CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020579

TRADE NAME: Flomax 0.4 mg capsules

GENERIC NAME: Tamsulosin hydrochloride

SPONSOR: Boehringer Ingelheim Pharmaceuticals, Inc.

APPROVAL DATE: 04/15/97

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-579

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Mr. Peter P. Fernandes, M.Pharm.
Associate Director, Drug Regulatory Affairs
P.O. Box 368
Ridgefield, CT 06877

APR 15 1997

Dear Mr. Fernandes:

Please refer to your new drug application dated April 15, 1996, received April 15, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flomax™ (tamsulosin hydrochloride) Capsules, 0.4 mg.

We acknowledge receipt of your submissions dated May 21, June 28, July 11, August 6 and 16, and December 13 and 18, 1996; and January 10 and April 1, 10, 14 (2) and 15 (3), 1997. The User Fee goal date for this application is April 15, 1997.

This new drug application provides for the use of Flomax for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated April 15, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician and patient labeling dated April 15, 1997, and the draft carton and container labeling dated October 7, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-579. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated April 10, 1997. These commitments, along with any completion dates agreed upon, are listed below.

Please submit protocols, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application a status summary of your commitments. The status summary should include expected completion and submission dates and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Terri F. Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APR 14 1997

DIVISION DIRECTOR MEMO TO FILE

Date: April 14, 1997

NDA: 20-579

Product: Flomax (tamsulosin hydrochloride)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

****

This new drug application was submitted April 15, 1996 for Flomax (tamsulosin hydrochloride) as indicated for treatment of the signs and symptoms of benign prostatic hypertrophy (BPH). I concur with Dr. Jolson, Deputy Director, as well as the NDA review team that this application is approvable.

Several issues raised in the review process and described in the action package require clarification.

Issues related to appropriate dosing, description of selectivity for specific alpha receptors, adequate information regarding the risk of orthostatic hypotension and elimination of references to statistical testing at time points other than those intended per protocol have been discussed with the review team and with the sponsor. Appropriate labeling, which addresses these concerns, is now included in the action package.

In terms of Phase IV commitments recommended by the review team:

> I agree with the proposal to allow the submission of information related to *in vitro* dissolution and metabolic testing to be post-approval. The sponsor has performed this study and we anticipate submission of results within the next six months.
>
> The biopharmaceutics review also raises the issue of a possible drug interaction study between tamsulosin and other alpha-adrenergic blocking agents.
>
> > On discussion with the biopharmaceutics review team it seems that this was a misunderstanding of the MO reviewer's concern for possible drug interactions of tamsulosin with a 5-alpha reductase inhibitor.

A drug interaction study between tamsulosin and other alpha-adrenergic blocking agents is not recommended as this product is specifically labeled (in the Drug-Drug Interactions section of the prescribing information) NOT to be used in combination with alpha-adrenergic blocking agents. The possible requirement for a drug interaction study of the combination of tamsulosin with a 5-alpha reductase inhibitor is discussed below.

The MO review raises two issues for possible post-approval consideration:

I agree with Dr. Jolson that the first issue--further quantifying the incidence of retrograde ejaculation--is not a required commitment for approval. The information regarding the observation of a dose-dependent effect on retrograde ejaculation is included in the current label.

Unless the sponsor intends to make claims regarding the combined safety and effectiveness of tamsulosin in combination with a 5-alpha reductase inhibitor, I collude that this sponsor should not be required to undertake such a study. We look forward to the results of an NIH sponsored study which is evaluating the efficacy of other approved alpha adrenergic blocking agents in combination with finasteride (a 5-alpha reductase inhibitor) for this indication.

Recommendation

I concur with the review team to recommend approval for this application and have forwarded the action package to Dr. Bilstad, Director, ODE II, for review and final recommendation.

D Williams 4-14-97

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products
HFD-580

cc:
NDA 20-538
HFD-580
JFourcroy/HJolson/LRarick/TRumble\\wpfiles\20579.d

APR - 9 1997

Group Leader Memorandum

NDA:	**20-579**
Drug and indication:	**Flomax™ (tamsulosin hydrochloride) for treatment of the signs and symptoms of benign prostatic hypertrophy (BPH)**
Dose:	**0.4 mg orally once daily (two 0.4 mg capsules once daily for men who fail to respond to the 0.4 mg dose)**
Applicant:	**Boehringer Ingelheim Pharmaceuticals, Inc.**
Submission received:	**April 15, 1996**
Date of MO review:	**April 4, 1997**
Date of Memorandum:	**April 5, 1997; revised April 8, 1997**

In this application, the sponsor requests approval for a selective adrenergic receptor antagonist for the treatment of the signs and symptoms of benign prostatic hypertrophy (BPH). The sponsor claims that this α-antagonist is more selective for the 1a receptors of the prostatic smooth muscle than for receptors at other sites. In support of the request for approval, the sponsor has submitted the results of five controlled studies of which two studies (US92-03A and US93-01) provide the primary evidence of safety and efficacy. Together, these two studies randomized 1486 men with the signs and symptoms of BPH to receive either tamsulosin 0.4 mg or 0.8 mg, or placebo for 13 weeks of treatment. Primary efficacy parameters included: 1) changes from baseline in total American Urological Association (AUA) Symptom Score, and 2) changes from baseline in peak urine flow rate.

I concur with Dr. Fourcroy, the primary medical reviewer, that this application is approvable and that the efficacy of this product based on the previously noted efficacy parameters is comparable to other products in its class. Tolerability with this product during the conduct of the clinical trials was generally acceptable, however notable adverse experience with dosing includes: orthostasis and associated symptoms (as with other products in this class) and retrograde ejaculation.

Issues of note at the time of this regulatory action include:

1. **Dosing**

The sponsor has requested that the label provide a recommendation for dose escalation to 0.8 mg for men who fail to respond to the 0.4 mg dose. Unfortunately, in the clinical trials, men were randomized to the lower and higher dose, rather than allowing for titration-to-effect. Not surprising, these trial detected no significant differences in

efficacy between the 0.4 and 0.8 mg doses. However, because there were small numerical trends in favor of the 0.8 mg dose, it would seem reasonable to offer the higher dose to non-responders provided that the label and promotion are explicitly clear that 0.4 mg is the recommended initial dose.

2. Phase IV requests

As noted in the biopharmaceutics reviews, the sponsor will be requested to conduct appropriate

Additionally, Dr. Fourcroy raises two interesting research questions in her review: (1) further quantifying the incidence of retrograde ejaculation, and (2) studying the efficacy of this product in combination with a 5-alpha reductase inhibitor. Requests for commitments to undertake these studies will not be requested at this time because: (1) the observation of a dose-dependent effect on retrograde ejaculation is already discussed in the label; and (2) while the efficacy of other α-antagonists with finasteride is being evaluated by an ongoing NIH study, this investigation was not a phase IV commitment for the respective sponsors. Further, from the safety perspective, there is no *in vitro* evidence of an effect of finasteride on the metabolism of tamsulosin in pooled human liver microsomes. Therefore, because tamsulosin in combination with a 5-alpha reductase inhibitor is likely to used clinically, the sponsor will be encouraged to study the safety and efficacy of tamsulosin combination therapy, however a phase IV commitment will not be requested.

3. Selectivity

The sponsor has requested that tamsulosin be designated as selective for alpha 1a receptors. (Of the two approved comparable products for BPH, only doxazosin makes the similar claim of alpha 1c selectivity). Based on Dr. El Hage's interpretation of the submitted data, it appears that tamsulosin binds to alpha 1 receptors in the human prostate more selectively than to those in the aorta; additionally there is data demonstrating that the alpha receptors in the human prostate are approximately 60-70% of the alpha 1a subtype. In the absence of clearly interpretable preclinical data, this human data provides at least indirect evidence to support the sponsor's claim of selectivity. Further, because current literature suggests that the 1a subtype is identical to 1c, Dr. El Hage recommends that the doxazosin label be updated to reflect the current status of the nomenclature for these receptor subtypes.

4. Labeling

Substantive labeling issues to be resolved at the time of this memo include the following:

a. Providing balanced information on the potential for orthostasis with this product. The sponsor proposes a label that provides a warning about the

potential for syncope and hypotension (as with other drugs in this class) however provides the very low "reporting" rates of this adverse event. To provide balance, we have requested that the sponsor additionally include data about the much higher frequency of detection of orthostasis on serial testing to alert the prescriber that orthostatic symptoms may be encountered more frequently during marketing.

b. Need for clarification regarding the lack of significant differences in efficacy between the 0.4 mg and 0.8 mg doses (and the observation of higher rates of retrograde ejaculation at the 0.8 mg dose).

c. Elimination of references to statistical testing at timepoints other than at the primary endpoint (13 weeks).

Heidi Jolson M.D.

Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-579
HFD-580/LRarick/JFourcroy/HJolson

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DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-579 Trade (generic) names Flomax (tamsulosin HCl)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

2/28/97
Date

cc: Orig NDA
HFD-550 Div File
NDA Action Package

13.0 PATENT INFORMATION

Patent Number:	4,731,478 Expires October 27, 2004 Type of Patent: This patent covers the drug per se and the pharmaceutical formulation thereof.
Patent Number	4,703,063 Expires October 27, 2004 Type of Patent: This patent also covers the drug per se.
Patent Number:	4,772,475 Expires February 27, 2006 Type of Patent: This patent covers the controlled release pharmaceutical composition.
Patent Number:	4,868,216 Expires September 19, 2006 Type of Patent: This patent covers producing alpha adrenergic antagonistic action in a host. Thus this patent covers the proposed indication for the subject product.

Certification

The undersigned hereby certifies that on information and belief the above patent information is correct and that in the opinion of applicant and to the best of its knowledge, applicant enjoys such protection with claims for its drug product and drug substance as well as for the approved use thereof sought in this application.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By: _____

Robert P. Raymond
Attorney for Applicant
Registration No. 25,089

Date: March 29, 1996

Tamsulosin Hydrochloride Capsules, 0.4 mg

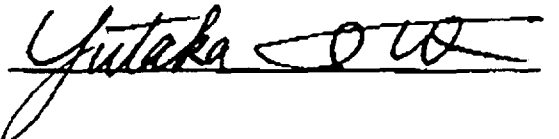
NEW DRUG APPLICATION
Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877

CERTIFICATION: DEBARRED PERSONS

CERTIFICATION REQUIREMENT

Section 306(K)(1) of the Act; 21 U.S.C.335a(k)(1)

The undersigned certifies, that, Yamanouchi U.S.A. Inc.
did not and will not use in any capacity the services of any person
debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with
Tamsulosin Hydrochloride Capsules.

Signature 

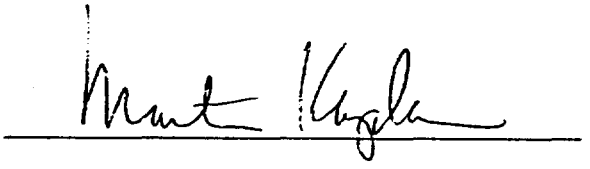
Name of Responsible Official : Yutaka Ito, D.V.M.
Vice-President, New Drug Development
Yamanouchi U.S.A., Inc.

Mailing Address: Yamanouchi U.S.A., Inc.
10 Bank Street, Suite 790
White Plains, NY 10606

CERTIFICATION REQUIREMENT

SECTION 306(K)(1) OF THE ACT: 21 U.S.C.335a(k)(1)

The undersigned certifies, that, to the best knowledge and belief of the undersigned, Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], in connection with Tamsulosin Hydrochloride Capsules.

Signature 

Name of Applicant: Martin Kaplan, M.D., J.D.
Director, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Mailing Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O.Box 368
Ridgefield, CT 06877

APR - 5 1997

MEDICAL OFFICER'S REVIEW OF TAMSOLUSIN NDA
NDA 20-579

Table of Contents

1.1.1 NDA 20-579

1.1.2 Medical Officer Review

1.1.3 Submission April 15, 1996

1.1.4 Review completed March 22, 1997

1.2 Drug name

1.2.1 Generic name Tamsulosin hydrochloride

1.2.2 Proposed trade name - Flowmax

1.3 Sponsor - Boehringer Ingelheim

1.4 Pharmacologic Category: Defined by sponsor as an adrenergic receptor antagonist type - *alpha* 1c

1.5 **Proposed Indication:**

Treatment of patients with the signs and symptoms associated with benign prostatic hyperplasia (BPH).

1.6 Dosage form(s) and route(s) of administration:
0.4 mg capsules in a Modified Release form to be taken orally once a day.
Patients taking 0.8 mg dose will take two capsules orally once a day.

1.7 NDA Drug Classification - S

1.8 Important Related Drugs - see review of drug treatment for BPH and the current approved and investigational studies with adrenoceptor antagonists on page A-5.

1.9 Related Reviews See reviews of statistics and biopharm.

2 Table of Contents - See page A-1

3 Material Reviewed

and electronic versions submitted by sponsor
volume 1.1 - the entire NDA is well indexed.

Volumes Reviewed

Volume	Trial	Dat
1.0011	Application Summary	
1.098-1.369	Clinical Data	
1.098 and 1.099 1.188 synopsis 1.188 - 1.219	US92-03A*	U95-3258
	US93-01*	U95-3259
	91-HAR-01	U95-3276
1.345		
Volume 1 - 90 (1 and 2)	Safety Update 1	October 23, 1996
Volume 1 - 10 (1 and 2)	Safety Update 2	January 31, 1997
	92-HAR-02	U95-3277

	92-HAR-01	U95-3278
	Extension US92-03B	U95-3260
Volume 1 (of 90) 10/24/96	Safety Update I	
Volume 1 1/97	Safety Update II	

*Pivotal trials

There were a total 47 clinical trials with tamsulosin.

4 Chemistry/Manufacturing Controls

See Chemistry review.

5 Animal Pharmacology/Toxicology

See Pharmacology Review

6 Clinical Background

Treatment of BPH

Benign prostatic hyperplasia or hypertrophy (BPH), or lower urinary outlet obstruction, is a chronic and progressive condition; it is not one disease but represents a common pathway of multiple problems. The term lower urinary tract dysfunction in men should be used for men with lower urinary tract symptoms or other manifestations thought to be prostate-related , but with insufficient evidence to merit the more specific term bladder outlet obstruction.

Although the growth of the prostate with age is now well documented, less than twenty-five percent of men will require therapeutic intervention for the growth of the prostate. Many variables enter into the decision and the symptoms for which intervention is required will vary widely between each individual. These factors will include behavioral and social expectations, anatomic location of the prostatic growth, and histological elements of the prostate, e.g. neural, stromal, or epithelial.

The stromal and epithelial components of the prostate that obstruct the bladder outlet have been referred to respectively as the dynamic and the mechanical portion of the obstruction. The size of the prostate or prostate volume is not a predictor of obstructive or irritative symptoms. No matter what is the prostate volume it is the gland around the prostatic or posterior urethra which can block or obstruct the passage of urine from the bladder. This obstruction or lower tract dysfunction can be purely mechanical or secondary to dynamic changes in the tone of the muscle cells within the prostate gland.

Mechanical obstruction. The epithelial portion of the prostate gland probably represents approximately 30% of the total prostate gland when histologically evaluated. It is this epithelial component which is exquisitely sensitive to the metabolite of testosterone, dihydrotestosterone. Finasteride or PROSCAR was designed to intervene with the prostate volume growth by blocking the epithelial or adenomatous portion of the prostate by blocking the metabolism of testosterone to dihydrotestosterone. In addition to the continuous growth of the epithelial or adenomatous portion of the prostate, there are probably some areas of the posterior urethra where the increased tissue is more critical in obstructing the flow of urine. One important area may be at the transitional zone of the prostatic urethra. This may be the site of renewing prostate stem cells.

If outlet obstruction and the associated symptoms depended only on the overgrowth of epithelial cells it would be expected that the majority of men with symptoms would benefit from this therapy. It is known from the Finasteride studies that the benefit of blocking dihydrotestosterone is of benefit to only 1 in 10 men. Recent unpublished data suggests that prostatic tissue response may not be distributed evenly throughout the prostate tissue. Some areas of the tissue may appear atrophied and others unchanged. Some men may also benefit from the use of LHRH analogs, e.g., leuprolide, directed to diminishing the volume of the prostate.

Dynamic obstruction The second major component of outlet obstruction is the dynamic portion. The smooth muscle cells and the true capsular components and perhaps other cellular components of the prostate are rich in alpha adrenergic receptors. These receptors are abundant in the prostate and bladder neck and the endothelial cells of the prostatic region. There is evidence that increased tone of these cells contributes to their tonic contraction. The use of adrenergic blockers is based on the concept that relaxation of the stromal components is thought to relax and widen the posterior urethra, prostatic tissue and the bladder neck. Similar to treatment of the adenomatous component of the prostate it is not expected that this treatment will be of benefit to each individual although there is a higher percentage of stromal cells with adrenergic receptors in the prostate gland than epithelial cells. It is also expected that if blocking this adrenergic component is effective it will be so in a small proportion of men. The lasting effect of this treatment is unknown since the epithelial components of the prostate continue to grow.

THE PLACEBO EFFECT AND THE PROSTATE. The role of the placebo effect in all trials evaluating the response to drug therapy and the prostate is tremendous. The placebo response has ranged from 30 to 50%. Controlled trials without a large placebo response should be suspect. A comparison can be made to the Ornish effect and relaxation of the capillaries in the heart with behaviorial modification. A reduction of stress should lead to a relaxation of the adrenergic tone and a decreasing resistance of the cells (endothelial or prostatic muscle) with

alpha receptors. Relaxation of these cells should lead not only to improved symptoms or irritation and obstruction but improve the flow of urine. Education is also an important element involved in treatment of BPH with placebo or watchful waiting. Voiding is a complex phenomenon and requires contraction of the vesical or bladder muscle while relaxing the urethral component. Synergistic voiding patterns must include a contraction of the bladder or vesical muscle in concert with the relaxation of the urethral muscle and prostatic capsule. Voiding patterns and thus irritative symptoms improve with improved patterns of voiding and by avoiding dysynergia. Individuals with high stress or little time often do not coordinate this pattern appropriately. Many men who were treated for BPH may not have needed any treatment and might have benefited from "watchful waiting" and/or stress reduction.

Approved and Investigational drug treatments for BPH

Generic name	Trade name	Current	IND/NDA
5 alpha reductase inhibitors			
Epristeride (SKF 105657)	not active	inhibitor not in trials	
Finasteride*	Proscar	inhibitor	NDA 20-180
G1198745			
191704			
320236			
300502			
306089			

Alpha Adrenoceptor Antagonists			
alfuzosin			IND
doxazosin*	Cardura		NDA20-371
GI 123818			IND
indoramin			not in U.S.
prazosin	Minipress		not BPH
RS 97078			IND
RS 70-0004 /alpha 1L	(RS-100975)		IND
SB216,469			IND
tamsulosin (YM617)	Flowmax	Yamanouchi/BI	NDA20-579
terazosin*	Hytrin	Abbott	NDA20-223

* *Approved drug treatments for BPH*

Other modes of investigational therapy		
SB 217242		Endothelin Receptor antagonist

History of Alpha adrenergic receptors

Alpha 1 adrenergic receptors are found in the prostate and bladder neck and appear to mediate the contraction of the smooth muscle at the bladder neck, prostastic capsule and the prostate. These drugs e.g. terazosin and doxazosin,appear to be currently the most commonly prescribed medications for men with symptoms of lower outlet obstruction.

The use of alpha 1 adrenergic antagonists or selective antagonists followed the use of the alpha blockers for the treatment of BPH in 1976 by Marco Caine in Israel. Phenoxybenxamine was the first such drug used. Terazosin is one of many alpha 1 selective antagonists. Others include: prazosin (minipress - approved in several countries for BPH), doxazosin (Cardura- approved for hypertension and BPH symptoms) , and alfuzosn (Italy/France), indoramin, and nicergolin. Current research suggests that future antagonists will be more selective and block specific alpha 1a subtype receptors. This has not yet occurred.

The alpha adrenergic antagonists are thought to selectively block the alpha 1 adrenergic receptors without affecting the alpha 2 adrenergic receptor. Prazosin, terazosin, and doxazosin are the agents available for the treatment of hypertension and others are being developed, e.g. trimazosin. Investigational drugs such a ketanserin, indoramin, and urapidil may owe a major portion of their antihypertensive effects to blockade of these receptors.

The preliminary work on these receptors was originally done at Johns Hopkins by Drs Lepor and Shapiro and Dr Marco Caine in Israel. There has been ongoing work with many adrenergic blockers both in this country and outside of the U.S.

The current terminology of the alpha adrenoceptor antagonists is in flux . Three native alpha1-adrenoceptors with high affinity for prazosin are termed alpha1A, alpha1B and alpha 1D. The cloned counterparts are now termed alpha1a, alpha1b, and alpha1d. A recent review suggests that alpha 1A-AR (formerly alpha 1C) subtypes mediates contraction of human prostatic smooth muscle. The fingerprint of the alpha1L-AR is characterized by the low affinity for prazosin.

The term selective may be a misnomer as there still appears to be some confusion regarding the classification of these receptors and the corresponding antagonists. The original subdivision of the alpha 1 adrenoceptors was

derived principally from ligand-binding studies and the affinity for prazosin. Improved selectivity should be seen with decreased effects associated with generalized endothelial cell relaxation causing hypotension. Tamsulosin may be the most potent in abolishing a response. The order of potency appears to be tamsulosin, prazosin, alfusozin, terazosin and doxazosin.

The mechanism of action of AR drugs is thought to be relaxation of the appropriate stromal components in and around the prostate and thereby widening the prostatic urethra.

Safety profile of alpha blockers.

The safety issues include the effects of alpha 1 adrenoreceptor antagonists, e.g., asthenia (tiredness), dizziness, edema, postural hypotension, and weight gain. Of these, postural hypotension has been the most important adverse effects of these compounds. It is important to titrate the initial doses of both terazosin and doxazosin because of the first dose effect of these compounds. This has been noted in the label of each of these drugs. The adverse experiences of dizziness may encourage the patient to take smaller doses of the drug or perhaps an ineffective dose. Retention of water, hyperprolactinemia and mammary gland proliferative changes have been noted in animal but not human studies.

Previous Clinical Trials:

The primary endpoints used in BPH trials have been the improvement demonstrated in the measurements of the peak urinary flow and the improvement in the symptom scores using a validated instrument. These were the primary endpoints for the finasteride trials. The terazosin trial did not use a validated symptom score but measured symptom improvement using the Boyarsky score which was developed in the 1970s.

An interesting characteristic of patients in BPH trials is the large placebo effect. Between 30 and 50% of the patients have clinical improvement of the signs and symptoms of BPH. Patients willingly remain on clinical trials even while on placebo. This may also reflect the large variability of signs and symptoms with size of the prostate gland.

The first drug to be approved for the treatment of BPH was finasteride (Proscar). Finasteride inhibits the conversion of testosterone to dihydrotestosterone and diminishes the volume and epithelial cell component of prostate. Adrenergic receptor (AR) antagonists were first approved for the treatment of hypertension. This class of drugs does not alter the androgen profile nor diminish the volume of the prostate but acts by relaxing the adrenergic receptors in the stroma and smooth muscle of the prostate and the bladder neck. The first AR antagonist

approved for the treatment of symptomatic benign prostatic hyperplasia was terazosin (Hytrin). In the terazosin studies sponsored by Abbott three pivotal studies were submitted: M87-005, M87-012, and M89-370. There were a total of 671 patients - 414 on active drugs and 257 on placebo. The second AR antagonist to be approved for this indication was doxazosin (Cardura). In the doxazosin studies sponsored by Pfizer three pivotal studies were submitted: 421, 488, and 490. There were a total of 609 patients - 460 on active drugs and 149 on placebo.

The following chart outlines the peak urinary flow and symptom scores at baseline and the treatment changes for the three drugs approved for the treatment of symptomatic BPH. The total symptom score range from 0 - 27 points for the AUA score, 7 - 39 for the Boyarsky score (Boy) and 0 - 36 for the Merck score. The accepted normal peak urinary flow is ≥15 ml/sec.

Comparison of Approved BPH Drugs

Drug	Qmax ml/sec at Baseline Rx(Pbo)	Qmax ml/sec change at endpoint Rx(Pbo)	SSX at Baseline Rx(Pbo)	SSX change at endpoint Rx(Pbo)
doxazosin (**Cardura**)	10.8 (10.3) 9.6 (9.9) 9.8 (9.7)	2.8 (0.6) 2.6 (2.1) 2.9(0.7)	26.1/25.8) 16.5 (15.0) 14.2 (15.6) AUA / Boy	4.0 (2.9) 6.0 (3.9) 5.7 (2.5)
terazosin (**Hytrin**)	8.6 (8.8) 8.4 (8.8) 9.0 (9.9)	2.6 (1.2) 2.9 (1.4) 3.1 (0.9)	10.0 (9.7) 10.9 (13.5) 11.1 (11.0) Boyarsky	4.4 (2.1) 5.2 ((1.4) 4.6 (3.5)
finasteride (**Proscar**)	9.6 (9.6) 9.2 (8.6)	1.6 (0.2) 1.3 (0.4)	10.1 (9.8) 10. 6 (10.2) Merck	3.9 (2.5) 2.6 (1.0)

Peak Urinary Flow-Qmax ml/sec, Symptom Score - SSX (negative numbers);
Rx = treated;Pbo = placebo.
The three trials for doxazosin are 421, 488 and 490 and for terazosin 005, 012, and 377. The two trials for finasteride were International - 507 and Domestic - 508.

Prostate Cancer Issues

Prostate cancer and BPH may share characteristics and it is important to delineate the two diseases. An upper limit of Prostate Specific Antigen (PSA) of 4 or 10 ng/mL has been an exclusion in clinical trials. There is no evidence that drugs other than 5 alpha reductase inhibitors alter PSA serum levels. Age and race specific reference ranges may provide more accurate exclusion criteria.

6.1 Foreign experience with tamulosin:

Approved in Japan, The Netherlands, Finland, France, Denmark, Sweden, New Zealand. The drug has not been withdrawn from investigation or marketing in any country.

6.2 Human Pharmacology, Pharmacokinetics, Pharmacodynamics
see Pharmacology review.

6.5 Other background information:

The sponsor provided a but computer problems made it mostly unaccessable. The original IND was filed by Eli Lilly in 1987. The ownership was transferred from Yamanouchi to Boerhinger Ingelheim 11/28/94.

7 Description of Clinical Data
See listing of data sources under material review on page A-2.

7.1 Post-Marketing Experience
Note the countries were tamsulosin is approved (6.3).

8 Clinical Studies

The sponsor has submitted eleven controlled clinical trials. A total of 3497 patients were randomized in 10 controlled short-term studies which were conducted in the United States, Europe and Japan. (1881 patients in the United States, 955 Europe and 618 Asia for a total of 3454 - Safety Update of October 1996.) The emphasis of this review is on studies 92-03A and 93-01; these are the two pivotal trials.

Tamsulosin Controlled Clinical Trials		
Study	Time	Alternate name
US92-03A*	13 weeks (0.4/0.8 mg)	U95-3258
US93-01*	13 weeks (0.4/0.8 mg)	U95-3259
91-HAR-01	12 weeks (0.4 mg)	U95-3276
92-HAR-02	12 weeks (0.4 mg)	U95-3277
92-HAR-01	12 weeks (0.4 mg/alfuzosin 2.5 mg bid/tid)	U95-3278
Dose-Finding Studies		
US90-01	8 weeks (.1/.2 mg)	U95-3256
90-HAR-01	4 weeks (.2,4,.6 mg)	U95-3273
M6172/8051	4 weeks (.1,.2,.4mg)	U95-3287
M6173/BCT1	4-6 wks (0.2 mg)	U95-3288
M5173/BCT2	16 weeks (O.2 mg 0/chloramadinone 25 mg BID	U95-3289
US92-03B	40 weeks (0.4/0.8mg) Long range extension	U95-3260

**Conducted in U.S.*

As of the cutoff date for the Safety Update 2 (January 1997) a total of 6336 patients or volunteers were included in a total of 68 clinical studies conducted during the development of tamsulosin. The following table notes the extension studies of the controlled clinical trials.

Tamsulosin Extension Studies			
Protocol	# Patients	Mean Rx weeks	Range weeks
US93-04	949	68.6	
01085	604	144.5	
92HAR-02	355	113.1	
02HAR-03	160	1155.2	
M6173/LLN1	136	40.6	

8.1 Trial # US92-03A - Tamsulosin CR-M

Tamsulosin Pivotal Trial				
US 92-03A Other names YM617 U95-3258	39 investigators 10 clinical centers	Ages Mean age 58.6	• 0.8 mg q.d. (12 weeks) after 0.4 mg q.d. (1 week) • 0.4 mg q.d. x 13 weeks • Placebo 13 weeks	— N= 248 254 254
Dates: November 2, 1992 - October 4, 1993				

This was a multicenter placebo-controlled study in patients with the signs and symptoms of benign prostatic hyperplasia which included three treatment groups - two dosages groups, 0.4 mg q.d. and 0.8 mg q.d. of Modified Release Tamsulosin and one placebo group. After 4 weeks of a single-blind placebo baseline evaluation period, patients were randomly assigned to one of the three treatment groups. All patients were treated with 2 placebo capsules in the morning for 4 weeks.

Principal Urologists and Centers:

Michael Witt, Murray Lieberman, Larry Frank, Robert Dowling, Preston Packer, Andrew Moore, George Ellis, Barry Krumholz, Israel Barken and Richard Bruneel. The study centers were located in Atlanta, Bethesda, Dallas, Fort Worth, Hollywood, Indianapolis, Orlando, Phoenix, San Diego, and Tampa.

The patients who met the inclusion criteria were randomly assigned to one of the following therapies:

- 0.8 mg q.d. for 12 weeks after 1 week of 0.4 mg q.d.
- 0.4 mg q.d. for 13 weeks
- Placebo q.d. for 13 weeks

8.1.1 Objectives

1. To confirm the effectiveness of 0.4 mg q.d. and 0.8 mg q.d. of tamsulosin for use in the treatment of patients with the signs and symptoms of benign prostatic hyperplasia (BPH).

2. To confirm the safety of 0.4 mg q.d. and 0.8 mg q.d. of tamsulosin in patients with BPH.

The primary response variables for the evaluation of efficacy were Total Symptom Score (AUA) and Peak Urine Flow Rate (Q_{max}) at the final visit (Endpoint #1) during the double-blind treatment period relative to the baseline value. All other efficacy evaluations were considered supportive.

8.1.2 Design

This was a double-blind, randomized, parallel-design, multicenter Phase III clinical trial in which tamsulosin was compared to placebo for the treatment of the signs and symptoms of infravesical obstruction associated with benign prostatic hyperplasia.

8.1.3 Protocol

The patients were screened at 14 study centers. During the first four weeks, all patients who satisfied the requirements at the screening visit and Visit 1 were treated with placebo and underwent further evaluations, e.g., urodynamic measurements, determination of post-void residual urine volumes, and urine tests. Medication and visit compliance were assessed. Concomitant medications that could interfere with the activity of tamsulosin, or influence the symptoms associated with BPH were not allowed (see inclusion and exclusion criteria).

For this study male patients had to be at least 45 years old with the signs and symptoms of BPH. At each of the three visits in the single-blind placebo evaluation period, which were visits 1-3, the patient was required to have: a total score on the AUA Symptom Score questionnaire for BPH ≥ 13; and bladder outlet obstruction defined as a peak urine flow rate (Q max) ≥ 4 and $\leq$ 15 ml/sec as measured by the Dantec Urodyn 2000 machine. During this testing procedure, the patient was required to void a total urine volume of $\geq$ 125 mL.

Each patient was to be in the study for approximately 17 weeks. This included 4 weeks of placebo during the baseline period, and 13 weeks of double-blind therapy (91 days).

A total of 7446 patients were screened, of which 3574 entered the single-blind placebo evaluation period at Visit 1. 1934 patients (54%) failed to meet the study entry criteria, 387 (11%) patients discontinued because of laboratory abnormalities on randomization measurement and 403 (11%) patients discontinued for other reasons. See Table below, which shows the number of patients included and analyzed in Study 92-03.

Study 92-03				
92-03A	Tamsulosin		Placebo	Total
	0.8 mg	0.4 mg		
Randomized	248	254	254	756
Randomized Patients Discontinuing Study	50	41	47	138
Safety Population	248	254	254	756
Efficacy-Analyzable	199	199	207	605
Completed Study	198	213	207	618
<4weeks	28	26	26	
Took prohibited med 1-3 wk	19	30	19	
US92-03B extension				
enrolled in US 92-03B	144	142	132	418
Safety population	139	139	128	406
Intent-to-treat population	135	138	127	400
Number pts in SAF pop who discontinued therapy	38	19	26	
Number of patients that completed 03B	101	120	102	323

The patients who are qualified at the end of the placebo evaluation period were randomly assigned to one of the following 3 treatment groups. During the 13-week double-blind period, each patient returned to the study center 5 times to be evaluated for the efficacy and safety of their treatment.

The patients were blinded for the entire study period [4 weeks of placebo evaluation + 13 weeks of double-blind treatment period]. The investigator was blinded throughout the 13 weeks of treatment.

All of the medications for the placebo baseline period, and the 13-week double-blind treatment period were to be identical in appearance and

packaged in an identical manner. Patients took 2 capsules once a day throughout the entire study period. These were to taken orally approximately 30 minutes after breakfast.

Dosing Regime	
Dose	**Capsules - 0.4 mg**
0.8 mg dose:	2 capsules
0.4 mg dose:	one capsule + one placebo capsule
placebo dose:	two placebo capsules

A set of individual key codes in a sealed envelope was provided to the investigator for emergency use.

The results of the tests performed at Visit 3 were used to establish the baseline. The other results used for baseline were the Visit 2 post-void residual urine volume. At each follow-up visit, and at the end of the double-blind therapy, efficacy and safety measurements were performed.

After all assessments have been completed at Visit 10, patients were offered the opportunity to enter in an open-label long-term extension study. They received the same double-blind regimen and dose as in 92-03A.

8.1.3.1 Population, procedures

Enough patients were to be screened in order to achieve at least 690 patients to qualify for randomization, receive at least one dose of double-blind medication, and provide at least some follow-up efficacy evaluations. After completing the placebo evaluation period eligibility requirements, patients were randomly allocated to one of the three treatment groups, so there would be approximately 230 patients per treatment group.

Inclusion Criteria:

Males who are 45 years of age.

Patients from whom written informed consent is obtained before performing screening examinations or tests.

Patients with a total score on the AUA Symptom Index for BPH of 13 at each of the 3 visits (Visits 1, 2, and 3).

Bladder outlet obstruction as defined by a peak urine flow rate (Qmax) 4 and 15 ml/sec as measured by the Dantec Urodyn machine. The peak urine flow rate was required to be within this range at each of the 3 visits (Visits 1, 2, and 3).

Patients who had to be able to void a total volume of 125 ml at each of the 3 visits (Visits 1, 2, and 3). If the patient fails to void 125 ml and his Qmax is 15 ml/sec or less at either visit during the placebo evaluation period, another uroflowmetry test will be performed. It was advised that the patient wait about 3 hours after the first test, but the patient could attempt this second test when he felt ready. The second test had to be performed on the same calendar day as the first test. A test performed on another calendar day was not acceptable.

A post-void residual urine volume of <300 ml at Visit 2.

Patients must be able to follow protocol procedures including the return visit schedule and the completion of tests related to safety and efficacy.

Exclusion Criteria:

Patients with any of the following characteristics will be excluded from the study:

Patients with a history of an allergy to alpha blockers, alpha/beta blockers or patients who have had a "first dose hypotensive episode" upon starting therapy with an alpha blocker.

Patients who are currently being treated or who, in the last 3 months, have been treated with Proscar®.

Patients who participated in an investigational drug study within the last 3 months.

Patients taking medication in the following classes and unable to discontinue prior to Visit 2 and for the duration of the study:

a) Alpha adrenergic blocking drugs
b) Alpha adrenergic agonists
c) Drugs with anticholinergic activity (including antihistamines)
d) Antispasmodics
e) Parasympathomimetic and cholinomimetic

Peripheral or central neurologic disease including:

transient ischemic attacks, stroke, dementia, multiple sclerosis, spinal cord injury, recurrent episodes of dizziness, vertigo, or loss of consciousness, clinically evident diabetic neuropathy, brain and/or spinal cord tumors.

History of a pathological fall (unintentional change in body position) occurring under circumstances in which normal homeostatic mechanisms would ordinarily maintain stability, or syncope during the last year.

Ambulation requiring assistance (i.e., canes, walkers, etc.).

More than one episode of angina during the prior 6 months.

Documented myocardial infarction (by EKG) during the prior 6 months or evidence of a myocardial infarction on EKG whose age cannot be determined.

New York Heart Association class III or IV congestive heart failure

Prosthetic heart valves, cardiac devices or prior history of endocarditis.

Either of the following findings confirmed by repeated orthostatic tests

I. Diastolic blood pressure < 65 mm Hg in supine position.

ii. Diastolic blood pressure < 65 mm Hg 3 minutes after standing.

iii. Pulse rate > 120 beats per minute 3 minutes after standing.

iv. The presence of physiological or clinical symptoms with a change in posture.

Clinically significant cardiac arrhythmias as diagnosed by EKG whether or not accompanied by symptoms (e.g., dizziness, presyncope, syncope, unsteadiness).

Intravesical obstruction due to:

a) Vesical neck contracture
b) Clinical suspicion of prostate carcinoma
c) Muellerian duct cysts
d) Urethral obstruction due to stricture/valves/sclerosis or urethral tumor
e) Inflammatory or infectious conditions
f) Bladder calculi
g) Detrusor-sphincter dyssynergia

Prior TURP or open prostatectomy.

History of instrumentation of the urinary tract (cystoscopy or catheterization) within 30 days prior to the start of the study.

Prior pelvic surgery for malignancy or bowel resection.

History or diagnosis of genitourinary malignancy.

History of an episode of urinary retention within three months prior to the start of the study.

Patients with the current diagnosis of either bladder, ureter, or kidney stones.

Patients with a history of drug and/or alcohol abuse within 1 year.

Patients with the current diagnosis of the prostatitis, which should be determined by the following procedure:

If the prostate is boggy in consistency and tender on the digital prostate examination, the prostatic secretions should be applied to a glass microscope slide, a cover slip will be placed, and the slide examined under a high power lens. If there are 10 bacteria and/or white cells per high power field, a presumptive diagnosis of prostatitis will be made.

Exclusion During the Placebo Evaluation Period:

Patients who show poor compliance in the initial placebo period by:

1) not returning medication cardboard sleeves at either Visit 2 or 3
2) having taken <80% or >120% of prescribed doses during any visit interval between Visit 1 and 3

Instrumentation of the urinary tract (cystoscopy or catheterization)

Any surgical procedure which requires general anesthesia

Postural symptoms during the initial placebo period, e.g., lightheadedness (on more than three occasions), fainting, blurring or loss of vision, profound weakness, or unsteadiness, with or without a change in blood pressure and/or pulse rate.

Unresolving changes in the blood pressure or pulse at any of the visit during the placebo evaluation period as defined by the following:

a. The diastolic blood pressure decreases below 60 mm Hg

b. A tachycardia of >120 beats per minute

Patients with poorly controlled diabetes mellitus [urine positive for glucose (>1+) on each of 2 urinalyses during the placebo evaluation period].

Patients whose results for any of the following clinical laboratory tests exceed the limits below:

Hemoglobin: <12.0 g/dl
Leukocytes: <2,500/mm^3

Liver Enzymes: More than twice the established upper limit of normal for the testing laboratory.

Urinary tract infection during the placebo evaluation period (i.e., a single positive urine culture yielding pathogenic bacteria 10^5 CFU per milliliter in a properly obtained, clean voided urine specimen which has been cultured within 2 hours after voiding).

An episode of acute urinary retention.

Hydronephrosis (demonstrated on abdominal ultrasound) or other abnormality of the kidneys, ureters, or bladder.

Evidence of renal dysfunction [elevated creatinine (>2.1 mg/dl)]

Patients with clinical evidence (hard nodules or suspicious areas of the prostate on digital examination), clinical suspicion of prostatic carcinoma, or an acid phosphatase 2 times the upper limits of normal or PSA values >6.0 ng/ml. The patient was to be discontinued from the study and referred to his urologist for future evaluation. The patient could be considered for future studies if his urologist provided documentation of a urological evaluation (which includes transrectal ultrasound and multiple biopsies of the prostate) that showed the patient to be free of prostatic carcinoma.

If PSA values were > 4.0 ng/ml but ≤ 6.0 ng/ml the patient was to be considered for continuation in this clinical study if he met all of the following three criteria:

1. The digital rectal examination of the prostate does not reveal any clinical evidence (hard nodules or suspicious areas of the prostate) of prostatic carcinoma
2. The results of the transrectal ultrasound examination are negative (i.e., no signs of a prostatic carcinoma)
3. The PSAD is < 0.10

8.1.3.2 Endpoints

The changes from baseline in the total AUA symptom score and the peak urine flow rate (Qmax) were used as primary efficacy parameters.

If a patient demonstrated the following symptomatic or urodynamic improvements, he was considered as a responder, and the response rate was compared among the treatment groups:

- An improvement (decrease) in the total AUA symptom score of at least 25% from the baseline score.
- An improvement (increase) in the peak urine flow rate (Qmax) of at least 30% from the baseline score.

Other urodynamic parameters (average flow rate, voiding time, flow time, time to maximum flow and voided volume), the total Boyarsky symptom score and each individual symptom score (both the AUA and the Boyarsky) were analyzed as secondary parameters of efficacy.

Patient's overall condition during the double-blind period compared with that of Visit 3 was also evaluated as Investigator's Global Assessment.

The observation at the final evaluable double-blind visit for each patient, provided the visit occurred either on the last day of double-blind medication dosing or on the day after the last day of double-blind medication dosing or if the last dosing day is unknown, the available data on the closest prior visit during the double-blind period i[illegible] as the endpoint. This was the primary endpoint for the study analysis.

A validated Quality of Life questionnaire was used to assess the effect of therapy. (The validation of all questions included in this instrument have not been verified.)

All patients were monitored for safety (vital signs, orthostatic test and information on adverse events) at each visit. At selected visits, the patients had a 12-lead EKG, and clinical laboratory tests performed.

8.1.3.3 Statistical considerations

See statistical review. Approximately 230 patients/group were to be evaluated for safety and efficacy on an intent-to-treat basis. For a specific pairwise treatment group comparison, the sample size was to provide 90% power to detect statistical significance at the two-sided p = 0.05 level for differences of about 30% of the expected standard deviation. A separate efficacy analysis was to be applied to those patients completing the study according to the protocol.

8.1.4 Results

756 patients entered study 92-03A. Of these, 138 dropped out and 618 completed the Phase III study. The sponsor notes that there was greater improvement in each of the tamsulosin treatment groups relative to the placebo group for all four primary efficacy parameters. These included: total AUA symptom score, the percentage of patients with≥25% improvement in total AUA symptom score, peak urine flow rate and the percentage of patients with ≥30% improvement in peak urine flow rate.

8.1.4.1 Patient Disposition, comparability

Demographic

	Demographics 92-03A		
Total N	248	254	254
Mean age	59.0	57.3	59.5
≤64	74%	70%	72%
Race			
Caucasian	92%	91%	90%
Black	6%	8%	10%
Asian/other	2%	2%	0
Disease Severity			
Severe≥20	121 (49%)	118 (46%)	114 (45%)
Moderate 8-19	127 (51%)	136 (54%)	140 (55%)
Boyarksy at baseline	10.7	11.1	11.0

Severity of disease based on AUA symptom score

There was a comparable distribution in ages among the three treatment arms.

8.1.4.2 Efficacy endpoint outcomes

The peak or maximum urinary flow rate was evaluated at each visit during the study at four to eight hours after with study medication using the Dantec Urodyn 1000 machine. The time-point used for the evaluation coincided with the estimated peak plasma level. The peak urine flow rate in this study

was measured during the estimated time of peak plasma concentration of drug or 4 to 8 hours after dosing.

A responder could be measured in several ways. One measurement noted the patients with percentage changes (30%) from baseline and a second measurement noted the percentage of patients who had an improvement of ≥3 mL/sec.

Mean change from Baseline to Endpoint #1

Qmax (mL/sec)

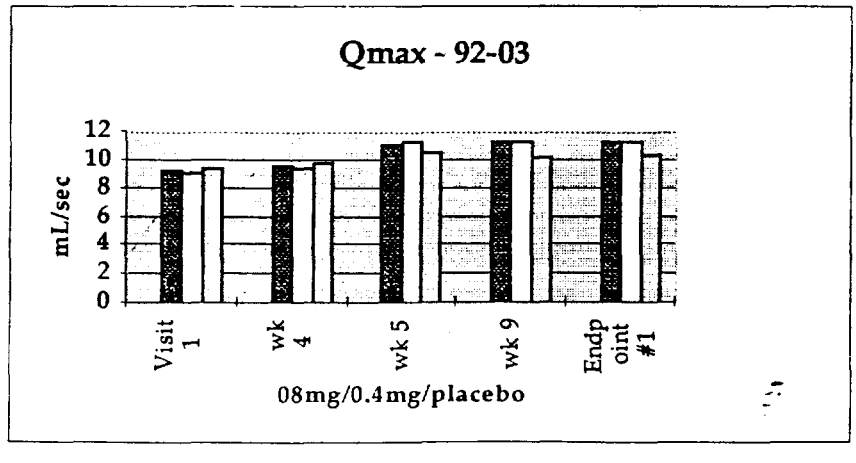
	Dose	Mean Baseline	N=#	Mean Change	RX- PBO	N=##
Qmax						
	0.8	9.57	247	1.78*	1.26	247
	0.4	9.46	254	1.75*	1.23	254
	placebo	9.75	254	0.52		253
Percentage Responders (30% from baseline)						
	0.8	36%	p=0.001	(vs placebo)	15%	88/247
	0.4	31%	p=0.002	(vs placebo)	10%	79/254
	placebo	21%				54/253

Percentage responders (EFF^)	
0.8	75 (38%)
0.4	59 (30%)
placebo	44 (21%)

*# at baseline ## at endpoint #1 * p value =0.001*

^ EFF- Efficacy analyzable population.

The chart below demonstrates the changes from Baseline to Endpoint 1 in the three treatment arms respectively from left to right: 0.8 mg, 0.4 mg and placebo in the peak flow rate. There is no difference between the 0.8 and 0.4 mg doses.



Peak Urine Flow Rate Responders
Improvement of > 3 mL/sec (ITT)

Visit	0.8 mg	0.4 mg	placebo	0.8 vs pbo	0.4 vs pbo	0.8 vs 0.4
Visit 4 week 5	27% 68/246	30% 77/254	21% 53/252	.121	.017	.406
Visit 5	21% 71/231	33% 81/242	14% 33/240	** .001	** .001	.144
Visit 7	35% 12/215	31% 69/236	19% 42/225	.018	.005	.208
Visit 8 week 12	33% 67/206	285 61/218	16% 34/211	.001	.003	.289
Endpoint #1	33% 81/247	29% 74/254	19% 48/253	.001 **	.007	0.341

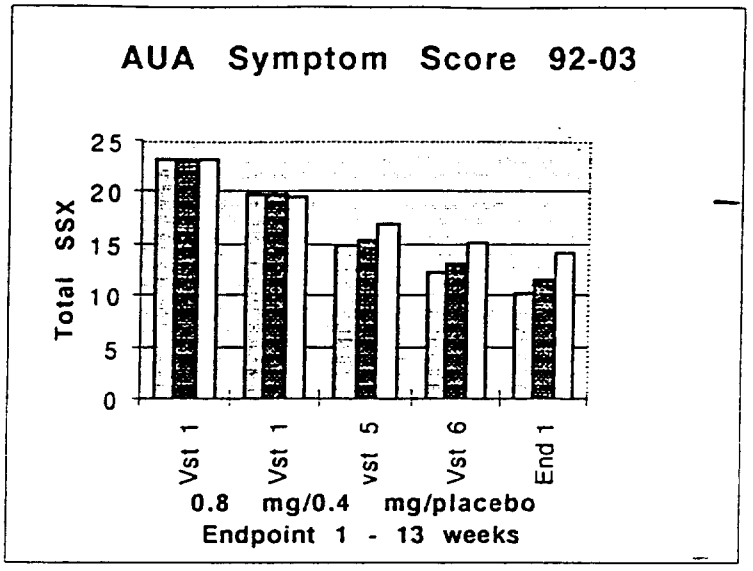
* p≤0.05 ** p ≤0.001

Symptom improvement using both the AUA validated score and the and Boyarsky score.
{Total AUA score 0 - 35 points;Total Boyarsky Score - 27 points}

	Dose	BL Score	N= #			N=##
AUA Score	0.8	19.9	247	-9.6*	-4.1	236
	0.4	19.8	254	-8.3*	-2.8	246
	placebo	19.6	254	-5.5		246
Boyarsky	0.8	10.7		-5.2*	-2	234
	0.4	11.1		-4.8*	-1.6	242
	placebo	11		-3.2		244
25% Responders from Baseline (30%)						
	0.8	74%*	(71% 168)		23%	175/237
	0.4	70%*	(65% 160)		19%	171/246
	PBO	51%	(46% 112)			126/246

 # N at Baseline ##N at Endpoint #1
**p value vs placebo ≤0.001 ** p value 0.4 vs 0.8 0.020*

At visit 5 which was one week after start of drug the AUA score improved by -5.1, -4.3 and - 2.6 (0.8, 0.4 and placebo respectively). The chart below notes the improvement in symptom scores (decreasing total symptom score) from Baseline to Endpoint one. The bars on the chart on the next page read from left to right - 0.8 mg, 0.4 mg and placebo (white). There is only a slight difference between the improvement of 0.8 and 0.4 at endpoint.



Improvment in both Flow Rate (≥30%) and AUA Symptom Score (25%):

The sponsor calculated how many patients had both a ≥30% improvement in Qmax and a 25% improvement in Symptom Score. There was a total of 160 out of 728 patients who demonstrated improvement in both of these parameters. Sixty one of these patients were on the 0.8 mg dose, 71 on 0.4 mg dose and 28 on placebo. There is no data regarding the improvement of these patients related to the severity of these patients at baseline.

Quality of Life Parameters:

The Total Quality of Life score (TGOL) was defined as the sum of all 5 index scores. Questions 1 - discomfort, 2, worrying, 3 bothersome,4 worry, and 5 limitation of activity. (The Quality of Life (QOL) scores only used the sum of questions 1,2,3, and 5.) The validation of these instruments is not available.

At Endpoint #1 the 0.8 mg versus placebo was p=0.001. There was a statistical difference between 0.4 and 0.8mg dose and the 0.4mg dose was not statistically significant. The Quality of Life instrument was used on visits 3, 5 and 10. Five questions were graded on a 4 point scale. The sponsor states that significant differences in total quality of life were observed after 1 week on 0.4 mg.
The sponsor notes that for all Quality of Life parameters except for the individual score for 'worry' and for post-void residual the change from baseline to Endpoint #1 was significantly greater in the 0.8 mg group versus the placebo. In those patients dosed at 0.4 mg the same parameters except for the individual score for limitations was significantly greater than placebo.

The Investigator's Global Assessment was evaluated at visit 5, 8 and 10 and measured on a 4 point scale: 0 - worsened; 1 - exhibited no change; 2 - slightly improved; 3 - improved; and 4 - markedly improved. Improvement (markedly

improved + improved) in the Intent-to-Treat (IIT) population from baseline was 63% (0.8 mg), 53% (0.4 mg) and 51% (placebo). No further evaluation was done. Although the sponsor notes that these were statistically significant changes at the 0.050 level they were not overwhelming changes. There is no data regarding the method of accumulating this data.

8.1.4.3 Safety comparisons

Overview of Safety Results during Double Blind phase with Tamsulosin Protocol 92-03A

	0.8 mg	0.4 mg	Placebo
N= Safety population	248	254	254
N= Treatment AEs (%)	180 (73%)	165 (65%)	151 (59%)
Total Number of Patients Discontinued			
Total Discontinued	50 (20%)	41 (16%)	47 (19%)
N= Serious AEs (%)	6 (2%)	4 (2%)	3 (1%)
N= DC due to AEs (%)	31 (13%)	18 (7%)	22 (9%)
N= clinical significant orthostatic hypotension	2 (1%)	1 (<1%)	

First Dose Effect

There did not appear to be any increased treatment emergent adverse events with the initiation of the 0.4 mg dose at visit 5 or with the increase to the 0.8 mg dose. Patients were to be confined for 8 hours during the 1st dose of the drug.

Orthostatic changes

The sponsor has provided a review of blood pressure measurements and pulse rate pre-dose and four and eight hours post dose at visit 4. All patients were on the 0.4 mg dose at this point. A positive orthostatic test defined as a decrease in standing > 20 mm Hg (criterion 1) or decrease in diastolic on standing ≥10 mmHg and standing DBP<65mmHg (criterion 2). Criterion 3 was increase in pulse rate ≥20 bpm and PR> 100 bpm.

	Pre-dose	4 hours post-dose	8 hours post-dose
Criterion 1			
0.8 mg	3 /248 (1%)	9/245 (4%)	7/244 (3%)
0.4 mg	12 /254 (5%)	14/254 (6%)	6/251(2%)
placebo	4/254 (2%)	5/253 (2%)	7/250 (3%)
From sponsor's table			

There are few drug-related first dose changes or orthostatic changes with the initiation of drug therapy. However when the two active treatment groups are combined there is a 12% incidence of a positive orthostatic test observed between 4 or 8 hours in patients who received 0.4 mg of tamsulosin as compared to 6% of

patients treated with placebo. It is not clear if there is a statistical difference in the incidence of positive orthostatic testing in the 65-74 year old. The sponsor states that there is an 8% incidence of positive testing in this age group. However, a listing of the patients meeting the criteria for a positive orthostatic test on first exposure does not show a higher incidence in the older patient.

Other markers that may reflect drug-related vasodilation or volume changes include asthenia, headaches, rhinitis, and dizziness. Although the changes are not as pronounced as with other andrenergic blockers they remain important safety issues. Rhinitis may also reflect increased infection in this group.

	0.8 mg	0.4 mg	placebo
N=	248	254	254
Asthenia	13 (5%)	12 (5%)	5 (2%)
Rhinitis	37 (15%)*	31 (12%)*	14 (6%)
Dizziness	28 (11%)*	25 (10%)	13 (5%)
Infection	25 (10%)*	23 (9%)*	13 (5%)
Abnormal Ejaculation	44 (18%)*#	15 (6%)*	0

** statistically significant from placebo: # 0.8 mg vs 0.4 mg statistically significant*

There did not appear to be any statistical differences between baseline and any visit in the number of patients with a positive orthostatic test. There did not appear to be any injuries or falls related to orthostatic changes.

There were four cases of syncope - all of which resolved. 2 in the placebo arm and one each in the 0.8 and 0.4 mg doses. Three patients in the 0.8 mg dose and one in the 0.4 mg dose and none in the placebo group discontinued because of hypotension.

One patient had a myocardial infarction and chest pain and was discontinued. He was 65 years old and had a treatment duration of 48 days. The investigators did not believe the event was related to drug.

Four cases of syncope which appeared to resolve:
- patient - a 51 year old patient who reported that he blacked out subsequent to his last visit. He had tried to blow out his birthday candles but could not extinguish them since they were trick candles.
- patient - a 50 year old patient who had a vaso-vagal response to venipuncture.
- patient - a 62 year old patient reported on visit 7 symptoms descriptive of a seizure or possible convulsion while mowing his lawn. The relationship to study drug considered remote.

- patient had an abnormal junctional rhythm that was not clinically significant on report. After the first dose of study medication the patient experienced heartburn several hours after his first dose and slight vertigo upon standing eight hours post-dosing.

Abnormal ejaculation:

Abnormal ejaculation is clearly drug and dose related. The mechanism of retrograde ejaculation is probably related to smooth muscle relaxation at the bladder neck. Abnormal ejaculation included absence of ejaculate, altered viscosity and decreased volume all of which are related to retrograde ejaculate and loss of bladder neck integrity. Six patients withdrew because of this problem, all of which were in the highest dose.

Other adverse events:

Thirteen patients randomized into the double-blind treatment period experienced other serious adverse events which included skin melanoma, hernia, carcinoma, gastrointestinal disorder, ventricular extra systoles (patient , cholecystitis, back pain , and an accidental injury. None of these appeared to be clearly drug related. Nor there were no significant changes in PSA that appeared to be drug related. There were no significant changes in any of the other clinical laboratory tests.

Synopsis of US 92-03B (completed 22 July 1994) - A long term, Phase III multicenter placebo controlled study of 20 months.

This study is the extension of US 92-03A and provided additional efficacy and safety data. Completion of the 17 week Phase III study 92-03A was the main eligibility requirement to enter 92-03B, the 40 week study. Enrollment was entirely optional and voluntary. Those patients who entered continued to be treated with the same medication and dosage to which they had been previously randomized. All visits during the double blind treatment period were scheduled at 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, and 40 weeks after study entry. A total of 618 patients completed study 92-03A and a total of 418 of the original 756 patients (55%) who were randomized enrolled at visit L1. See table on page B-18.

The objectives were to determine the long-term safety and to compare the results to 92-03a to determine if the patient's initial response to therapy remained constant, decreased, or increased while the patient is maintained on the same dose during the 40 weeks of the study.

Three different baselines were used in the data analyses. The placebo baseline in the 17 week study, results obtained during the double-blind treatment period of the 17 week study and the results observed at the final visit of the 17 week study

(Baseline #1). Endpoint #3 for the patients who completed the study was the observation at Visit L11, or the closest previous evaluable double-blind ovservation instead if the L11 was unavailable. L11 (Endpoint 3) was the equivalent of Endpoint 1 for the 92-03B extension and was 58 weeks after the initiation of the study. The ITT population consisted of randomized patients who received at least one dose of double blind study medication and had any follow-up safety data.

	Tamsulosin		Placebo	TOTAL
	0.8 mg	0.4 mg		
Randomized to 92-03A	248	254	254	756
Completed	198	213	207	618
US92-03B				
Enrolled	144	142	132	418
Safety Population	139	139	128	406
Intent-to-Treat Population	135	138	127	400
Number of Patients in SAF population who disc rx	38	19	26	83
Number of Patients completed	101	120	102	323

The following tables note the changes in uroflow parameters and symptom scores using the same measurements as 92-03a. The baseline scores do not appear to reflect the baseline data of the patients' measurement at Endpoint L11 but rather the baseline of all of the patients entered into 92-03a.

Results for Uroflow Parameters 92-03B

	Dose	Baseline 92-03a	N= 92-03a	Endpt #3 92-03b	N= 92-03b
Qmax					
	0.8	9.57	247	2.10*	133
	0.4	9.46	254	1.69*	136
	placebo	9.75	254	0.43	123
% Rspdrs					
	0.8			39%	52/133
	0.4			40%	55/136
	placebo			22%	27/123

* $p \leq 0.050$

The sponsor has not provided the baseline data for those measured at endpoint L11.

Results for Symptom Parameters 92-03b

	Dose	BL Score 92-03a	N=	Endpt #3 92-03b	N=
AUA	0.8	19.1	247	-9.7*	132
	0.4	19.8	254	-9.4*	137
	placebo	19.6	254	-6.5*	123
≥25% Responders					
	0.8	(74%)	175/237	78%	103/132
	0.4	(70%)	171/246	81%	111/137
	placebo	(51%)	126/246	59%	72/123

** statistically significant at 0.050 level*

The data from the extension is interesting but there is no data from the baseline of the extension (endpoint #1) to compare to Endpoint #3. At best one can note that the patients that continued throughout the entire study appeared to have continued maintenance of the benefits first achieved from the drug.

The safety profile in the extension did not differ greatly from 92-3a. All serious events were considered by the investigator to be either not related or remotely related to study drug. Only one serious event, gynecomastia, was considered by the investigator to be possibly related to study drug.

8.1.5 Reviewer's Comments

Efficacy: The sponsor has demonstrated that the use of either 0.4 mg or 0.8 mg of tamsulosin per day improves peak urinary flow and/or symptoms as measured by the AUA symptoms scores. This improvement is statistically better than the placebo response at Endpoint 1. There is a 7% to 13% improvement over placebo in peak urinary flow rates responders (> 3 mL/sec). The sponsor has provided additional data that the percentage of responders from baseline is approximately 20% greater than placebo in symptom improvement. In addition, approximately 22% of all patients improved in both symptoms and peak urinary flow. Four percent of those who improvement in both symptoms and peak urinary flow were on placebo.

Safety: The safety profile appears satisfactory with few patients noting orthostatic changes with the initiation of the drug either at 0.4 mg or 0.8 mg. The most significant safety features include rhinitis, dizziness and abnormal ejaculation. Both the rhinitis and dizziness may reflect changes in the blood volume. These

effects are not as pronounced as seen in other adrenoceptor blocker drugs, e.g. terazosin. The profile of orthostatic hypotension with first dose appears to be improved with this drug. The abnormal ejaculation, which is primarily retrograde ejaculation, is dose related with 18% noted at the 0.8 mg dose. This will be annoying and noticeable to many patients but does not represent a safety problem except when fertility is desired.

8.2 Trial # US 93-01 - Tamsulosin modified release in patients with signs and symptoms of benign prostatic hyperplasia.

Protocol 93-01				
US 93-01 Alternate names YM617 U95-3258	14 primary Centers	Ages Mean age 58.6	• 0.8 mg q.d. (12 weeks) after 0.4 mg q.d. (1 week) • 0.4 mg q.d. x 13 weeks • Placebo 13 weeks	N= 735 randomized to – db-rx - 622 efficacy - 731 ITT - 731 safety
Dates: April 26, 1993 - December 29, 1993				

The principal urologists at 14 Centers include: Charles Scott, MD (Atlanta); Murray Lieberman, MD (Bethesda); Larry Frank, MD (Dallas); Robert Dowling, MD (Fort Worth); Preston Packer, MD (Hollywood); Andrew Moore, MD (Indianapolis); Reginald Bruskewitz, MD (Madison); Steven Kaplan, MD (Manhattan); Herbert Lepor, MD (Milwaukee); George Ellis, MD (Orlando); Barry Krumholz, MD (Phoenix); Israel Barken, MD (San Diego); Perincherry Narayan, MD (San Francisco); Richard Brunelle, MD (Tampa)

This second Phase III protocol (93-01) incorporates all of the amendments that were made to the US92-03A protocol. The dosing regimen in this protocol is identical to the one used in Protocol US92-03A. The modifications that were made to this protocol deal with the schedule of follow-up visits and the elimination of the special monitoring of the patients after they receive their first dose of double-blind medication. The rationale for the elimination of the monitoring of the patient's vital signs after the first dose was based on a review of the accumulated safety experience. This included a review of the adverse events, electrocardiograms, changes in vital signs, and orthostatic tests on the first dosing day in the U.S., and adverse experiences profile in Europe and Japan.

8.2.1 Objectives

To confirm the safety and effectiveness of 0.4 mg q.d. and 0.8 mg q.d. of tamsulosin for use in the treatment of patients with the signs and symptoms of benign prostatic hyperplasia (BPH).

8.2.2 Design

This was a multicenter (14 sites), randomized, double-blind, placebo-controlled, parallel group Phase III clinical trial. Out-patients who had the signs and symptoms of infravesical obstruction were screened. If they met the basic requirements of the study, they underwent a 4-week single-blind placebo evaluation period.

8.2.3 Protocol

During the evaluation period, the patient's baselines were established, patient's compliance to study medication was determined, and additional testing was done to insure that the patient met the requirements of the protocol. Those patients who met all of the enrollment criteria and returned for a Visit 3 evaluation were assigned a specific medication kit number that corresponded to the randomization schedule which was comprised of tamsulosin 0.8 mg q.d., tamsulosin 0.4 mg q.d., or placebo q.d. For the single-blind placebo period, clinical and safety assessments were performed at Visit 1 (within 8 days after screening visit), Visit 2 (12 to 16 days after Visit 1) and Visit 3 (26 to 30 days after Visit 1). For the double-blind phase, clinical and safety assessments were performed at Visit 4 (5 to 9 days after Visit 3), Visit 5 (12 to 16 days after Visit 3), Visit 6 (33 to 37 days after Visit 3), Visit 7 (61 to 65 days after Visit 3), and Visit 8 (89 to 93 days after Visit 3).

Although patients were not randomized to a double-blind treatment group until they had satisfied baseline evaluation criteria at the end of the single-blind phase, patient information for the single-blind placebo evaluation phase has been displayed by their assigned drug for reporting purposes. Those patients who were withdrawn from the trial prior to treatment randomization have been classified as non-randomized. Medications were scheduled to be taken 30 minutes after breakfast throughout the entire study.

The efficacy population included all patients in the intent-to treat population who had been taking study medication for at least 4 weeks since the start of double-blind therapy and were not classified as being major violators of the protocol or study procedures. The intent-to-treat population included all patients who had taken at least one dose of double-blind medication, had a baseline efficacy assessment performed,

and had a minimum of one follow-up primary or secondary efficacy evaluation after the administration of double-blind dosing.

Seven hundred thirty-five patients were randomized to double-blind therapy. Two of these patients were not dosed with double-blind medication, and 2 of these patients did not provide any information after randomization. The safety population was composed of 731 patients who had the required post-baseline efficacy data to qualify them for inclusion in the intent-to-treat population.

8.2.3.1 Population, procedures

There were 731 patients in the intent-to-treat population, of whom 622 patients qualified for inclusion into the efficacy analyzable population. Efficacy population: Patients in the intent-to-treat population who had been taking study medication for at least 4 weeks since the start of double-blind therapy and were not classified as being major violators of the protocol or study procedures.

Patients 93-01 Protocol					
	Tamsulosin				
	0.8 mg	0.4 mg	Placebo	Non-Randomized	TOTAL
Evaluated at Visit 1	245	249	241	741	1476
Treated with Single-Blind Therapy	245	249	241	682	1417
Randomized to Double-Blind Therapy	245	249	241	---	735
Treated with Double-Blind Therapy	244	249	240	---	733
Randomized Patients Discontinuing Study	39	33	32	---	104
Completed Study	206	216	209	---	631

8.2.3.2 Endpoints

The primary response variables for the evaluation of efficacy were the Total Symptom Score (AUA) and Peak Urine Flow Rate (Q_{max}) at the final visit (Endpoint #1) during the double-blind treatment period relative to the baseline value. As in protocol 92-03A,a 'responder' was defined by an improvement (decrease) in the total AUA symptom score of at least 25% from the baseline and an improvement (increase) in the peak urine flow rate of at least 30% from baseline. Secondary efficacy measures were changes from baseline in other uroflowmetry

measurements which included the Boyarsky symptom scores and investigator's global assessments.

Endpoint 1 was defined at the observation at the final evaluable double-blind visit for each patient, provided the visit occurred either on the last day of double-blind medication dosing or on the day after the last day of double-blind medication dosing (if the last dosing day is unknown, the available data on the closest prior visit during the double-blind period is used as the endpoint). This was the primary endpoint for the study analysis.

Endpoint 2 was defined as the observation at the final evaluable visit including discharge/follow-up visit, regardless of the number of days from the last day of double-blind medication dosing. This was the secondary endpoint for the study analysis. In most cases Endpoint 2 was similar if not identical to Endpoint 1.

8.2.3.3 Statistical considerations - See statistical review

8.2.4 Results

8.2.4.1 Patient Disposition, comparability

	Demographics 93-01 A		
	0.8 mg	0.4mg	placebo
Total N	244	248	239
Mean age	58.3	58.6	58.1
≤64	77%	76%	78%
	44-79	45-77	45-79
Race			
Caucasian	95%	94%	94%
Black	4%	6%	4%
Asian/other	2%	0%	2%
Disease Severity			
Severe≥20	43%	36%	44%
Moderate 8-19	55%	605	54%
Boyarsky	10.0	10.21	10.65
AUA S SX	18.2	17.9	19.2

Severity of disease based on AUA symptom score

The inclusion and exclusion criteria are the same as noted on page B-5 for protocol 92-03A.

8.2.4.2 Efficacy endpoint outcomes

Peak or maximum urinary flow rate:

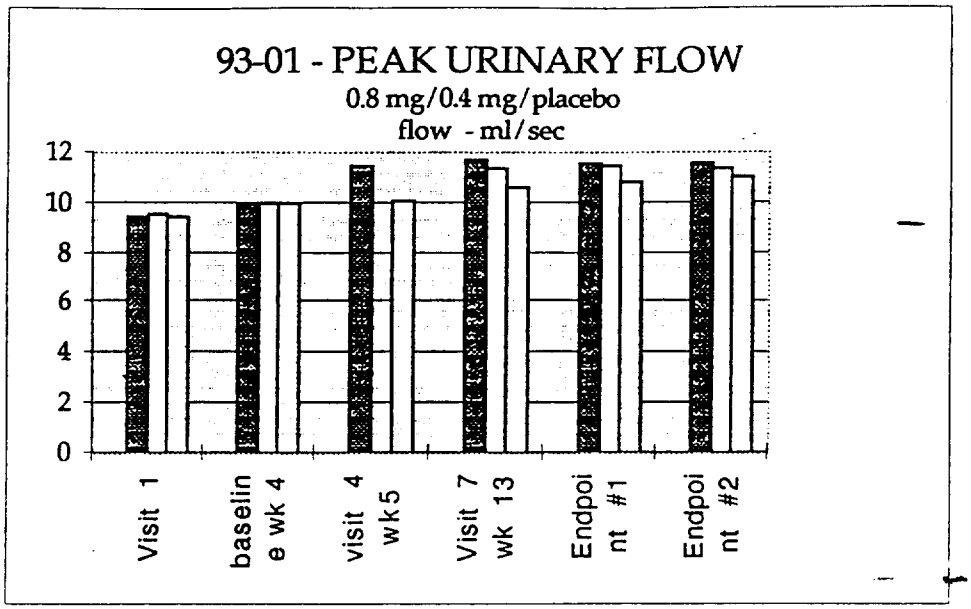
Uroflow measurements were done at each visit. A voided volume of at least 125 mL was required for the reading to be acceptable. All testing was done with a Dantec Urodyn 1000 machine. The peak urinary flows were measured at the estimated peak plasma concentration of the drug (between 4- 8 hours after dosing) at visits 4 and 5 and the estimated trough plasma concentration (24-27 hours after dosing) at Visits 6, 7, and 8. Note that this is different from the previous protocol that measured maximum urinary flow rate at the expected peak plasma concentration of tamsulosin.

The change of the peak urine flow rate was statistically significant after one week of treatment of 0.4 mg per day. The patients in the tamsulosin 0.8 mg had an improvement over the placebo group in the peak urine flow rates at each of the study visits whether the tests were conducted at the presumed peak or trough of tamsulosin plasma levels. The patients in the 0.4 mg demonstrated improvement over placebo when the measurements were conducted at the estimated peak plasma concentration at visits 4 and 5 and at only one trough measurement (visit 8).

Peak Urinary Flow Responses (ITT)						
	Dose	Baseline	Endpoint 1	Change	difference from placebo	N=
Qmax						
	0.8	9.96	0.007**	1.79	0.86	237
	0.4	9.94	0.64	1.52	0.59	244
	placebo	9.95	-	0.93	-	235
Responders ≥30%						
	0.8		0.27*	33%	9%	78/237
	0.4		0.019*	34%	10%	82/244
	placebo		-	24%	-	56/235

*P value - dose vs placebo ** p≤0.01 * p≤0.05*

The chart on the next page shows the changes from the baseline week 4 to Endpoint 1 and 2. Although all three arms (0.8 mg, 0.4 mg and placebo respectively) improved, the improvement in the treated arms was greater than placebo.



The tables below identify the peak urine flow responses for each treatment arm at each visit and the differences of each from placebo. The first table shows the percentage of patients in each group with improvement of ≥3 ml/sec and the second table by an improvement of ≥30%.

93-01 Peak urine flow rate responders with improvement of ≥3 ml/sec ITT

Visit	0.8 mg	0.4 mg	placebo	0.8 vs pbo	0.4 vs pbo	0.8 vs 0.4
Visit 4	27% 64/234	33% 78/240	13%	**	**	-
Visit 5 wk 6	43% 96/224	29% 67/233	14% 32/227	**	**	**
Visit 6 wk 9	26% 55/215	25% 56/225	16% 34/217	*	*	-
Visit 7 wk 13	32% 67/210	29% 64/219	18% 38/212	**	**	-
Visit 8 wk 17	30% 71/237	30% 72/244	23% 53/235	*	-	-
Endpoint #1	30% 71/237	30% 72/244	23% 53/235	-	-	-
Endpoint #2	28% 69/243	28% 69/245	23% 54/239	-	-	-

** p≤0.05 ** p ≤0.01 - = not significant*

93-01 Peak urine flow rate responders with improvement of >30% from baseline ITT

Visit	0.8 g	0.4 mg	placebo	0.8 vs pbo	0.4 vs pbo	0.8 vs 0.4
Visit 4 wk 5	32% 74/234	37% 89/240	17% 39/232	** 0.001	** 0.001	0.220
Visit 5 wk 6	46% 102/224	31% 72/233	17% 39/227	** 0.001	** 0.001	** 0.002
Visit 6 wk 9	31% 66/215	28% 62/225	18% 39/217	** 0.003	* 0.018	0.535
Visit 7 wk 13	33% 69/210	32% 69/219	21% 44/212	** 0.004	* 0.010	0.783
Visit 8 wk 17	32% 66/206	33% 71/216	23% 48/208	* 0.034	* 0.027	0.816
Endpoint #1	33% 78/237	34% 82/244	24% 56/235	* 0.027	* 0.019	0.891
Endpoint #2	30% 74/243	33% 82/245	24% 57/239	0.092	0.019	0.486

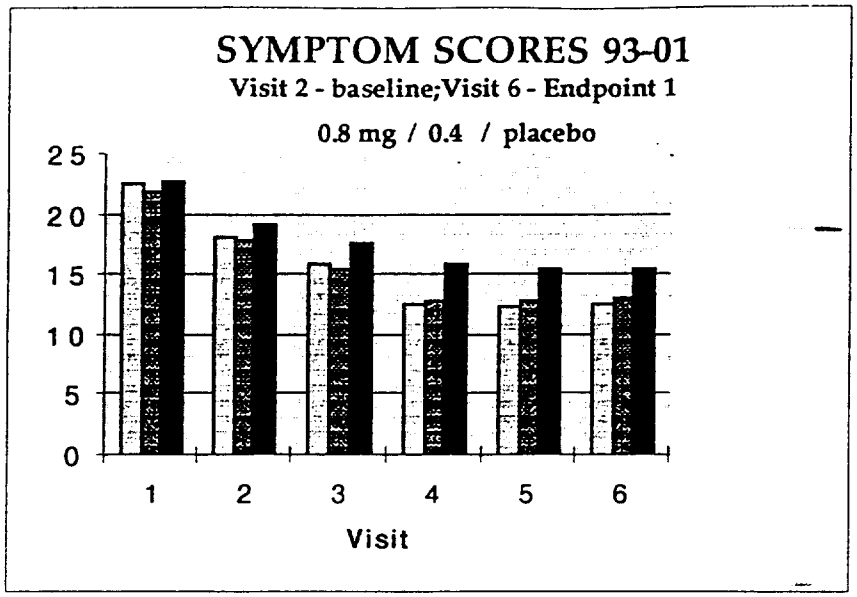
** p≤0.05 ** p ≤0.01*

The following tables and chart demonstrate the improvement by dose from baseline to endpoint in symptom scores and the percentage of responders. Improvement is a decrease in total scores from the baseline to endpoint.

Symptom improvement - AUA and Boyarsky

	Dose	BL Score	Endpoint # 1	difference from placebo	N=
AUA	0.8	18.2	- 5.76	2.16 **	238
	0.4	17.9	-5.09	1.49 **	244
	placebo	19.2	- 3.60	-	235
AUA >25% Responders					
	0.8		56%	16%**	124/238
	0.4		55%	15%**	133/244
	placebo		40%	-	95/235
Boyarsky Total SSX	0.8	10.01	-3.25	1.36**	237
	0.4	10.21	-2.97	0.99**	24[illegible]
	placebo	10.65	-1.89		23[illegible]
Boyarsky obstructive sx	0.8	5.84	-2.44	1.44 **	237
	0.4	6.02	-2.18	0.78**	244
	placebo	6.31	-1.40		235

*** p≤0.01* p≤0.05 #Endpoint 1 used.*



93-01 AUA Symptom Responders Improvement ≥ 30%

Visit	0.8 mg	0.4 mg	placebo	0.8 vs pbo	0.4 vs pbo	0.8 vs 0.4
Visit 4	19%	25%	14%	-	**	-
Visit 5	35%	39%	25%	*	**	-
Visit 6	42%	44%	29%	**	**	-
Visit 7 week 13	48%	50%	34%	**	**	*
Visit 8	56%	50%	34%	**	**	-
Endpoint #1	52%	48%	32%	**	**	-
Endpoint #2	52%	46%	33%	**	**	-

** p≤0.05 ** p ≤0.01 - not significant*

Improvement in both Flow Rate (≥30%) and AUA Symptom Score (25%):

The sponsor calculated how many patients had both a ≥30% improvement in Qmax and a 25% improvement in Symptom Score. There were a total of 122 (17% overall) patients with improvement in both of these parameters {49 (0.8 mg), 49 (0.4 mg) and 24 on placebo}.

Quality of Life Parameters:

The total quality of life score was defined as the sum of all 5 index scores. Although statistically significant within two weeks of treatment (on the 0.8 mg dose) the clinical significance of this small improvement is not clear. The validation or the method of presenting this instrument to the patient has not been included although the sponsor states that it has been validated. It appears to be a similar

instrument to others that have been validated. The same quality of life questionnaire was administered at each of the visits. See table below.

93-01 Quality of Life Score (IT)
change from baseline

Visit	0.8 mg	0.4 mg	placebo	0.8 vs pbo	0.4 vs pbo	0.8 vs 0.4
Visit 3 baseline	4.82	4.63	4.90			
Visit 4	-0.62	-0.48	-.25	*	-	-
Endpoint #1	-1.40 (238)	-0.95 (244)	-0.56 ((235)	**	-	-

** p≤0.05 ** p ≤0.01 ;- not significant*

In addition, the investigators did an Investigator Global Assessment which has not been reviewed.

8.2.4.3 Safety comparisons

The following table is an overview of the safety results during the double-blind phase of 93-01.

Overview of Safety Results during Double Blind Phase with Tamsulosin

	0.8 mg	0.4 mg	Placebo
N= Safety population	244	248	239
N= Discontinuing	39 (16%)	33 (13%)	32 (13%)
N= Treatment AEs (%)	188 (77%)	194 (78%)	181 (76%)
N= Serious AEs (%)	8 (3%)	7 (3%)	9 (4%)
N= DC due to AEs (%)	30 (12%)	22 (9%)	20 (8%)

- First Dose Effect: The sponsor states that no "first dose effects" were reported either at the time of the first dose when the patients were confined to the medical facility or were contacted by telephone at later doses or when dosing was increased from 0.4 to 0.8 mg.

- Orthostatic changes: Testing was performed at each of the visits. Between 1% and 4% of the patients had decreases ≥ 20 mm Hg of systolic blood pressure upon standing. There were no statistically significant differences among the three treatment groups. Visit 5 all patients were started on 0.4 mg dose. Visit 6 was the time the patients randomized to 0.8 mg switched from the 0.4 mg to the 0.8 mg dose. The sitting pulse rate was comparable among all three treatment groups at baseline The 0.8 mg tamsulosin group showed statistically but not clinically significant mean changes from baseline at Visit 5 only (1 week after treatment - all on 0.4 mg dose).

Patients with a Positive Orthostatic Test

	0.8 mg	0.4 mg	placebo
visit 5	12 (5%)	9(4%)	2 (1%)

visit 5 is the first dose of drug - all received 0.4 mg

- The mean differences upon standing systolic blood pressure ranged from 0.1 to 4.7 mmHg and were not considered clinically significant.

- There were no statistically significant or clinically meaningful differences from baseline between any two treatments at any visit. At visit 5 the 0.8 mg group showed statistically but not clinically significant mean change (increase of 2.7 bpm) from baseline for the sitting pulse rate.

Another problem related to hypovolumia includes dizziness. There was an increased incidence of 11% (28/248), 10% (25/254) and 5% (13/254)at the 0.8, 0.4 and placebo doses respectively. There did not appear to be any falls related to orthostatic changes. It is unclear if the incidence of rhinitis is related to volume changes in any way. The incidence of rhinitis was 15% (37/248) , 12% (31/254) and 6% (14/254){0.8, 0.4 and placebo}.

- Two patients had myocardial infarctions on short term exposure. One patient was on placebo and the second was on treatment for 7 days (0.4mg). The MI resolved.

- Twelve patients had normal or non-clinically significant abnormal EKGs at baseline which became clinically significantly abnormal at one of the post-baseline visits. This included 4 patients on 0.8 mg, 5 patients on 0.4 mg and 3 patients on placebo. The EKG changes in patients randomized to the 0.8 mg included: bradycardia on visit 6 , 7 and 8; premature ventricular beats prior to drug and being discharged from study; atrial fibrillation prior to drug usage; and ventricular bigeminy prior to drug usage. The EKG changes in patients randomized to the 0.4 mg dose included: Mobitz type II second degree block removed from study prior to visit 5; nonspecific ST-T wave changes; anteroseptal infarction prior to drug usage; atrial fibrillation and sinus bradycardia possibly drug related; First degree heart block at screening at baseline and on Visit 6 profound sinus bradycardia and was dropped from the study. Abnormal changes in patients randomized to the placebo group included: nonprogressive ST-T wave changes, ischemic T wave inversions and first-degree block with sinus bradycardia.

- Serious events in individual patients included chest pain, adenocarcinoma of the lung, acute myocardial infarction, skin cancer, neutropenia, abdominal aortic aneurysm, and diverticulosis, fracture with hospitalization, dizziness, blurred vision, bradycardia, hypotension, prostate cancer, chest pain with coronary occlusion with bypass surgery, second degree A-V block, pneumonia, lung cancer

mass, vomiting, hepatitis c, inverted T wave, decreased visual acuity, angina, coronary thrombosis, by-pass surgery, carcinoid tumor, renal mass, atrial fibrillation, skin cancer, surgery of the left thumb, coronary stenosis, with crescendo angina, syncope, urinary retention with TURP cardiac arrhythmias, dizziness (near syncope, and dizziness with syncopal episode. There is no evidence these events were clearly drug related although dizziness blurred vision, hypotension and coronary disease could well be related to drug.

- There were no significant changes related to PSA.
- One patient in the 0.4 mg dose was diagnosed with prostate cancer.
- There were no drug related changes in other clinical parameters.

Abnormal Ejaculation (retrograde ejaculation) :

- The adverse events coded to abnormal ejaculation were shown to be associated with tamsulosin treatment and were dose dependent.

Protocol 93-01
Adverse Events

	0.8 mg 244	0.4 mg 248	Placebo 239
Asthenia	29 (12%)	27 (11%)	22 (9%)
Rhinitis	50 (20%)*	35 (14%)	26 (11%)
Dizziness	56 (23%)*	50 (20%)	37 (15%)
Somnolence	19 (8%)*	10 (4%)	7 (3%)
Abnormal Ejaculation	45 (18%)*	27 (11%)*	1 (<1%)

* *statistically significant compared to placebo*

- Discontinued patients were comparable among all three treatment groups: 9 (4%) , 5 (2%) and 4 (2%) patients withdrew during the double-blind treatment period because of dizziness. (0.8, 0.4 and placebo respectively.)

- Six patients in the 18% (44/248) of the patients in the 0.8 mg group and 6% (15/254) of patients in the 0.4 mg 0.8 mg group withdrew due in part to abnormal ejaculation.

8.2.5 Reviewer's Comments

Efficacy: The sponsor has provided data demonstrating that both 0.8 and 0.4 mg doses of tamsulosin improved peak urinary flow and AUA symptom scores over placebo. There does not appear to be a difference between the two doses. Approximately 20% more treated patients than patients on placebo had a 25% response from baseline in AUA symptom scores. Ten to thirteen percent more

patients than patients on placebo had an improvement ≥ 3 mL/sec in peak urinary flow.

Approximately 122 patients (17% overall) had improvement in both the primary endpoints (17%). This included 49/238 patients on 0.8 mg , 49/244 on 0.4 mg and 24/ 235 on placebo. Approximately 10% more patients on drug than placebo had a total improvement of ≥30% change on peak urinary flow and 25% change on total AUA score.

Safety: The safety profile in this clinical trial was similar to that seen in 92-03. Rhinitis, dizziness and abnormal ejaculation were the primary adverse events. Only abnormal ejaculation was clearly drug and dose related.

9 Overview of Efficacy - Comparative results between studies

Sponsor's Statement

The sponsor has provided data demonstrating improvement in the following primary and secondary endpoints:

- An improvement in the peak urinary flow rates from baseline and greater improvement than placebo;

- An improvement in the total AUA measured Symptom Score from baseline and greater improvement than placebo;

- An improvement (decrease) in the total AUA symptom score of at least 25% from the baseline; and

- An improvement (increase) in the peak urine flow rate (Qmax) of at least 30% from the baseline.

All of the identified efficacy endpoints were statistically significantly greater than placebo. However, there is no clear and consistent advantage between the 0.8 and 0.4 mg doses although there may be some patients that will benefit from the higher dose. The final changes in peak urinary flow rates and AUA symptom score changes does not suggest that this compound is more effective than previously approved adrenoceptor blockers, e.g., terazosin or doxazosin.

It was calculated that 160 patients had improvement in both parameters from a total of 728 patients in protocol 92-03a and a total of 122 patients (total 717) in protocol 93-01. The following tables summarize the "complete" responders in each of the two pivotal trials.

Protocol 92-03a

	≥30% change Q max	% ≥3mL/sec ITT	≥25 change (30%) AUA	AUA + Q max
0.8	36% 88/247	33% 81/247	74% 175/237	26% 61/236
0.4	31% 79/254	29% 74/254	70% 171/246	29% 71/246
Placebo	21% 54/253	19% 48/253	51% 126/246	11% 28/246

Protocol 93-01

	≥30% change Q max	% ≥3mL/sec ITT	≥25 change (30%) AUA	AUA + Q max
0.8	33% 78/237	30% 71/237	56% (52%) 124/238	21% 49/238
0.4	34% 82/244	30% 72/244	55% (48%) 133/244	20% 49/244
Placebo	24% 56/235	23% 53/235	40% (32%) 95/235	10% 24/235

The following table outlines the actual numbers from Baseline to Endpoint for the two primary clinical endpoints for the two pivotal trials, 92-03a and 93-01.

Tamsulosin Changes from Baseline in Qmax and AUA SX				
Protocol	Qmax	Endpoint 1	AUA Sx	Endpoint 1
92-03a				
0.8 mg	9.57	1.78	19.9	-9.6
0.4 mg	9.46	1.75	19.9	-8.3
placebo	9.75	0.52	19.8	-5.5
93-01				
0.8 mg	9.96	1.79	18.2	-5.76
0.4 mg	9.94	1.52	17.9	-5.09
placebo	9.95	0.93	19.2	-3.60

10 Overview of Safety

The safety profile of this compound is satisfactory. Rhinitis (that may be a reflection of volume changes), dizziness, and abnormal ejaculation are the most important events noted. The safety profile appears to be somewhat improved over the previous compounds in this class. (See table on page 35 comparing the safety profile of all of the adrenoreceptor antagonists). Orthostatic hypotension appears to be less of a problem with this antagonist. There does not appear to be a major first pass effect with the initiation or first dose of this compound. Pulse rates do not appear to be changed. Minimal changes related to hypovolemia or orthostatic changes are noted. Even though few changes are noted this should be viewed with caution when the drug reaches the market. Orthostatic testing should be continued in these patients, particularly in the older population who may be more sensitive to volume changes.

If this compound is more selective, this selectivity is manifested in the receptors of the bladder neck. There is a drug related relaxation of the bladder neck seen particularly at the 0.8 mg dose which is manifested as retrograde ejaculation or abnormal ejaculation. This may be troubling to patients if they are not informed of this possibility. It can also be a cause of male infertility. The true incidence of retrograde ejaculation is not known in this population and should be evaluated as a phase IV commitment. The evaluation of post-ejaculate urine samples could easily determine the true incidence of bladder neck relaxation.

There are no significant changes in PSA nor prostate volume. There is no reason why this drug should cause changes in either the volume of the prostate or the PSA.

There were no cases of priapism noted in these clinical trials. One mechanism of action of priapism includes the adrenoceptor and priapism is seen with all other AR antagonists.

Comparison to other alpha adrenergic blockers, e.g. terazosin and doxazosin.

The response seen with tamsulosin is similar to the changes noted in the clinical trials of the two approved alpha adrenoreceptor antagonists, terazosin and doxazosin. The magnitude of change in all three of the clinical trials is similar. The reduction in total symptom score, whether measured with Boyarksy score or AUA score, appeared to be similar in all the studies. Standardized measurements of peak urinary flow were similar in all three studies (Q max in ml/sec). The table on next page shows the changes from baseline to the endpoint in the pivotal trials of all three adrenergic antagonists: doxazosin, terazosin and tamulosin.

Comparison of Clinical Trials with AR Antagonists

Protocol Doxazosin/Terazosin	Doxazosin (placebo)	Terazosin (placebo)	Tamsulosin Protocol	Tamsulosin 0.8 mg (pbo) 0.4 mg
	Change to Endpoint from Baseline			
Qmax				
421/005	2.8 (0.6)	3.1 (0.9)	**92-03**	**1.7** (0.5) 1.7
488/012	2.6 (2.1)	2.9 (1.4)	**93-01**	**1.7** (0.9) 1.5
490/377	2.9 (0.7)	2.6 (1.2)		
AUA SSX				
488/ -	6.0 (3.9)		**92-03**	**9.6** (5.5) 8.3
490/ -	5.7 (3.2)		**93-01**	**5.8** (3.6) 5.1
Boyarsky SSX				
- /005		4.4 (2.1)	**92-03**	**5.2** (3.2) 4.8
- /012		5.2 (1.4)	**93-01**	**3.2** (1.8) 3.0
- /377		4.6 (3.5)		

All symptom score improvements are a negative number.

Below is a summary of the important safety features of each of the adrenoceptor antagonists.

Comparison of Safety Profile			
	Doxazosin /PBO	**Terazosin /PBO**	**Tamsulosin /PBO**
Body as a whole Asthenia	-	7.4%/3.3%	0.7%/0,6% 6.1%/5%
Cardiovascular Hypotension Palpitation Postural hypotens.	1.7%/0 1.2%/0.3%	0.6%/0.6% 0.9%/1.1% 3.9%/0.8%	0.2 -1%/0.2% 1.2%/0.6% 0.2-1%/0.2%
Nervous System Dizziness	15.6%/9.0%	9.1%/4.2%	11 - 23% / 5 - 15%
Somnolence	3%/1.0%	3.6%/1.9%	2.5%/1.5%
Respiratory System Rhinitis/Nasal Congestion	3%/1%	1.9%/0.0%	11 - 20%/6.9 -11%
Special Senses Visual	1.4%/0.7%	1.3%/0.6%	
Impotence		1.6%/0.6%	1.2%/1.5%
Retrograde Ejac	-	-	18%*/0% 18%*/<1%
Priapism **post marketing**	- 5	- 12	-

* 0.8 mg dose

Safety Updates:

The sponsor has provided two updates which included data on 1600 patients in the five U.S., European, and Japanese long-term uncontrolled trials of approximately 2 years in duration. The Safety Update (II) extension included only those studies closely monitored for safety and efficacy of tamsulosin. This included studies US 93-04, 01085, 92HAR-02, 92-HAR-03, and M6173/LLN1. There are no major changes in the updates compared to the original submissions.

The following notes are from the safety report of November 20, 1996

- a circulatory collapse of a patient on tamsulosin (Alna), dimethindene maleate (Fenistil) and brisenin (reserpine).

The safety report of January 28, 1997 notes the following:

- a 75 year old male in Germany on 0.4 mg. On the night after the first intake of tamsulosin the patient had a syncopal episode and was unconscious for several

hours. As a consequence of the episode the patient fell and sustained an injury to the cervical vertebral column. This is may be an example of orthostatic hypotension.

- a German patient entered a double-blind study had a fatal mycocardial infarction.

11 Labeling Review

The labeling review will added separately.

12 Conclusions

The sponsor has provided data from two well-controlled clinical trials demonstrating improvement in the signs and symptoms of BPH with tamsulosin treatment. There does not appear to be a difference between the two doses, 0.4 or 0.8 grams. The changes were similar to those seen with the two approved drugs, terazosin and doxazosin. The sponsor is recommending the 0.4 mg once daily dose for the treatment of the signs and symptoms of BPH with possible adjustment to 0.8 mg once daily.

The safety profile is somewhat better than previous antagonists as seen in the clinical trials. The compound appears to be only modestly more selective than the previous compounds and although few changes were noted associated with decreased blood volume, e.g. dizziness and orthostatic hypotension, it is possible that with more drug use more of these events will be seen. The one major difference relates to the effect on the receptors of the bladder neck causing retrograde ejaculation. The incidence of retrograde ejaculation may be higher than reported and should be evaluated.

Careful education should continue to be included for the patient regarding the dangers of possible hypotension and blood pressure changes.

Patients should understand the importance of continual monitoring for signs and symptoms of prostate growth and/or prostate cancer. This drug will not retard the growth of the prostate nor alter the risk for prostate cancer.

13 Recommendations

It is recommended that tamsulosin (Flowmax) is approvable for the treatment of symptoms of benign prostatic hyperplasia. There appears to be little advantage between the two doses, 0.4 or 0.8 mg. However, there may be a few patients who will benefit from a higher dose. The safety profile is similar except for abnormal ejaculation. Therefore, it is recommended that patients be maintained on the 0.4 mg dose unless they do not respond to this dose.

This compound is not recommended for the treatment of hypertension. It has not been studied for that indication.

The dose-relationship with bladder neck relaxation as evidenced by the high percentage of complaints of retrograde ejaculation would suggest a higher incidence of retrograde ejaculation than reported. It would be helpful for the sponsor to evaluate this possibility in a small study checking for sperm in post-ejaculate urine specimens as a Phase IV study.

Many clinicians combine the use of an adrenoceptor antagonist with a 5 alpha reductase inhibitor for the treatment of BPH. For this reason it would be helpful for the sponsor to compare the two compounds in a controlled study as a Phase IV commitment.

Jean L. Fourcroy, M.D., PhD
Medical Officer
March 22, 1997/HFD-580/JFourcroy/DShames/HJolson

See 'group leader's memo' dated 4/5/97
for additional comments.

HJolson M.D. 4/5/97

NDA 20-579
Flomax™
Tamsulosin HCl

Safety Update review is included in the Medical Officer Review.

APR 7 1997

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-579
Compound:	Flomax ™ (Tamsulosin Hydrochloride) Capsules 0.4 mg
Submission Dates:	April 15, 1996 August 16, 1996
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Type of Submission:	New Molecular Entity (NME) Amendment No. 000BB
Code:	1S
Reviewers:	Raymond Miller, Ph.D. Ene Ette, Ph.D.
Consultant:	K. Gary Barnette, Ph.D. (*In Vitro* Drug Metabolism Issues)

I. SYNOPSIS

On April 15, 1996, Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-579 Flomax™ (tamsulosin hydrochloride) Capsules 0.4 mg. Tamsulosin hydrochloride is an alpha$_1$ adrenoceptor blocking agent which exhibits a high degree of selectivity for alpha$_{1c}$ receptors in the human prostate. Tamsulosin has been formulated as a extended release formulation and is to be supplied in capsules containing 0.4 mg of tamsulosin hydrochloride for oral administration. The proposed indication for Flomax™ is the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

The pharmacokinetics of tamsulosin and the extended release formulation proposed for marketing (CR-M) were examined in 21 studies in humans following single and/or multiple (q.d. or b.i.d.) dosing. These studies addressed issues related to mass balance, absorption, absolute/relative bioavailability, food effects, distribution and protein binding, metabolism/excretion, single/multiple dose pharmacokinetics and dose proportionality, kinetics in the elderly, disease states such as renal or hepatic impairment, pharmacodynamic-drug interactions, and the bioequivalence of the final formulation. Dose-finding, population-PK, and PK/PD relationships were examined in BPH patients. *In vitro* dissolution information and assay validation data were also included.

The overall results of the submitted information indicate;

- ***Formulation:*** The "modified release" term proposed by the sponsor to describe their formulation is not currently defined by the USP and cannot be used by the sponsor.
- ***Dissolution:*** The proposed *in vitro* dissolution method and specifications are inappropriate.
- ***Assays:*** The validations of the analytical methods used to determine tamsulosin and its metabolites in plasma and urine are appropriate.
- ***Isomers:*** Tamsulosin (R(-) isomer) does not undergo chiral inversion to the S(+) isomer *in vivo*.
- ***Protein Binding:*** Tamsulosin is extensively plasma protein bound (94% to 99%), primarily to alpha-1-acid glycoprotein (AAG) in humans, with linear binding over a wide concentration range.
- ***Bioavailability:*** Tamsulosin is extensively absorbed from the gastrointestinal (GI) tract, with an absolute bioavailability (F) of 92%. The relative bioavailability of FLOMAX™ 0.4 mg capsules is 75% when compared to an oral solution.
- ***Food Effect:*** Administration of tamsulosin extended-release formulation with food results at steady state in a delay in T_{max} to six to seven hours and a decrease in C_{max} (by 40% to 70%) and AUC_t (by

30%) in both young and older volunteers. The effects of food on the pharmacokinetics of tamsulosin are consistent regardless of whether tamsulosin is administered with a light breakfast or a high-fat breakfast.

- ***Bioequivalence***: The bioequivalence of three different batches of the same extended-release formulation (CR-M) of tamsulosin used in the two U.S. pivotal Phase III trials, study US92-03A and study US93-01 were compared to a to-be-marketed batch. The results indicate that three batches are bioequivalent.
- ***Linearity/Dose Proportionality:*** Tamsulosin exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing. Dose proportionality was also demonstrated over the 0.4 to 0.8 mg q.d. dose range at steady-state.
- ***Special Populations:***

  Elderly: Cross-study comparisons of tamsulosin overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin may be prolonged in geriatric males compared to young healthy male volunteers. However, no dose adjustment is needed with age.

  Hepatic/Renal Impairment: No dosage adjustment is necessary when tamsulosin is administered to patients with moderate hepatic dysfunction. Patients with renal impairment (creatinine clearances above 10 mL/min/1.73m^2) do not require a dosage adjustment of tamsulosin. No changes are predicted in the efficacy, safety, or tolerability of tamsulosin when administered to subjects with hepatic or renal impairment.
- ***Metabolism:*** Tamsulosin is extensively metabolized by enzymes in the liver, followed by Tamsulosin is excreted in urine and feces, primarily in the form of metabolites with only a small fraction (about 10%) excreted unchanged.
- ***Interactions:*** No dosage adjustments are necessary when tamsulosin is administered concomitantly with Procardia XL®, atenolol or enalapril, digoxin, theophylline, and furosemide. However, potential drug interactions may exist with warfarin and cimetidine and caution should be exercised with concomitant administration of these drugs and tamsulosin.
- ***PK/PD:*** Based on PK/PD analysis, the 0.4 mg daily dose provides the optimal combination of efficacy and tolerability in most patients.

II. COMMENTS

Dissolution:

1. The proposed dissolution method and specifications are not acceptable. The sampling time as well as the speed of rotation are inappropriate to ensure that all the lots that are released would have a satisfactory performance.
2. The sponsor should provide full individual and mean dissolution data and profiles from at least 12 units in three media N HCl, water, and phosphate buffer pH 6.8 using USP apparatus at a speed not exceeding rpm. If the solubility is a problem and sink conditions are not obtained, the sponsor may consider increasing the dissolution volume up to mL. Also, samples should be obtained hourly until complete dissolution is achieved or a plateau is reached.
3. Once the requested dissolution information is submitted and reviewed by the Agency , a dissolution method with the appropriate specifications will be recommended for FLOMAX™ capsules.

Metabolism:

4. The sponsor has not adequately assessed the enzyme(s) primarily or secondarily responsible for the metabolism of tamsulosin.

5. The sponsor should conduct appropriate *in vitro* drug metabolism studies to characterize the that catalyze the metabolism of tamsulosin.
6. The sponsor should submit their proposed protocol(s) for the *in vitro* drug metabolism studies for comments prior to initiation of the studies.

Labeling:

7. The proposed pharmacokinetic section of the labeling is not acceptable. The sponsor should revise their labeling to incorporate the changes recommended in pages 25-28 of this review.

III. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed NDA 20-579 for FLOMAX™ (tamsulosin hydrochloride) Capsules 0.4 mg that was submitted on April 15, 1996. Based on the review of the overall information included in this submission, OCPB is of the opinion that the provided analytical and pharmacokinetic data are appropriate and acceptable. However, before a final recommendation is given, the sponsor needs to address the Dissolution, Metabolic, and Labeling Comments listed above.

If the Division of Reproductive and Urologic Drug Products (HFD-580) considers that the sponsor has provided adequate efficacy and safety information for approval of NDA 20-579, FLOMAX™, then OCPB is of the opinion that the requested *in vitro* dissolution and metabolic testing can be performed post-approval (Phase IV Commitment).

Regarding the *in vitro* dissolution test, OCPB will accept the proposed dissolution method and specifications on the interim basis in order to permit the release of the product. However, the sponsor should provide the requested dissolution information within 3 months of NDA's approval date.

With respect to the metabolic data requested in Comments 4 to 6 above, it is recommended that the sponsor submit within a month of NDA's approval date their proposed metabolic protocol(s) for review and comments. The complete study report should be submitted within 6 months of approval date and at that time the labeling should be updated as appropriate to incorporate the additional metabolic information.

In addition, due to the fact that interactions between FLOMAX™ and other alpha-adrenergic blocking agents could be expected, OCPB recommends that the sponsor conducts a Phase IV drug-drug interaction study to determine the pharmacokinetic and pharmacodynamic interactions that may occur between FLOMAX™ and these agents.

Please convey the Recommendation and Dissolution, Metabolism, and Labeling Comments to the sponsor.

R. Miller, Ph.D. R. Miller 3/31/97
Pharmacometrics, OCPB

E. Ette, Ph.D. 4/7/97
Pharmacometrics, OCPB

RD Initialed by Angelica Dorantes, Ph.D., Team Leader. AD 3/8/97
FT signed by Angelica Dorantes, Ph.D., Team Leader. A Dorantes 4/8/97

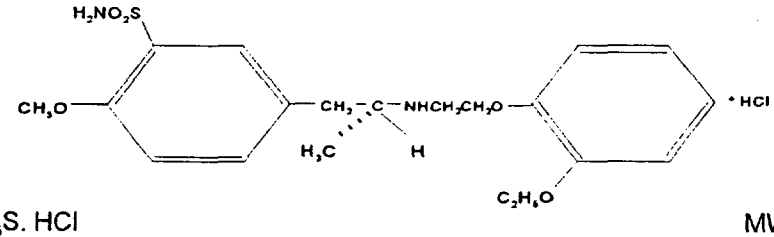
cc: **NDA 20-579, HFD-580 (Fourcroy, Rumble), HFD-870 (ML.Chen, Dorantes, Miller, Ette, Barnette), Drug file, (CDR Barbara Murphy).**

TABLE OF CONTENTS:

IV. Background

Tamsulosin [(R)(-)-5-[2-[[2-(ethoxyphenoxy)ethyl]amino]-propyl]-2-methoxybenzene sulfonamide] is the hydrochloride salt of a weak base. The molecular weight, empirical formula, and chemical structure of tamsulosin are described in Figure 1.

FIGURE 1



$C_{20}H_{28}N_2O_5S.\ HCl$ MW: 444.98

Tamsulosin is a benzene sulfonamide derivative with one chiral center and is manufactured as the (R)-stereoisomer. The drug substance is manufactured at the Yamanouchi facility in Takahagi, Japan. The drug product consists of a gelatin capsule filled with coated granules which provide an extended release profile. The outer granule coating provides acid resistance, and dissolution of the granule itself is retarded by enteric-soluble material mixed into the granulation. The drug product is manufactured by Yamanouchi at Nishine, Japan.

As January 1996, tamsulosin hydrochloride capsules has received marketing approval in: Japan, Netherlands, France, Finland, Denmark, Sweden, and New Zealand (Table 1).

Table 1. Foreign Approval History

Country	Sponsor	Date of Approval
Japan	Yamanouchi Pharmaceutical Co.	August 1993
Sweden	Yamanouchi Europe	February 1995
The Netherlands	Yamanouchi Europe	April 1995
	Boehringer Ingelheim	January 1996
Finland	Yamanouchi Europe	August 1995
New Zealand	Yamanouchi Europe	December 1995
France	Yamanouchi Europe	December 1995
	Boehringer Ingelheim	December 1995
Denmark	Yamanouchi Europe	January 1996

Tamsulosin is an alpha$_1$-adrenoceptor antagonist proposed for use in the treatment of urinary obstruction and irritation secondary to detrusor instability, increased urethal resistance and mechanical compression of the urethal lumen associated with benign prostate hypertrophy (BPH). BPH is characterized by progressive enlargement of the prostate leading to urinary tract irritation and disturbance in urinary bladder outflow. The use of medical therapy for the treatment of the signs and symptoms of BPH, a condition unique to men over the age of 45 years, with an alpha$_1$ adrenoceptor antagonist is a concept that has been developing over the past few years. Alpha$_1$ antagonists are approved for the treatment of the signs and symptoms of BPH in Europe and at the present time, two alpha$_1$ antagonists (doxazosin and terazosin) are approved for this indication in the United States.

V. Formulation

It is stated in the submission that the to-be-marketed formulation (CR-M) of the extended release granules was

used in all controlled clinical studies and virtually all the definitive pharmacokinetic studies. The to-be-marketed formulation of tamsulosin extended-release capsule is included in Table 2, below.

Table 2.

Component	Ingredient	Amount of Ingredient (mg)
Core Granules	tamsulosin HCl ✓	
	microcrystalline cellulose ✓	
Granule Coating	triacetin ✓	
Capsule Excipients	calcium stearate ✓	
	talc ✓	
Total Fill Weight		
Capsule Shell	gelatin ✓	
	FD&C Blue No. 2 ✓	
	titanium dioxide ✓	

It should be noted that, the 0.1 and 0.2 mg dosage forms used in some of the pharmacokinetic studies reviewed herein reportedly differ from the to-be-marketed 0.4 mg dosage form only in that they have 1/4 and ½ of the quantity of the to-be-marketed granules in smaller capsules.

Reviewer Comment:

1. *Although 0.1 and 0.2 mg dosage forms are used in some of the pharmacokinetic studies reviewed herein, approval is sought only for the 0.4 mg dosage form of tamsulosin.*

VI. Analytical Methodology

The original HPLC tamsulosin assay was developed by Yamanouchi Pharmaceutical Co. Ltd., Japan (YM-1) and later extended (YM-2). The YM-2 method was used by Yamanouchi Pharmaceutical Company and by to quantitate tamsulosin in plasma during the early clinical development program. More recently, , employed an HPLC assay with fluorescence detection. The method was validated for both plasma and urine and was used for the majority of pharmacokinetic studies conducted in the United States. It should be noted that, although the tamsulosin concentrations from Yamanouchi tended to be slightly higher than those from the magnitude of the difference was comparatively small.

Table 3 presents the *in vivo* analytical methods and laboratories in clinical studies to support the pharmacokinetic development of Tamsulosin in the United States. Cross validation of tamsulosin plasma assays were carried out between the four analytical laboratories and five different methods. Plasma samples from clinical study US92-03A containing high, medium and low concentrations of tamsulosin were sent to the other laboratories for blinded chromatographic analysis are included in Table 4.

Table 3.

Method			YM-2	YM-2	YM-2	YM-1
Assay site	(conc ng/mL)	USA	Europe	Japan	Japan Yamanouchi	Japan
Precision %	High	2.4 (50)	3.3 (19)	1.4 (15)	2.1 (40)	2.29 (40)
	Medium	4.3 (8)	5.5 (8)	1.4 (5)	1.4 (25)	2.93 (25)
	Low	9.5 (1)	4.3 (1.6)	8.0 (1)	7.1 (1.5)	7.26 (1.5)
Accuracy %	High	102	98.6	98.7	101.5	96.4
	Medium	92.9	97.5	100	106	96.9
	Low	104	96.3	96.7	98.1	90.6
(ng/mL)		0.5	0.5	0.5	0.5	0.5
Study #		92-03A, 92-04, 92-05, 93-02, 93-03, 93-05, 93-06, 93-07, 93-08, 93-09, 93-10, 94-02, 94-03	92-01A, 90-01A, 90-HAR-02, 93-HAR-01	89-01	555/7	125/0014

Table 4. Summary of Assay Comparison Results

Sample Pool	Statistic		YM-2	YM-2	YM-2 Yamanouchi	YM-1
High	Mean (ng/mL)	37.2	38.62	38.32	39.7	38.83
	C.V. %	1.21	6.76	1.53	1.92	2.83
Medium	Mean (ng/mL)	11.42	11.79	12.53	12.52	12.17
	C.V. %	1.29	1.49	9.65	2.34	6.95
Low	Mean (ng/mL)	2.35	-	2.72	2.61	2.44
	C.V. %	1.47	-	9.58	10.22	3.86

Reviewer Comments:

1. *Low concentrations at Simbec could not be quantitated. In general there appears to be good agreement between the methods.*
2. *The assays used appear appropriate and overall the validations presented are accepted. See individual study summaries for the comments on the validation for each study.*

VII. *In Vitro* Dissolution Testing

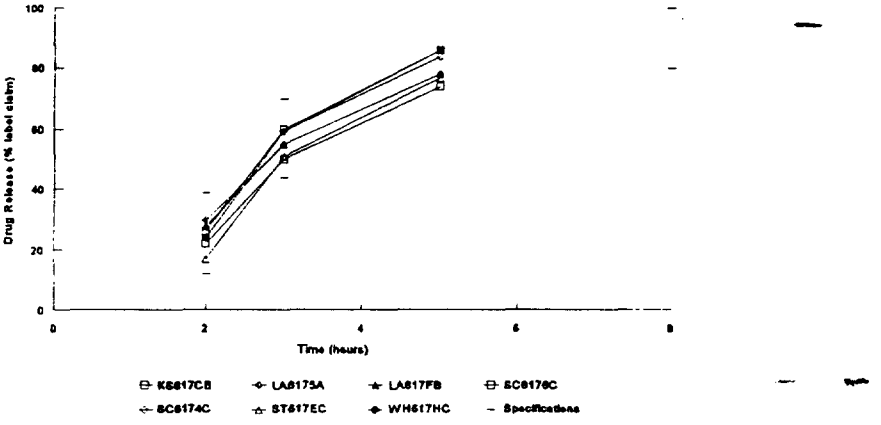
The following *in vitro* dissolution testing method is proposed by the sponsor:

Apparatus: USP Type 2 (Paddle Method)
Speed of rotation: rpm
Media: h (6 polysorbate 80, pH 1.2); h (phosphate buffer, pH 7.2)
Volume: 500 mL
Specifications:

Sampling times	% label claim
hours	%
hours	%
hours	%

Figure 2 includes the mean dissolution data from batches of the to-be-marketed formulation used in the clinical and pharmacokinetic studies reviewed herein.

Figure 2.



Reviewer Comments:

1. *The paddle speed of rpm is very high which explains the very rapid dissolution that is seen (complete dissolution in hours). This may also make it difficult to discern unacceptable lots. A paddle speed of rpm is preferred and the sponsor should be requested to submit data at that speed.*

2. *The dissolution data from hours for the clinically tested batches is not submitted and it is unclear why the hour time point is included in the release specifications.*

3. *The timing of samples is unusual and the sponsor should be requested to submit full dissolution profiles with more frequent sampling (perhaps every hours) in order to select the appropriate time points. A measurement at one hour may also be helpful.*

4. *The choice of polysorbate 80 instead of N HCl should be justified.*

5. *The dissolution specifications are relatively wide and should be tightened especially when variability in the dissolution results are not a factor.*

6. *If solubility is a problem, perhaps increasing the volume to 900 mL may resolve this problem.*

VIII. Pharmacokinetic/Pharmacodynamic Studies

The pharmacokinetics of tamsulosin and the extended release formulation proposed for marketing (CR-M) were examined in 21 studies in humans following single and/or multiple (q.d. or b.i.d.) dosing. These studies addressed issues related to mass balance, absorption, absolute/relative bioavailability, food effects, distribution and protein binding, metabolism/excretion, single/multiple dose pharmacokinetics and dose proportionality, kinetics in the elderly, disease states such as renal or hepatic impairment, pharmacodynamic-drug interactions, and the bioequivalence of the final formulation. Dose-finding, population-PK, and PK/PD relationships were examined in BPH patients.

A summary of the pharmacokinetic and pharmacodynamic studies is presented in Table 5.

Table 5. Study Summary

Study #	Design	Dose	Population	Pg #
93-HAR-01	ABSOLUTE BIOAVAILABILITY: Single dose, two-way crossover	0.4 mg controlled release (CR-M) 0.125 mg IV	10 healthy ♂	62
89-01	RELATIVE BIOAVAILABILITY: Multiple dose, single blind, randomized, crossover	0.4 mg CR-M q.d., 7 days 0.1 mg solution B.I.D., 7 days	24 healthy ♂	58
B9V-LC-GSAD	RELATIVE BIOAVAILABILITY: Single dose, randomized	0.4 mg CR-M q.d., fasted 0.4 mg CR-M q.d., fed 0.2 mg IR q.d. 0.4 mg CR-M, B.I.D.	8 healthy ♂	56
94-02	FORMULATION BIOEQUIVALENCE: Single dose, 3 treatment, 3 period, 5 sequence crossover	0.4mg CR-M commercial batch 0.4mg CR-M clinical batch (ST617DC) 0.4mg CR-M clinical batch (ST6174C)	28 healthy ♂	64
7/0014	DOSE PROPORTIONALITY: placebo-controlled, dose rising	CR-M 0.1, 0.4, 0.8 mg CR-M 0.2, 0.6, 1.0 mg Placebo	16 healthy ♂	67
555/7	MASS BALANCE: Single dose	0.2 mg C^{14}-Tamsulosin oral solution	4 healthy ♂	71
94-03	FOOD EFFECT: Single and multiple dose, double blind, sequential	CR-M (0.4 mgq.d. x 2 days followed by 0.8 mg q.d. x 11 days) Placebo x 13 days	24 middle aged, elderly ♂ 12 middle aged, elderly ♂	74
92-01A	MULTIPLE DOSE PK: Placebo controlled, double blind	CR-M (0.4 mg q.d. x 5 days followed by 0.8 mg q.d. x 14 days) placebo x 19 days	18 middle aged, elderly ♂ 6 middle aged, elderly ♂	92
92-04	RENAL IMPAIRMENT: Single dose PK	CR-M 0.4 mg	12 ♂ renal impaired 6 ♂ normal renal function	107
92-05	HEPATIC INSUFFICIENCY: Single dose PK	CR-M 0.4 mg	8 ♂ hepatic insufficiency 8 ♂ normal hepatic func.	113
90-01A	PHASE II DOSE FINDING (Phase II): Multiple dose	CR-M 0.2 mg, BID x 8 weeks CR-M 0.2 mg, QD x 8 weeks CR-M 0.1 mg, BID x 8 weeks CR-M 0.1 mg, QD x 8 weeks Placebo, BID x 8 weeks	10 ♂ w/ BPH 5 ♂ w/ BPH 9 ♂ w/ BPH 9 ♂ w/ BPH 6 ♂ w/ BPH	116
90-HAR-02	PK/PD STUDY (Phase II)	CR-M 0.4 mg, QD x 8 days	13 ♂ w/ BPH	118
92-03A	POPULATION PK (Phase III): Pivotal clinical study	0.4 mg QD x 1 week followed by 0.8 mg QD x 12 weeks Placebo x 13 weeks	185 ♂ w/ BPH 189 ♂ w/ BPH	120

A. PHARMACOKINETICS

a) **Absolute Bioavailability:**

The absolute bioavailability of the 0.4 mg extended-release formulation was determined in Study 93-HAR-01. The results are included in Table 6.

Table 6. Pharmacokinetic Parameters for Tamsulosin Following Oral Administration of 0.4 mg Extended-Release Formulation and a 0.125 mg Intravenous Infusion Over Four Hours.

	0.125 mg Intravenous Infusion (n=10)	0.4 mg Extended Release (n=10)
AUC (ng*h/mL)	173 ± 88	181 ± 108
F (%)	-	100 ± 19
C_{max} (ng/mL)	22.8 ± 6.8 (normalized to a 0.4 mg dose)	15.5 ± 5.0
T_{max} (h)	-	5.0 (4.0 - 6.0) median (range)
λ_z $t_{½}$ (h)	6.8 ± 3.5	22.0 ± 23.0
CL (L/h)	2.88 ± 1.44	-
V_{ss} (L)	16 ± 4	-

Reviewer Comment:

1. *The mean (± SD) absolute bioavailability of the 0.4 mg extended-release formulation is 100% ± 19, the median absolute bioavailability is 92% and the range from this study was %. Therefore, the data appear to be highly variable and non-normally distributed.*

b) **Relative bioavailability**

Administration of a single dose (Study B9V-LC-GSAD) and multiple doses (Study US89-01) of FLOMAX under fasted conditions resulted in a median T_{max} of 4 to 5 hours compared to 1 hour after immediate release formulation as well as oral solution. Extent of absorption is similar for the two formulations resulting in a 50% lower C_{max} (Figure 3 and Table 7).

FIGURE 3: Mean Plasma Profile for Tamsulosin on Day 5 (fed) after solution 0.1 mg bid and 0.4 mg q.d. extended Release Formulation (Extracted from Study US89-0).

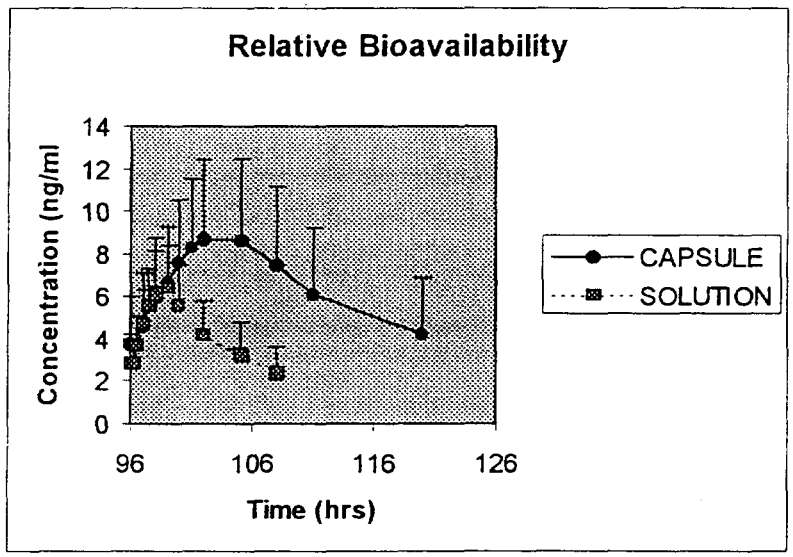


Table 7.

Parameter	0.4 mg q.d. Extended Release	0.1 mg b.i.d Solution	90% CI
AUC (ng*h/mL)	199.1 ± 94.1	239.2 ± 78.8	72-95
Cmax (ng/mL)	17.1 ± 7.3	9.1 ± 2.3	
Tmax (h)	4.0 (3.0-6.0)	1.0 (0.3-2.0)	
Cmin (ng/mL)	4.0 ± 2.6	2.6 ± 1.2	
t½ (h)		7.1 ± 3.7	

Reviewer Comments:

1. *Extent of absorption after oral administration of extended release formulation is approximately 25% lower than that of the oral solution . This is reflected in the reduced AUC and decreased fraction excreted unchanged (27% decrease).*

2. *Food reduces the extent of absorption of tamsulosin after solution by about 10% and after extended release formulation by about 26%. The extended release form is relatively consistently absorbed and displays adequate delayed absorption properties.*

c) **Bioequivalence:**

In Study 94-02, the bioequivalence of the batches that were used in the two U.S. pivotal Phase III trials, study US92-03A (Batch Number = SC6174C) and study US93-01 (Batch Number = SC617DC) were compared to a commercial batch intended for marketing (Batch Number = WH617HC). The results of comparing the pharmacokinetic parameters by ANOVA on the log-transformed data are included in Table 8.

Table 8

Parameter	Batch WH617HC	Batch SC6174C	90% CI
AUC∞	180.0 ± 65.5	180.0 ± 68.1	93.0 - 109
Cmax	14.4 ± 4.21	15.0 ± 4.45	86.0 - 106
Tmax	4.93 ± 0.90	5.36 ± 0.99	—
Parameter	**Batch WH617HC**	**Batch SC617DC**	**90% CI**
AUC∞	180 ± 65.5	190.0 ± 81.1	89.0 - 104
Cmax	14.4 ± 4.21	15.0 ± 5.19	89.0 - 107
Tmax	4.93 ± 0.90	5.36 ± 0.73	

Reviewer Comment: *The commercial batch (WH617HC) is bioequivalent to two of the batches (SC6174C and SC617DC) used in the pivotal clinical trials.*

d) **Single Dose:**

The pharmacokinetic profile of tamsulosin after a single dose of Flomax™ 0.4 mg controlled release capsules to 10 young (18-29 yoa) healthy males in Study US93-HAR-01 is included in Figure 4. The single dose pharmacokinetic parameters from the various studies reviewed herein are included in Table 9 .

Figure 4. Mean Plasma Tamsulosin Levels after administration of the to-be-marketed formulation (Study US93-HAR-01)

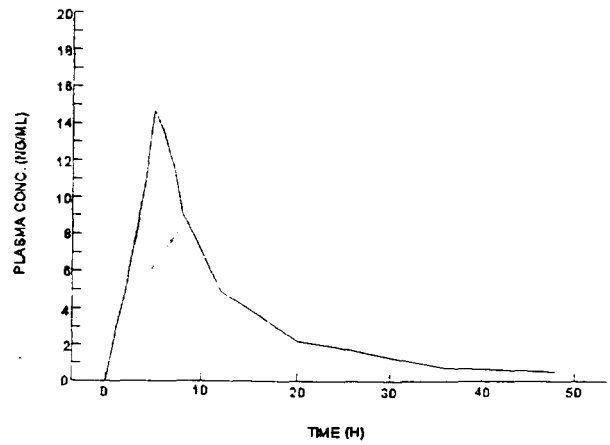


Table 9.

Study	n	Subject Age Range	Dose	Fed (+) or	Cmax	Tmax	AUC	T½
"Young" Subjects								
93-HAR-01	10		0.125 IV	-	22.8 ± 6.8	-	173 ± 88	6.8 ± 3.5
			0.4 CR	-	15.5 ± 5.0	5 (4-6)	181 ± 108	22.0 ± 23.0
B9V-LC-GSAD	8		0.2 IR	-	38.0 ± 9.8	1 (0.5-2)	280 ±104	6.4 ±3.3
			0.4 CR	-	19.6 ± 5.4	4.5 (4-6)	271 ± 114	11.7 ± 3.5
			0.4 CR	+	9.6 ± 2.5	9 (4-24)	215 ± 89	13.7 ± 3.4
US94-02	30		0.4 CR	-	14.4-15.0	5	180-190	8.9-9.4
125/0014	12		0.1-1.0 CR	-	15.5-21.0	3.5-5	168-203	8.1-11.4
555/7			0.2 IR	-	24.0 ± 2.4	0.8 (0.6-1)	66 [illegible]	[illegible] ± 0.8
US93-09			0.4 CR	1h before meal	13.9 ± 4.3	3 (2-3)	132 ± 55	21 12.6
"Middle-Aged to Elderly" Subjects								
US94-03	22		0.4 CR	+	9.8 ± 2.9	6 (2-10)	Not Done	Not Done
90-HAR-02	13		0.4 CR	-	9.9 ± 3.7	9 (6-28)	255 ± 151	14.1 ± 8.2
US92-04	6		0.4 CR	-	14.8 ± 2.8	4.5 (3-6)	192 ± 69	13.8 ± 4.0
US92-05	8		0.4 CR	-	18.8 ± 10.2	4.5 (3-5)	246 ± 146	16.1 ± 4.9

e) **Multiple Dose:**

The multiple dose pharmacokinetic parameters from the studies reviewed herein are included in Table 10.

Table 10.

Study	Subject Age	n	Dose	Fed (+) or	Cmax	Tmax	AUC	T½
"Young" Subjects								
US89-01		23	0.1 IR	-	9.1 ± 2.3	1 (0.3-2)	239 ± 79	7.1 ± 3.7
			0.1 IR	+	6.9 ± 2.2	2 (0.5-4)	205 ± 77	6.7 ± 2.4
			0.4 CR	-	17.1 ± 7.3	4 (3-6)	199 ± 94	ND
			0.4 CR	+	10.1 ± 4.8	6 (2-9)	151 ± 82	ND
US93-08		9	0.8 CR	+	12.9 ± 4.4	6 (2-12)	176 ± 68	228 ± 5.7
"Middle-Aged and Elderly" Subjects								
US94-03		22	0.8	+	14.9 ± 5.2	7 (3-12)	220 ± 98	ND
			0.8	+	14.6 ± 5.5	6.5 (3-10)	225 ± 109	ND
			0.8	-	20.8 ± 7.8	5 (2-7)	279 ± 129	14.9 ± 3.8
90-HAR-02		12	0.4	-	17.4 ± 12.4	9 (4-28)	290 ± 179	ND
US92-01A		18	0.4	+	10.8 ± 3.7	6 (4-12)	96 ± 34	ND
		17	0.8	+	11.6 ± 4.2	6 (2-10)	105 ± 38	ND
		16	0.8	-	14.1 ± 4.8	2 (2-6)	124 ± 48	ND
US90-01A		9	0.1	+	10.8 ± 6.4	5 (4-10)	76 ± 46	ND
		5	0.2	+	13.2 ± 5.2	5 (2-6.8)	83 ± 25	ND
		9	0.1	+	6.6 ± 1.9	4 (2-10)	52 ± 12	ND
		10	0.2	+	11.2 ± 5	3 (2-7.9)	47 ± 26	ND
US92-03A		374	0.4,0.8	+	ND	ND	ND	32.8 ± 5.3

Additionally, the measured accumulation of tamsulosin (55% to 75% for C_{max} and AUC) following administration of 0.8 mg q.d. to middle-aged to older volunteers for five days (Study US94-03) was similar to the predicted estimate of 50%.

f) **Dose proportionality:**

The results of Study 125/0014 that consisted of administration of ascending, single doses (0.1 to 1.0 mg) of the extended-release formulation to 12 young volunteers (n=6 per dose) are presented in Table 11.

Table 11: Mean (SD) Pharmacokinetic Parameters for Tamsulosin Following Single Oral Doses (0.1 mg - 1.0 mg) of Extended-Release Formulation (Study 125/0014)

Tamsulosin [illegible]	[illegible]	[illegible] [2]	$AUC_{(0-36)}$ [1] (ng*h/mL)	AUC_{∞} [1] (ng*h/mL)	t½ (h)	fe (%)	Cl [3]
0.1 mg	[illegible]	[illegible] 5.0)	169 (95)	Not Done	Not Done	6.3 (5.1)	0.17 [illegible]
0.2 mg	19.6 (4.4)	5.0 (3.0-5.0)	179 (46)	192 (50)	8.1 (2.1)	6.3 (2.8)	0.14 (0.07)
0.4 mg	16.5 (8.6)	5.0 (4.0-5.0)	162 (76)	184 (81)	11.4 (1.4)	10.3 (2.4)	0.28 (0.09)
0.6 mg	21.0 (4.1)	3.5 (3.0-5.0)	191 (48)	203 (52)	9.5 (0.6)	6.5 (3.0)	0.15 (0.08)
0.8 mg	15.5 (6.5)	5.0 (4.0-6.0)	153 (80)	168 (90)	10.0 (2.9)	8.5 (2.5)	0.25 (0.08)
1.0 mg	16.8 (4.2)	4.5 (4.0-5.0)	161 (36)	174 (40)	10.2 (1.7)	8.4 (2.6)	0.22 (0.10)

[1] Normalized to a 0.4 mg dose.
[2] Median (range)
[3] Based on supplementary analyses done during preparation of the NDA.

It should be noted that the Pearson Correlation Coefficient for C_{max} and $AUC_{(0-36)}$ (not dose-normalized) as a function of dose were 0.856 and 0.837, respectively (data not shown).

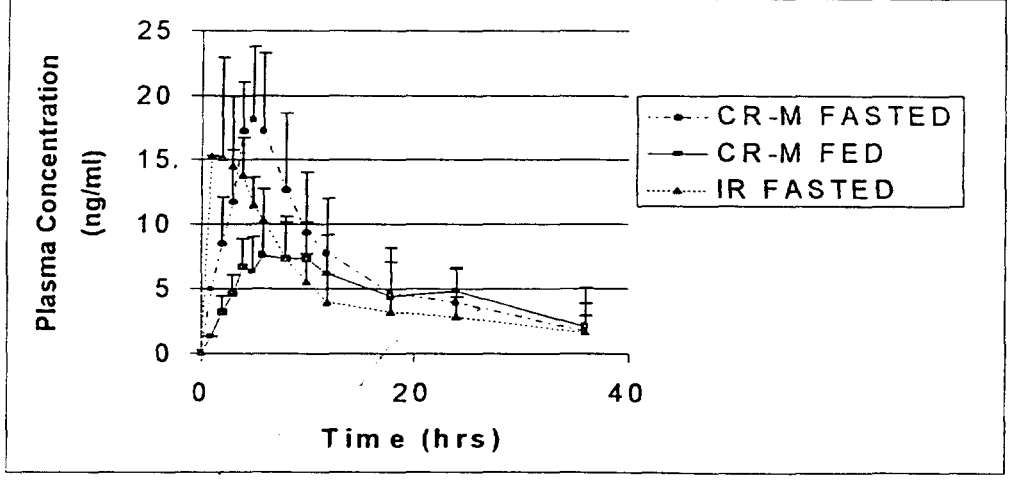
Reviewer Comment:

1. Tamsulosin shows dose proportionality within the clinical dose range.

g) **Food effect:**

The effect of food on the to-be-marketed formulation of tamsulosin and immediate release tamsulosin was assessed in Study B9V-LC-GSAD. The mean ± SD plasma concentrations are represented in Figure 6 below.

Figure 5.



In addition, Study 94-03 compared the bioavailability of tamsulosin with a light breakfast, a heavy breakfast and fasting in young to older volunteers at steady state. The results are presented in Table 12.

Table 12. Mean ± SD Pharmacokinetic Parameters and Comparative Statistics for 0.8 mg q.d. Tamsulosin

	Light Breakfast (A)	High-Fat Breakfast (B)	Fasting ©	Ratio (90% CI)[1]	
				B/A	C/A
$AUC_{(0-24)}$ (ng*h/mL)	440 ± 195	449 ± 217	557 ± 257	101 (97,106)	127 (121,133)
C_{max} (ng/mL)	29.8 ± 10.3	29.1 ± 11.0	41.6 ± 15.6	97 (91,104)	139 (130,149)
C_{min} (ng/mL)	12.3 ± 6.7	13.5 ± 7.6	13.3 ± 7.4	-	-
C_{max}/C_{min} Ratio	2.7 ± 0.7	2.5 ± 0.8	3.6 ± 1.1	-	-
T_{max} (h)	7.0 (3.0,12.0)[2]	6 5 (3.0,10.0)[2]	5.0 (2.0,7.0)[2]	96 (85,108)	77 (69,87)
$t_{½}$ (h)		-	14.9 ± 3.9	-	-

[1] 90% confidence interval on ge[illegible] a[illegible] ratio (% [illegible] sing light breakfast as the reference.
[2] Median (range).

Reviewer Comments:

1. *The proposed dosing of Flomax™ is with food.*
2. *The effects of food on the pharmacokinetics of tamsulosin are comparable when administered with a light or high-fat breakfast.*
3. *The fluctuation of plasma tamsulosin levels from the peak and trough concentrations are diminished when dosed with food. However, the clinical significance of this is unknown.*

h) **Metabolism:**

Mass Balance

After administration of a radiolabeled dose of tamsulosin to four healthy volunteers (555/7), 76% of administered radioactivity was recovered in the urine and 21% in the feces within 168 hours, with less than 10% recovered as unchanged drug in the urine.

In Vivo Drug Metabolism

Tamsulosin is extensively metabolized by enzymes in the liver, followed by The metabolic pathways identified in humans that are catalyzed by enzymes include; Phase II metabolism includes the of some of these metabolites of tamsulosin.

In Vitro Drug Metabolism Testing

Two *in vitro* drug metabolism tests were conducted by the sponsor in human liver microsomes. Study US95-3365 was an *in vitro* interaction study conducted to assess the effect of amitriptyline, diclofenac, salbutamol, glibenclamide, finasteride, warfarin and SKF 525-A on the metabolism of tamsulosin and correlation with marker substrate to identify the enzyme primarily responsible for the metabolism of tamsulosin. In Study US95-3371 an assessment of the effect of warfarin and diclofenac on the binding and metabolism of tamsulosin in human liver microsomes.

Reviewer Comments:

1. *The pharmacokinetic profile of the metabolites was not assessed in any of the pharmacokinetic studies.*
2. *Pre-clinical studies showed that some of the metabolites have comparable activity to the parent compound (data not shown, see Pharmacology/Toxicology Review by Dr. Jeri El Hage, Division of Reproductive and Urologic Drug Products, HFD-580).*
3. *In vitro drug metabolism and drug interaction testing was conducted by the sponsor and have been reviewed by Dr. K. Gary Barnette, Division of Pharmaceutical Evaluation II, Office of Clinical*

Pharmacology and Biopharmaceutics. Dr. Barnette's review is included as Attachment 3. The following significant comments were made:

- *The raw data from these studies is not submitted for review. Therefore, reanalysis of these data is not possible.*
- *The assay used to estimate the levels of each analyte (tamsulosin and metabolites and marker substrate metabolites) in this in vitro drug metabolism study is not properly validated. Therefore, the confidence one can have in any of the conclusions herein, is considerably limited.*
- *The concentration of tamsulosin used in these in vitro drug metabolism studies ng/mL) is times the Cmax at steady state from a 0.8 mg dose of the to-be-marketed formulation of tamsulosin (≈30 ng/mL).*
- *Diclofenac and Warfarin appear to activate the metabolism of tamsulosin in pooled liver microsomes. The mechanism of activation is not addressed by the sponsor. It should be noted that Diclofenac and Warfarin are primarily metabolized by and are not reported to induce metabolism by any mechanism.*
- *Amitriptyline, primarily metabolized by appears to have little effect on tamsulosin metabolism.*
- *The rationale the sponsor uses to identify as the primary catalyzing enzyme of tamsulosin, correlation of metabolism of a marker substrate with the disappearance of tamsulosin is inappropriate.*
- *Interaction studies with glibenclamide (Drug Saf. 1995, 13: 105-122) and finasteride (Drug Metab Dispos. 1995, 23: 1126-1135) both reportedly metabolized by showed no interaction with tamsulosin.*

i) **Isomer/Chiral Analysis:**

In a study in 22 middle-aged to older volunteers (US94-03), no S(+) isomer was detected in plasma samples collected at the approximate time of C_{max}.

Reviewer Comment:

1. *The to-be-marketed formulation of tamsulosin hydrochloride contains only the R(-) isomer and this isomer does NOT undergo chiral inversion to the S(+) isomer in vivo.*

j) **Protein binding:**

In vitro experiments have demonstrated that tamsulosin binds to specific and relatively high affinity binding sites on alpha-1-acid glycoprotein. Though highly bound, perturbations in binding (that might arise as a result of drug- or disease-interactions) are not expected to affect the efficacy or safety of tamsulosin, since unbound or active concentrations remain relatively constant, regardless of the magnitude of change in binding (Table 13).

Table 13. *In Vitro* Protein Binding of Tamsulosin at Different Concentrations in Humans, Rats, and Dogs by two separate methods (Ultrafiltration and Ultracentrifugation)

Plasma Concentration of Tamsulosin	Percent of Tamsulosin Bound to Plasma Proteins					
	Ultrafiltration Method (n=3)			Ultracentrifugation Method (n=3)		
	Human	Rat	Dog	Human	Rat	Dog
20 ng/mL	ND	ND	ND	93.7 (1.0)	81.0 (0.1)	92.7 (0.9)
60 ng/mL	ND	ND	ND	95.4 (0.4)	81.8 (0.2)	89.6 (1.3)
200 ng/mL	98.9 (0.0)	80.6 (0.4)	90.2 (1.2)	95.0 (0.4)	81.9 (0.5)	92.2 (1.0)
600 ng/mL	99.1 (0.1)	79.0 (0.4)	90.3 (0.0)	94.9 (0.2)	80.2 (0.0)	90.8 (0.1)

Note: Values are mean (SD) for ultrafiltration method and mean (standard error) for ultracentrifugationmethod.

Reviewer Comments:

1. *Tamsulosin is extensively plasma protein bound (94% to 99%), primarily to alpha-1-acid glycoprotein (AAG) in humans.*

2. *Protein binding appears linear over a wide concentration range. ng/mL).*

B. SPECIAL POPULATIONS:

a) **Hepatic Insufficiency:**

In a single dose study (US92-05) in eight subjects with moderate hepatic impairment and eight normal subjects, it was observed that the unbound fraction of tamsulosin was 150% higher in subjects with hepatic impairment (with a resultant 45% increase in oral clearance) due to a reduction in plasma alpha-1-acid glycoprotein levels, but differences in intrinsic clearance of unbound drug were modest (30%; Table 14). The modest difference in intrinsic clearance indicated that concentrations of unbound (active) tamsulosin would remain relatively unchanged with hepatic impairment (in spite of large changes in unbound fraction).

b) **Renal Impairment:**

In a single dose study (US92-04) in 12 subjects with moderate to severe renal impairment and 6 normal subjects, a % decrease in oral clearance was observed, which was considered to be the combined result of age-related decreases in intrinsic clearance %) and decreases in unbound fraction (%) related to increases in alpha-1-acid glycoprotein associated with renal dysfunction. Since changes attributable to decreased renal function were restricted to a decrease in unbound fraction due to the increase in alpha-1-acid glycoprotein levels, results of this study predicted that concentrations of unbound (active) drug would remain unchanged with renal impairment. Again, the predicted lack of a clinically significant effect was supported by the absence of changes in safety measurements in renally impaired subjects (Table 14).

Table 14. Mean ± SD Pharmacokinetic Parameters Following Single Dose Administration of Tamsulosin 0.4 mg to Fasted Adult Male Volunteers with Renal (Study US92-04) or Hepatic Function (Study US92-05)

	Renal Study			Hepatic Study	
	Normal	Moderately	Severely	Normal	Hepatic
No. of Subjects	6	6	6	8	8
Cl_{cr} (mL/min/1.73m^2)	106 ± 10	54 ± 10[1]	14 ± 4[1]	-	-
ICG CL (L/h)	-	-	-	41 ± 10[2]	25 ± 17[2]
AUC (ng*h/mL)	192 ± 69	397 ± 197	286 ± 167	246 ± 146	144 ± 61
C_{max} (ng/mL)	14.8 ± 2.8	20.5 ± 4.5	16.7 ± 7.1	18.8 ± 10.2	12.5 ± 6.1
T_{max} (h)[3]	4.5	5.0	6.0	4.5	4.0
CL/F (L/h/kg)	0.026 ± 0.011	0.015 ± 0.009	0.025 ± 0.015	0.028 ± 0.021	0.041 ± 0.016
CL_{nr} (L/h/kg)	2.30 ± 0.7	1.57 ± 1.08	2.12 ± 0.80	2.59 ± 1.59	1.75 ± 0.91
fu (%)	1.1 ± 0.3	0.9 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	2.5 ± 1.9
$t_{½}$ (h)	13.8 ± 4.0	20.2 ± 5.6	18.0 ± 4.9	16.1 ± 4.9	13.6 ± 5.5
CL_R (L/h)	0.251 ± 0.075	0.100 ± 0.033[1]	0.045 ± 0.027[1]	0.234 ± 0.181	0.663 ± 0.388[2]

Note: Normal renal function: CL_{cr} >90 mL/min/1.73m^2 ; Mild-moderate renal impairment: 30≤ CL_{cr} <70 mL/min/1.73m^2; Moderate-severe renal impairment: 10≤ CL_{cr} <30 mL/min/1.73m^2. [1] Renal Study: Significantly different from normal subjects (P-value <0.050), [2] Hepatic Study: Significantly different from normal subjects (P-value <0.050), [3] Median.

Reviewer Comments:

1. *No dosage adjustment is necessary when tamsulosin is administered to patients with hepatic dysfunction (Grades A and B, Child-Pugh's classification).*

2. *Patients with renal impairment (creatinine clearances above mL/min/ m^2) do not require a dosage adjustment of tamsulosin.*

c) **Age:**

A cross-study comparison of tamsulosin AUC showed that following administration of 0.8 mg q.d. extended-release formulation to older subjects (study US94-03; 55-75 years), a moderate increase in bioavailability was

observed, with a % increase in dose-normalized AUC measured under fasted conditions at steady-state compared to AUC in young volunteers (study US89-01; data not shown). It is stated by the sponsor that this change is likely related to a modest decrease in intrinsic clearance with advancing age (study US92-04).

Reviewer Comment: *Dose need not be adjusted for age.*

C. PHARMACOKINETIC DRUG INTERACTIONS:

Table 15. Summary of Pharmacokinetic Drug Interaction Studies.

Study #	Design	Dose	Population	Pg #
US93-07	Digoxin (Lanoxin®) - Tamsulosin	Placebo x 8 days followed by 0.4 mg QD x 2 days	10 ♂	98
US93-08	Furosemide (Lasix®) - Tamsulosin	0.4 mg QD x 2 days followed by 0.8 mg QD x 5 days	10 ♂ (5 test/5 placebo)	100
US93-09	Cimetidine (Tagamet®) - Tamsulosin	Placebo + 0.4 mg QD (days 2, 8) + cimetidine 400 mg	10 ♂	103
US93-10	Theophylline - Tamsulosin	Placebo + 0.4 mg QD (days 3,4) followed by 0.8 mg	9 ♂	105

a) **Digoxin:**
The pharmacokinetic effect of tamsulosin on a single IV dose of digoxin (0.5 mg administered over 30 minutes) in healthy volunteers was assessed in Study US93-07. The results of this study are included in Table 16.

Table 16. Mean (CV%) Pharmacokinetic Parameters and Ratio (SE) from Iterative 2-Stage Analysis

	Digoxin alone (placebo)	Digoxin plus tamsulosin (test)	Ratio (Placebo/Test)
Vss (L)	618 (10.7%)	640 (3.52%)	1.05 (0.04)
Clrenal (L/h)	9.24 (13.6%)	9.46 (15.5%)	1.02 (0.02)
Cltotal (L/h)	11.8 (16.8%)	11.3 (17.7%)	0.966 (0.009)
t½ (h)	44.0 (21.2%)	46.7 (17.7%)	1.08 (0.045)
AUC0-∞ (ng*h/mL)	43.6 (15.6%)	45.2 (16.0%)	1.01 (0.007)

Reviewer Comments:
1. *Study US93-07 resulted in no change in the pharmacokinetics of digoxin in comparison to the pharmacokinetic profiles in the absence of concomitant tamsulosin.*
2. *Dosage adjustments are not necessary when tamsulosin is administered concomitantly with digoxin.*

b) **Theophylline:**
The effect on the pharmacokinetics of a single IV dose of theophylline (5 mg/kg administered over 30 minutes) in healthy volunteers [n=10] by 0.4 mg/day tamsulosin for two days, followed by tamsulosin 0.8 mg/day for five to eight days was assessed in Study US93-10. The results of this study are included in Table 17.

Table 17. Mean (CV%) Pharmacokinetic Parameters

	Theophylline alone (placebo)	Theophylline plus tamsulosin (test)
AUC0-∞ (ng*h/mL)	85.1 (27.2%)	83.2 (34.7%)
Clt (L/h/kg)	0.0629 (25.7%)	0.0661 (25.9%)
Vd (L/kg)	0.493 (8.04%)	0.518 (10.3%)
t½ (h)	5.68 (19.9%)	5.85 (35.5%)

Reviewer Comments:

1. *The data presented herein indicates that concomitant dosing of theophylline and tamsulosin resulted in no change in the pharmacokinetics of theophylline.*
2. *Dosage adjustments are not necessary when tamsulosin is administered concomitantly with digoxin or theophylline.*

c) **Furosemide:**

Study US93-08 evaluated the pharmacokinetic and pharmacodynamic effect of furosemide (single 20 mg IV dose) on tamsulosin 0.8 mg/day (steady-state). The results of this study are included in Table 18.

Table 18. Mean (CV%) Pharmacokinetic Parameters

	Tamsulosin alone (placebo)	Tamsulosin with Furosemide (test)	p
Tlag (h)	1.89 (12.4%)	1.74 (3.17%)	
Ka (h-1)	0.178 (24.8%)	0.143 (30.7%)	
Vss/F (L)	36.6 (9.26%)	37.7 (34.8%)	
Clt/F (L/h)	2.32 (30.7%)	3.42 (41.7%)	<0.001
t½ (h)	22.8 (25.0%)	18.5 (33.2%)	0.0552
SHAM Analysis			
AUC0-23h (ng*h/mL)	351 (38.7%)	314 (50.5%)	0.064
Cmax (ng/mL)	25.7 (34.3%)	22.1 (40.7%)	0.579
Tmax (h)	6.44 (43.3%)	6.44 (13.7%)	0.169

Reviewer Comments:

1. *Tamsulosin had no effect on the pharmacodynamics (urinary excretion of electrolytes) of furosemide (data not shown).*
2. *Although furosemide produced a % reduction in tamsulosin C_{max} and AUC, these changes do not warrant adjustment of the tamsulosin dosage.*

d) **Cimetidine:**

The effects of cimetidine at its maximal clinically recommended dose on the pharmacokinetics of a single 0.4 mg dose of tamsulosin was investigated in study US93-09 in ten healthy volunteers (age range 21-38 years). The results of this study are included in Table 19.

Table 19. Mean (CV%) Pharmacokinetic Parameters

	Tamsulosin alone (placebo)	Tamsulosin plus Cimetidine (test)	p-value
Fitted Pharmacokinetic Parameters			
Tlag (h)	0.613 (58.7%)	0.589 (83.0%)	
ka (h-1)	0.172 (33.2%)	0.125 (47.3%)	
Vss/F (L)	28.8 (18.5%)	22.1 (24.9%)	0.00630
Clt/F (L/h)	2.33 (40.2%)	1.62 (29.5%)	0.00368
t½ (h)	21.5 (58.7%)	25.3 (68.2%)	0.296
AUC∞ (ng*h/mL)	196 (36.1%)	266 (27.4%)	0.0019

Table 19. (Continued)			
SHAM Analysis			
AUC∞ (ng*h/mL)	182 (34.6%)	249 (29.4%)	0.00361
Clt/F (L/h)	2.51 (41.4%)	1.76 (34.1%)	0.00361
Vz/F (L)	38.8 (35.3%)	29.2 (40.4%)	0.0043
t½app (h)	11.7 (34.0%)	11.6 (21.1%)	0.285
Tmax (h)	2.9 (11.5%)	3.7 (56.2%)	0.523
Cmax (ng/mL)	13.9 (31.1%)	12.7 (20.2%)	0.584

Reviewer Comments:

1. *Treatment with cimetidine (400 mg every six hours for six days) resulted in a significant decrease (26%) in the clearance of tamsulosin which resulted in a moderate increase in tamsulosin AUC_4 (44%).*
2. *Although the sponsor suggests that the safety profile does not warrant dosage adjustment this has not been shown for a patient taking doses larger than 0.8 mg.*

D. PHARMACODYNAMIC DRUG INTERACTION STUDIES

A summary of the PD drug interaction studies included in this submission is presented in Table 20.

Table 20.

Study #	Design	Dose	Population	Pg #
US93-02	Nifedipine (ProcardiaXL®) - Tamsulosin	nifedipine + 0.4 mg tamsulosin, QD followed by 0.8 mg QD x 7 days Placebo x 14 day + nifedipine	11 ♂ previously stabilized on nifedipine (7 test/4 placebo)	76
US93-03	Atenolol (Tenormin®) - Tamsulosin	atenolol + 0.4 mg tamsulosin, QD x 7 days followed by 0.8 mg QD x 7 days Placebo x 14 day + atenolol	12 ♂ previously stabilized on atenolol (8 test/4 placebo)	84
US93-05	Enalapril (Vasotec®) - Tamsulosin	enalapril + 0.4 mg tamsulosin QD x 7 days followed by 0.8 mg QD x 7 days Placebo x 14 day + enalapril	10 ♂ previously stabilized on enalapril (6 test/4 placebo)	94
US93-06	Warfarin Sodium (Coumadin®) - Tamsulosin	warfarin + 0.4 mg tamsulosin QD x 5 days followed by 0.8 mg QD x 5 days Placebo x 10 day + warfarin	6 ♂ (3 test/3 placebo)	96

a) <u>Nifedipine (Procardia XL®):</u>

A pharmacodynamic interaction study between nifedipine and tamsulosin in 11 (7 test and 4 placebo) hypertensive subjects (Study US93-02) whose blood pressure was controlled with stable doses of Procardia XL® for at least three months was conducted. The effect of tamsulosin on blood pressure and pulse rate (change from baseline) is included in Table 21.

Reviewer Comments:

1. *There were eight of subjects enrolled in the treatment arm of Study US93-02. However, only seven subjects completed the study, one subject was discontinued due to abnormal urinalysis on Day 11 and prior history of renal stones.*
2. *Based on change from baseline in seven evaluable test subjects and comparison to placebo (n=4), no clinically significant effects on blood pressure and pulse rate were observed*

Table 21.

		Baseline (Placebo)	Change from Baseline	
		Day 4	Day 11	Day 19
Systolic Blood Pressure (mm Hg)	Tamsulosin	134.3 - 147.0	-11.0 to -3.8	-11.7 to +2.6
	Placebo	127 - 144.5	-10.0 to +4.0	-11.0 to +3.0
Diastolic Blood Pressure (mm Hg)	Tamsulosin	87.3 - 95.8	-5.8 to +2.8	-8.9 to +3.1
	Placebo	77.0 - 94.5	-6.0 to +4.0	-7.0 to +5.0
Pulse Rate (bpm)	Tamsulosin	71.5 - 79.8	-2.5 to +7.8	-6.1 to +8.9
	Placebo	70.0 - 79.5	-10.0 to +5.5	-12.0 to +2.8

3. *Additionally, no significant orthostatic effects or changes in ECG were observed in comparison to placebo.*
4. *No dosage adjustments are necessary when tamsulosin is administered concomitantly with Procardia XL®.*

b) **Atenolol:**

In Study US93-03 a pharmacodynamic interaction of atenolol and tamsulosin was assessed in 12 hypertensive subjects (8 test and 4 placebo) previously stabilized on atenolol for at least 3 months. The results of this study is included in Table 22.

Table 22.

		Baseline (Placebo)	Change from Baseline	
		Day 4	Day 11	Day 19
Systolic Blood Pressure (mm Hg)	Tamsulosin	129.8 - 140.0	-14.8 to +1.5	-20.3 to +11.5
	Placebo	137.5 - 150.5	-18.5 to +6.5	-21.5 to +1.0
Diastolic Blood Pressure (mm Hg)	Tamsulosin	81.5 - 93.3	-11.5 to +0.5	-9.5 to +1.8
	Placebo	82.5 - 92.5	-4.5 to +2.0	-7.5 to +2.5
Pulse Rate (bpm)	Tamsulosin	54.9 - 64.0	-5.0 to +7.4	-5.8 to +6.1
	Placebo	49.5 - 64.0	-6.5 to +5.8	-9.8 to +6.8

Reviewer Comments:

1. *Based on the results of Study US93-03, no clinically significant effect of coadministration of tamsulosin and atenolol on blood pressure and pulse rate were observed.*
2. *No dosage adjustments are necessary when tamsulosin is administered concomitantly with atenolol.*

c) **Enalapril:**

A pharmacodynamic interaction of enalapril and tamsulosin in 10 hypertensive subjects stabilized on enalapril for at least 3 months was conducted (US93-05). The results of the interaction on blood pressure and pulse rate are included in Table 23.

Table 23.

		Baseline (Placebo)	Change from Baseline	
		Day 4	Day 11	Day 19
Systolic Blood Pressure (mm Hg)	Tamsulosin	124.8 - 138.0	-6.7 to +9.0	-8.3 to +14.0
	Placebo	123.5 - 128.5	-5.0 to +10.0	-8.5 to +5.5
Diastolic Blood Pressure (mm Hg)	Tamsulosin	76.8 - 94.3	-7.0 to +10.7	-8.0 to +14.3
	Placebo	76.0 - 90.5	-8.0 to +3.5	-7.0 to +3.5
Pulse Rate (bpm)	Tamsulosin	63.5 - 73.9	-5.2 to +6.8	-2.0 to +4.7
	Placebo	72.0 - 74.5	-7.0 to +6.0	-4.0 to +9.0

Reviewer Comments:

1. *Based on the results of Study US93-05, no clinically significant effect of coadministration of tamsulosin and Enalapril on blood pressure and pulse rate were observed.*
2. *No dosage adjustments are necessary when tamsulosin is administered concomitantly with enalapril.*

d) **Warfarin:**

The pharmacodynamic effect of treatment with tamsulosin (0.4 mg q.d. for five days followed by 0.8 mg q.d. for five days), in healthy volunteers (age range years) receiving warfarin was assessed in Study US93-06. It should be noted that eight subjects were enrolled and randomized to the test arm (dosing of tamsulosin and warfarin) and 4 subjects to the placebo arm (dosing of placebo and warfarin). However, only 3 subjects in each arm completed the study. The reasons for discontinuation from the study are included in Table 24.

Table 24: Summary of Reasons for Discontinuation

Subject Number	Number of Days on Warfarin	Number of Days on Double-Blind Medication	PT value (sec)	Laboratory Findings
TAMSULOSIN GROUP				
	13	3	21.3	Increase in PT
	11	1	21.5	Increase in PT *
	14	4	21.9	Increase in PT
	11	1	16.5	Urine RBCs > 100 on 8/20/93, urine blood +3, Probable urinary tract infection*
	11	1	21.3	Increase in PT *
PLACEBO GROUP				
	14	4	21.5	Increase in PT

* Based on PT or laboratory tests prior to the initiation of double-blind therap

The pharmacokinetic effect of tamsulosin on warfarin was assessed by taking trough levels of warfarin (and tamsulosin) from the 6 subjects that completed the study. The results of this assessment is included in Table 25. The warfarin and tamsulosin doses and prothrombin times at the end of the dosing interval for each subject enrolled (just prior to the next dose) are included in Table 26.

Table 25. Plasma Warfarin and Tamsulosin Conc. From the 6 Subjects that Completed the Study.

		DB Day 1[a]	DB Day 6		DB Day 11	
Subject	Warfarin	Warfarin Plasma	Warfarin Plasma	Tamsulosin Plasma	Warfarin Plasma	Tamsulosin Plasma
TAMSULOSIN TREATMENT GROUP						
PLACEBO TREATMENT GROUP						

[a] The dose remained constant during the double-blind treatment period.
[b] All plasma determinations of tamsulosin concentration were 0 on DB1 as the blood was withdrawn predose of double-blind medication. Trough value after 5 days of dosing with tamsulosin 0.4 mg and 0.8 mg q.d.[4]

Table 26. Warfarin Dose and Prothrombin Times

	TAMSULOSIN-TREATED SUBJECTS								PLACEBO-TREATED SUBJECTS			
Study Day Tamsulosin Dose	01	03	04	06	07	09	10	11	02	05	08	12
BASELINE DAY												
0 -	3mg 11.9sec	3mg 11.8sec	3mg 11.3sec	3mg 11.3sec	3mg 11.5sec	3mg 12.0sec	3mg 11.8sec	3mg 12.4sec	3mg 12.0sec	3mg 11.8sec	3mg 11.9sec	3mg 12.0sec
PLACEBO EVALUATION DAYS												
PE 8 0 mg	4 mg 17.4sec	5 mg 16.4sec	5 mg 15.5sec	6 mg 15.0sec	7 mg 13.7sec	7 mg 16.8sec	5 mg 18.1sec	6 mg 14.4sec	4 mg 17.4sec	6 mg 15.7sec	7 mg 14.1sec	7 mg 15.1sec
PE 9 0 mg	4 mg 19.4sec	5 mg 19.6sec	5 mg 16.7sec	6 mg 16.7sec	7 mg 15.8sec	7 mg 19.9sec	5 mg 19.5sec	6 mg 17.4sec	4 mg 18.0sec	6 mg 17.7sec	7 mg 15.9sec	7 mg 18.2sec
PE 10 0 mg	4 mg 19.0sec	5 mg 19.0sec	5 mg 16.6sec	6 mg 17.0sec	7 mg 15.9sec	7 mg 19.8sec	5 mg 18.6sec	6 mg 18.2sec	4 mg 17.0sec	6 mg 18.6sec	7 mg 16.3sec	7 mg 17.7sec
DOUBLE-BLIND DOSING DAYS												
DB 1 0.4 mg	3mg 20.3sec	– 21.5sec	5mg 17.7sec	6mg 18.1sec	– 16.5sec	– 21.3sec	4mg 19.7sec	6mg 18.1sec	4mg 17.0sec	4mg 20.6sec	7mg 16.9sec	6mg 19.6sec
DB 2 0.4 mg	3mg 21.0sec	# 19.5sec	5mg 18.2sec	6mg 19.2sec	# 16.5sec	# 20.0sec	4mg 20.1sec	6mg 17.2mg	4mg 16.5sec	4mg 19.9sec	7mg 17.6sec	6mg 18.8sec
DB 3 0.4 mg	– 21.3sec	# 16.8sec	5mg 19.4sec	6mg 20.3sec	# 15.6sec	# 18.0sec	4mg 20.2sec	6mg 16.8sec	4mg 17.3sec	4mg 20.6sec	7mg 18.1sec	6mg 17.7sec
DB 4 0.4 mg	# 20.3sec	# 14.1sec	5mg 20.0sec	– 21.9sec	# 14.1sec	# 14.8sec	4mg 20.8sec	6mg 17.9sec	4mg 18.0sec	– 21.5sec	7mg 19.5sec	6mg 17.7sec
DB 5 0.4 mg	# 16.7sec	–	5mg 19.7sec	# 20.7sec	–	–	4mg 20.3sec	6mg 18.0sec	4mg 19.3sec	# 20.3sec	7mg 19.8sec	6mg 17.7sec
DB 6 0.8 mg	# 13.6sec	–	5mg 19.7sec	# 18.0sec	–	–	4mg 18.6sec	6mg 18.2sec	4mg 18.3sec	# 16.3sec	7mg 20.8sec	6mg 17.8sec
DB 7 0.8 mg	–	–	5mg 19.4sec	# 14.4sec	–	–	4mg 17.5sec	6mg 19.2sec	4mg 18.6sec	# 14.0sec	7mg 20.4sec	6mg 17.8sec
DB 8 0.8 mg	–	–	5mg 18.6sec	–	–	–	4mg 16.3sec	6mg 18.7sec	4mg 18.7sec	–	7mg 19.5sec	6mg 16.9sec
DB 9 0.8 mg	–	–	5mg 18.3sec	–	–	–	4mg 16.1sec	6mg 17.7sec	4mg 16.9sec	–	7mg 20.7sec	6mg 17.5sec
DB 10 0.8 mg	–	–	5mg 19.0sec	–	–	–	4mg 16.3sec	6mg 14.3sec	4mg 16.9sec	–	7mg 20.4sec	6mg 15.7sec
DB 11 Placebo	–	–	– 18.6sec	–	–	–	– 16.4sec	– 13.6sec	– 16.5sec	–	– 20.7sec	– 13.6sec
DB 12 None	–	–	– 16.3sec	–	–	–	– 14.9sec	– 13.5sec	– 15.5sec	–	– 19.2sec	– 12.5sec
DB 19 None	–	–	– 11.8sec	–	–	–	– 11.5sec	– 12.5sec	– 12.1sec	–	– 12.1sec	– 11.8sec

– No dose of warfarin
Measurement taken after the dosing of warfarin was discontinued

Reviewer Comments:

1. *It is unclear why the sponsor increased the warfarin dose from the 3 mg dose, on which the subject was stabilized, when the subjects were going from "Baseline" (no tamsulosin or placebo dose) to the "Placebo Evaluation Days".*
2. *From the trough tamsulosin and warfarin concentration data from the 6 subjects that completed the study (3 subjects on test, 3 on placebo), it appears that tamsulosin may have an interactive effect on the warfarin levels. Consequently, the assessment and conclusions of the pharmacokinetic effect of warfarin on tamsulosin are equivocal.*
3. *The discontinuation of 4 out of 5 subjects that did not complete the study on tamsulosin treatment was due to increased prothrombin time (a significant adverse event).*
4. *Since the drug interaction studies (in vivo PK/PD and in vitro drug metabolism) between warfarin and tamsulosin are inconclusive, it is recommended that the label includes this potential interaction.*

E. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS:

The rationale for the dosage regimen proposed for marketing was arrived at through a series of clinical studies that evaluated several different doses and dosing regimens of tamsulosin [studies US90-01A, 90-HAR-02, US92-03A]. Of these, study US92-03A provides the clearest evidence from a PK/PD perspective of the suitability of the proposed dosing regimen based on a population PK/PD analysis of tamsulosin concentration and efficacy data.

Plasma samples were obtained (between 4 and 8 hours after the dose) on visits 5, 6 (one sample each) and visit 10 (two samples). The population pharmacokinetics was characterized by the iterative two stage analysis using ADAPT II. No covariates were significant in describing differences between subjects and were not incorporated in the pharmacokinetic model. Pharmacokinetic parameters are similar to previously determined values in normal, adult male volunteers (Table 27).

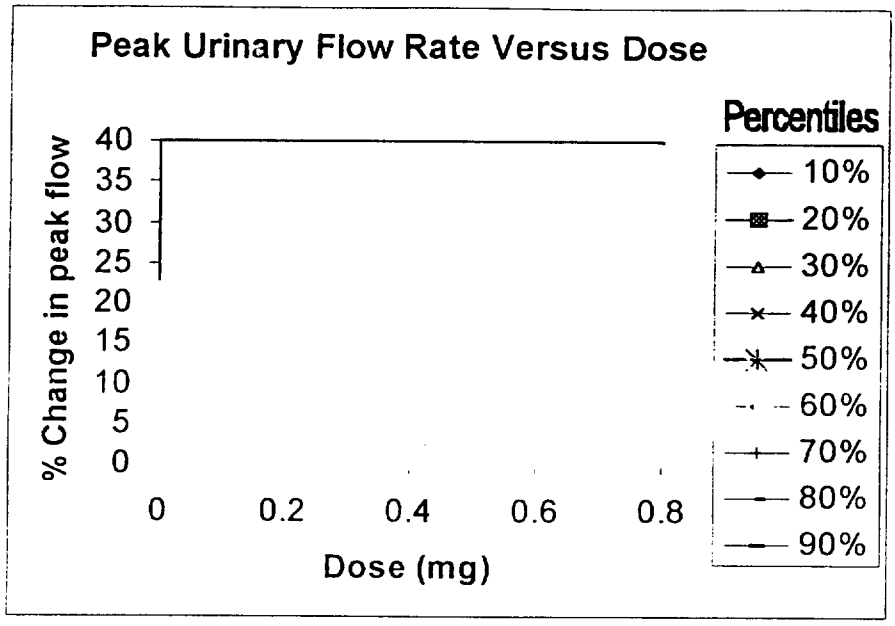
TABLE 27. Mean (SD) Model-Fitted Pharmacokinetic Parameters for Tamsulosin Following Administration of 0.4 mg q.d. and 0.8 mg q.d. to BPH Patients

Pharmacokinetic Parameter	Mean (SD)
V_c/F (L)	12.1 (6.6)
V_{SS}/F (L)	36.2 (10.1)
CL/F (L/h)	2.17 (0.98)
$t_{½}$ (h)	32.8 (5.3)

Note: Parameters generated using population pharmacokinetic methods. Data from 374 patients were included.

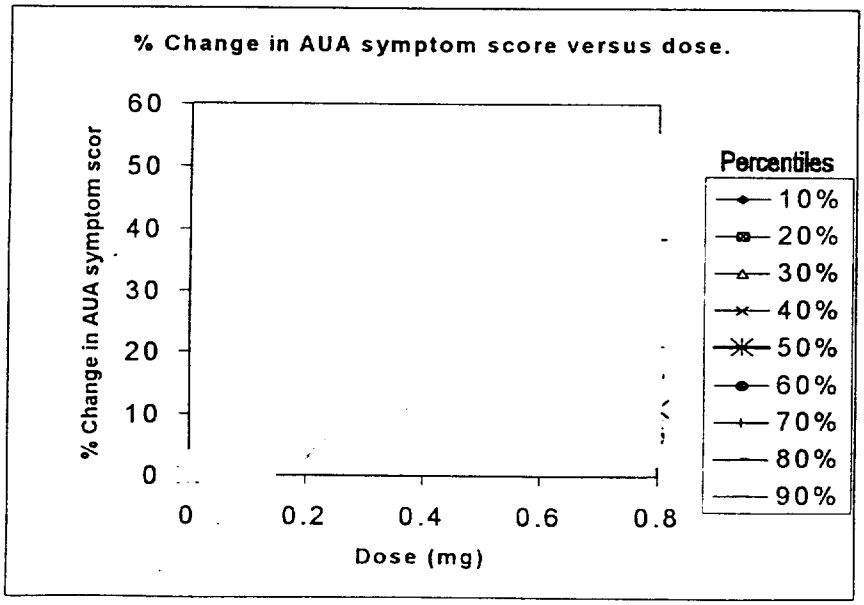
The primary efficacy parameters were: **(a)** the change in Total AUA Symptom Score from Baseline to Endpoint; **(b)** the percentage of patients having a 25% or more improvement in Total AUA Symptom Score from Baseline to Endpoint; © the change in peak urine flow rate (Q_{MAX}) from Baseline to Endpoint; and **(d)** the percentage of patients with 30% or more improvement in Q_{MAX} from Baseline to Endpoint. Peak and average urinary flow rate and time to peak flow rate were considered for pharmacodynamic modeling. There was no systematic change in time to peak flow with either time on study or assigned regimen. Using predicted concentration as a measure of exposure a sigmoid Emax model best described the peak and average urinary flow rate. Predicted changes in peak urinary flow rate are depicted in Figure 7.

FIGURE 6



As can be seen, there was only modest improvement in peak flow, at doses beyond 0.4 mg per day and, at doses of 0.2, 0.4, 0.6 and 0.8 mg, the percent of patients predicted to experience at least a 30% improvement in flow, were approximately 11, 20, 24 and 24% respectively. Symptom score was modeled as a function of time (improvement) as well as drug concentration. The data was best described with an Emax model with an underlying improvement in symptom score with time (placebo effect). Percent improvement in symptom score related to dose is presented in Figure 8.

FIGURE 7



It could be demonstrated that symptom scores showed only slight drug-related improvements above doses of 0.4 mg daily for a majority of subjects. However, on comparison of the predicted improvement in scores at the 90th percentile, a modestly larger improvement was seen at the 0.8 mg daily dose compared to the 0.4 mg daily tamsulosin dose (54.3% versus 47.6%, respectively). At higher doses a small incidence of abnormal ejaculation was observed but no other serious side effects. The 0.4 mg daily dose provides the optimal combination of efficacy and tolerability in most patients. Increasing the dose is unlikely to provide additional benefit in terms of peak urinary flow, however, in some patients a larger dose may further improve symptoms.

Safety was assessed while the patients were confined for 8 hours during the first day of double-blind study medication and during the duration of the clinical study. Safety was assessed primarily on the basis of: **(a)** treatment emergent adverse events; **(b)** serious adverse events; © orthostatic test results; **(d)** sitting vital signs (blood pressure and pulse rate); **(e)** laboratory determinations including prostate specific antigen and acid phosphatase (change from Baseline, shifts from Baseline, and newly emergent clinical abnormalities); **(f)** EKGs (shifts from Baseline and newly emergent clinically significant abnormalities); and physical examination. The incidence of patients that displayed a positive orthostatic hypotension test was very small on all visits (generally 1 to 3%), and could not be modeled.

Reviewer Comment:

1. *The 0.4 mg daily dose provides the optimal combination of efficacy and tolerability in most patients. Increasing the dose is unlikely to provide additional benefit, however, in some patients a larger dose may further improve symptoms.*

IX. LABELING

Labeling Comments:

1. The following changes are recommended for the **"PHARMACOKINETICS"** section of the labeling:

Pharmacokinetics

The pharmacokinetics of tamsulosin have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

Absorption:

Absorption of tamsulosin from FLOMAX™ 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food: Time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when FLOMAX™ is administered with food. The delay in T_{max} when FLOMAX™ is administered with food has the desirable effect of smoothing the tamsulosin plasma concentration profile, thereby reducing fluctuation of the plasma peak and trough concentrations with multiple dosing. Taking FLOMAX™ under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentration (C_{max}) compared to fed conditions (Figure XX).

COMMENT TO THE SPONSOR:

A Figure that illustrates the mean (SD) plasma profile for tamsulosin following administration of a single dose of FLOMAX in fasting and fed conditions should be included.

The effects of food on the pharmacokinetics of tamsulosin are consistent regardless of whether FLOMAX™ is taken with a light breakfast or a high fat breakfast (Table XX).

TABLE XX. *MEAN PHARMACOKINETIC PARAMETERS FOLLOWING DAILY (Q.D.) DOSING WITH FLOMAX™ 0.4 MG ONCE DAILY OR 0.8 MG ONCE DAILY WITH A LIGHT BREAKFAST, HIGH FAT BREAKFAST OR FASTED.*

Pharmacokinetic Parameter	0.4 mg q.d. to healthy volunteers (age range 18-32 years)		0.8 mg q.d. to healthy volunteers (age range 55-75 years)		
	Light Breakfast	Fasted	Light Breakfast	High Fat Breakfast	Fasted
AUC (ng·hr/mL)	151	199	440	449	557
T_{max} (hours)	6.0	4.0	7.0	6.5	5.0
C_{max} (ng/mL)	10.1	17.1	29.8	29.1	41.6
C_{min} (ng/mL)	3.8	4.0	12.3	13.5	13.3
C_{max}/C_{min} Ratio	3.1	5.3	2.7	2.5	3.6

: area under the tamsulosin plasma time curve over the dosing interval; T_{max}: median [illegible] concentration; C_{max}: observed maximum tamsulosin plasma concentration; C_{min}: observed minimum concentration. Coefficients of variation (%CV) for C_{max} and AUC generally ranged from 35%-53%, collectively.

COMMENT TO THE SPONSOR:
Table 3 needs to be updated to incorporate; SD, No. of subjects, Cl, and T1/2. In addition, it is recommended to change the order of PK parameters as follows; Cmin, Cmax, Cmax/Cmin, Tmax, T1/2, Cl, and AUC.

Distribution
The mean steady-state apparent volume of distribution of tamsulosin after intravenous administration to ten healthy male adults was 16 L, which is suggestive of distribution into extracellular fluids in the body. Additionally, whole body autoradiographic studies in mice, rats and dogs indicate that tamsulosin is widely distributed to most tissues including kidney, prostate, liver, gall bladder, heart, aorta, and brown fat, and minimally distributed to the brain, spinal cord, and testes.

Tamsulosin is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1-acid glycoprotein (AAG) in humans, with linear binding over a wide concentration range (ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin had no effect on the extent of binding of these drugs.

Metabolism
There is no enantiomeric bioconversion from tamsulosin [R(-) isomer] to the S(+) isomer in humans. Tamsulosin is extensively metabolized by enzymes in the liver and less than % of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Additionally, the enzymes that primarily catalyze the Phase I metabolism of tamsulosin have NOT been identified. Therefore, possible interactions with other metabolized compounds can not be discerned with current information. The metabolites of Tamsulosin undergo extensive Phase II prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor for treatment of BPH). However, *in vitro* testing of the tamsulosin interaction with diclofenac and warfarin were equivocal.

Excretion
On administration of a radiolabeled dose of tamsulosin to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces

(21%) over 168 hours.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin in plasma ranged from five to seven hours. Because of absorption rate-controlled pharmacokinetics with the FLOMAX™ modified release formulation, the apparent half-life of tamsulosin is approximately 9 to 13 hours in healthy volunteers and to 14 to 15 hours in the target population. Tamsulosin undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Special Populations

Geriatrics (Age): Cross-study comparisons of FLOMAX™ overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin may be slightly prolonged in geriatric males compared to young healthy male volunteers. Intrinsic clearance is independent of tamsulosin binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal Dysfunction: The pharmacokinetics of tamsulosin have been compared in 6 subjects with mild-moderate ($30 \le CL_{cr} < 70$ mL/min/1.73m^2) or moderate-severe ($10 \le CL_{cr} < 30$ mL/min/1.73m^2) renal impairment and 6 normal subjects ($CL_{cr} > 90$ mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in FLOMAX™ dosing. However, patients with endstage renal disease ($CL_{cr} < 10$ mL/min/1.73m^2) have not been studied.

Hepatic Dysfunction: The pharmacokinetics of tamsulosin have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification; Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in FLOMAX™ dosage.

Drug-Drug Interactions:

Warfarin: A definitive drug-drug interaction study between tamsulosin and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX™.

Cimetidine: The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single FLOMAX™ 0.4 mg dose was investigated in ten healthy volunteers (age range years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin which resulted in an increase in tamsulosin AUC (44%). Therefore, FLOMAX™ should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Nifedipine, Atenolol, Enalapril: In three studies in hypertensive subjects (age range · years) whose blood pressure was controlled with stable doses of Procardia XL®, atenolol or Enalapril for at least three months, FLOMAX™ 0.4 mg for seven days followed by FLOMAX™ 0.8 mg for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments are not necessary when FLOMAX™ is administered concomitantly with Procardia XL®, atenolol, or Enalapril.

Digoxin and Theophylline: In two studies in healthy volunteers (n=10 per study; age range years), receiving FLOMAX™ 0.4 mg/day for two days, followed by FLOMAX™ 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when FLOMAX™ is administered concomitantly with digoxin or theophylline.

Furosemide: The pharmacokinetic and pharmacodynamic interaction between FLOMAX™ 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range years). FLOMAX™ had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced a % reduction in tamsulosin C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the FLOMAX™ dosage.

2. Include the following information as appropriate in the **"PRECAUTIONS"** section of the labeling.

The pharmacokinetic and pharmacodynamic interactions between FLOMAX™ and other alpha-adrenergic blocking agents have not been determined. However, possible interactions may be expected and FLOMAX™ should NOT be used in combination with alpha-adrenergic blocking agents.

The pharmacokinetic interaction between cimetidine and FLOMAX™ was investigated. The results indicate significant changes in tamsulosin clearance (26% decrease) and AUC (44% increase). Therefore FLOMAX™ should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

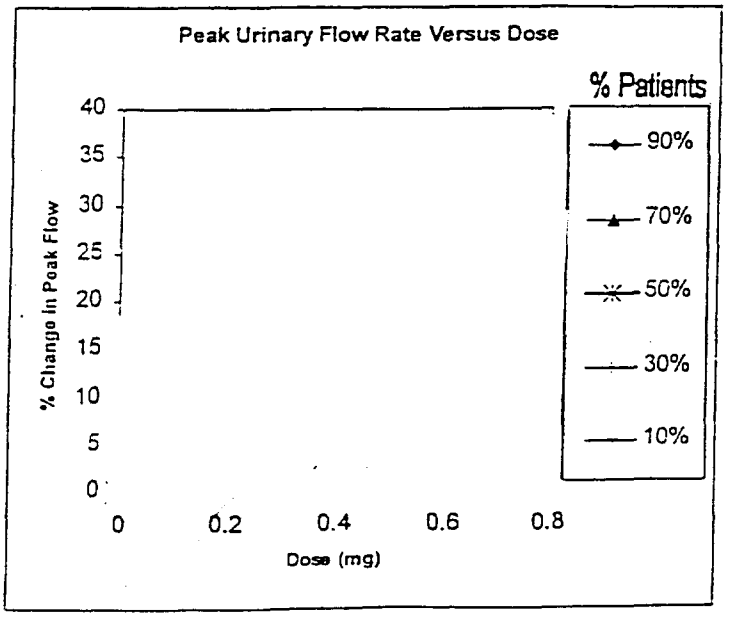
Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX™.

(See details of drug-drug interaction studies in the PHARMACOKINETIC section).

3. Include the following information and Figure in the **"CLINICAL"** section of the labeling.

A pharmacokinetic/pharmacodynamic correlation analysis was performed on data from a subset of the population (374/502 patients) included in clinical trial US92-03A. The results of this analysis indicate that no significant increase on peak urinary flow exixts between doses of 0.4 and 0.8 mg of FLOMAX (Figure XX). Therefore, the 0.8 mg dose may be required in only a small number of treated patients.

FIGURE XX



X. ATTACHMENT 1

Sponsor's Proposed Labeling

NDA 20-579

25 pages (30-54)
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XI. ATTACHMENT 2

Individual Studies

NDA 20-579

RELATIVE BIOAVAILABILITY

Study No: B9V-LC-GSAD

Study Title: Pharmacokinetics and Safety of Single and Multiple Doses

Investigator and study site:

Objective(s): To 1) evaluate the single dose pharmacokinetics of the modified release formulation of tamsulosin; and 2) evaluate the safety of single doses and multiple doses of the formulation, with particular emphasis on supine and standing blood pressure and pulse rate.

Study design: Single-blind study in eight healthy male subjects, conducted in two phases. The first phase was a randomized, three-way crossover, single dose [illegible]netic study. Treatments were 0.4 mg tamsulosin immediate release formulation (fasted), [illegible]ation (fasted), and modified release formulation (fed). The second phase was a multiple, ascending dose safety study without pharmacokinetic measurements.

Subjects: Eight healthy, male subjects were enrolled and completed the study. The mean (± standard error) age of subjects was 43 (± 3) years and the mean weight was 78.1 (± 2.3) kg.

Formulation, dosage, and administration: Subjects were dosed with 0.4 mg tamsulosin (two 0.2 mg capsules of modified release formulation of tamsulosin HCl; fasted), 0.4 mg tamsulosin (two 0.2 mg capsules of modified release formulation of tamsulosin HCl; fed), and 0.2 mg of an immediate release formulation of tamsulosin (fasted) in random order, with approximately 72 hours washout between doses. Subjects were fed a standard breakfast 30 minutes before dosing (fed) or were fasted overnight (fasted). The second phase was a multiple, ascending-dose safety study of the modified release formulation. The dose advancement schedule was tamsulosin 0.1 mg b.i.d for one day, 0.2 mg b.i.d. for one day, and 0.4 mg b.i.d. for ten days. The 0.2 mg capsules of tamsulosin (Lot No. CT-9682-8A) were manufactured using the same processes as proposed for commercial production, except that a coating pan was used for the coating process.

Blood Sampling: In the single dose phase, venous blood samples (10 mL each) for determination of tamsulosin plasma concentrations were collected prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, and 36 hours following dosing with the modified release formulation, and prior to (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours following dosing with the immediate release formulation. Plasma was separated and frozen until analysis.

Analysis: An HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-60 ng/mL); mean recovery (79% for 44 determinations); sensitivity (LOQ) of 0.5 ng/mL; quality control samples (CV% of 31.4%, 8.6%, 4.4%, and 3.3%, and accuracy of 118.1%, 103.9%, 101.6%, and 105.8% at concentrations of 0.5, 2, 7, and 12 ng/mL, respectively).

Data analysis: Pharmacokinetic parameters were calculated using non-compartmental methods. Tabular presentations, descriptive statistics (number of subjects, mean, standard deviation, coefficient of variation) and graphical analyses were used to evaluate the data.

Results: In the single dose phase of the study, a decrease in dose-normalized C_{max} (48%), no change in dose-normalized AUC_{∞}, and an increase in T_{max} (median increase of 3.8 hours) were observed for the 0.4 mg modified release formulation (fasted), compared to the 0.2 mg immediate release formulation (fasted) (Table 28). An increase in C_{max} (104%) and AUC_{∞}(26%), and a decrease in T_{max} (median decrease of 4.5 hours) were observed when 0.4 mg modified release formulation was administered in the fasted state, compared to fed (Table 28 and Figure 8). Mean (harmonic) terminal half-lives of 11.7, 13.7, and 6.4 hours were obtained

following administration of 0.4 mg fasted, 0.4 mg fed, and 0.2 mg immediate release, respectively. The prolonged estimates of half-life obtained for the modified release formulation compared to the immediate release formulation suggest that the modified release formulation provides sustained release and that the terminal half-life is reflective of the absorption rather than the elimination process. Tamsulosin was well tolerated following single dose administration. After dose advancement two of the eight subjects required dose reductions from 0.4 mg twice daily to 0.2 mg twice daily.

Sponsors Conclusion: The bioavailability of the modified release formulation was similar to the immediate release formulation when both were administered in the fasted state, but the rate of absorption was slower for the modified release formulation. Administration of the modified release formulation with food resulted in a decreased rate and extent of absorption of tamsulosin compared to the fasted state. Tamsulosin was well tolerated when administered in single doses up to 0.4 mg in the fed or fasted state.

Reviewer: ...d release form is relatively consistently absorbed and displays ... delayed ...se of 0.8 mg daily should be considered with caution.

TABLE 28: Mean (Standard Deviation) Single Dose Pharmacokinetic Parameters for Tamsulosin Following Administration of 0.4 mg Modified Release Formulation (Fed and Fasted State) and 0.2 mg Immediate Release Formulation in the Fasted State

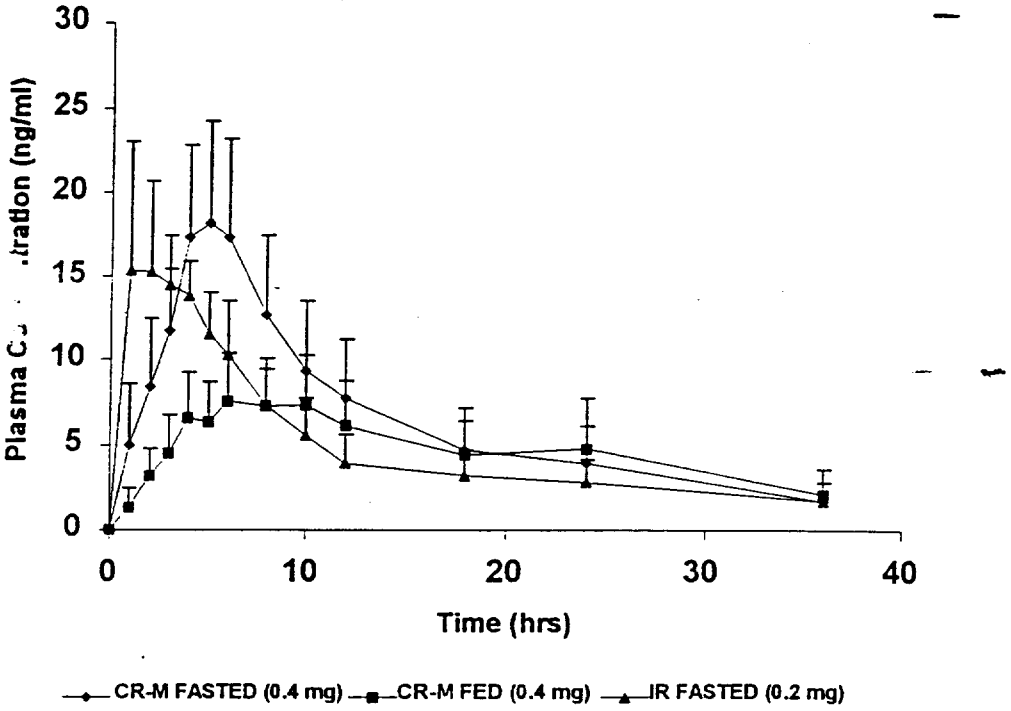
	0.4 mg Modified Release			0.2 mg Immediate Release	Ratio (MR:IR)[4]
	Fed	Fasted	Ratio (Fasting:Fed)	Fasted	Fasted
AUC_∞(ng*h/mL)	215 (89)	271 (114)	1.26	280 (104)[1]	0.97
C_{max} (ng/mL)	9.6 (2.5)	19.6 (5.4)	2.04	38.0 (9.8)[1]	0.52
T_{max} (h)	9.0 (4,24)[2]	4.5 (4.0,6.0)[2]	-	1.0 (0.5,2.0)[2]	-
λ_z (h^{-1})	0.051 (0.013)	0.059 (0.018)	-	0.108 (0.055)	-
$t_{½}$ (h)	13.7 (3.4)[3]	11.7 (3.5)[3]	0.85	6.4 (3.3)[3]	1.83
CL/F (L/h)	1.96 (0.71)	1.63 (0.80)	0.83	1.51 (0.61)	1.08
V_β/F (L)	-	-	-	32.0 (15.5)	-

1 Normalized to a 0.4 mg dose.
2 Median (range)
3 Harmonic mean
4 Confidence intervals not computed on ratio as part of study report

MR = modified release; IR = immediate release

Note: Subjects received a high fat meal a half-hour prior to dosing (fed) or were fasted overnight (fasted).

FIGURE 8: Mean (Standard Error) Plasma Profile for Tamsulosin Following Single Dosing with 0.4 mg Modified Release Formulation (Fasted and Fed) and 0.2 mg Immediate Release Formulation (Extracted from Study B9V-LC-GSAD)



Study No. US89-01

Study Title: A Single Blinded, Multiple Dose, Steady State, Two-Way Crossover, Pharmacokinetic and Pharmacodynamic Comparison of YM617 Administered as 400 mcg of Modified Release Formulation Once a Day Versus a 100 mcg Solution Every 12 Hours Under Fed and Fasting Conditions

Investigator:

Objective(s): 1) To confirm the pharmacokinetics of tamsulosin under fed and fasted conditions; 2) to define the relationship of plasma drug concentrations to blood pressure and heart rate at steady state; 3) to study the occurrence of orthostatic hypotension in normal volunteers and its relationship to plasma drug concentrations of tamsulosin; and 4) monitor tamsulosin activity on cardiac electrophysiology.

Study design: Single-blind, double-dummy, multiple-dose, randomized, two-period crossover under fed and fasted conditions in 24 healthy male subjects, with a minimum of seven days washout between periods.

Population: Twenty-four healthy, male subjects were enrolled; 23 subjects completed the study. One subject was discontinued from the study on Day 2 of the first period (no study drug administered) because of orthostatic changes in blood pressure and pulse. The mean (± standard error) age of subjects was 24 (± 1) years and the

mean weight was 77.1 (± 1.9) kg, respectively. As a result of a dosing error, one subject received an evening dose of tamsulosin solution while on 0.4 mg q.d. modified release tamsulosin treatment, while another subject received an extra dose of placebo solution.

Formulation, dosage, and administration: Subjects received two 0.2 mg capsules of tamsulosin (modified release formulation of tamsulosin HCl) once daily, or a 0.1 mg tamsulosin HCl solution administered twice daily. Placebo capsules and placebo solution were also administered to blind the subjects to the treatment. Each period consisted of a baseline evaluation day (Day 1), five days of dosing in the fed state (Days 2-6), and one day of dosing in the fasted state (Day 7). Subjects received a high calorie, medium fat breakfast (615-755 calories, 14-23g protein, 87-136g carbohydrate, 15-25g fat) a half-hour prior to dosing (fed condition), or were fasted overnight and up to 3.5 hours following dosing (fasted condition).

Blood Sampling: Venous blood samples (10 mL each) were drawn for tamsulosin plasma concentrations prior to dosing (0 hour) .. ', 3, 4, 5, 6, 9, 12, 15, and 24 hours following dosing with tamsulosin capsules, and prior to dosing (. id 25 0.5, . 1.5, 2, 3, 4, 6, 9, and 12 hours following dosing with tamsulosin solution on Days 5, 6, and 7. In addition, pre-dose samples were collected on Days 2, 4, and 8 for trough levels. Urine samples were collected prior to dosing on Day 2 and over the 0-12 and 12-24 hour intervals on Days 5, 6, and 7. Blood samples were centrifuged immediately after collection at 2000 rpm for 10 min at 10°C, and plasma was separated. Plasma samples were stored at approximately -20°C until assayed. Three 10 mL aliquots of urine samples from each collection interval were stored at approximately -20°C until assayed.

Assays: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-50 ng/mL); mean recovery (75.7%, 59.5%, and 56.9% at concentrations of 0.5, 1.0, and 5.1 ng/mL, respectively); sensitivity (LOQ) of 0.5 ng/mL; validation quality control samples (CV% was not greater than 15%, and accuracy was within ±15% at concentrations of 1.5, 25, and 40 ng/mL, respectively). A validated HPLC assay with ultraviolet detection was used for tamsulosin urine samples; Standard curve (5.2-520 ng/mL); mean recovery (45.5-64.3% at concentrations of 5.2-520 ng/mL); sensitivity (LOQ) of 5 ng/mL; intra- and inter-day validation quality control samples (CV% of <15% and accuracy within ±15% at concentrations of 15, 250 and 400 ng/mL, respectively).

Analysis: Non-compartmental techniques were used to determine tamsulosin pharmacokinetic parameters ($AUC_{(0-12)}$ (solution), $AUC_{(0-24)}$ (modified release), C_{max}, C_{min}, and T_{max}). Duncan's multiple range test was used to determine attainment of steady-state (C_{min}). Pharmacokinetic parameters ($AUC_{(0-12)}$, $AUC_{(0-24)}$, and C_{max} adjusted for differences in dose) were compared between treatments using ANOVA, and 90% confidence intervals were computed on the ratio of the means.

Results: The pharmacokinetics of the modified release formulation and tamsulosin solution were compared under fed and fasting conditions. Steady-state was achieved by Day 5 for both formulations. At steady-state (Day 6), the bioavailability of the modified release formulation was 73% that of the solution ($AUC_{(0-24)}$ vs $AUC_{(0-12)}$; after dose correction) under fed conditions and 84% that of the solution under fasted conditions (Table 29 and Figure 9). Half-lives of tamsulosin solution were similar on Days 5, 6, and 7 (6.7-7.8h).

A significant increase in the extent of absorption ($AUC_{(0-24)}$ or $AUC_{(0-12)}$) was observed for the modified release formulation and solution (32% and 15% increase, respectively) when administered under fasted conditions compared to fed. A significant increase in C_{max} and decrease in T_{max} was also observed under fasted conditions (69% and 32% increase in C_{max}, and 33% and 50% decrease in median T_{max}, for the modified release formulation and solution, respectively) indicating an increase in the rate of absorption with fasting. The higher concentrations observed in the fasted state were also reflected in the higher mean peak/trough ratio (C_{max}/C_{min}; 71% increase) under fasted compared to fed conditions. On Day 6, fe (%) in urine was 27% lower for the modified release formulation compared to the solution. No significant differences were observed in fe (%) between the fed and fasted state (Day 6 vs Day 7) for the solution, but the modified release formulation showed

a 26% increase on fasting, compared to fed.

There is a trend to an increase in positive tilt response with dosing tamsulosin. The observed difference was judged to be medically insignificant by the principal investigator. Two instances of priapism were reported in one subject. One episode persisted for 1.5 hours and the other episode persisted for 2.2 days.

Conclusion: At steady-state, the bioavailability of the modified release formulation was 73% that of the solution, under fed conditions. A significant increase in the rate and extent of absorption was observed for the modified release formulation and the solution under fasted conditions compared to fed. Tamsulosin was well tolerated.

Reviewers Comment: The extent of absorption of the modified release formulation is reduced with respect to the oral solution. This is reflected in the reduced AUC and decreased fraction excreted unchanged (27% decrease). Food reduces the extent of absorption of tamsulosin after solution by about 10% and after modified release formulation by about 26%. Tamsulosin shows a trend toward a positive tilt response which the principal scientist considers not medically relevant, however, this should taken into account in considering other studies.

TABLE 29: Mean (Standard Deviation) Steady-State Pharmacokinetic Parameters and Comparative Statistics for Tamsulosin Following Administration of 0.4 mg Modified Release Formulation and 0.1 mg Solution in the Fed (Day 6) and Fasted State (Day 7) (Extracted from Tables B8-B12, B25-B27, and B35-B36, Study US89-01)

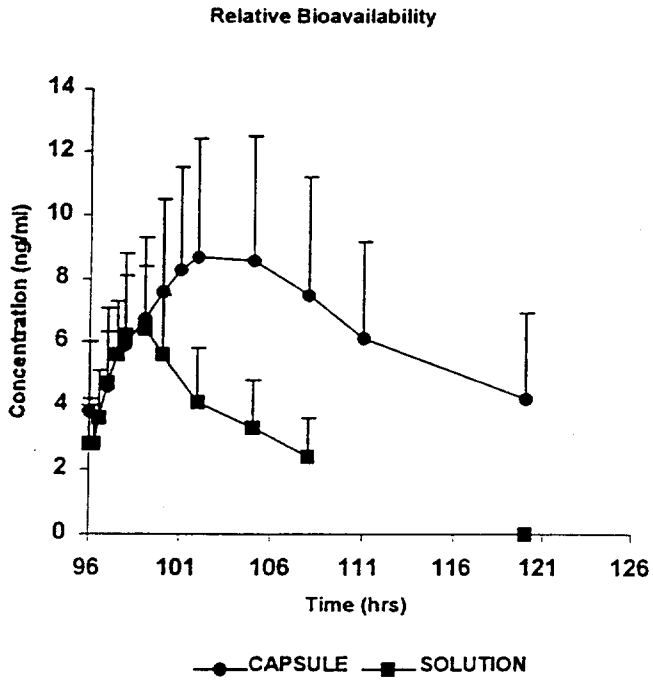
	0.4 mg Modified Release (q.d.)			0.1 mg Solution (b.i.d.)			Ratio (90% CI)[2-4] MR:Solution	
	Fed Day 6	Fasted Day 7	Ratio (90% CI)[2,3] Day 7:Day 6	Fed Day 6	Fasted Day 7	Ratio (90% CI)[2,3] Day 7:Day 6	Day 6	Day 7
AUC (ng*h/mL)[1]	151.1 (8	199.1 (94.1)	132 (12? 140)	204.8 (76.8)[5]	239.2 (78.8)[5]	115 (110,119)	73 (61,86)	84 (72,95)
C_{max} (ng/mL)	16.. (4.8)	17.1 (7.3)	15? (154, 184)	6.9 (2.2)	9.1 (2.3)	132 (126,139)	-	-
T_{max} (h)	6.0 (2.0,9.0)[6]	4.0 (3.0,6.0)[6]	-	2.0 (0.5,4.0)[6]	1.0 (0.3,2.0)[6]	-	-	-
C_{min} (ng/mL)	3.8 (2.5)	4.0 (2.6)	-	2.2 (1.2)	2.6 (1.2)	-	-	-
C_{max}/C_{min} Ratio	3.1 (1.0)	5.3 (2.2)	-	-	-	-	-	-
$t_{½}$ (h)	-	-	-	6.7 (2.4)	7.1 (3.7)	-	-	-
fe (%)	8.5 (4.3)	10.7 (3.7)	126 (111,141)	11.6 (3.8)	12.7 (4.7)	110 (101,119)	73 (64,82)	84 (74,95)
CL_R (L/h)[2]	0.27 (0.09)	0.25 (0.10)	-	0.27 (0.09)	0.28 (0.08)	-	-	-

[1] $AUC_{(0-24)}$ for 0.4 mg modified release or $AUC_{(0-12)}$ for solution.
[2] Based on supplementary analyses done during preparation of the NDA.
[3] 90% confidence interval on least squares mean ratio (%).
[4] Based on dose-normalized values.
[5] Normalized to a 0.4 mg dose.
[6] Median (range).

CI = Confidence Interval; MR = modified release; fe (%) = fraction of dose excreted in urine (%).

Note: Subjects received a high calorie, medium fat breakfast a half-hour prior to dosing on Day 6, and were fasted overnight on Day 7.

FIGURE 9: Mean Plasma Profile for Tamsulosin on Day 5 (fed), Day 6 (fed), and Day 7 (fasted) of 0.4 mg q.d. Dosing with the Modified Release Formulation (Extracted from Study US89-01)



ABSOLUTE BIOAVAILABILITY

Study No. 93-HAR-01
Study Title: Absolute Bioavailability Study of Tamsulosin Hydrochloride (0.4 mg) After Single Dose Oral Administration to Healthy Male Volunteers

Investigator and Study Site:

Objectives: The study was performed: (1) to evaluate the absolute bioavailability of tamsulosin modified release formulation; and (2) to assess the primary pharmacokinetics of intravenously delivered tamsulosin.

Subjects: Ten healthy, young male subjects were enrolled into the study. One subject withdrew for personal reasons and was replaced. The mean (± standard deviation) age of subjects was 22.2 (± 3.4) years and the mean weight was 78.0 (± 7.9) kg.

Study Design: This was an open-label, randomized, single-dose, two-period crossover study in ten healthy, young, male subjects, with a washout of at least one week between periods.

Formulation, Dosage and Administration: Subjects received an oral dose of 0.4 mg of tamsulosin (0.4 mg capsule of modified release formulation of tamsulosin HCl (Lot. No. ST617EC) administered with 200 mL water) and an intravenous infusion of 0.125 mg tamsulosin (infused over four hours), administered on two

different occasions in a randomized fashion. The intravenous formulation consisted of 0.15 mg tamsulosin HCl in 2 mL isotonic buffer (Lot No. TB6171A), diluted with saline before infusion. Subjects were fasted overnight prior to dosing and for 4.5 hours following oral dosing or the start of infusion.

Blood Sampling and Assay: Venous blood samples (10 mL each) for determination of tamsulosin plasma concentrations were collected prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 4.25, 4.5, 5, 6, 7, 8, 10, 12, 16, 20, 24, and 36 hours following the start of intravenous infusion, and prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours after oral dosing. Plasma samples were stored at approximately -20°C until assayed.
A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); standard curve (0.5-20 ng/mL); mean recovery (91.1%, 66.9%, 86.0%, 71.1%, and 65.8% at concentrations of approximately 2, 5, 10, 15, and 20 ng/mL, respectively; n=5 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); validation quality control samples (CV% of 5.3%, 4.3%, 5.5%, and [illegible] accuracy of 94.4%, 96.3%, 97.5%, and 98.6% at concentrations of approximately 0.5, 2, 10, [illegible], respectively).

Data Analysis: Tamsulosin pharmacokinetic parameters were estimated using modeling techniques (two-compartment model; oral dosing or intravenous infusion) as well as non-compartmental techniques.

Results: Tamsulosin profiles showed a biexponential decline following intravenous infusion, with a mean distribution half-life of 1.2 hours. Estimates of terminal half-lives were highly variable and ranged from hours, with a median value of 5.2 hours (Table 30). Mean total clearance was 48mL/min and the steady state volume of distribution was estimated at 16 liters. Oral administration resulted in peak plasma levels at 4-6 hours, followed by biexponential decay. Estimates of terminal half-lives were highly variable and ranged from hours, with a median value of 13.1 hours. The prolonged estimates of half-life obtained for the modified release oral formulation, compared to intravenous administration, suggest that half-life is determined by absorption rather than the elimination processes. The absolute bioavailability (F) of the modified release formulation administered under fasted conditions was estimated to be approximately 92% (median value) (Table 30).
Tamsulosin demonstrated an acceptable safety and tolerability profile following oral and intravenous administration

Table 30: Mean (Standard Deviation) Single Dose, Non-Compartmental and Model-Fitted Pharmacokinetic Parameters for Tamsulosin Following Oral Administration of 0.4 mg Modified Release Formulation (Fasted) and a 0.125 mg Intravenous Infusion Over Four Hours

	0.125 mg Intravenous Infusion	0.4 mg Modified Release
AUC_{∞} ng*h/mL)	173 (88) [151 (73,367)][3,4]	181 (108) [145 (64,363)][3]
AUC_{last} (ng*h/mL)[1]	168 (75) [151 (73,309)][3,4]	157 (78) [141 (64,320)][3]
F (%)	-	100 (19) [92 (85,115)][3]
C_{max} (ng/mL)	22.8 (6.8)[4]	15.5 (5.0)
T_{max} (h)	-	5.0 (4.0,6.0)[3]
λ_1 $t_{1/2}$ (h)[2]	1.2 (0.6)	-
λ_z $t_{1/2}$ (h)[2]	6.8 (3.5) [5.2 (3.6,14.0)][3]	22.0 (23.0) [13.1 (5.3,76.1)][3]
CL (L/h)	2.88 (1.44)	-
V_{β} (L)	21 (6)	-
V_{ss} (L)[2]	16 (4)	-

1 $AUC_{(0-36)}$ for intravenous infusion and $AUC_{(0-48)}$ for oral formulation.
2 Model-fitted parameters.
3 Median (range)
4 Normalized to a 0.4 mg dose.

Sponsor's Conclusion: Plasma concentrations showed biexponential decline, with a median terminal half-life of 5.2 hours following intravenous administration and a 13.1 hours following oral administration. The absolute bioavailability of the modified release formulation administered under fasted conditions was very high and was estimated to be approximately 92% (median value).
Reviewer's Comment: The reviewer agrees with the Sponsor's conclusions. However, there is considerable variability in the terminal-half life estimates.

BIOEQUIVALENCE

Study YM617US94-02

Study Title: Assessment of bioequivalence (BE) of three batches of tamsulosin hydrochloride 0.4 mg capsule (commercial scale batch and two batches used in the U.S. Phase III, double-blind, pivotal studies) in normal male volunteers.

Investigator:

Objective: The objective of the study was to assess the BE of three batches of tamsulosin hydrochloride capsules. One was a commercial scale batch and the other two batches were used in the U.S. Phase III, double-blind, placebo-controlled, pivotal studies.

Subjects: Twenty eight normal male volunteers ranging from yr (mean: 26.3 yr) participated in the study with informed consent.

Study Design: This was a single dose (0.4 mg) , randomized, three treatment, three period, six sequence, cross over study

Formulation: The following formulations were used: commercial scale batch of 0.4 mg tamsulosin hydrochloride capsule (lot no.: WH617HC), clinical batch of 0.4 mg tamsulosin hydrochloride capsule (lot no.: SC6174C, used in Study YM617US92-03A), clinical batch of 0.4 mg tamsulosin hydrochloride capsule (lot no.: ST617DC, used in Study YM617US93-01).

Drug Administration, Blood Sampling and Assay: A single dose of tamsulosin hydrochloride was administered 4 h prior to a meal and following an ove[illegible]
Blood was sampled predose and at specified times [illegible] assay with fluorescence detection was used for tamsulosin (plasma samples); [illegible] mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 2.5%, 2.4%, and 9.7%, and accuracy of 99%, 98%, and 97% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively).

Data Analysis: Pharmacokinetic analysis was by noncompartmental approach. Comparison of mean pharmacokinetic (PK) parameters was by ANOVA on log-transformed parameters.

Results: The commercial batch was bioequivalent with the two clinical batches (Tables 31 and 32).

Table 31. Pharmacokinetic Parameters of Commercial Batch #WH617HC/Clinical Batch #SC6174C

Parameter	Mean ± SD Commercial Scale Batch	Mean ± SD Clinical Batch	90% CI of the Ratio Commercial/Clinical
$AUC_{(0-t)}$ (ng.h/ml)	167.0 ±60.5	169 ±62.4	91.0 - 108%
$AUC_{(0-\infty)}$ (ng.h/ml)	180.0 ±65.5	180.0 ±68.1	93.0 - 109%
Cmax (ng/ml)	14.4 ±4.21	15.0 ±4.45	86.0 - 106%
Tmax (h)	4.93±0.90	5.36 ±0.99	-

Table 32. Pharmacokinetic Parameters of Commercial Batch #WH617HC/Clinical Batch #SC617DC

Parameter	Mean ± SD Commercial Scale Batch	Mean ± SD Clinical Batch	90% CI of the Ratio Commercial/Clinical
$AUC_{(0-t)}$ (ng.h/ml)	167.0 ±60.5	177.0 ±72.2	89.0 - 105%
$AUC_{(0-\infty)}$ (ng.h/ml)	180.0 ±65.5	190.0 ±81.1	89.0 - 104%
Cmax (ng/ml)	14.4 ±4.21	15.0 ±5.19	87.0 - 107%
Tmax (h)	4.93±0.90	5.36 ±0.73	-

Sponsor's Conclusion: The commercial scale batch (#WH617HC) and the clinical batches (#SC6174C and

#ST617DC) of tamsulosin 0.4 mg modified release formulation (capsules) were determined to be bioequivalent. For all key parameters, the 90% confidence intervals on the mean ratios of commercial batch to clinical batch were well within the 80-125% (log-transformed data) limits used for the assessment of bioequivalence.

Reviewer's Comment: The commercial and clinical batches of tamsulosin 0.4 mg capsules were bioequivalent.

DOSE PROPORTIONALITY
Study No. 125/0014
Study Title: A Single Rising Dose Safety Tolerance and Pharmacokinetic Study of YM-617 in Healthy Male Volunteers

Investigator and Study Site:

Objective: The objective of this study was to evaluate the safety, tolerance, and pharmacokinetics following single rising oral doses of tamsulosin (modified release formulation) at six dose levels in healthy male volunteers.

Subjects: Sixteen healthy, young male subjects completed the study. The mean (± standard deviation) ages of tamsulosin and placebo subjects were 27.0 (± 2.8) and 25.0 (± [illegible] years, respectively, and the mean weights were 70.0 (± 9.5) and 65.3 (± 7.9) kg, respectively.

Study Design: Double-blind, randomized, placebo-controlled, single, ascending dose study in two groups of eight subjects. Two subjects in each group were randomized to placebo and six subjects were randomized to tamsulosin at three dose levels.

Formulation, Dosage and Administration: Subjects on tamsulosin in the first group received a 0.1, 0.4, and 0.8 mg dose, and subjects in the second group received a 0.2, 0.6, and 1.0 mg dose, during periods 1, 2, and 3, respectively. Subjects were fasted overnight and up to four hours following dosing. Tamsulosin was administered with 150-200 mL water, as 0.1 mg or 0.2 mg capsules of modified release formulation of tamsulosin HCl. Progression to a higher dose was dependent on the safety and tolerance data at the previous dose level. An interval of seven days was allowed between successive doses to each subject.

Blood Sampling and Analysis: Venous blood samples for tamsulosin plasma concentrations were collected prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 30, and 36 hours following each dose. A total of 480 mL blood was collected from each subject. Blood samples were centrifuged, plasma was separated and stored at -20°C until assayed.
Urine was collected over the periods -2-0, 0-6, 6-12, 12-24, and 24-36 hours following dosing with tamsulosin. Two 20 mL aliquots were removed and stored at -20°C until assayed.
A validated HPLC assay with fluorescence detection (dansyl-derivative of tamsulosin) was used for tamsulosin (plasma samples); standard curve (0.5-80 ng/mL); mean recovery (88.7%, 80.3%, and 71.5% at concentrations of 5, 3, and 15 ng/mL, respectively); sensitivity (LOQ) of 0.5 ng/mL; validation quality control samples (CV% not greater than 15% and accuracy within ±15% at concentrations of 1.5, 40, and 60 ng/mL, respectively).
A validated HPLC assay with ultraviolet detection was used for tamsulosin urine samples; Standard curve (5.2-520 ng/mL); mean recovery (45.5-64.3% at concentrations of ng/mL); sensitivity (LOQ) of 5 ng/mL; intra- and inter-day validation quality control samples (CV% of <15% and accuracy within ±15% at concentrations of 15, 250 and 400 ng/mL, respectively).

Data Analysis: The dose proportionality of C_{max} and $AUC_{(0-36)}$ were assessed using Pearson's correlation coefficient.
Mean observed values and mean change from baseline values were computed for vital signs. The numbers and percentages of subjects in different categories were calculated for categorical safety parameters.

Results: C_{max} and $AUC_{(0-36)}$ increased linearly with dose over the dose range studied (Table 33 and Fig. 10 & 11). T_{max} ranged from 3-6 hours and mean terminal half-life ranged from hours. These parameters did not vary significantly with increasing doses of tamsulosin. Urinary excretion of unchanged tamsulosin (% dose) was minimal and ranged from %.
The plasma protein binding of tamsulosin was also estimated in four subjects on 0.8 mg tamsulosin. Of the four

subjects, only two had sufficiently high concentrations of free tamsulosin to allow estimation of binding percentage. Protein binding in these subjects ranged from % at tamsulosin concentrations of ng/mL (ultracentrifuge method).
Tamsulosin was well tolerated in this study. Mild to moderate instances of lightheadedness were observed in some subjects at the 0.6-1.0 mg doses and one episode of asymptomatic hypotension was observed in one subject at the 1.0 mg dose.

Table 33.
Mean (Standard Deviation) Pharmacokinetic Parameters for Tamsulosin Following Single Oral Doses (0.1 mg - 1.0 mg) of Modified Release Formulation Administered under Fasted Conditions

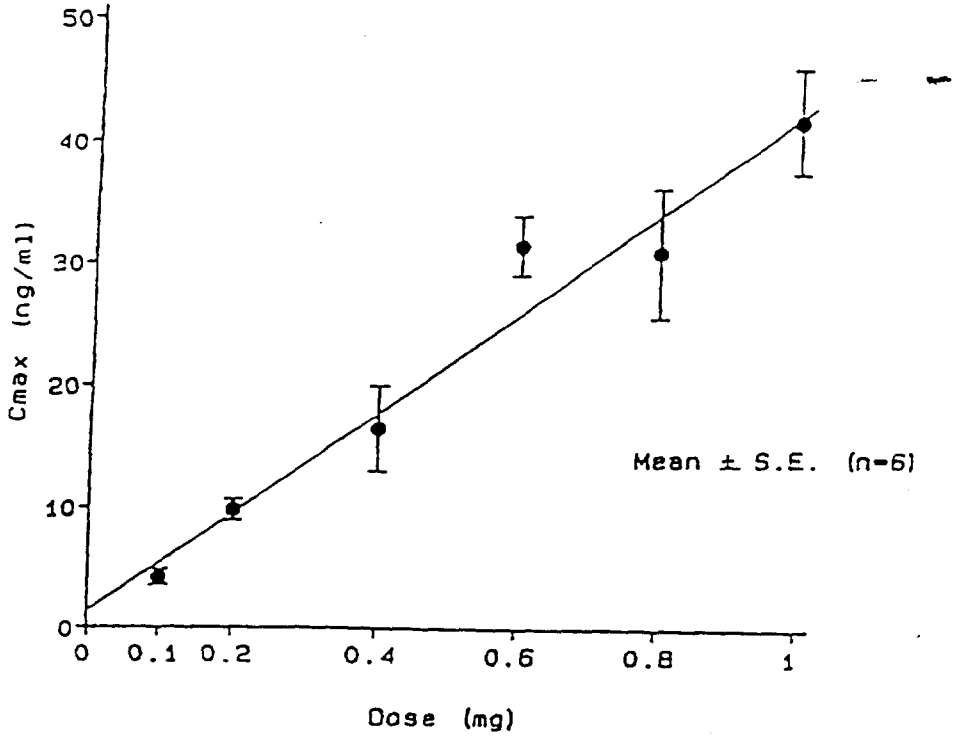
Tamsulosin Dose	C_{max}[1,2] (ng/mL)	T_{max}[3] (h)	$AUC_{(0-36)}$[1,2] (ng*h/mL)	AUC_{∞}[1] (ng*h/mL)	$t_{½}$ (h)	fe (%)	CL_R (L/h)
0.1 mg	16.8 (6.9)	5.0 (4.0,5.0)	169 (95)	*	*	6.3 (5.1)	0.17 (0.08)
0.2 mg	19.6 (4.4)	5.0 (3.0,5.0)	179 (46)	192 (50)	8.1 (2.1)	6.3 (2.8)	0.14 (0.07)
0.4 mg	16.5 (8.6)	5.0 (4.0,5.0)	162 (76)	184 (81)	11.4 (1.4)	10.3 (2.4)	0.28 (0.09)
0.6 mg	21.0 (4.1)	3.5 (3.0,5.0)	191 (48)	203 (52)	9.5 (0.6)	6.5 (3.0)	0.15 (0.08)
0.8 mg	15.5 (6.5)	5.0 (4.0,6.0)	153 (80)	168 (90)	10.0 (2.9)	8.5 (2.5)	0.25 (0.08)
1.0 mg	16.8 (4.2)	4.5 (4.0,5.0)	161 (36)	174 (40)	10.2 (1.7)	8.4 (2.6)	0.22 (0.10)

* Parameters were not estimable.
1 Normalized to a 0.4 mg dose.
2 Pearson Correlation Coefficient for C_{max} and $AUC_{(0-36)}$ (not dose-normalized) as a function of dose were 0.856 and 0.837, respectively.
3 Median (range)
Note: One group of subjects received 0.1 mg, 0.4 mg, and 0.8 mg tamsulosin while another group received 0.2 mg, 0.6 mg, and 1.0 mg tamsulosin.

Sponsor's Conclusion: The pharmacokinetics of tamsulosin were linear over the mg dose range. Tamsulosin was well tolerated over the mg dose range.

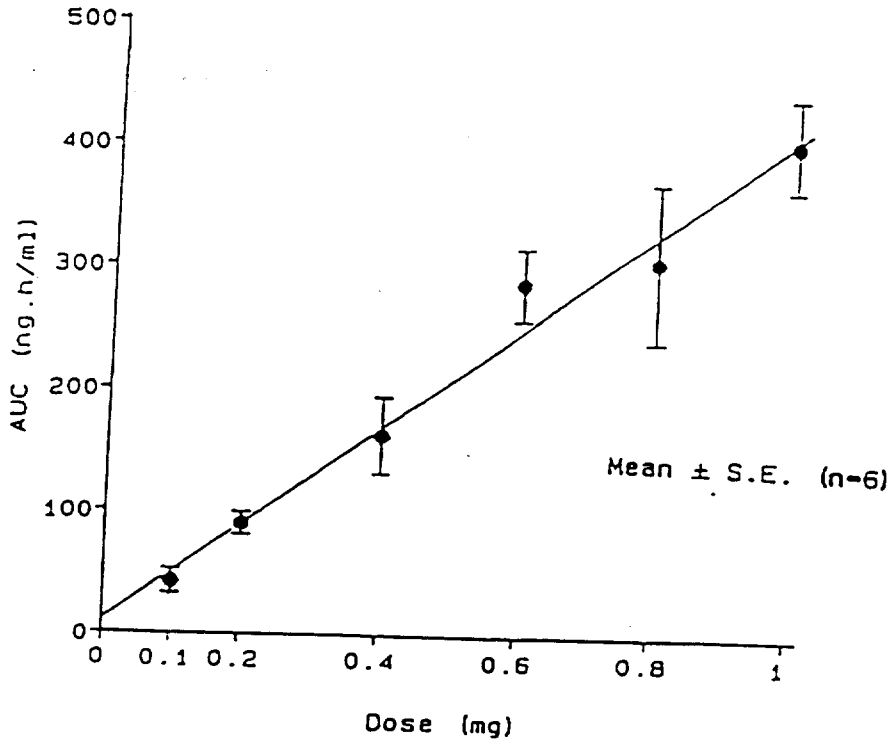
Reviewer's Comment: Dose linearity of tamsulosin in the 0.1 - 1.0 mg range was established. Some subjects had mild to moderate instances of lightheadedness at the 0.6-1.0 mg doses and one episode of asymptomatic hypotension was observed in one subject at the 1.0 mg dose.

Fig. 10: Dose Proportionality of C_{max} Following Administration of Single, Ascending Doses (0.1-1.0 mg) of Tamsulosin to Healthy, Young Volunteers



Relationship between dose and Cmax in humans dosed with YM617 as a controlled release formulation.

Fig. 11: Dose Proportionality of $AUC_{(0-36)}$ Following Administration of Single, Ascending Doses (0.1-1.0 mg) of Tamsulosin to Healthy, Young Volunteers



Relationship between dose and AUC0-36h in humans dosed with YM617 as a controlled release formulation.

MASS BALANCE

Study No. 555/7
Study Title: (^{14}C)-YM 12617-1: A Study of the Absorption, Metabolism, and Excretion Following Oral Administration to Healthy Human Volunteers

Investigator and Study Site:

Objectives: The objectives were to: (1) define the plasma and whole blood concentration versus time curve for total radioactivity for ^{14}C-tamsulosin when administered orally to healthy male volunteers; (2) describe the pharmacokinetics of tamsulosin following oral administration; and (3) obtain mass balance for excretion of ^{14}C-tamsulosin by quantifying urinary and fecal excretion.

Subjects: Four healthy, male subjects were enrolled and completed the study. The mean age of subjects was 42 years (range 36-53 years) and the mean weight was 82.8 kg (range 78.7-87.3 kg).

Study Design: Open-label, single-dose study in four healthy, male subjects.

Formulation, Dosage and Administration: Subjects were administered a solution of 0.2 mg ^{14}C-tamsulosin as a single oral dose, following an overnight fast.
The solid ^{14}C-tamsulosin HCl had a stated radiochemical purity of >98% and a specific activity of 73.2 μCi/mg and was stored in the dark at approximately 0-4°C until used. Prior to dosing, 0.2 mg ^{14}C-tamsulosin HCl (approximately 14.6 μCi) was dissolved in 50 mL water and administered to each subject.

Sample Collection and Analysis: Venous blood samples (16 mL each) for measurement of total radioactivity and tamsulosin and/or metabolite concentrations in plasma and whole blood were collected prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours following dosing. Blood urine and fecal samples were collected up to 168 hours following dosing.
An aliquot of blood (2 mL) was used for measurement of radioactivity in blood. The remaining blood (14 mL) was centrifuged at 1500 g for 10 minutes, and plasma was separated and divided. One aliquot was stored at 4°C until completion of radioactivity determinations in plasma after which it was stored at -20 °C; the other aliquot was stored at -20°C until assayed.
All voided urine was collected for measurement of total radioactivity and tamsulosin and metabolite concentrations, prior to dosing (aliquot only) and over the 0-6, 6-12, 12-24, 24-30, 30-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hour intervals following dosing. Weight and pH were recorded, and an aliquot (20 mL) was used for radioactivity determinations. A further aliquot (100 mL) was stored at -20°C until assayed and the remainder discarded.
All voided feces was collected for measurement of total radioactivity, prior to dosing (sample only) and over the 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hour intervals following dosing. Samples were weighed and stored at -20°C until radioactivity was determined.
Total radioactivity (^{14}C) in blood, plasma, urine, and fecal homogenate extracts was measured using liquid scintillation counting.
A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); standard curve (0.5-50 ng/mL); mean recovery (60.3 %, 63.3%, and 63.0% at concentrations of 1.5, 25, and 40 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); validation quality control samples (CV% was not greater than 15%, and accuracy was within ±15% at concentrations of 1.5, 25, and 40 ng/mL, respectively).
Tamsulosin and its metabolites in plasma and urine were measured using a HPLC assay with a combination of ultraviolet and radioactivity detection. Ultraviolet detection was used to separate the eluate into metabolite fractions based on the retention time of non-radiolabeled standards mixed in with the sample, followed by measurement of radioactivity of each of these fractions. Conjugates were measured by subjecting the HPLC

eluates to hydrolysis (using β-glucuronidase, sulfatase and/or HCl), followed by analysis of the samples using the HPLC assay with combined ultraviolet/radioactivity detection.

Data Analysis: Non-compartmental analysis was used to determine pharmacokinetic parameters for total radioactivity and unchanged drug.

Results: Plasma and whole blood concentrations of total radioactivity increased rapidly to 14.0 and 7.0 ng equiv./mL at 1 hour and 0.5 hours post-dose, respectively. Levels then declined rapidly over the first 4 hours followed by a more gradual decline, falling below detectable levels by 36 hours. The mean terminal half-lives of radioactivity in plasma and blood were 11.8 and 9.1 hours, respectively.
Within 168 hours of drug administration, 76.4% of administered radioactivity was recovered in the urine and 21.4% in the feces. Most renally eliminated radioactivity was recovered within 24 hours post-dose (62.2% of dose), while fecal elimination was more protracted (up to 96 hours), suggesting the occurrence of biliary excretion. Tamsulosin was extensively metabolized, with urinary excretion of unchanged drug accounting for only 8.74% of the total dose (Table 34). Metabolic pathways included

followed by of some of these metabolites (Fig. 3). A total of 11 metabolites were identified in urine, of which the metabolite was the major identifiable metabolite. Ten of these metabolites were also identified in plasma, though in small amounts (Table 34).

Fig. 12: Possible Metabolic Pathways of Tamsulosin (Glu-glucuronide, Sul-sulfate)

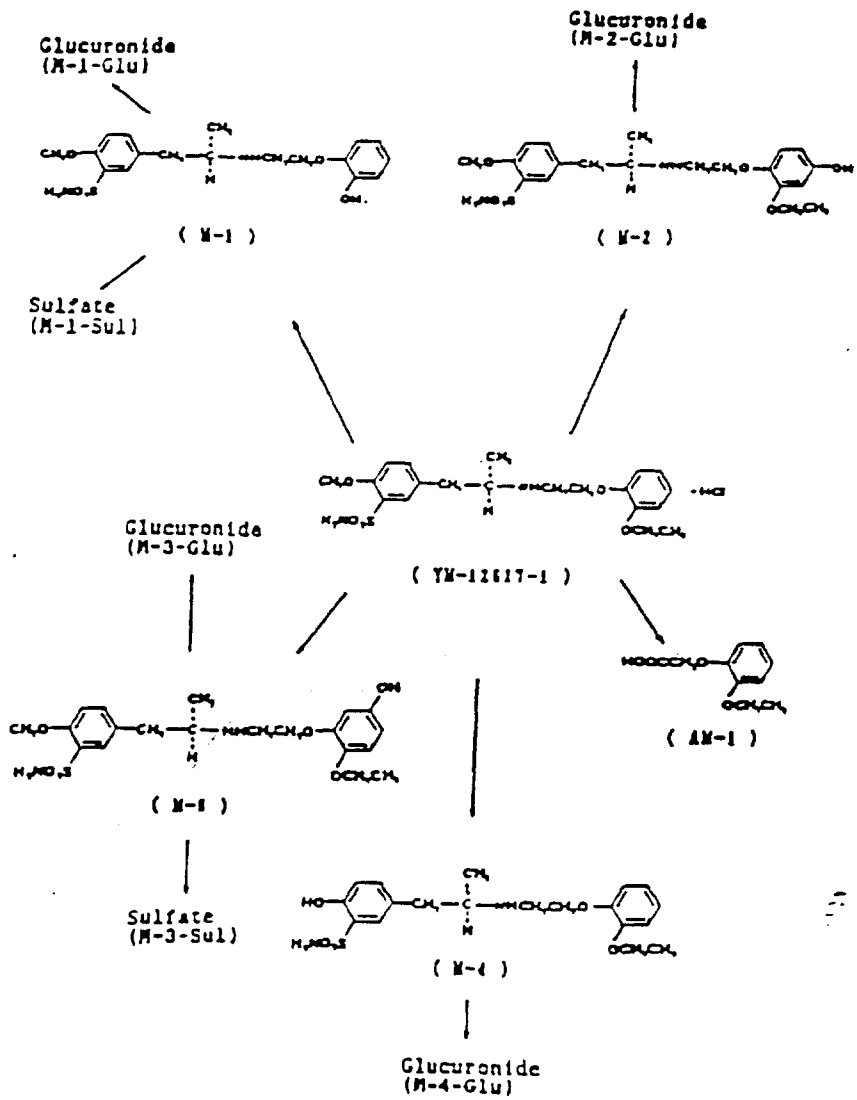


Table 34.

Percentages of Unchanged Drug and Metabolites in Plasma Urinary Excretion of Unchanged Drug and Metabolites over 24 Hours After a Single Oral Dose of ^{14}C-tamsulosin in Humans

Compound Identity[1]	Percentage of Total Plasma Radioactivity (%)[2]	Urinary Excretion (% of Dose)[3]
	Humans[1]	Humans
	81.01	8.74 (0.65)
	1.55	0.15 (0.03)
	0.27[4]	1.24 (0.27)
	2.41	15.72 (1.23)
	0.78	0.35 (0.09)
	0.34	0.01 (0.02)
	0.45	4.14 (0.57)
	ND	2.21 (0.30)
	0.34	0.58 (0.13)
	0.66	3.56 (0.62)
	1.69	7.55 (0.76)
Subtotal[5]	89.50	44.30 (2.80)
Others[6]	5.72	9.86 (1.86)
Polar Metabolites[7]	4.78	8.17 (1.34)
Total	100.00	62.33 (0.86)

1 See Fig. 3

2 The plasma pool between 0.5 and 4 hours post-dose was used. Its radioactivity was equivalent to 11.5 ng/mL of tamsulosin.

3 Data represent the mean (standard deviation) for four subjects.

4 The figure represents the two metabolites combined because they could not be separated.

5 Unchanged drug and identified metabolites combined.

6 Unidentified metabolites

7 The fraction not adsorbed to SEP-PAK C18 cartridges and consequently not recovered.

ND: Not detected; Glu: glucoronide; Sul: sulfate.

Note: Dose of tamsulosin administered was 0.2 mg (Study 555/7).

Note: Mean (standard deviation) urinary and fecal excretion of radioactivity accounted for 76.44 (1.31) % and 21.39 (1.70) % of the administered dose, respectively.

Sponsor's Conclusion: Following oral dosing, tamsulosin was extensively metabolized and eliminated in the urine and feces, with less than 10% of the total dose excreted unchanged in the urine. A total of 10-11 metabolites were identified in urine and plasma. ^{14}C-Tamsulosin in solution form (0.2 mg) was, in general, safe and well tolerated in this study.

Reviewer's Comments: Within 168 h of a single oral dose of labelled tamsulosin, a mean of 97.8% of administered radioactivity was recovered in urine (76.4%) and feces (21.4%).

FOOD EFFECT STUDY
Study No. US94-03
Study Title: A Double Blind, Single and Multiple Dose Study to Assess the Bioavailability and Safety/Tolerance of Tamsulosin (YM617) in the Target Population under Fasted and Two Fed Conditions

Investigator and Study Site: —

Objectives: The study was design to :(1) determine the bioavailability of the modified release formulation of tamsulosin after an initial 0.4 mg dose (with a light breakfast); (2) compare the bioavailability at steady-state (0.8 mg q.d. dosing) after administration under fasted and two different fed conditions (a light breakfast and a high-fat breakfast); (3) confirm the safety and tolerance of 0.8 mg of tamsulosin administered after an overnight fast in the target population; and (4) obtain blood samples on selected Study Days in order to determine if biotransformation of tamsulosin [(-) isomer] to the (+)isomer takes place *in vivo*.

Subjects: Thirty four healthy, middle-aged to elderly male subjects were enrolled into the study. The mean (± standard deviation) ages of subjects on tamsulosin and placebo were 63.9 (± 4.9) years and 62.9 (± 5.1) years, respectively, and the mean weights were 87.9 (± 11.4) kg and 88.7 (± 10.4) kg, respectively.

Study Design: This was a randomized, double-blind, placebo-controlled, multiple dose study in middle-aged to elderly, healthy male subjects. Following a single-blind placebo treatment day (Day 0), subjects were randomized to tamsulosin (24 subjects) or placebo (12 subjects). Subjects on tamsulosin received 0.4 mg q.d. tamsulosin HCl modified release formulation for 2 days (Days 1 and 2), followed by 0.8 mg q.d. for 11 days (Days 3-13). Subjects on placebo received placebo during the entire period. Subjects were fed a light (1.5 ounces of cereal, 2 pieces of toast, and 8 ounces of skim milk; Days 0-9, 11, and 12) or high-fat breakfast (two eggs, 2 slices of bacon, 4 ounces of home fried potatoes, 2 pieces of toast with 1 pat of butter each, and 8 ounces of whole milk; Day 10) half-an-hour prior to dosing, or were fasted overnight (Day 13; no food administered until four hours post-dosing).

Formulation: The 0.4 mg capsules of tamsulosin were from a clinically tested batch (Lot. No. SC6174C); the 0.2 mg capsules were made of a 1:1 mixture of tamsulosin modified release granules and placebo granules (Lot. No. SC6176C).

Sample Collection and Analysis: Venous blood samples (10mL each) for determination of tamsulosin plasma concentrations were collected prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 17.5, and 24 hours after dosing on Days 1, 7, 10, and 13, with an additional sample drawn at 36 hours following dosing on Day 13. On Days 5, 6, 8, 9, 11, and 12 , blood samples were drawn prior to dosing for trough concentrations. Blood samples were also collected at 4.5 hours post-dosing on Days 7, 10, and 13 to determine whether biotransformation of tamsulosin [R(-) isomer] to the S(+) isomer occurred. Plasma samples were stored at approximately -20°C until assayed.
A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 3.2%, 3.7%, and 7.6%, and accuracy of 103%, 101%, and 103% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively).
A HPLC assay with MS/MS detection was used for determination of tamsulosin enantiomers in plasma; Standard curve (0.5-50 ng/mL for each enantiomer); mean recovery (65% and 77% for (+)enantiomer and (-)enantiomer, respectively); sensitivity (LOQ) of 0.5 ng/mL for each enantiomer; specificity (no interfering peaks for tamsulosin enantiomers or internal standard); quality control samples (CV% of <8%, and accuracy of within ±8.5% at concentrations of 2.0, 12.5 and 40 ng/mL for each enantiomer).

Data Analysis: Non-compartmental analysis was used to determine tamsulosin pharmacokinetic parameters. Pharmacokinetic parameters (C_{max}, T_{max}, and $AUC_{(0-24)}$) were compared between treatments (light or heavy

breakfast or fasting) using ANOVA, and 90% confidence intervals were computed on the ratio of the means. An acceptance interval of 80-125% on the ratio of the means was used to establish equivalence between treatments.

Results: Based on dose-normalized values, $AUC_{(0-24)}$ showed an accumulation of 76% and C_{max} values showed an accumulation of 54% on Day 7 compared to Day 1 (Table 35). Based on tamsulosin trough concentrations, steady state was achieved by the fifth day of 0.8 mg q.d. dosing (Day 7). Median T_{max} values were comparable on Days 1 and 7. The mean $t_{½}$ of tamsulosin was 14.93 hours, based on estimates obtained on Day 13.

No differences were observed in rate and extent of absorption (based on comparable estimates of C_{max}, T_{max}, and $AUC_{(0-24)}$), regardless of whether tamsulosin was administered after a light or high-fat breakfast (Table 36). In contrast T_{max} occurred about 2 hours earlier, and C_{max} and $AUC_{(0-24)}$ were 39% and 27% higher, respectively, when tamsulosin was administered in the fasted state, compared to administration after a light breakfast. Thus, administration under fasted conditions resulted in an increase in the rate and extent of absorption of tamsulosin.

No (+) [illegible] was [illegible] (limit of sensitivity of the assay, 0.5 ng/mL) in plasma samples collected at 4.5 hours [illegible] dicating that tamsulosin is not converted *in vivo* to the (+)isomer. No significant [illegible] measurements were observed between tamsulosin or placebo under fasted conditions. A relatively higher incidence of dizziness (29% [7/24] in tamsulosin group, 8% [1/12] in placebo group) and postural hypotension (33% [8/24] in tamsulosin group, 8% [1/12] in placebo group) was observed after the first dose of tamsulosin (0.4 mg administered under fed conditions) compared to placebo, in spite of a lower overall exposure (28%of steady-state, based on AUC) to study drug after the first dose compared to steady-state (0.8 mg).

Table 35.

Mean (Standard Deviation) Pharmacokinetic Parameters and Comparative Statistics for 0.4 mg q.d. (Single Dose, Fed) and 0.8 mg q.d. (Steady-State, Fed) Tamsulosin

	Day 1 0.4 mg[1]	Day 7 0.8 mg q.d.[2]
$AUC_{(0-24)}$ (ng*h/mL)	122 (41)	440 (195)[3,5]
C_{max} (ng/mL)	9.8 (2.9)	29.8 (10.3)[4,5]
C_{min} (ng/mL)	-	12.3 (6.7)
C_{max}/C_{min} Ratio	-	2.7 (0.7)
T_{max} (h)	6 (2,10)[6]	7.0 (3.0,12.0)[6]
$t_{½}$ (h)	-	-

[1] First dose.
[2] Fifth day of 0.8 mg q.d. dosing.
[3] Accumulation ratio of 176 (33) percent, based on a comparison of dose-normalized $AUC_{(0-24)}$ versus $AUC_{(0-24)}$ on Day 1.
[4] Accumulation ratio of 154 (34) percent, based on a comparison of dose-normalized C_{max} versus C_{max} on Day 1.
[5] Theoretical accumulation ratio = 149 (21) percent based on $t_{½}$ estimates under fasted conditions.
[6] Median (range).

Note: A light breakfast was administered ½ hour prior to dosing on both days.
Note: Day 1: first day of 0.4 mg q.d. dosing; Day 7: fifth day of 0.8 mg q.d. dosing.

Table 36.

Mean (Standard Deviation) Pharmacokinetic Parameters and Comparative Statistics for 0.8 mg q.d. (Steady-State, Fed Versus Fasting) Tamsulosin

	0.8 mg q.d. Tamsulosin			Ratio (90% CI)[2]	
	Light Breakfast (A)	High-Fat Breakfast (B)	Fasting C	B/A	C/A
$AUC_{(0-24)}$ (ng*h/mL)	440 (195)	449 (217)	557 (257)	101 (97,106)	127 (121,133)
C_{max} (ng/mL)	29.8 (10.3)	29.1 (11.0)	41.6 (15.6)	97 (91,104)	139 (130,149)
C_{min} (ng/mL)	12.3 (6.7)	13.5 (7.6)	13.3 (7.4)	-	-
C_{max}/C_{min} Ratio	2.7 (0.7)	2.5 (0.8)	3.6 (1.1)	-	-
T_{max} (h)	7.0 (3.0,12.0)[3]	6.5 (3.0,10.0)[3]	5.0 (2.0,7.0)[3]	96 (85,108)	77 (69,87)
$t_{½}$ (h)	-	-	14.9 (3.9)	-	-

[1] Single dose, light breakfast.
[2] 90% confidence interval on geometric least squares mean ratio (%), using light breakfast as the reference.
[3] Median (range).
CI = Confidence Interval
Note: A: Day 7 (fifth day of 0.8 mg q.d. dosing); B: Day 10 (eighth day of 0.8 mg q.d. dosing); C: Day 13 (eleventh day of 0.8 mg q.d. dosing).

Sponsor's Conclusion: The pharmacokinetics of tamsulosin were comparable following administration of a 0.8 mg dose after a light or a high-fat breakfast. Subjects exhibited an increased rate and extent of absorption when tamsulosin was administered under fasted conditions, compared to the fed state (light or high-fat breakfast). Tamsulosin [(-)isomer] was not converted to the (+)isomer *in vivo*. No significant differences in safety measurements were observed between tamsulosin or placebo under fasted conditions. In this study, the first 0.4 mg dose was noted to produce mild to moderate dizziness or postural hypotension in some subjects
Reviewer's Comments: Light or hig fat breakfast had similar effects on tamsulosin pharmacokinetics. The extent of availability of the drug was increased 27% by food, while Cmax was increased 39%. There was no *in vivo* conversion of tamsulosin [(-)isomer] to the (+)isomer.

DRUG INTERACTION

Nifedipine - Atenolol Study
Study No. US93-02
Study Title: A Placebo-Controlled Double-Blind Evaluation of the Concomitant Administration of Two Dose Levels of Tamsulosin on the Pharmacodynamic Profile of Nifedipine (Procardia XL®) in Subjects with Essential Hypertension
Investigator and Study Site:

Objective: To determine the effects of concomitant administration of tamsulosin (multiple dose; 0.4 mg q.d. and 0.8 mg q.d.) on the pharmacodynamic profile of nifedipine (Procardia XL®; once daily formulation) in hypertensive subjects on a stable maintenance dose of nifedipine.
Subjects: Twelve hypertensive subjects were enrolled; eleven subjects completed the study. One subject in the tamsulosin treatment group was discontinued on Day 15 (0.8 mg q.d. tamsulosin treatment period) because of abdominal pain and hematuria. This was judged to be unrelated to study drug. The mean (± standard deviation) ages for the tamsulosin and placebo groups were 58.9 (± 5.5) and 54.5 (± 5.3) years, respectively.

and the mean weights were 89.7 (± 11.1) and 79.3 (± 17.1) kg, respectively.

Study Design: This was a double-blind, parallel, placebo-controlled, pharmacodynamic study performed in twelve subjects with idiopathic or essential hypertension, on a stable dose of nifedipine (Procardia XL®) for a minimum of three months.

Formulation, Dosage and Administration: After a placebo run-in period (Days 1-5; single-blind), subjects were randomized (double-blind) to tamsulosin (eight subjects) or placebo (four subjects), while continuing on their established dosage of nifedipine (Procardia XL®). After treatment for seven days with 0.4 mg q.d. (two capsules of 0.2 mg modified release formulation of tamsulosin HCl; Days 6-12), the tamsulosin dose was stepped up to 0.8 mg q.d. for seven days (two capsules of 0.4 mg modified release formulation of tamsulosin HCl; Days 13-19). Doses of nifedipine ranged from mg q.d. (mean 48.75 mg/day) in the tamsulosin group and 3 .5 mg/day) in the placebo group. Tamsulosin, placebo, and nifedipine were administered er after breakfast.
The 0.4 mg cap were from a clinically tested batch (Lot. No. SC6174C); the 0.2 mg capsules were made of a 1:1 mixture of tamsulosin modified release granules and placebo granules (Lot. No. SC6176C).

Measurements and Sample Collection: Sitting vital signs (systolic and diastolic blood pressure, and pulse rate) were monitored daily, with more frequent monitoring over a 24-hour period on Days 4 (placebo), 11 (sixth day of 0.4 mg q.d. dosing) and 19 (seventh day of 0.8 mg q.d. dosing). Orthostatic tests (supine to standing vital signs) and ECG were measured on selected days including those prior to and following a change in dosage, and 10-hour Holter was monitored immediately following a change in dosage.
Venous blood samples (10 mL for each analyte) were drawn prior to dosing with tamsulosin on Days 12 and 13 (0.4 mg q.d. tamsulosin) and Days 19 and 20 (0.8 mg q.d. tamsulosin) for determination of steady-state tamsulosin trough concentrations, and prior to dosing with nifedipine on Days 6, 13, and 20 for nifedipine trough concentrations. Blood draws and sample processing was done under yellow lighting to prevent degradation of nifedipine. Plasma samples were stored at -20°C until assayed.

Assay: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 0.3%, 0%, and 2.5%, and accuracy of 101%, 98%, and 92% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively).
A validated HPLC assay with ultraviolet detection was used for nifedipine (plasma samples); Standard curve (1 - 100 ng/mL); mean recovery (87.7%, 91.0%, and 92.7% at concentrations of 50, 15, and 2 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 1 ng/mL; specificity (no interfering peaks for nifedipine or internal standard); in-process quality control samples (CV% of 2.6%, 3.3%, and 9.1%, and accuracy of 98%, 99%, and 96% at concentrations of 50, 15, and 2 ng/mL, respectively).

Data Analysis: Descriptive statistics of values and of change in values from Baseline were computed for continuous pharmacodynamic and safety parameters. Changes in pharmacodynamic parameters like sitting vital signs (including actual values, areas under the curve, and/or changes from Baseline) and orthostatic tests were compared between the tamsulosin and the placebo groups. Descriptive statistics were computed for nifedipine and tamsulosin trough concentrations.

Results: No clinically significant differences were observed in change from baseline estimates (Day 4 versus Days 11 and 19) of mean 24-hour blood pressures (systolic and diastolic) or pulse rate, between tamsulosin and placebo in terms of mean values and calculated AUC (Table 37 & 38, Fig. 13 - 16), indicating that tamsulosin does not affect blood pressure control by Procardia XL®. Orthostatic tests for tamsulosin and placebo yielded maximum mean systolic blood pressure changes (supine to standing) of -9.5 and -5.0 mmHg, maximum mean diastolic blood pressure changes of +4.7 and +10.5 mmHg, and maximum mean changes in pulse rate of

+11.1 and +12.5 beats/min, respectively, over the course of the study (Table 39). These results indicate the absence of a first dose effect following initiation of therapy or increase in dose of tamsulosin. Results from Holter monitoring and ECG measurements also did not demonstrate any differences between tamsulosin treatment and placebo.

Mean trough (pre-dose) plasma concentrations of tamsulosin in the tamsulosin treatment group reflected attainment of steady-state by Day 12 (at 0.4 mg q.d.) and Day 19 (at 0.8 mg q.d.) (Table 40). Following treatment with tamsulosin, mean trough concentrations of nifedipine in the tamsulosin group did not change significantly from baseline (Day 6 versus Days 13 and 20), indicating the absence of a clinically significant influence of tamsulosin on the pharmacokinetics of nifedipine.

No significant differences in safety measurements were observed on administration of nifedipine (Procardia XL®) in the presence or absence of tamsulosin (tamsulosin vs placebo group).

Table 37.

Mean Changes in Steady-State Vital Signs Following Treatment with Tamsulosin (0.4 mg q.d. (Day 11) and 0.8 mg q.d. (Day 19)) or Placebo, in the Presence of Concomitant Procardia XL®

	Mean Actual Values on Baseline Day	Mean Changes from Baseline Day	
	Day 4 (Placebo)	Day 11 (0.4 mg q.d.)	Day 19 (0.8 mg q.d.)
Systolic Blood Pressure (mmHg)			
Tamsulosin (n = 7-8)	134.3, 147.0	-11.0, -3.8	-11.7, +2.6
Placebo (n = 4)	127.0, 144.5	-10.0, +4.0	-11.0, +3.0
Diastolic Blood Pressure (mmHg)			
Tamsulosin (n = 7-8)	87.3, 95.8	-5.8, +2.8	-8.9, +3.1
Placebo (n = 4)	77.0, 94.5	-6.0, +4.0	-7.0, +5.0
Pulse Rate (bpm)			
Tamsulosin (n = 7-8)	71.5, 79.8	-2.5, +7.8	-6.1, +8.9
Placebo (n = 4)	70.0, 79.5	-10.0, +5.5	-12.0, +2.8

Note: Data presented are the ranges in mean values (across time points) for 12 measurements over a 24-hour period.

Note: Subjects in the Placebo group received placebo on all study days.

Note: Day 11 - sixth day of 0.4 mg q.d. dosing; Day 19 - seventh day of 0.8 mg q.d. dosing.

Table 38. Mean Changes in Area under the Curve ($AUC_{(vital\ signs)}$) of 24 h Vital Signs from Baseline Day to Tamsulosin Treatment Days

		Mean AUC (mmHg·h) on Baseline Day	Mean Change (%) from Baseline Day	
		Study Day 4 (Placebo)	Study Day 11 (0.4 mg q.d.)	Study Day 19 (0.8 mg q.d.)
Systolic Blood Pressure	Tamsulosin	3388.07	-5.3%	-4.9%
	Placebo	3235.39	-2.1%	-3.3%
Diastolic Blood Pressure	Tamsulosin	2183.71	-2.9%	-2.9%
	Placebo	2077.74	+0.1%	-2.0%
Pulse Rate	Tamsulosin	1848.40	+2.5%	-1.3%
	Placebo	1822.05	-2.0%	-5.5%

Table 39: Orthostatic Test Results[1] on Days of Initiation/Change in Tamsulosin Dosing Regimen (Days 6 and 13) and at Steady-State (Days 12 and 18), Following Treatment with Tamsulosin or Placebo in the Presence of Concomitant Procardia XL®

	Mean Actual Values				
	Placebo (Baseline)	0.4 mg q.d.		0.8 mg q.d.	
	Day 5	Day 6	Day 12	Day 13	Day 18
Systolic Blood Pressure (mmHg)					
Tamsulosin (n = 7-8)	-4.7, +1.0	-0.8, +2.0	-5.2, -2.2	-9.5, 0.0	-8.3, +1.1
Placebo (n = 4)	-3.5, +0.5	-2.0, +4.0	-4.5, +1.5	-5.0, 0.0	-1.5, 0.0
Diastolic Blood Pressure (mmHg)					
Tamsulosin (n = 7-8)	+2.0, +3.0	+1.3, +4.7	-1.5, +2.2	+1.0, +3.0	-1.4, +3.4
Placebo (n = 4)	+0.5, +4.0	+4.0, +10.5	+1.5, +6.0	+3.0, +10.0	+2.5, +6.0
Pulse Rate					
Tamsulosin (n = 7-8)	+2.5, +7.5	+2.5, +5.5	+4.5, +8.0	+6.0, +10.3	+3.9, +11.1
Placebo (n = 4)	0.0, +5.5	-1.0, +4.0	+0.5, +6.5	+3.0, +12.5	+2.7, +3.5

[1] Standing minus supine measurements.

Note: Data presented are the ranges in mean values (across time points) for 3 measurements (4, 8, and 10 hours post-dose).

Note: Subjects in the Placebo group received placebo on all study days.

Note: Day 6 - first day of 0.4 mg q.d. dosing; Day 12 - seventh day of 0.4 mg q.d. dosing; Day 13 - first day of 0.8 mg q.d. dosing; Day 18 - sixth day of 0.8 mg q.d. dosing.

Table 40: Summary Statistics for Steady-State Plasma Trough (Pre-dose) Concentrations (ng/mL) of Tamsulosin and Nifedipine[1]

	Placebo	0.4 mg q.d. Tamsulosin[2]		0.8 mg q.d. Tamsulosin[2]	
	Day 6	Day 12	Day 13	Day 19	Day 20
Tamsulosin (Tamsulosin Group; [n = 7-8])					
Mean	-	6.23	5.46	10.26	10.33
SD		2.33	2.22	4.22	4.86
Median		5.78	5.58	8.47	9.44
Min.,Max.		4.14, 11.50	2.03, 9.74	6.36, 18.00	5.60, 20.30
Nifedipine (Tamsulosin Group; [n = 7-8])					
Mean	37.74	-	49.65	-	44.83
SD	27.63		36.86		22.46
Median	31.60		48.75		45.90
Min.,Max.	9.43, 81.30		2.78, 96.00		16.30, 83.10
Nifedipine (Placebo Group; [n = 4])					
Mean	22.45	-	20.98	-	27.60
SD	11.99		7.93		16.67
Median	21.10		20.65		25.90
Min.,Max.	9.30, 38.30		11.80, 30.80		10.80, 47.80

[1] Mean (SD) nifedipine dose in the Tamsulosin group was 48.75 (22.32) mg/day and in the Placebo group was 37.50 (15.00) mg/day.

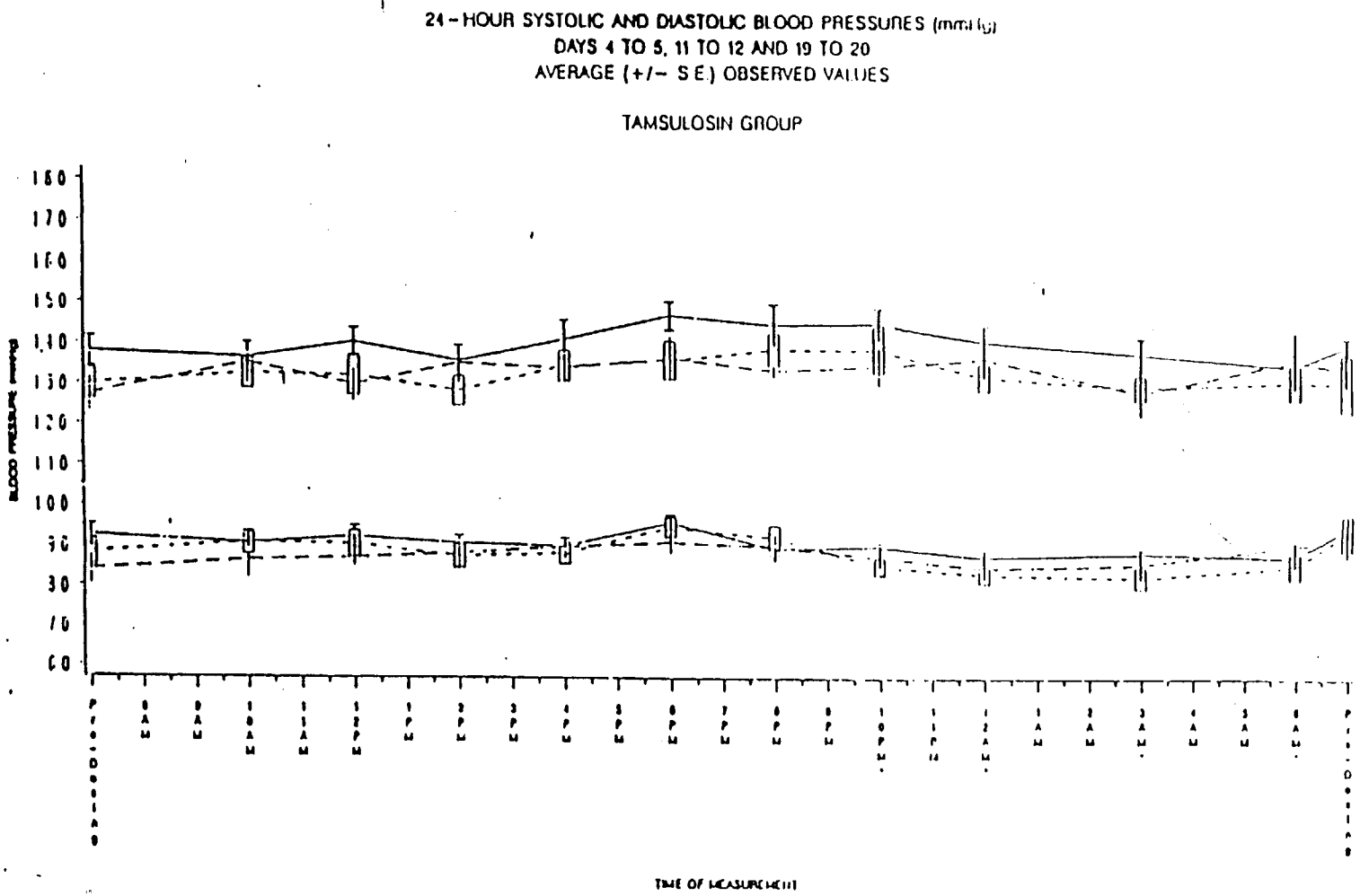
[2] Subjects in the Placebo group received placebo on all study days.

Note: Day 12 - trough level after six days of 0.4 mg q.d. dosing; Day 13 - trough level after seven days of 0.4 mg q.d. dosing; Day 19 - trough level after six days of 0.8 mg q.d. dosing; Day 20 - trough level after seven days of 0.8 mg q.d. dosing.

Sponsor's Conclusion: No significant interactions occur between tamsulosin and nifedipine. No dose adjustments are necessary when these drugs are administered concurrently.

Reviewer's Comment: The reviewer agrees with the Sponsor's conclusion.

Fig 13. Mean Steady-State 24-Hour Blood Pressures (Actual Values; mmHg) Following Treatment with Tamsulosin in the Presence of Concomitant Procardia XL*

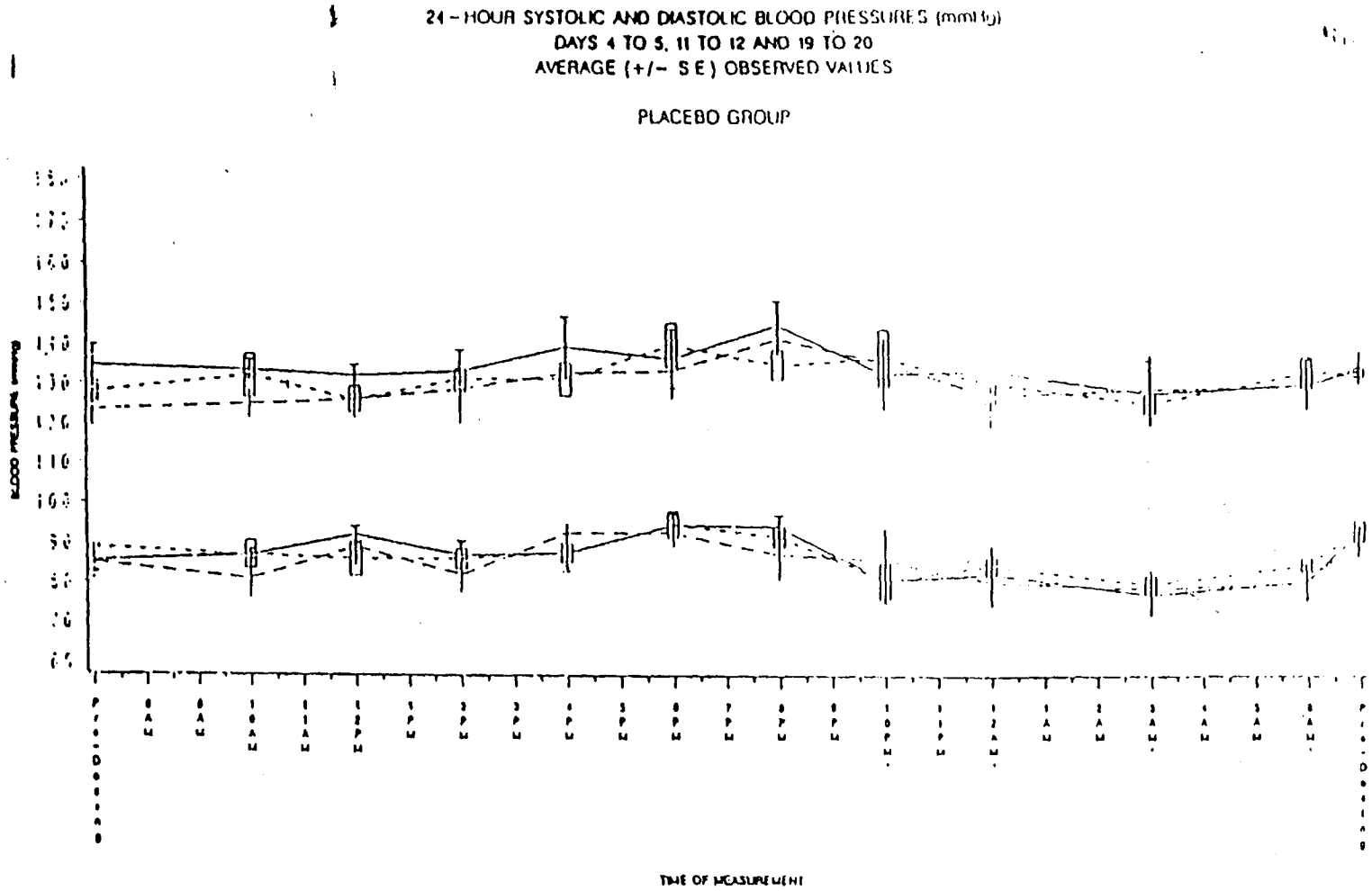


Note: _____ Day 4 to Day 5 _ _ _ _ _ Day 11 to Day 12 _ _ _ _ _ Day 19 to Day 20

Note: The upper set of lines corresponds to systolic blood pressure; the lower set corresponds to diastolic blood pressure

* Vital signs were taken while the subject was supine.

Fig. 14. Mean Steady-State 24-Hour Blood Pressures (Actual Values; mmHg) Following Treatment with Placebo in the Presence of Concomitant Procardia XL®

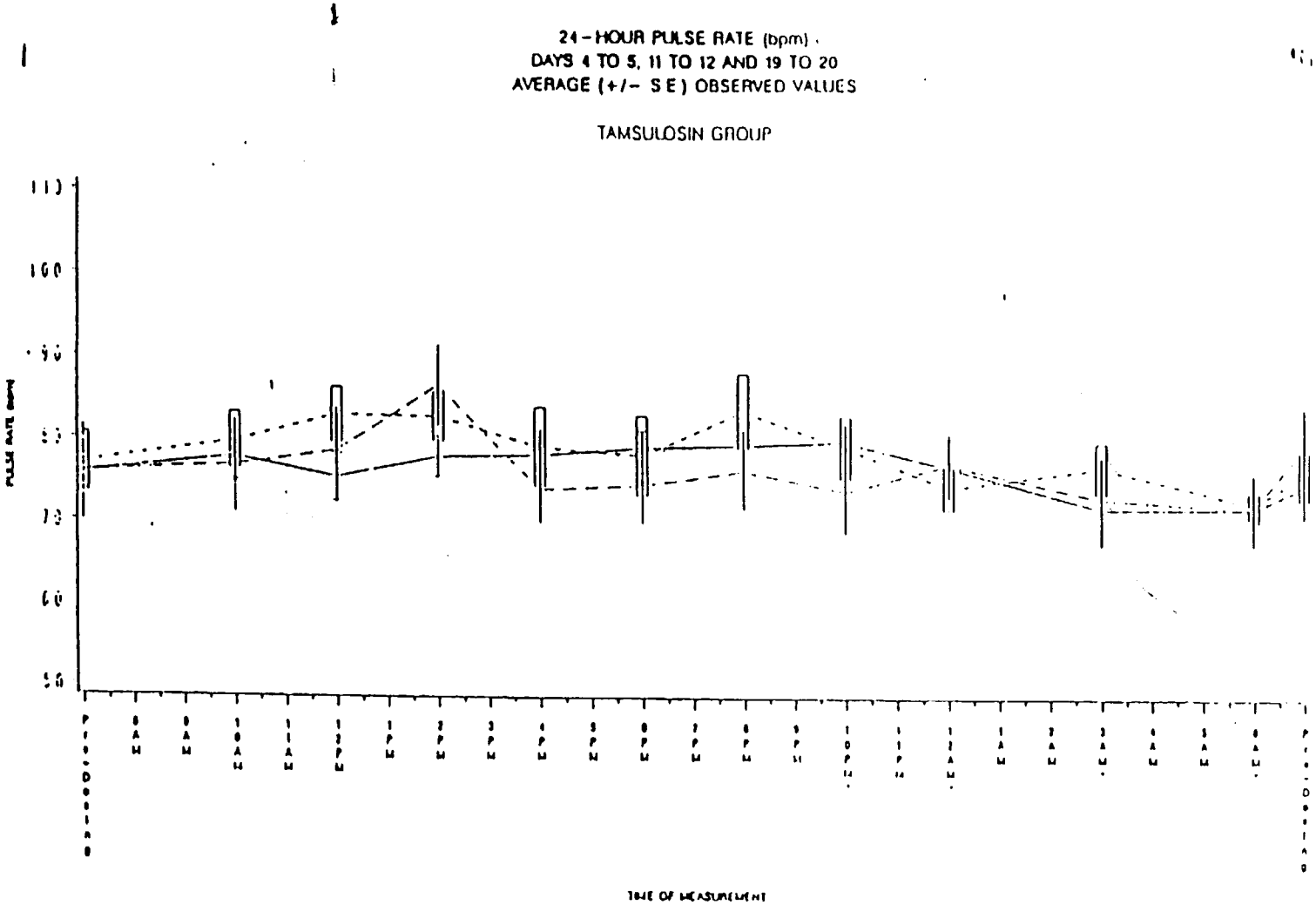


Note: _____ Day 4 to Day 5 _ _ _ _ _ Day 11 to Day 12 _ _ _ _ _ Day 19 to Day 20

Note: The upper set of lines corresponds to systolic blood pressure; the lower set corresponds to diastolic blood pressure

* Vital signs were taken while the subject was supine.

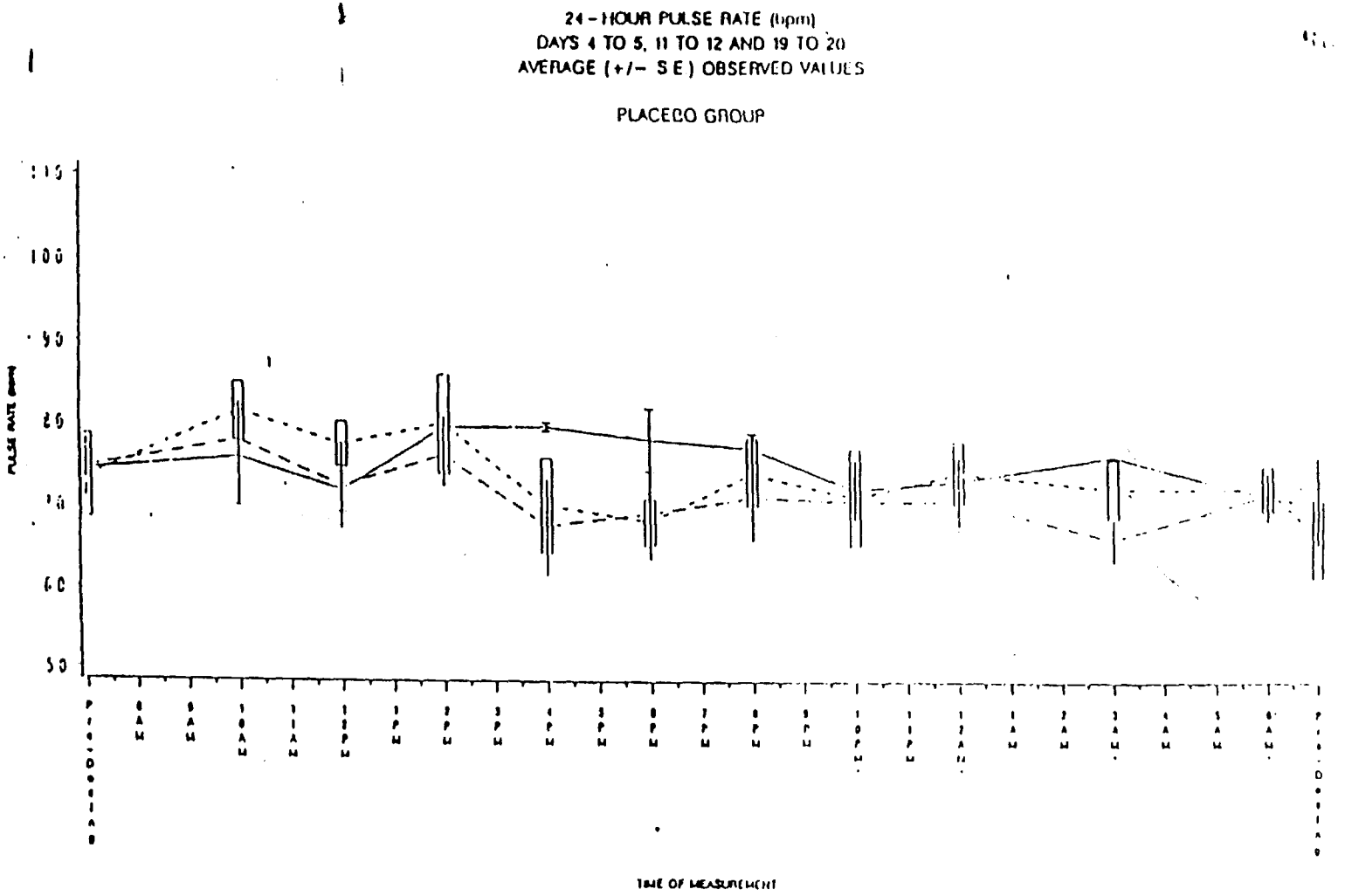
Fig. 15. Mean Steady-State 24-Hour Pulse Rates (Actual Values; bpm) Following Treatment with Tamsulosin in the Presence of Concomitant Procardia XL*



Note: _____ Day 4 to Day 5 _ _ _ _ Day 11 to Day 12 __ __ __ Day 19 to Day 20

* Vital signs were taken while the subject was supine.

Fig. 16. Mean Steady-State 24-Hour Pulse Rates (Actual Values; bpm) Following Treatment with Placebo in the Presence of Concomitant Procardia XL*



Note: _____ Day 4 to Day 5 _ _ _ _ Day 11 to Day 12 __ __ __ Day 19 to Day 20

* Vital signs were taken while the subject was supine.

Atenolol - Tamsulosin Study

Study No. US93-03
Study Title: A Placebo-Controlled Double-Blind Evaluation of the Concomitant Administration of Two Dose Levels of Tamsulosin (YM617) on the Pharmacodynamic Profile of Atenolol (Tenormin®) in Subjects with Essential Hypertension

Investigator and Study Site:

Objective: To determine the effects of concomitant administration of tamsulosin (multiple dose; 0.4 mg q.d. and 0.8 mg q.d.) on the pharmacodynamic profile of atenolol in hypertensive subjects on a stable maintenance dose of atenolol.

Subjects: Twelve hypertensive subjects were enrolled and completed the study. The mean (± standard deviation) ages for the tamsulosin and placebo groups were 57.2 (± 6.0) and 66.5 (± 9.5) years, respectively, and the mean weights were 92.9 (± 14.2) and 91.1 (± 15.1) kg, respectively

Study Design: This was a double-blind, parallel, placebo-controlled, pharmacodynamic study in 12 subjects with essential hypertension, on a stable dose of atenolol for a minimum of three months.

Formulation, Dosage and Administration: After a placebo run-in period (Days 1-5; single-blind), subjects were randomized (double-blind) to tamsulosin (eight subjects) or placebo (four subjects), while continuing on their established dosage of atenolol (Tenormin® or generic). After treatment for seven days with 0.4 mg q.d. (two capsules of 0.2 mg modified release formulation of tamsulosin HCl; Days 6-12), the dosage of tamsulosin was stepped up to 0.8 mg q.d. for seven days (two capsules of 0.4 mg modified release formulation of tamsulosin HCl; Days 13-19). Doses of atenolol ranged from mg q.d. in the tamsulosin and placebo groups (mean doses of 50.00 and 56.25 mg/day in the respective groups). Tamsulosin, placebo, and atenolol were administered approximately 30 minutes after breakfast.
The 0.4 mg capsules of tamsulosin were from a clinically tested batch (Lot. No. SC6174C); the 0.2 mg capsules were made of a 1:1 mixture of tamsulosin modified release granules and placebo granules (Lot. No. SC6176C). Subjects were dosed with the same brand of atenolol (Tenormin® or generic) that they had been using prior to the study.

Measurements and Sample Collection: Sitting vital signs (systolic and diastolic blood pressure, and pulse rate) were monitored daily, with more frequent monitoring over a 24-hour period on Days 4 (placebo), 11 (sixth day of 0.4 mg q.d. dosing) and 19 (seventh day of 0.8 mg q.d. dosing). Orthostatic tests (supine to standing vital signs) and ECG were measured on selected days including those prior to and following a change in dosage, and 10-hour Holter was monitored immediately following a change in dosage.
Venous blood samples (10 mL for each analyte in separate tubes) were drawn prior to dosing with tamsulosin on Days 12 and 13 (0.4 mg q.d. tamsulosin) and Days 19 and 20 (0.8 mg q.d. tamsulosin) for determination of steady-state tamsulosin trough concentrations, and prior to dosing with atenolol on Days 6, 13, and 20 for atenolol trough concentrations. Plasma samples were stored at -20°C until assayed.

Assays: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 6.7%, 1.1%, and 4.7%, and accuracy of 94%, 95%, and 97% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively).
A validated HPLC assay with fluorescence detection was used for atenolol (whole blood samples); standard curve (10 -1000 ng/mL); mean recovery (62.0%, 61.9%, and 66.0% at concentrations of 800, 150, and 15 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 10 ng/mL; specificity (no interfering peaks for atenolol or internal standard); in-process quality control samples (CV% of 7.6%, 2.8%, and 6.5%, and accuracy of 101%, 102%, and 108% at concentrations of 800, 150, and 15 ng/mL, respectively; n=2).

Data Analysis: Descriptive statistics of values and of change in values from Baseline were computed for continuous pharmacodynamic and safety parameters. Changes in pharmacodynamic parameters like sitting vital signs (including actual values, areas under the curve, and/or changes from baseline) and orthostatic tests were compared between the tamsulosin and the placebo groups. Descriptive statistics were computed for atenolol and tamsulosin trough concentrations.

Results: No clinically significant differences were observed in change from Baseline estimates (Day 4 versus Days 11 and 19) of mean 24-hour blood pressures (systolic and diastolic) or pulse rate, between tamsulosin and placebo in terms of mean values and calculated AUC (Table 41 & 42, Fig. 17 - 20), indicating that tamsulosin does not affect blood pressure control by atenolol. Orthostatic tests yielded a maximum mean systolic blood pressure change (supine to standing) of -10.3 and -16.0 mmHg, a maximum mean diastolic blood pressure change of +6.2 and +11.5 mmHg, and a maximum mean change in pulse rate of +9.[illegible] beats/min, for tamsulosin and placebo, respectively, over the course of the study (Table [illegible] these [illegible] the absence of a first dose effect following initiation of therapy or increase in dose of tamsulosin. [illegible]results [illegible]n Holter monitoring and ECG measurements also failed to demonstrate any differences between tamsulosin treatment and placebo.

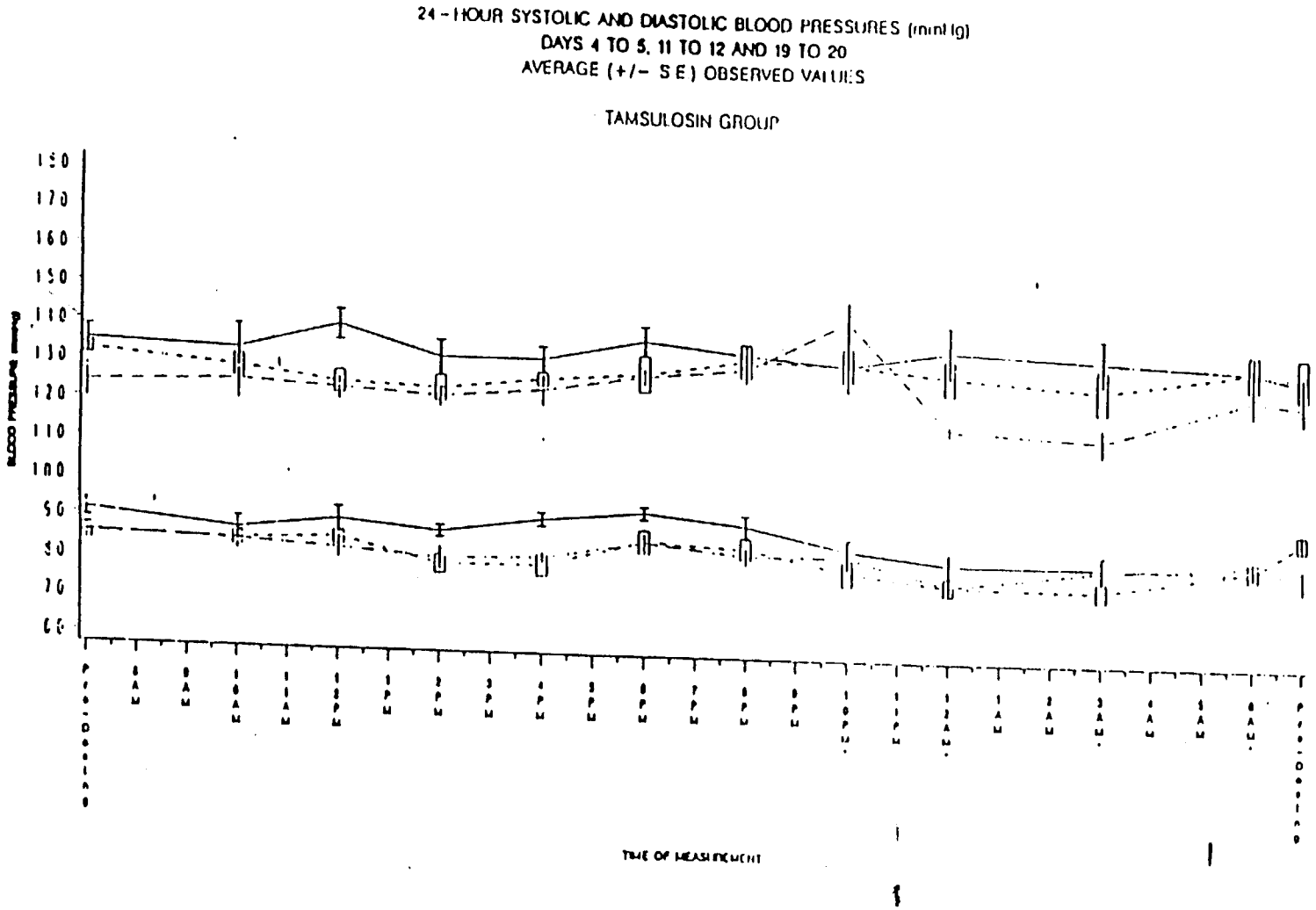
Mean trough (pre-dose) plasma concentrations of tamsulosin in the tamsulosin treatment group reflected attainment of steady-state by Day 12 (at 0.4 mg q.d.) and Day 19 (at 0.8 mg q.d.) (Table 44). Following treatment with tamsulosin, mean trough concentrations of atenolol in the tamsulosin group did not change significantly from baseline (Day 6 versus Days 13 and 20), indicating the absence of a clinically significant influence of tamsulosin on the pharmacokinetics of atenolol. Mean trough concentrations of atenolol appeared elevated in the placebo group (66.0-69.5 ng/mL; mean dose of 56.3 mg q.d.) compared to the tamsulosin group (35.0-40.0 ng/mL; mean dose of 50.0 mg q.d.). These elevated mean concentrations were accounted for by significantly higher concentrations of atenolol (ranging from ng/mL) in two subjects within the placebo group, as compared to a range of ng/mL for the remaining two subjects.

No significant differences in safety measurements were observed on administration of atenolol in the presence or absence of tamsulosin (tamsulosin vs placebo group).

Sponsor's Conclusion: No significant interactions occur between tamsulosin and atenolol. No dose adjustments are necessary when these drugs are administered concurrently.

Reviewer's Comment: No significant interaction between tamsulosin and atenolol was observed. Adjustment of atenolol dose is not required on the institution of tamsulosin therapy.

Fig. 17. Mean Steady-State 24-Hour Blood Pressures (Actual Values; mmHg) Following Treatment with Tamsulosin in the Presence of Concomitant Atenolol

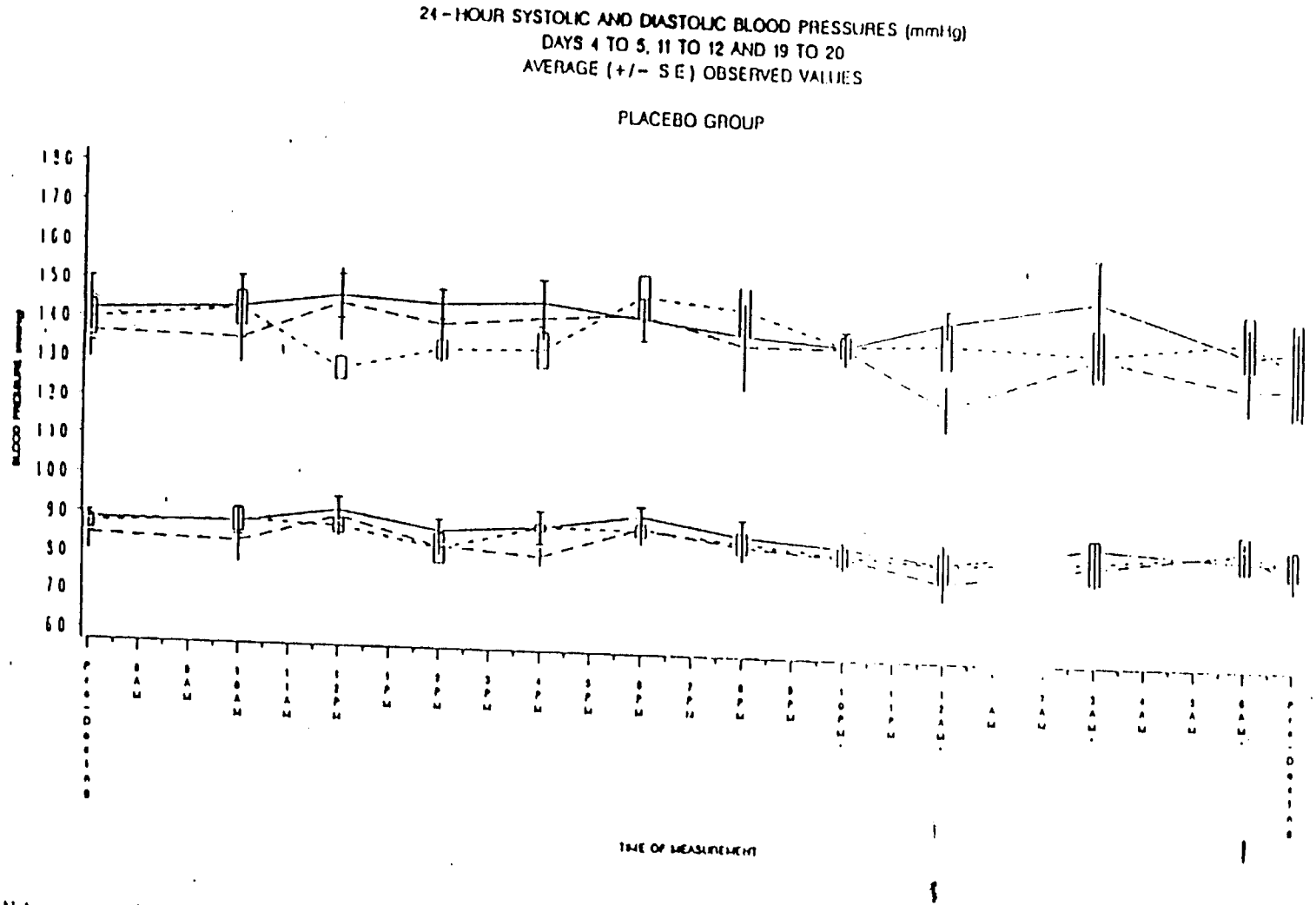


Note: _____ Day 4 to Day 5 _ _ _ _ Day 11 to Day 12 — — — Day 19 to Day 20

Note: The upper set of lines corresponds to systolic blood pressure; the lower set corresponds to diastolic blood pressure

* Vital signs were taken while the subject was supine.

Fig.18. Mean Steady-State 24-Hour Blood Pressures (Actual Values; mmHg) Following Treatment with Placebo in the Presence of Concomitant Atenolol



Note: _____ Day 4 to Day 5 _ _ _ _ _ Day 11 to Day 12 — — — Day 19 to Day 20

Note: The upper set of lines corresponds to systolic blood pressure; the lower set corresponds to diastolic blood pressure

* Vital signs were taken while the subject was supine.

Fig. 19. Mean Steady-State 24-Hour Pulse Rates (Actual Values; bpm) Following Treatment with Tamsulosin in the Presence of Concomitant Atenolol

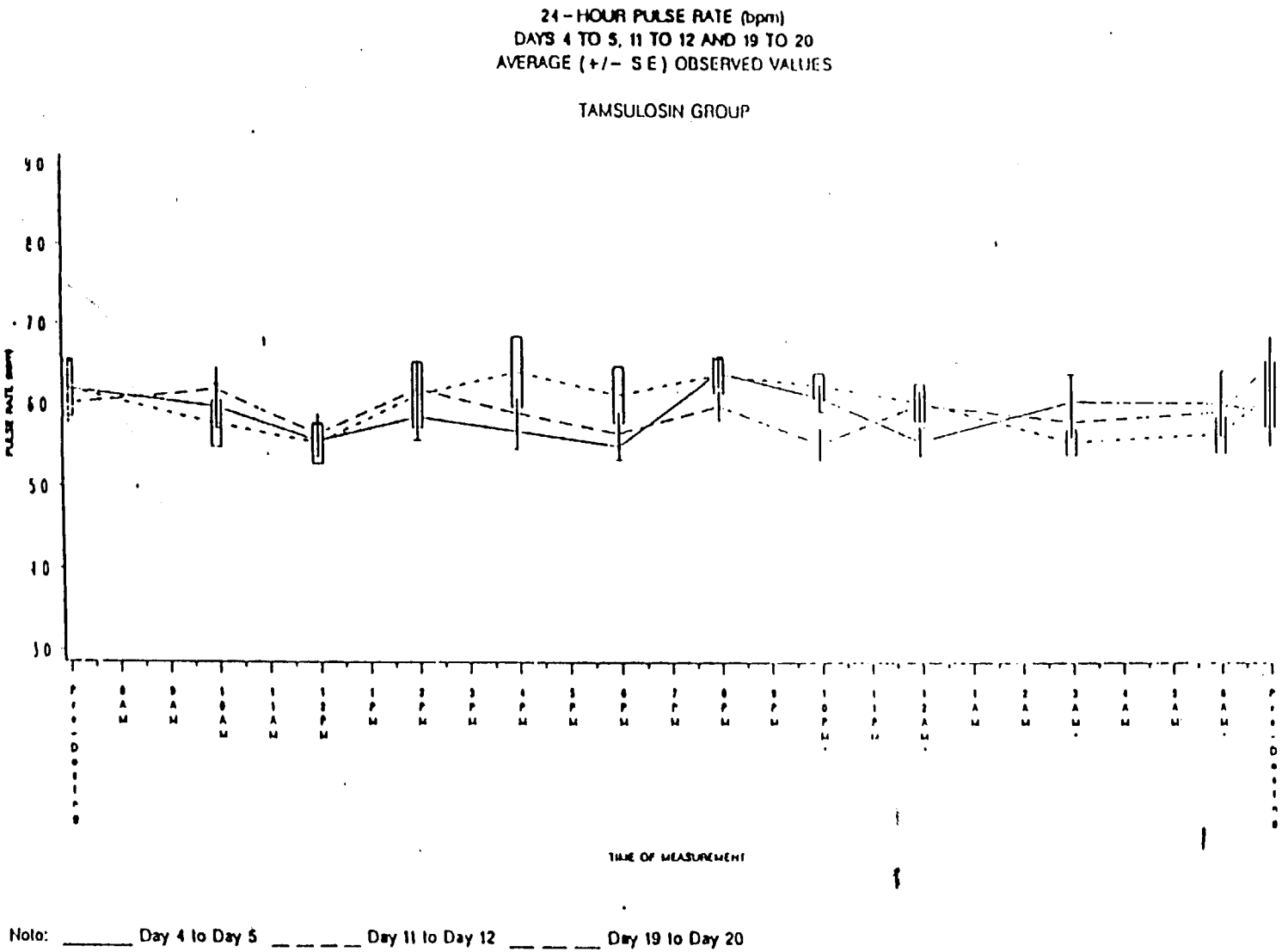
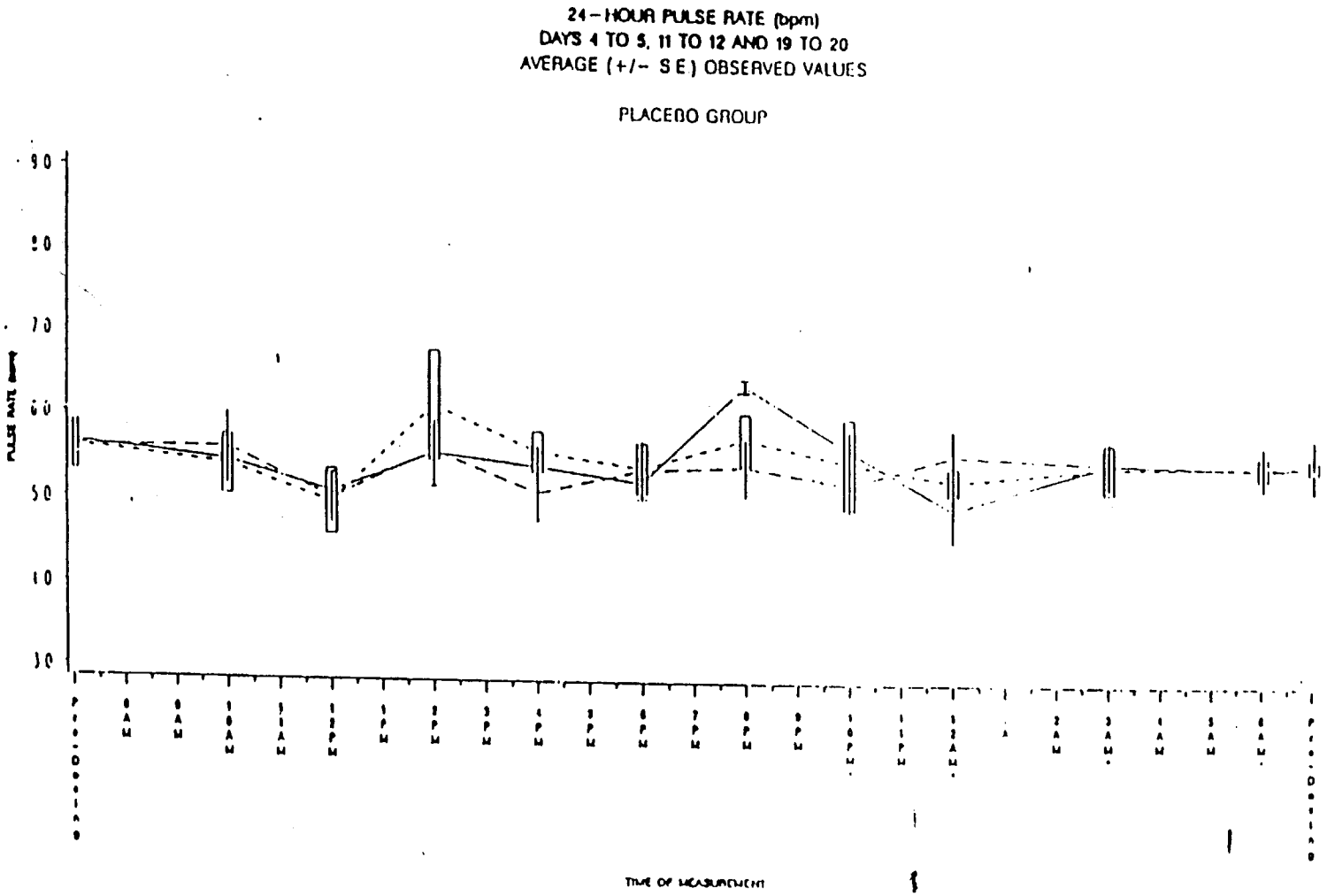


Fig. 20. Mean Steady-State 24-Hour Pulse Rates (Actual Values; bpm) Following Treatment with Placebo in the Presence of Concomitant Atenolol



Note: _____ Day 4 to Day 5 _ _ _ _ _ Day 11 to Day 12 _ _ _ _ _ Day 19 to Day 20

* Vital signs were taken while the subject was supine.

Table 41. Mean Changes in Steady-State Vital Signs Following Treatment with Tamsulosin (0.4 mg q.d. (Day 11) and 0.8 mg q.d. (Day 19)) or Placebo, in the Presence of Concomitant Atenolol

	Mean Actual Values on Baseline Day	Mean Change from Baseline Day	
	Day 4 (Placebo)	Day 11 (0.4 mg q.d.)	Day 19 (0.8 mg q.d.)
Systolic Blood Pressure (mmHg)			
Tamsulosin (n = 8)	129.8, 140.0	-14.8, +1.5	-20.3, +11.5
Placebo (n = 4)	137.5, 150.5	-18.5, +6.5	-21.5, +1.0
Diastolic Blood Pressure (mmHg)			
Tamsulosin (n = 8)	81.5, 93.3	-11.5, +0.5	-9.5, +1.8
Placebo (n = 4)	82.5, 92.5	-4.5, +2.0	-7.5, +2.5
Pulse Rate (bpm)			
Tamsulosin (n = 8)	54.9, 64.0	-5.0, +7.4	-5.8, +6.1
Placebo (n = 4)	49.5, 64.0	-6.5, +5.8	-9.8, +6.3

Note: Data presented are the ranges in mean values (across time points) for 12 measurements over a 24-hour period.

Note: Subjects in the Placebo group received placebo on all study days.

Note: Day 11 - sixth day of 0.4 mg q.d. dosing; Day 19 - seventh day of 0.8 mg q.d. dosing.

Table 42. Mean Changes in $AUC_{(vital\ signs)}$ of 24 h Vital Signs from Baseline Following Tamsulosin Treatment

Table 43. Orthostatic Test Results[1] on Days of Initiation/Change in Tamsulosin Dosing Regimen (Days 6 and 13) and at Steady-State (Days 12 and 18), Following Treatment with Tamsulosin or Placebo in the Presence of Concomitant Atenolol

	Mean Actual Values				
	Placebo (Baseline)	0.4 mg q.d.		0.8 mg q.d.	
	Day 5	Day 6	Day 12	Day 13	Day 18
Systolic Blood Pressure (mmHg)					
Tamsulosin (n = 8)	-8.8, -6.0	-7.7, +1.0	-7.0, +1.0	-10.3, -3.5	-8.3, -4.0
Placebo (n = 4)	-7.0, +0.5	-3.5, +4.0	-0.5, +16.0	-16.0, +3.5	-5.5, -1.0
Diastolic Blood Pressure (mmHg)					
Tamsulosin (n = 8)	+1.3, +4.0	+1.6, -5.2	+0.0, +4.7	-2.0, +2.5	-1.5, +6.2
Placebo (n = 4)	-8.0, +2.0	[illegible]	+2.5, +[illegible]	-1.5, +3.5	-4.0, +1.5
Pulse Rate (bpm)					
Tamsulosin (n = 8)	+1.4, +4.9	+4.6, +6.1	+4.2, +6.9	+3.5, +5.5	+2.4, +9.3
Placebo (n = 4)	+1.5, +3.7	+2.5, +3.2	+2.0, +5.5	-0.5, +[illegible]	+2.2, +7.2

[1] Standing minus supine measurements.

Note: Data presented are the ranges in mean values (across time points) for three measurements (four, eight, and ten hours post-dose).

Note: Subjects in the Placebo group received placebo on all study days.

Note: Day 6 - first day of 0.4 mg q.d. dosing; Day 12 - seventh day of 0.4 mg q.d. dosing; Day 13 - first day of 0.8 mg q.d. dosing; Day 18 - sixth day of 0.8 mg q.d. dosing.

Table 44. Summary Statistics for Steady-State Plasma Trough (Pre-dose) Concentrations (ng/mL) of Tamsulosin and Atenolol[1]

	Placebo	0.4 mg q.d. Tamsulosin[2]		0.8 mg q.d. Tamsulosin[2]	
	Day 6	Day 12	Day 13	Day 19	Day 20
Tamsulosin (Tamsulosin Group; [n = 8])					
Mean	-	3.27	3.55	9.22	10.38
SD		1.48	1.71	4.07	4.32
Median		3.57	3.41	8.29	10.02
Min.,Max.		1.08, 5.59	1.55, 7.13	4.23, 16.80	4.43, 18.30
Atenolol (Tamsulosin Group; [n = 8])					
Mean	35.53	-	34.99	-	39.93
SD	15.61		15.61		18.22
Median	36.25		34.25		39.80
Min.,Max.	12.4, 55.2		14.5, 60.7		17.8, 73.4
Atenolol (Placebo Group; [n = 8])					
Mean	69.53	-	66.63	-	66.03
SD	38.12		41.20		35.68
Median	69.80		62.00		68.80
Min.,Max.	32.5, 106.0		28.5, 114.0		29.1, 97.4

[1] Mean (SD) atenolol dose in the Tamsulosin group was 50.00 (23.14) mg/day and in the Placebo group was 56.25 (31.46) mg/day.

[2] Subjects in the Placebo group received placebo on all study days.

Note: Day 12 - trough level after six days of 0.4 mg q.d. dosing; Day 13 - trough level after seven days of 0.4 mg q.d. dosing; Day 19 - trough level after six days of 0.8 mg q.d. dosing; Day 20 - trough level after seven days of 0.8 mg q.d. dosing.

Multiple Dose Study

Study No. US92-01A
Study Title: A Phase I, Placebo-Controlled Study of the Safety of Modified Release Tamsulosin in Subjects of the Target Population Demographics

Investigator and Study Site:

Objectives: The primary objective of this study was to confirm the safety of a once daily dose of 0.4 mg and 0.8 mg of tamsulosin modified release formulation in subjects with demographics similar to the drug's target population. The secondary objectives were to (1) study the pharmacokinetics of 0.8 mg q.d. of tamsulosin in relation to 0.4 mg q.d. under fed conditions; and (2) to study the effects of food on the pharmacokinetics of 0.8 mg q.d. tamsulosin, in subjects with demographics similar to the drug's target population.

Study Design: This was a double-blind, randomized, parallel, placebo-controlled trial of tamsulosin in middle-aged to elderly subjects.

Subjects: Twenty-four healthy, middle-aged to elderly male subjects were enrolled and 21 subjects completed the study. One subject on placebo was discontinued after dosing on Day 2 due to ECG abnormalities. Two subjects on tamsulosin were discontinued on Days 8 and 17, respectively, because of atrial fibrillation and elevated liver function tests (alanine aminotransferase levels), respectively. The median (range) ages of subjects on tamsulosin and placebo were 62.6 (55 - 74) years and 63 ( ) years, respectively, and the mean weights were 80.5 (± 73.4 - 92.3) kg and 86.9 (±79.0 - 100.6) kg, respectively.

Formulation, Dosage and Administration: Twenty-four subjects were randomized to tamsulosin or placebo (18 subjects on tamsulosin and 6 subjects on placebo). Subjects on tamsulosin received placebo for 1 day (Day 1), 0.4 mg q.d. tamsulosin for 5 days (two 0.2 mg capsules (Lot No. LA617FB) of modified release formulation of tamsulosin HCl; Days 2-6), and 0.8 mg q.d. for 14 days (four 0.2 mg capsules of modified release formulation of tamsulosin HCl; Days 7-20). The placebo group received placebo during the entire period. Tamsulosin or placebo was administered to subjects half-an-hour after a standardized light breakfast ("fed" condition), except for the last day of dosing (Day 20), when they were administered half-an-hour prior to breakfast ("delayed meal").

Blood Sampling and Analysis: Venous blood samples (10 mL each) for determination of tamsulosin plasma concentrations were collected prior to dosing (0 hour) and at 2, 4, 6, 8, 10, and 12 hours following dosing on Days 6, 14, and 20. Plasma samples were stored at approximately -20°C until assayed.
A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); standard curve (0.5-20 ng/mL); mean recovery (91.1%, 66.9%, 86.0%, 71.1%, and 65.8% at concentrations of 2, 5, 10, 15, and 20 ng/mL, respectively; n=5 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 18.3%, 15.3%, 5.6%, and 3.3%, and accuracy of 100%, 107%, 104%, and 106% at concentrations of 0.5, 3.1, 11.4, and 17.5 ng/mL, respectively).

Data Analysis: Non-compartmental analysis was used to determine tamsulosin pharmacokinetic parameters. Parameters (C_{max}, T_{max}, and $AUC_{(0-12)}$) were compared between treatments (0.4 mg q.d. versus 0.8 mg q.d.; 0.8 mg q.d. fed versus 0.8 mg q.d. delayed meal) using ANOVA, and 90% confidence intervals were computed on the ratio of the means. T_{max} (untransformed) was compared between treatments using the Kruskal-Wallis test.

Results: The pharmacokinetics were linear over the 0.4 mg to 0.8 mg q.d. dose range under fed conditions. Dose proportionality was observed in both C_{max} and $AUC_{(0-12)}$ following a doubling in dose from 0.4 mg to 0.8 mg. No significant changes were observed in T_{max} following this increase in dose.
A comparison of the 0.8 mg q.d. regimen under 'delayed meal' versus fed conditions showed a significant increase in C_{max} (23%) and $AUC_{(0-12)}$ (18%) with a delayed meal (Table 45). A delay in meals also resulted in a significant decrease in T_{max}, with median T_{max} occurring at two hours, as opposed to six hours under fed conditions.
In general, tamsulosin was well tolerated in this study, both at initiation of therapy with 0.4 mg q.d. and when the

dose level was increased to 0.8 mg q.d. Two serious adverse events were reported in tamsulosin subjects, resulting in subject discontinuations from the study; a trial fibrillation in one subject (judged by the investigator to be remotely related to study drug) and an increase in ALT to more than three times the upper limit of the reference range in one subject (judged by the investigator to be possibly related to study drug).

Table 45. Mean (Standard Deviation) Steady-State Pharmacokinetic Parameters for Tamsulosin Following Administration of 0.4 mg q.d. in the Fed State and 0.8 mg q.d. in the Fed State and Under Conditions of Delayed Meals[1] (Extracted from Appendices 6.1.2.0 and 6.1.4.1; Study US92-01A)

	0.4 mg Fed (A)	0.8 mg Fed (B)	0.8 mg Delayed Meal (C)	Ratio (90% CI)[2] B/A[5]	Ratio (90% CI)[2] C/B
$AUC_{(0-12)}$ (ng·h/mL)	96 (34)	105 (38)[3]	124 (48)[3]	111 (101,122)	118 (107,130)
C_{max} (ng/mL)	10.8 (3.7)	11.6 (4.2)[3]	14.1 (4.8)[3]	107 (93,122)	123 (107,141)
T_{max} (h)	6.0 (4.0,12.0)[4]	6.0 (2.0,10.0)[4]	2.0 (2.0,6.0)[4]	-	-

[1] Subjects were dosed ½ hour before (delayed meal) or ½ hour after (fed) breakfast.
[2] 90% confidence interval on geometric least squares mean ratio (%).
[3] Normalized to a 0.4 mg dose.
[4] Median (range).
[5] Based on dose-normalized values; supplementary analyses done during preparation of the NDA.
CI = Confidence Interval
Note: A-Day 6 (fifth day of 0.4 mg q.d. dosing); B-Day 14 (eighth day of 0.8 mg q.d. dosing); C-Day 20 (fourteenth day of 0.8 mg q.d. dosing).

Sponsor's Conclusion: The pharmacokinetics of tamsulosin were linear over the 0.4 mg to 0.8 mg q.d. dose range under fed conditions. No significant changes were observed in T_{max} following an increase in dose under fed conditions. Comparison of the 0.8 mg q.d. regimen under 'delayed meal' versus fed conditions showed a significant increase in C_{max} and $AUC_{(0-12)}$ and decrease in T_{max} with a delay in meals. The two dose levels of tamsulosin (0.4 mg q.d. and 0.8 mg q.d.) were well tolerated throughout the study, both at initiation of therapy with 0.4 mg q.d. and when the dose level was increased to 0.8 mg q.d.

Reviewer's Comment: "Delayed meal" caused a significant increase in C_{max} (23%) and $AUC_{(0-12)}$ (18%) when compared to fed conditions. The pharmacokinetics of tamsulosin were linear over the 0.4 mg to 0.8 mg q.d. dose range under fed conditions.

Study Number: US93-05

Study Title: A Placebo-Controlled Double-Blind Evaluation of the Concomitant Administration of Two Dose Levels of Tamsulosin (YM617) on the Pharmacodynamic Profile of Enalapril (Vasotec®) in Subjects with Essential Hypertension

Investigator:

Objectives: The objective of this study was to determine the effects of concomitant administration of tamsulosin (at a dose of 0.4 mg and 0.8 mg) and enalapril on the pharmacodynamic profile of enalapril in subjects with essential hypertension who were on a stable maintenance doses of enalapril for at least three months.

Study Design: The trial was designed as a randomized, parallel design, double-blind, placebo-controlled study. Eight subjects were randomly assigned to the tamsulosin treatment and 4 subjects were randomly assigned to the placebo treatment.

Subjects: Twelve subjects with essential hypertension who were on stable maintenance doses of enalapril for at least three months were assigned a study number and enrolled into the study. Of the 12 subjects, 8 were randomly assigned to tamsulosin and 4 to placebo. Ten subjects completed the study, two subjects who were randomized to tamsulosin were discontinued from the study. The first subject had abnormalities in his electrocardiogram (sinus bradycardia, inferiolateral ST abnormalities, possible ischemia) at screening which increased while still in the placebo evaluation period, he was then discontinued prior to the start of tamsulosin dosing. The second subject developed hematuria of moderate severity and was discontinued from the study after receiving tamsulosin 0.4 mg q.d. for 4 days.

Formulation: Study medications were capsules filled with modified release granules of tamsulosin or placebo granules. The 0.4 mg capsules of tamsulosin were from a clinically tested batch (Lot. No. SC6174C); the 0.2 mg capsules were made of a 1:1 mixture of tamsulosin modified release granules and placebo granules (Lot. No. SC6176C). Placebo capsules, 0.2 mg and 0.4 mg tamsulosin capsules were identical in appearance and supplied in identical packaging in blister cards.

Dosage and administration: All subjects received placebo (two capsules) for the first five days of the study. On Study Day 6, the subjects randomized to tamsulosin began dosing with tamsulosin 0.4 mg (two capsules of tamsulosin 0.2 mg) for seven days. In these subjects, on Study Day 13, the dose of tamsulosin was increased to 0.8 mg (two capsules of tamsulosin 0.4 mg) for seven days. The subjects in the placebo group continued to be treated with placebo throughout the entire study period. All these dose regimens were administered concomitantly with the subject's usual daily dose of enalapril.

Blood Sampling: Blood samples were obtained for the determination of the trough plasma concentration of tamsulosin and/or enalaprilat before dosing on the following days: Study Day 6:10 ml for enalaprilat, Study Day 12: 10 ml for tamsulosin, Study Day 13: 20 ml for tamsulosin and enalaprilat, Study Day 19: 10 ml for tamsulosin, Study Day 20: 20 ml for tamsulosin and enalaprilat.

Pharmacodynamic Parameters: Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) were measured over a 24-hour period on Study Days 4, 11, and 19. Sitting vital signs were measured after the subjects were sitting for 5 or more minutes at pre-dose, 10 a.m., 12 noon, 2 p.m., 4 p.m., 6 p.m., 8 p.m. and pre-dose the following day. Supine vital signs were measured at 10 p.m., 12 midnight, 3 a.m. and 6 a.m.

Analysis:A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL,

respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 8.6%, 3.7%, and 4.8%, and accuracy of 94%, 97%, and 101% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively). A validated radioimmunoassay with a ^{125}I-enalaprilat tracer was used for enalaprilat (plasma samples); Standard curve (8 -200 µg/mL); sensitivity (LOQ) of 8 µg/mL; specificity (no significant cross-reactivity with enalapril: <0.6%); in-process quality control samples (CV% of 25.2%, 19.2%, and 6.6%, and accuracy of 119.7%, 111.4%, and 110.6% at concentrations of 8, 25, and 100 µg/mL, respectively).

Results: In the subjects randomized to tamsulosin, the mean trough plasma concentration of enalaprilat in the tamsulosin group was 9.1, 9.3 and 8.2 ng/ml at the end of placebo-evaluation phase (before administration of the dose on Study Day 6), at the end of 0.4 mg q.d. tamsulosin-treatment period (before administration of the dose on Study Day 13) and 0.8 mg q.d. tamsulosin-treatment period (before administration of the dose on Study Day 20), respectively. At the same time points, the mean trough plasma concentration of enalaprilat in the placebo group was 7.7, 5.9 and [illegible] ml, respectively. The mean trough plasma concentration of tamsulosin was, reflecting its dose proportionality, 7.6 ng/ml and 9.9 ng/ml at the end of 0.4 mg q.d. treatment period and at the end of 0.8 mg q.d. treatment period, respectively.

The following Table 46, gives the results of vital sign measurements over 24 hours on selected study days, the ranges of mean observed values on the baseline day, and the ranges of mean changes from baseline day to tamsulosin treatment days are presented. None of the changes suggests a clinically important difference between the tamsulosin group and the placebo group. Range of the mean changes in vital signs (none were significant) at each time point over 24-hours from baseline day to tamsulosin treatment days are summarized in the following table:

Table 46.

		Mean Actual Value on Baseline Day	Mean Change from Baseline Day	
		Study Day 4 (Placebo)	Study Day 11 (0.4 mg q.d.)	Study Day 19 (0.8 mg q.d.)
Systolic Blood Pressure (mmHg)	Tamsulosin	124.8 - 138.0	-6.7 - +9.0	-8.3 - +14.0
	Placebo	123.5 - 128.5	-5.0 - +10.0	-8.5 - +5.5
Diastolic Blood Pressure (mmHg)	Tamsulosin	76.8 - 94.3	-7.0 - +10.7	-8.0 - +14.3
	Placebo	76.0 - 90.5	-8.0 - +3.5	-7.0 - +3.5
Pulse Rate (bpm)	Tamsulosin	63.5 - 73.9	-5.2 - +6.8	-2.0 - +4.7
	Placebo	62.0 - 74.5	-7.0 - +6.0	-4.0 - +9.0

Sponsor's Conclusions: In a select population of subjects with essential hypertension, the administration of tamsulosin with enalapril did not significantly alter the pharmacodynamic effects of enalapril. The concomitant administration of tamsulosin and enalapril did not produce a clinically significant lowering of blood pressure and resulted in an acceptable adverse event profile. The results of this study indicate that a dose adjustment would not be necessary in the target population when the two agents are administered concomitantly.

Reviewer Comments: The plasma levels indicate that there is no pharmacokinetic interaction in either direction.

Study Number: US93-06

Study Title: A Placebo-Controlled Double-Blind Evaluation of the Effects of the Concomitant Administration of Two Dose Levels of Tamsulosin (YM617) (0.4 mg q.d. and 0.8 mg q.d.) on the Pharmacodynamic Profile of Warfarin Sodium (Coumadin®)

Investigator:

Objectives: The objective of this study was to determine the influence of co-administration of tamsulosin (at doses of 0.4 mg q.d. and 0.8 mg q.d.) on the pharmacodynamic activity (prolongation of coagulation time) of warfarin.

Study Design: The study was divided into two phases. The first phase was used to establish a dose of warfarin that would cause anticoagulation and a stable prolonged PT. The subjects that achieved a stable prolonged PT were entered into the double-blind portion of the study. Following stabilization of PT to >30% of baseline a stable PT was defined as one with not more than a 2-second variation on two separate days. During the second phase of this study, double-blind medication was administered. The twelve eligible subjects were randomly assigned to either tamsulosin or placebo treatment plus their established daily warfarin dose. The eight subjects that were randomized to tamsulosin were dosed with tamsulosin at 0.4 mg q.d. for 5 days followed by 0.8 mg q.d. for 5 days.

Subjects: Six subjects completed the study: three subjects who were randomized to tamsulosin and three to placebo. Six subjects were discontinued from the study after the start of the double-blind therapy, 5 on tamsulosin and one on placebo. Of the five subjects on tamsulosin, 3 were discontinued because of laboratory results from samples obtained prior to the first dose of tamsulosin; two of the three for increases in PT over the narrow range defined in the protocol and one due to the development of an infection.

Formulation: Test materials were capsules that contained tamsulosin hydrochloride (YM617) 0.2 mg and 0.4 mg in a modified release formulation and identical placebo capsules. All capsules (placebo and tamsulosin 0.2 mg and 0.4 mg capsules) were identical in appearance and supplied in identical packaging. The warfarin used in this study was the Coumadin® brand manufactured by Dupont Pharmaceuticals in 1 mg, 2 mg, and 5 mg tablets. The dosing of warfarin was open and not blinded.

Dosage and administration: Starting on Study Day 0, 18 subjects were dosed with warfarin until their PT was >30% over their Study Day 0 PT, but less than 20 seconds. The starting dose of warfarin was 3.0 mg. Dose adjustment of 1 or 2 mg of warfarin was based on the results of PT, judgment of the investigator, and the agreement of the investigator and sponsor. The first 12 subjects who had a stable prolonged PT (no more than a 2-second variation of their PT on two separate days) were enrolled into the double-blind portion of the study. After a stable prolonged PT had been established, the dose of warfarin was maintained for the remainder of the study until Study Day DB11. Twelve subjects were randomly assigned to either tamsulosin treatment or placebo treatment. Eight (8) subjects were dosed with tamsulosin at 0.4 mg q.d. for 5 days followed by 0.8 mg q.d. for 5 days. Four control subjects were dosed with placebo capsules for the duration of the study.

Blood Sampling: Blood samples for the determination of the plasma concentration of tamsulosin and warfarin were obtained prior to the morning dose of double-blind medication on Study Days DB1, DB6, and DB11. Additional blood samples were drawn before subjects were discontinued from the study. Blood samples for the determination of PT/PTT were drawn every morning of each Study Day around 7:00 am, before the morning dose of placebo.

Analytical Procedures: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 5.8%, 1.0%, and

9.8%, and accuracy of 88%, 94%, and 106% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively).

A validated HPLC assay with ultraviolet detection was used for warfarin (plasma samples); Standard curve (10 - 2000 ng/mL); mean recovery (88.4%, 91.6%, and 91.2% at concentrations of 1500, 150, and 20 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 10 ng/mL; specificity (no interfering peaks for warfarin or internal standard); in-process quality control samples (CV% of 3.7%, 1.4%, and 1.3%, and accuracy of 109%, 101%, and 105% at concentrations of 1500, 150, and 20 ng/mL, respectively).

Results: Warfarin dose and prothrombin times are presented in Table 47.

TABLE 47: WARFARIN DOSE AND PROTHROMBIN TIMES

	TAMSULOSIN-TREATED SUBJECTS								PLACEBO-TREATED SUBJECTS			
Study Day	01	03	04	06	07	09	10	11	02	05	08	12
0	3mg 11.9sec	3mg 11.8sec	3mg 11.3sec	3mg 11.3sec	3mg 11.5sec	3mg 12.0sec	3mg 11.8sec	3mg 12.4sec	3mg 12.0sec	3mg 11.8sec	3mg 11.9sec	3mg 12.0sec
PLACEBO EVALUATION DAYS												
WE8 0 mg	4 mg 17.4sec	5 mg 16.4sec	5 mg 15.5sec	6 mg 15.0sec	7 mg 13.7sec	7 mg 16.8sec	5 mg 18.1sec	6 mg 14.4sec	4 mg 17.4sec	6 mg 15.7sec	7 mg 14.1sec	7 mg 15.1sec
WE9 0 mg	4 mg 19.4sec	5 mg 19.6sec	5 mg 16.7sec	6 mg 16.7sec	7 mg 15.8sec	7 mg 19.9sec	5 mg 19.5sec	6 mg 17.4sec	4 mg 18.0sec	6 mg 17.7sec	7 mg 15.9sec	7 mg 18.2sec
WE10 0 mg	4 mg 19.0sec	5 mg 19.0sec	5 mg 16.6sec	6 mg 17.0sec	7 mg 15.9sec	7 mg 19.8sec	5 mg 18.6sec	6 mg 18.2sec	4 mg 17.0sec	6 mg 18.6sec	7 mg 16.3sec	7 mg 17.7sec
DOUBLE-BLIND DOSING DAYS												
DB1 0.4 mg	3mg 20.3sec	– 21.5sec	5mg 17.7sec	6mg 18.1sec	– 16.5sec	– 21.3sec	4mg 19.7sec	6mg 18.1sec	4mg 17.0sec	4mg 20.6sec	7mg 16.9sec	6mg 19.6sec
DB2 0.4 mg	3mg 21.0sec	# 19.5sec	5mg 18.2sec	6mg 19.2sec	# 16.5sec	# 20.0sec	4mg 20.1sec	6mg 17.2mg	4mg 16.5sec	4mg 19.9sec	7mg 17.6sec	6mg 18.8sec
DB3 0.4 mg	– 21.3sec	# 16.8sec	5mg 19.4sec	6mg 20.3sec	# 15.6sec	# 18.0sec	4mg 20.2sec	6mg 16.8sec	4mg 17.3sec	4mg 20.6sec	7mg 18.1sec	6mg 17.7sec
DB4 0.4 mg	# 20.3sec	# 14.1sec	5mg 20.0sec	– 21.9sec	# 14.1sec	# 14.8sec	4mg 20.8sec	6mg 17.9sec	4mg 18.0sec	– 21.5sec	7mg 19.5sec	6mg 17.7sec
DB5 0.4 mg	# 16.7sec	–	5mg 19.7sec	# 20.7sec	–	–	4mg 20.3sec	6mg 18.0sec	4mg 19.3sec	# 20.3sec	7mg 19.8sec	6mg 17.7sec
DB6 0.8 mg	# 13.6sec	–	5mg 19.7sec	# 18.0sec	–	–	4mg 18.6sec	6mg 18.2sec	4mg 18.3sec	# 16.3sec	7mg 20.8sec	6mg 17.8sec
DB7 0.8 mg	–	–	5mg 19.4sec	# 14.4sec	–	–	4mg 17.5sec	6mg 19.2sec	4mg 18.6sec	# 14.0sec	7mg 20.4sec	6mg 17.8sec
DB8 0.8 mg	–	–	5mg 18.6sec	–	–	–	4mg 16.3sec	6mg 18.7sec	4mg 18.7sec	–	7mg 19.5sec	6mg 16.9sec
DB9 0.8 mg	–	–	5mg 18.3sec	–	–	–	4mg 16.1sec	6mg 17.7sec	4mg 16.9sec	–	7mg 20.7sec	6mg 17.5sec
DB10 0.8 mg	–	–	5mg 19.0sec	–	–	–	4mg 16.3sec	6mg 14.3sec	4mg 16.9sec	–	7mg 20.4sec	6mg 15.7sec
DB11 Placebo	–	–	– 18.6sec	–	–	–	– 16.4sec	– 13.6sec	– 16.5sec	–	– 20.7sec	– 13.6sec
DB12 None	–	–	– 16.3sec	–	–	–	– 14.9sec	– 13.5sec	– 15.5sec	–	– 19.2sec	– 12.5sec
DB19 None	–	–	– 11.8sec	–	–	–	– 11.5sec	– 12.5sec	– 12.1sec	–	– 12.1sec	– 11.8sec

The PT increased with warfarin dosing, but the mean PT was similar in the 3 tamsulosin-treated subjects (18.83 seconds) and in the 3 placebo-treated subjects (18.97 seconds) at the end of the 0.4 mg dosing period (Study Day DB6). At the end of the 0.8 mg dosing period (DB11), the mean PT was 16.2 seconds in the tamsulosin-treated subjects and 16.93 seconds in the placebo-treated subjects.

The results of the determination of the plasma concentration of warfarin and tamsulosin in the subjects who completed the study are shown in Table 48. The dose of warfarin varied among the subjects as it was related to

their PT, but the dose of warfarin was constant during the double-blind dosing period for the individual subjects. None of the subjects in the tamsulosin treatment group had an increase in plasma warfarin concentrations during the DB treatment days and in fact the concentrations decreased. One subject (Subject in the placebo dosing group had an increase in his warfarin plasma concentration; the other two subjects had a decrease.

TABLE 48: PLASMA WARFARIN AND TAMSULOSIN CONCENTRATIONS

		DB Day 1[b]	DB Day 6		DB Day 11	
Subject Number	Warfarin Dose[a] (mg)	Warfarin Plasma Conc. (ng/ml)	Warfarin Plasma Conc. (ng/ml)	Tamsulosin Plasma Conc.[c] (ng/ml)	Warfarin Plasma Conc. (ng/ml)	Tamsulosin Plasma Conc.[d] (ng/ml)
TAMSULOSIN TREATMENT GROUP						
	5.0					
	4.0					
	6.0					
PLACEBO TREATMENT GROUP						
	4.0					
	7.0					
	6.0					

Sponsor's Conclusions: In a limited number of subjects, the results do not indicate that a dose adjustment of either warfarin or tamsulosin would be necessary when tamsulosin and warfarin are administered concomitantly.

Reviewer's Comments: It is difficult to draw definitive conclusions from the study as only half of the subjects completed it. The results are consistent with a low extraction ratio drug that is highly bound to serum proteins. If tamsulosin displaces warfarin from binding sites the total warfarin levels would decline, which appears to be the case, and the unbound concentration would remain the same, which appears to be reflected in the unchanged prothrombin time. However, the results are inconclusive and no inference can be made.

Study Number: US93-07

Study Title: A Placebo-Controlled Evaluation of the Effects of the Concomitant Administration of Tamsulosin (0.8 mg) on the Pharmacokinetic Profile of Intravenous Digoxin (Lanoxin®) in Normal Healthy Subjects.

Investigator:

Objectives: The objective of this study is to determine whether the concomitant administration of tamsulosin at a dose of 0.8 mg q.d. with digoxin will affect the pharmacokinetics of digoxin.

Study Design: This trial was an open label, sequential design, placebo-controlled study consisting of two periods. Each subject received placebo during Period 1 and tamsulosin during Period 2; thus, each subject served as his own control. On the second day of placebo dosing (Period 1), all subjects received a single intravenous 0.5 mg dose of digoxin. Blood was drawn and urine was collected over 96 hour period for digoxin pharmacokinetic determinations. This was repeated when all of the subjects were being dosed with 0.8 mg tamsulosin after they had reached a steady state. Tamsulosin blood concentrations were measured on the day of concomitant dosing with digoxin.

Subjects: Ten healthy male subjects with a mean age of 31.9 years were enrolled into the study. One subject was

discontinued on Study Day 11 due to an elevated SGOT and SGPT. The elevation of serum enzymes began while the subject was being treated with placebo and after a single intravenous dose of digoxin.

Formulation: Tamsulosin used in this study was a modified release formulation manufactured by Yamanouchi Pharmaceutical Company, Ltd. It was supplied in capsules containing 0.2 mg or 0.4 mg of tamsulosin hydrochloride, and matching placebo capsules, which were identical in appearance. Their lot numbers were 92-A22CC (0.2 mg tamsulosin capsules), 92-A44AA (0.4 mg tamsulosin capsules) (to be marketed formulations) and 92-A00BB (placebo capsules). Intravenous digoxin (Lanoxin®) was obtained from a licensed pharmacy.

Dosage and administration: Two placebo capsules were administered to all subjects on Study Days 1-8. Two capsules of 0.2 mg tamsulosin were administered on Study Days 9 and 10. Two capsules of 0.4 mg tamsulosin were administered on Study Days 11-18. All oral medications were taken approximately thirty minutes after breakfast. All subjects r[illegible] intravenous dose of 0.5 mg of digoxin over five minutes on Study Days 2 and 15 approxim[illegible] breakfast using a syringe infusion pump (Medifusion Inc, model 2001) and an indwelli[illegible]

Blood Sampling: On Study Days 2 and 15 serum concentrations of digoxin were measured at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, and 12 hours after an intravenous dosing of digoxin. On Study Days 3 through 6 and 16 through 19, serum digoxin concentrations were measured once daily at 24, 48, 72 and 96 hours post-dosing. Concentrations of digoxin in the urine were measured from 12- to 24-hour urine collections on the same days as serum digoxin determinations.

Analytical Procedures: Digoxin was analysed by fluorescence polarization immunoassay. Sensitivity was 0.2 ng/ml and accuracy 99.0-108.0%. Within run precision was 5.75%, 3.15%, 1.87% at concentrations 0.75, 1.5 and 3.5 ng/ml respectively. At these concentrations, between run precision was 4.29%, 2.3% and <1.% respectively. Tamsulosin was analysed by a validated HPLC method with fluorescence detector. For quality control samples the interday precision was 9.52% or better and mean accuracy was within the range of 92.9%-104%. At the minimum quantifiable level of 0.5 ng/ml the interday precision was 8.68% and accuracy was 106%.

Results: Ten subjects completed Period 1 of the study. Nine of the ten subjects completed Period 2. Subject was discontinued from the study on Study Day 11, after receiving two doses of tamsulosin. The reason for discontinuation was elevated SGOT and SGPT, which first occurred on Study Day 8, during the placebo treatment period. Digoxin serum and urine data were best fit by a linear, open, four compartment structural model. The parameter estimates agreed well with previously reported data in normal volunteers. Results of the two 1-sided hypothesis tests, on fitted parameters for digoxin, are shown in Table 49. The mean ratio, $\bar{x}_R$, contrasted the parameter values from Period 2 to those from Period 1. The mean of the Ln(ratio), $\bar{x}_{Ln(R)}$, was the statistic for which hypothesis testing was performed. All of the null hypotheses were rejected, the two study periods were equivalent in all of these parameters. The probability, that the true $\mu_{Ln(R)}$ for each parameter was within FDA guidelines, was greater than 0.998, for all values.

Table 49: **Equivalence of Fitted Digoxin Parameter Values Between Periods**

	Vss	CLt	CLr	AUC_{0-96}	$T½\lambda_z$
Mean Ratio, $\bar{X}_R$	1.05	0.966	1.02	1.01	1.08
SE of the $\bar{X}_R$	0.044	0.0092	0.024	0.007	0.045
Mean Ln(Ratio), $\bar{X}_{Ln(R)}$	0.0384	-0.0353	0.0215	0.00923	0.0687
SE of the $\bar{X}_{Ln(R)}$	0.0398	0.00939	0.0224	0.00681	0.0399
Probability*	> 0.999	> 0.999	> 0.999	> 0.999	0.998

* The *a posteriori* probability that the true μLn(R) is between Ln(0.8) and Ln(1.25).

The tamsulosin plasma concentration data were fit by a linear, open, three compartment structural model, with the oral input described by a first order process (ka) with a lag time (TLag) between administration of the study dose and the onset of systemic absorption. Parameter estimates agreed well with previously analyzed data obtained from young, normal volunteers. One patient was an outlier which was ascribed to initial poor absorption resulting from gastrointestinal problems.

Three subjects complained of being dizzy, lightheaded or having a flush upon standing during the orthostatic testing 6 hours after an intravenous digoxin administration with concomitant oral dose of tamsulosin 0.8 mg.

Sponsor's Conclusions: There is no evidence that oral tamsulosin causes any change in the single-dose pharmacokinetics of intravenous digoxin in normal volunteers.

Reviewer's Comments: The absence of a tamsulosin-digoxin interaction is limited to a single dose of digoxin administered intravenously. It is unclear if longterm treatment of the two drugs concomitantly might produce different results or if a pharmacodynamic interaction is feasible.

Study Number: US93-08

Study Title: A Double-blind, Placebo-controlled, Cross-over Study to Determine Interactions between Intravenous Furosemide (Lasix®) and Oral YM617 (0.8 mg) in Normal Healthy Subjects.

Investigator:

Objectives: The objectives of this study were, to determine whether there is an effect of tamsulosin (at a dose of 0.8 mg) on the pharmacodynamic activity of furosemide in healthy male subjects, and to determine whether there is an effect of furosemide on the steady-state pharmacokinetics of tamsulosin (0.8 mg).

Study Design: This study was a double-blind, placebo-controlled, two-way cross-over study conducted in ten (10) healthy male subjects. Subjects were randomly assigned to either tamsulosin or placebo for eight days when a 20

mg dose of intravenous furosemide was administered to all subjects. After 5 days washout the tamsulosin and placebo where crossed over and the procedure repeated.

Subjects: Out of ten subjects enrolled to the study, nine subjects completed both Study Periods. One subject (Subject was discontinued on Day A9 after the completion of Period 1 due to elevated serum enzymes, which occurred on Study Day A7. This subject received placebo treatment during Period 1 and was dosed with intravenous furosemide on Day A8.

Formulation: Study medications were capsules filled with either modified release granules of tamsulosin (to be marketed product) or placebo granules. The lot numbers were 92-A00BB (placebo capsules), 92-A22CC (0.2 mg tamsulosin capsules) and 92-A44AA (0.4 mg tamsulosin capsules). The intravenous form of furosemide (Lasix®) was obtained in sealed bottles from a licensed pharmacy and administered by the study personnel.

Dosage and a... ...ed two placebo capsules on the first day (Day 1) in each Study Period. On Study ... ...study eriod, the subjects randomized to tamsulosin in each Period (Group I in Period 1 and Group II in Period 2) were administered tamsulosin 0.4 mg (two tamsulosin 0.2 mg capsules) q.d. on Study Days 2 and 3, followed by 0.8 mg (two tamsulosin 0.4 mg capsules) q.d. on Study Days 4 through 8. The other subjects who were randomized to placebo were treated with placebo from Day 1 through Day 8 in that Study Period (either Period 1 or 2). There was a 5 day interval between Study Periods. All subjects received a single intravenous dose of 20 mg of furosemide over 2 minutes on Study Day 8 of each Study Period approximately one-half hour after breakfast.

Blood Sampling: Plasma concentrations of tamsulosin were determined on Study Days 7 and 8 of Periods 1 and 2, at pre-dose, 2, 4, 6, 8, 12 and 24 hours after dosing.

Furosemide Pharmacodynamics: The concentration of electrolytes in the urine were determined for 24 hours before (Study Days 7 of Periods 1 and 2) and after (Study Days 8 of Periods 1 and 2) the intravenous administration of a dose of furosemide. Urine was collected at hourly intervals for the first twelve hours and at four hour intervals for the next twelve hours.

Analytical Procedures: Tamsulosin was analysed by a validated HPLC method with fluorescence detector. For quality control samples the interday precision was % or better and mean accuracy was within the range of 92.9%-104%. At the minimum quantifiable level of 0.5 ng/ml the interday precision was % and accuracy was %.

Results:

Table 50 is a summary of the mean amounts of the four electrolytes, excreted over the merged collection intervals (0 to 6, 6 to 12, 12 to 18 hours), on each of the four days that urine was studied (Days 7 and 8 during placebo and during YM617). These data were analyzed by repeated measures ANOVA; each electrolyte was considered separately. In none of the preliminary analyses, was 'period' significant ($p > 0.05$).

The YM617 plasma concentrations, from Study Days 7 and 8, respectively, were best fit by a linear, open, three compartment model, with the oral input described by a first order process (ka) with a lag time (TLag) between administration of the study dose and the onset of systemic absorption. The tamsulosin plasma concentrations and fitted pharmacokinetic parameter values from Day 7, agreed well with earlier studies of tamsulosin in normal subjects. However, parameter values derived during concomitant furosemide administration (day 8), were significantly different. The mean (and SE), of the ratio of tamsulosin parameter values (Table 51), determined from Day 8 data divided by values from Day 7, were: Vss/F (total apparent steady-state volume), 1.1 (0.13); CLt/F (total apparent plasma clearance), 1.45 (0.084); $T\frac{1}{2}\lambda_z$ (terminal half-life), 0.82 (0.075); Tmax (time to maximal observed concentration), 1.2 (0.24); and Cmax (maximum observed concentration), 0.89 (0.08). Specifically, in these normal,

male volunteers, CLt/F was increased by ,% and T½λ_z was decreased by %, by a single IV dose of furosemide, 20 mg. The inequivalence and significant differences were probably due to a furosemide-associated increase in total oral clearance of tamsulosin.

Table 50: Amounts of Electrolytes Excreted

	0-6 hours (mEq)	6-12 hours (mEq)	12-18 hours (mEq)
Na^+ Excretion Patterns			
Placebo, alone	80.0	71.5	57.7
[illegible] alone	78.8	54.3	55.5
Placebo + Furosemide	143	37.3	40.6
YM617 + Furosemide	140	50.1	38.4
Cl^- Excretion Patterns			
Placebo, alone	81.1	65.3	54.6
YM617, alone	78	51.1	51.1
Placebo + Furosemide	176	30.6	28.2
YM617 + Furosemide	172	38.3	24.6
K^+ Excretion Patterns			
Placebo, alone	40.7	30.5	20.6
YM617, alone	41.7	24.3	19.8
Placebo + Furosemide	49.3	20.4	13.2
YM617 + Furosemide	43.7	22.0	9.38
Mg^{+2} Excretion Patterns			
Placebo, alone	3.96	3.90	4.36
YM617, alone	3.56	3.07	3.57
Placebo + Furosemide	4.42	2.52	3.02
YM617 + Furosemide	3.98	2.51	2.96

Table 51: Equivalence, Between Periods, of Fitted YM617 Parameter Values

	Vss/F	CLt/F	T½λ_z
Mean Ratio, $\overline{X}_R$	1.08	1.45	0.824
SE of the $\overline{X}_R$	0.13	0.084	0.075
Minimum	0.739	1.09	0.446
Median	0.872	1.47	0.892
Maximum	1.84	1.79	1.14
Mean Ln(Ratio), $\overline{X}_{Ln(R)}$	0.0239	0.360	-0.233
SE of the $\overline{X}_{Ln(R)}$	[illegible]	0.0596	0.103
Probability[a]	0.911	0.0256	0.463
p[b]	ND[c]	< 0.001	0.0552

[a] The *a posteriori* probability that the true $\mu_{Ln(R)}$ is between Ln(0.8) and Ln(1.25)
[b] The *a posteriori* probability that the true $\mu_{Ln(R)}$ is equal to zero
[c] Not done

Sponsor's Conclusions: There was no effect of tamsulosin (at a dose of 0.8 mg q.d.) on the pharmacodynamic activity of furosemide (excretion of electrolytes). Co-administration of a single IV dose of furosemide (20 mg) significantly increased CLt/F (by 45%) and decreased the terminal half-lives (by 18%) of tamsulosin. The concomitant administration of tamsulosin and intravenous furosemide did not cause any clinically detectable hypotension. Concurrent administration of tamsulosin and furosemide was well tolerated. The results of this study indicate that concomitant administration of tamsulosin and furosemide would not cause safety issues of clinical concern.

Reviewer's Comments: One patient showed signs of postural hypotension 6 hours after furosemide administration and may indicate that some pharmacodynamic interaction is possible. Safety is probably not an issue since the response to tamsulosin will be reduced.

Study Number: US93-09

Study Title: A Study on the Effect of the Concomitant Administration of Cimetidine Hydrochloride (Tagamet®) on the Pharmacokinetic Profile of a 0.4 mg Dose of Tamsulosin (YM617).

Investigator:

Objectives: The objective of this study was to determine if the concomitant administration of cimetidine will effect the pharmacokinetics of tamsulosin at a dose of 0.4 mg.

Study Design: This trial was a non-randomized, sequential design study.

Subjects: Ten subjects, with a mean age of 30.6 years, completed the study.

Formulation: Study medications were capsules filled with either modified release granules of tamsulosin (to be marketed product) or placebo granules. The lot numbers were 92-A00BB (placebo capsules) and 92-A44AA (0.4

mg tamsulosin capsules). Cimetidine Hydrochloride (Tagamet®) lot numbers 7763T26 and 7703T26 was used..

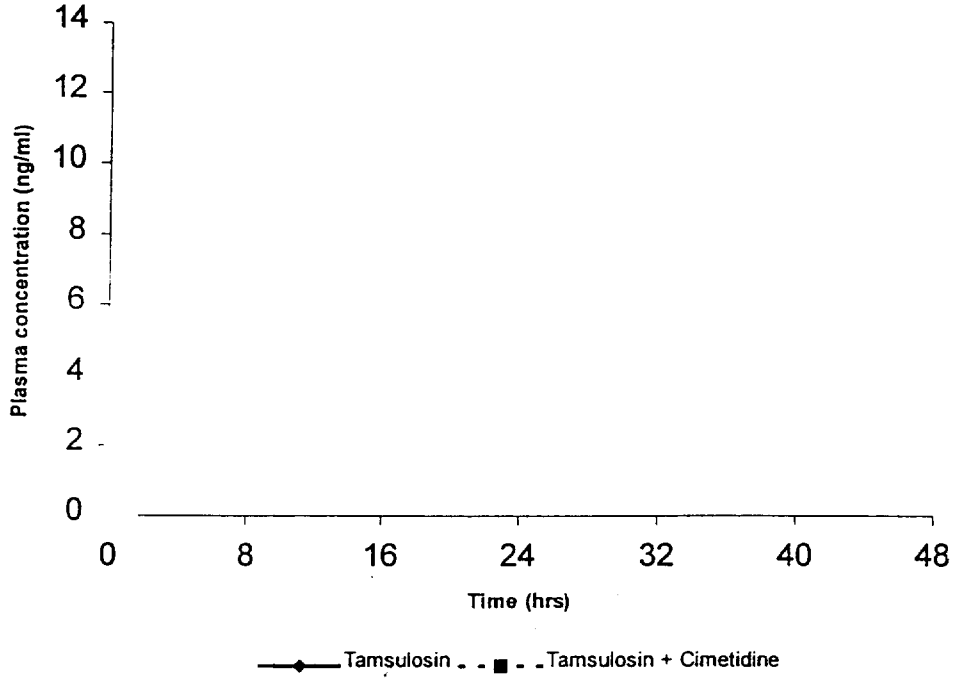
Dosage and administration: All 10 subjects were administered a 400 mg q6h dose of cimetidine on Study Days 5-10. Starting on Study Day 1, all subjects were dosed with a single daily dose of tamsulosin matching placebo except for Study Days 2 and 8, when tamsulosin 0.4 mg was administered. All subjects received a single oral 0.4 mg dose of tamsulosin, without concomitant administration of cimetidine on Study Day 2, and with concomitant administration of cimetidine on Study Day 8.

Blood Sampling: Plasma levels of tamsulosin were measured at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after tamsulosin dosing on Study Days 2 (without cimetidine) and 8 (with cimetidine).

Analytical Procedures: Tamsulosin was analysed by a validated HPLC method with fluorescence detector. For quality control samples the interday precision was % or better and mean accuracy was within the range of 92.9%-101% At the minimum quantifiable level of 0.5 ng/ml the interday precision was % and accuracy was %.

Results: The tamsulosin plasma concentrations were best fit by a linear, open, three compartment structural model, with the oral input function described by a first order process (ka) with a lag time (TLag) between administration of the study dose and the onset of systemic absorption. Figure 21, depicts the average plasma concentration profiles (and sd), in both study periods.

Figure 21. Average Tamsulosin plasma concentrations



Co-administration of cimetidine and tamsulosin was associated with a statistically significant decrease in the tamsulosin oral clearance (CLt/F) and steady-state distribution volume (Vss/F). The change in clearance, probably caused by inhibition of tamsulosin metabolism by cimetidine, was not accompanied by a significant increase in

terminal half-life. This was because the changes in CLt/F and Vss/F had off-setting effects on half-life. Because absolute bioavailability of tamsulosin is almost %, the increase in tamsulosin plasma concentrations and decrease in CLt/F and oral distribution volumes during co-administration of cimetidine, were unlikely to be related to an increase in oral availability. It could be speculated, that the mechanism of the cimetidine-associated decrease in volumes, may be decreased tissue uptake. The observed decrease in CLt/F would be predicted to provide a median (range), increase in average steady-state concentrations, of %. No significant or unexpected changes in vital signs, 12-lead EKGs, physical exams or clinical laboratories results were observed during post-dose testing.

Sponsor's Conclusions: It can be concluded that tamsulosin can be administered concomitantly with cimetidine without dose adjustment.

Reviewer's Comments: The sponsors conclusion that an increase of % in average steady-state tamsulosin concentrations would not be clinically important in most patients is based on the usual dose of 0.4 mg and the fact that a dose of 0.8 mg is still a low dose. No decision is made in the label for increasing the dose to 0.8 mg in which case a % increase in tamsulosin blood levels may be clinically important. A warning should be included in the label.

Study Number: US93-10

Study Title: A study to determine if the concomitant administration of tamsulosin (0.8 mg q.d.) affects the pharmacokinetic profile of theophylline (5 mg/kg).

Investigator: [redacted]

Objectives: The objective of this study was to determine if the concomitant administration of a 0.8 mg dose of tamsulosin at a steady state would affect the pharmacokinetics of theophylline (administered as 5 mg/kg over a minute intravenous infusion).

Study Design: This single-blind, crossover pharmacokinetic study was conducted in ten normal subjects.

Subjects: Ten healthy male subjects with a mean age of 27.3 years were enrolled into the study. One subject was discontinued on Study Day 1 due to an elevated platelet count. He was dosed with placebo capsules but did not receive tamsulosin nor theophylline.

Formulation: Study medications were capsules filled with either modified release granules of tamsulosin (to be marketed product) or placebo granules. The lot numbers were 92-A00BB (placebo capsules), 92-A22CC (0.2 mg tamsulosin capsules) and 92-A44AA (0.4 mg tamsulosin capsules). Theophylline was administered intravenously as Labophylline®

Dosage and administration: All subjects received two placebo capsules one-half hour after lunch on Study Day 0 and one-half hour after breakfast on Study Days 1, 2, and 10. Tamsulosin 0.4 mg [two (2) 0.2 mg tamsulosin capsules] was administered once daily during Study Days 3 and 4; the 0.8 mg q.d. dose [two (2) 0.4 mg tamsulosin capsules] was administered from Study Day 5 to Study Day 9. All subjects received a 5 mg/kg intravenous dose of theophylline one hour after the dose of placebo or tamsulosin by a 30 minute infusion (with an infusion pump) on Study Days 1 (placebo dosing day) and 9 (tamsulosin 0.8 mg q.d. dosing day).

Blood Sampling: On Study Days 1 and 9, plasma levels of theophylline were measured just before dosing and at 0.17 (10 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 1, 2, 4, 6, 8, 12, 16, and 24 hours after the start of the theophylline infusion. On Study Day 9, the plasma concentrations of tamsulosin were measured prior to dosing and

at 4, 6, and 8 hours after dosing.

Analytical Procedures: Plasma samples were analyzed for theophylline by validated HPLC assay. The mean accuracy was in the range of 96.5% -106%. The interday precision was % or better and the mean accuracy was in the range of 98.3%-104%. At the minimum quantifiable level of 0.2 ug/ml the mean interday precision was % and accuracy was %. Tamsulosin was analysed by a validated HPLC method with fluorescence detector. For quality control samples the interday precision was % or better and mean accuracy was within the range of 92.9%-104%. At the minimum quantifiable level of 0.5 ng/ml the interday precision was % and accuracy was %.

Results: There was no evidence that the oral dose of tamsulosin caused any change in the single-dose disposition of intravenous theophylline in normal male volunteers (See Table 52). The Day 9 mean tamsulosin Cmax and pre-dose concentrations agreed with other similar data in normal volunteers.

TABLE 52: Mean (Standard Deviation) Model-Fitted and Non-Compartmental Pharmacokinetic Parameters and Comparative Statistics for Theophylline, in the Presence and Absence of Concomitant Tamsulosin (Extracted from Study US93-10)

	Without Tamsulosin (Day 1)	With Tamsulosin (Day 9)	Mean Ratio[2,3] Day 9:Day 1
V_{ss} (L/kg)	0.493 (0.040)	0.518 (0.053)	1.05
V_β (L/kg)	0.491 (0.040)[1]	0.517 (0.068)[1]	1.05
CL (L/h/kg)	0.0629 (0.0162) 0.0626 (0.0158)[1]	0.0661 (0.0171) 0.0663 (0.0193)[1]	1.07 1.08
$t_{½}$ (h)	5.68 (1.13)	5.85 (2.08)	1.03
$AUC_{(0-24)}$ (μg•h/ml)	83.2 (19.5)[1]	75.3 (20.8)[1]	-
AUC_{∞} (μg•h/ml)	85.1 (23.1) 85.5 (23.1)[1]	83.2 (28.9) 83.2 (30.0)[1]	0.98 0.99
C_{max} (μg/ml)	9.85 (1.15)[1]	9.75 (1.71)[1]	0.99

[1] Parameters calculated using noncompartmental techniques.
[2] Mean by-subject ratio of parameters that underwent statistical testing.
[3] Differences were not statistically significant for all parameters tested (two one-sided t-tests testing for inclusion of the mean ratio within the 0.80-1.25 interval, α=0.05).
Note: Day 1 - 30 minute infusion of theophylline; Day 9 - 30 minute infusion of theophylline, fifth day of 0.8 mg q.d. dosing.

Sponsor's Conclusions: Concomitant administration of 0.8 mg of tamsulosin did not change the pharmacokinetic profile of theophylline. Concurrent administration of theophylline with tamsulosin results in an acceptable clinical laboratory and safety profile and thus no dose adjustment will be necessary for either drug.

Reviewer's Comments: The influence of theophylline administration on tamsulosin pharmacokinetics is not answered, however, the probability of a pharmacokinetic interaction is small.

TAMSULOSIN DISEASE INTERACTIONS

RENAL IMPAIRMENT
Study Number: US92-04

Study Title: A Study on the Evaluation of the Pharmacokinetic Profile of Tamsulosin in Subjects with Various Degrees of Renal Impairment.

Objectives: The objectives of this study were to determine the effect of renal impairment on the pharmacokinetics of a single oral 0.4 mg dose of tamsulosin in subjects with various degrees of renal function (creatinine clearance 10 to 70 mL/min/1.73m^2) as compared to the subjects with normal renal function (creatinine clearance over 90 mL/min/1.73m^2) and to try to establish the appropriate dose and schedule of tamsulosin for subjects with renal impairment.

Study Design: This study was designed as an open label, single-dose pharmacokinetic study of oral tamsulosin in 18 subjects with varying degrees of renal function.

Subjects: Twelve subjects with renal impairment [Group I, 6 subjects (8.4 ≤ mean CLcr ≤ 17.8 mL/min/1.73m^2); Group II, 6 subjects (35.3 ≤ mean CLcr ≤ 62.0 mL/min/1.73m^2)] and 6 subjects with normal renal function (Group III, 93.1 ≤ mean CLcr ≤ 119.4 mL/min/1.73m^2) were enrolled into the study. All subjects completed the study. Subjects with normal renal function (Group III) were matched to subjects in Group I on the basis of age (± 4 years) and smoking status.

Formulation: The drug was formulated as a modified release formulation and was supplied as tamsulosin 0.4 mg capsules (Lot. No. 92-A44AA) the to be marketed formulation.

Dosage: A single 0.4 mg oral dose (one 0.4 mg capsule) of tamsulosin was administered with 200 mL of water at approximately 8:00 a.m. on the day of dosing. The dose was administrated after an overnight fast.

Blood Sampling: Venous blood samples (10 mL) for the determination of plasma tamsulosin concentration were obtained prior to (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, and 72 hours post dosing.

Plasma Protein Binding: A venous blood sample (10 mL) for *in vitro* determination of percentage of protein bound and unbound tamsulosin was obtained prior to (0 hour) the administration of tamsulosin.

Urine Specimens: Urine samples for the determination of tamsulosin and its metabolites' concentrations in urine were collected at the following intervals: 0-12 hr, 12-24 hr, 24-48 hr, and 48-72 hr after tamsulosin administration.

Analytical Procedures: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 5.9%, 4.7%, and 9.7%, and accuracy of 100%, 97%, and 102% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively). A quantitative liquid chromatographic tandem mass spectrometric (LC-MS/MS) method was used for the measurement of tamsulosin and its metabolites, M1, M2, M3 and M4 in urine, and a semi-quantitative gas chromatographic tandem mass spectrometric (GC-MS/MS) method was used for the metabolite AM-1 in urine. For the measurement of conjugated metabolites, enzyme hydrolysis was performed prior to analysis for all analytes except AM-1. Concentrations of conjugated M1 were likely underestimated due to incomplete hydrolysis of this metabolite.

Results: Mean tamsulosin plasma-concentration time curve for all subjects in Groups I, II, and III are shown in Figure 22.

Figure 22 Mean Tamsulosin plasma concentration-time curve.

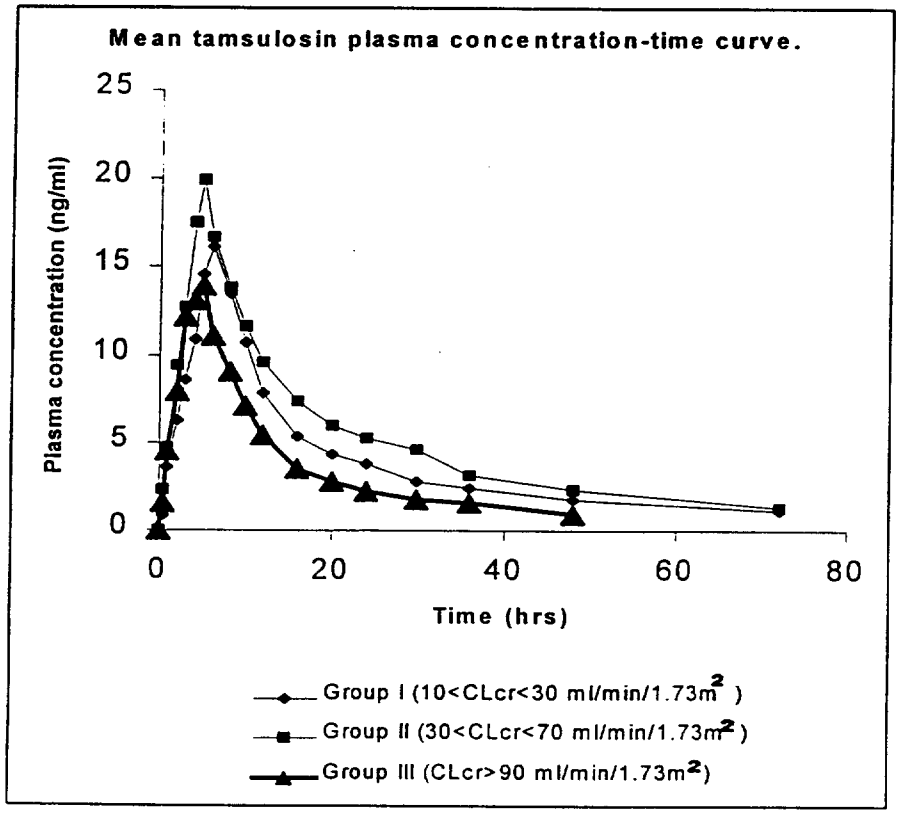


Table 53 represents the individual and mean % excretions of M-1, M-2, M-3, M-4, AM-1, and tamsulosin.

Table 53 Individual and mean % excretion of tamsulosin, M-1, M-2, M-3, M-4 and AM-1

	Tamsulosin	M-1	M-2	M-3	M-4	AM-1
Group I (10 ≤ CLcr < 30 mL/min/1.73m²)						
Mean	2.48	0.00			0.54	1.14
S.D.		0.00			0.40	0.65
%C.V.	43.6				73.98	56.71
Group II (30 ≤ CLcr < 70 mL/min/1.73m²)						
Mean	8.07	0.08	1.44	4.26	1.65	4.50
S.D.	1.96	0.20	0.90	3.26	1.01	3.57
%C.V.	24.27	244.95	62.31	76.44	61.29	79.24
Group III (CLcr > 90 mL/min/1.73m²)						
Mean	11.17	0.03	1.00	3.47	1.16	8.84
S.D.	3.28	0.03	0.21	1.96	0.42	7.08
%C.V.	29.31	112.10	21.21	56.51	36.35	80.13

There was essentially no excretion of the O-deethylation metabolite M-1 in urine in 14 out of 18 subjects. The greatest amount of M-1 excreted was less than 0.5% of the tamsulosin dose. The excretion of the para-hydroxylation metabolite M-2 accounted for 0.6%, 1.4%, and 1.0% of the tamsulosin dose in Group I, II, and III subjects, respectively. This metabolite was detected in 17 out of 18 subjects. M-2 is conjugated mainly to glucuronic acid. One of the major metabolites for tamsulosin excretion was the meta-hydroxylation metabolite M-3. This metabolite accounted for 2.2%, 4.3%, and 3.5% of the tamsulosin dose in Group I, II, and III subjects, respectively. This metabolite was detected in 17 out of 18 subjects. M-3 is conjugated mainly to glucuronic acid. The excretion of the demethylation metabolite M-4 accounted for 0.5%, 1.7%, and 1.2% of the tamsulosin dose in Group I, II, and III subjects, respectively. This metabolite was detected in all 18 subjects. M-4 is largely conjugated to glucuronic acid with a trace of M-4 possibly conjugated to sulfate. The excretion of the oxidative deamination metabolite AM-1 accounted for 1.1%, 4.5%, and 8.8% of the tamsulosin dose in Group I, II, and III subjects, respectively. This metabolite was detected in all 18 subjects.

Individual and mean tamsulosin pharmacokinetic parameters Cmax, Tmax, $t_{1/2}$, AUC_{0-}, Vdarea/F, CL/F, CLr, % excreted, CLint/F, Cb/Cu, and fu for Groups I, II, and III, are listed in Table 54.

Table 54 Individual and mean pharmacokinetic parameters

	CLcr (mL/min/1.73m²)	Cmax (ng/mL)	Tmax (h)	t½ (h)	AUC (mcg.h/L)	Vdarea/F (L/kg)	CL/F (L/h/1.73m²)	CL/F (L/h/kg)	CLr (L/h/1.73m²)	% excr	CLint/F (L/h/kg)	Cb/Cu	fu
Group I (10 ≤ CLcr < 30 mL/min/1.73m²)													
Median	14.8	18.10	6.00	18.79	287.20	0.46	1.31	0.0208	0.0292	2.3	2.150	89.8	0.011
Mean	13.5	16.70	5.67	18.02	285.75	0.61	1.74	0.0251	0.0383	2.5	2.120	98.7	0.011
S.D.	3.8	7.08	0.52	4.90	167.32	0.34	1.11	0.0152	0.0184	1.1	0.797	33.6	0.003
%C.V.	28.4	42.4	9.1	27.2	58.6	55.6	63.8	60.4	48.2	43.6	37.6	34.0	31.5
Minimum	8.4	5.69	5.00	10.04	86.73	0.33	0.67	0.0101	0.0248	1.1	0.960	65.4	0.007
Maximum	17.8	25.50	6.00	23.10	544.47	1.08	3.42	0.0452	0.0728	3.9	3.104	142.6	0.015
Group II (30 ≤ CLcr < 70 mL/min/1.73m²)													
Median	58.1	19.00	5.00	19.25	381.52	0.34	0.91	0.0129	0.0858	8.5	1.179	124.8	0.008
Mean	53.8	20.47	4.67	20.24	396.92	0.39	1.04	0.0146	0.0842	8.1	1.566	117.2	0.009
S.D.	9.9	4.49	0.52	5.56	196.87	0.15	0.55	0.0088	0.0280	2.0	1.075	27.8	0.003
%C.V.	18.4	21.9	11.1	27.5	49.6	40.0	53.3	60.4	33.3	24.4	68.6	23.8	29.6
Minimum	35.3	15.20	4.00	15.07	178.26	0.27	0.48	0.0068	0.0505	5.3	0.849	70.9	0.007
Maximum	62.0	26.80	5.00	30.13	761.37	0.69	2.09	0.0317	0.1179	10.8	3.691	145.8	0.014
Group III (CLcr > 90 mL/min/1.73m²)													
Median	106.9	15.10	4.50	12.81	204.13	0.42	1.72	0.0242	0.1824	11.5	2.349	100.0	0.010
Mean	106.3	14.83	4.50	13.80	192.46	0.50	1.96	0.0263	0.2078	11.2	2.301	92.6	0.011
S.D.	10.4	2.83	1.05	4.00	68.76	0.20	0.78	0.0109	0.0605	3.3	0.695	21.4	0.003
%C.V.	9.8	19.1	23.3	29.0	35.7	39.9	39.7	41.5	29.1	29.5	30.2	23.1	28.1
Minimum	93.1	10.80	3.00	9.12	105.21	0.30	1.14	0.0149	0.1793	6.3	1.517	59.1	0.009
Maximum	119.4	19.00	6.00	20.38	277.62	0.78	3.16	0.0436	0.3309	15.7	3.274	114.0	0.017

Creatinine clearance was significantly different between all 3 renal groups ($p<0.001$, Table 55). However, renal function did not significantly influence the disposition of tamsulosin. There was no significant relationship between CLcr and tamsulosin CL/F ($r=0.148$, $p=0.555$). There was no significant difference among the three renal groups in Cmax ($p=0.185$), $t_{1/2}$ ($p=0.098$), $AUC_{0-\infty}$ ($p=0.104$), Vdarea/F ($p=0.321$), CL/F ($p=0.178$), CLint/F ($p=0.370$), Cb/Cu ($p=0.345$), fu ($p=0.413$), and age ($p=0.171$, Table 55). Despite a lack of statistical significance in CLint/F, the slight reduction of CLint/F in Group II subjects appears to be influenced by age (Table 56). Tamsulosin CLint/F significantly decreases as subjects get older ($r=0.748$, $p<0.001$). Despite a lack of statistical significance, the median age in Group II subjects was 66.0 years compared to 50.0 and 50.5 years in Groups I and III, respectively. The similar ages in Groups I and III were because these subjects were matched for age as per the protocol. This age-related decrease in CLint/F was independent of renal function since CLcr did not significantly correlate with CLint/F ($r=0.055$, $p=0.847$, Table 56).

Table 55 **ANOVA results of pharmacokinetic parameters and demographic data between the three renal function groups**

Parameter	Sum of Squares	Degrees of Freedom	Mean Squares	F-Ratio	p	post-hoc tukey	p
CLcr							
Group	25959	2	12980	176	<0.001	Gp 1 vs Gp 2	<0.001
Residual	1104	15	73.6			Gp 1 vs Gp 3	<0.001
						Gp 2 vs Gp 3	<0.001
Cmax							
Group	98.8	2	49.4	1.89	0.185		
Residual	391	15	26.1				
Tmax		2		6.734*	0.034		
$t_{1/2}$							
Group	129	2	64.3	[illegible]	[illegible]		
Residual	354	15	23.6				
$AUC_{0-\infty}$							
Group	125729	2	62865	2.64	0.104		
Residual	357409	15	23827				
Vdarea/F							
Group	0.145	2	0.073	1.23	0.321		
Residual	0.889	15	0.059				
CL/F							
Group	2.76	2	1.38	1.94	0.178		
Residual	10.7	15	0.713				
CLr							
Group	0.092	2	0.046	28.9	<0.001	Gp 1 vs Gp 2	0.149
Residual	0.024	15	0.002			Gp 1 vs Gp 3	<0.001
						Gp 2 vs Gp 3	<0.001
% excreted							
Group	233	2	116	22.0	<0.001	Gp 1 vs Gp 2	0.002
Residual	79.4	15	5.29			Gp 1 vs Gp 3	<0.001
						Gp 2 vs Gp 3	0.084
CLint/F							
Group	1.66	2	0.830	1.07	0.370		
Residual	10.9	14	0.778				
Cb/Cu							
Group	1863	2	931	1.15	0.345		
Residual	11344	14	810				
fu							
Group	0.00001	2	0.00001	0.943	0.413		
Residual	0.00011	14	0.00001				
α_1 AGP							
Group	1795	2	898	4.34	0.033	Gp 1 vs Gp 2	0.996
Residual	3105	15	207			Gp 1 vs Gp 3	0.051
						Gp 2 vs Gp 3	0.060
Age							
Group	661	2	330	1.99	0.171		
Residual	2490	15	166				

Table 56 Linear regression analysis results

Regression (y = mx + b)	Coefficient	t value	p value	Sum of Squares	Degrees of Freedom	Mean Squares	F-Ratio	p	r^2
CLcr, CL/F				0.298	1	0.298	0.363	0.555	0.022
m = slope	0.003	0.602	0.556						
b = Constant	1.384	3.605	0.002						
Residual				13.155	16	0.822			
CLcr, CLr				0.085	1	0.085	44.034	<0.001	0.733
m = slope	0.002	6.636	<0.001						
b = Constant	0.007	0.399	0.695						
Residual				0.031	16	0.002			
CLcr, CLint/F				0.032	1	0.032	0.039	0.847	0.003
m = slope	0.001	0.197	0.847						
b = Constant	1.915	4.942	<0.001						
Residual				12.516	15	0.834			
α, AGP, Cb/Cu				6441.626	1	6441.626	14.284	0.002	0.488
m = slope	1.166	3.779	0.002						
b = Constant	21.909	0.988	0.339						
Residual				6764.676	15	450.978			
α, AGP, CL/F				4.012	1	4.012	6.800	0.019	0.298
m = slope	-0.029	-2.608	0.019						
b = Constant	3.557	4.555	<0.001						
Residual				9.441	16	0.590			
age, CL/F				2.894	1	2.894	4.385	0.053	0.215
m = slope	-0.030	-2.094	0.053						
b = Constant	3.139	4.074	0.001						
Residual				10.559	16	0.660			
age, CLint/F				7.021	1	7.021	19.057	<0.001	0.560
m = slope	-0.049	-4.365	<0.001						
b = Constant	4.529	7.515	<0.001						
Residual				5.527	15	0.368			
age, CLr				0.0003	1	0.0003	0.040	0.844	0.003
m = slope	>-0.001	-0.200	0.844						
b = Constant	0.126	1.558	0.139						
Residual				0.116	16	0.0072			
fu, CLint/F				0.436	1	0.436	0.540	0.474	0.039
m = slope	53.199	0.735	0.474						
b = Constant	1.426	1.826	0.088						
Residual				12.112	15	0.808			
fu, CL/F				5.899	1	5.899	12.034	0.003	0.445
m = slope	195.679	3.469	0.003						
b = Constant	-0.426	-0.700	0.494						
Residual				7.353	15	0.490			

Sponsors Conclusions: The pharmacokinetics of tamsulosin and its urinary metabolites were not significantly influenced by renal function. The primary elimination of tamsulosin is via nonrenal mechanisms. Despite a statistically significant difference in CLr and percent excretion of tamsulosin in the 3 renal groups, less than 12% of the dose is recovered in the urine with the predominate pathway of elimination occurring through nonrenal mechanisms. Group I subjects had a significantly lower CLr and significantly less excretion of tamsulosin in urine. Despite a lack of a significant difference in CLint/F, the reduction in CLint/F in Group II appears to be influenced by age explaining 56% of the variance (r^2) in tamsulosin Clint/F. Despite an age dependent decrease in CLint/F, patients with renal dysfunction would not require an adjustment in tamsulosin dosing because of the wide therapeutic window of tamsulosin.

Reviewer Comments: The results are consistent with the pharmacokinetics of the tamsulosin.

HEPATIC INSUFFICIENCY

Study Number: US92-05

Study Title: A Study on the Evaluation of the Pharmacokinetic Profile of Tamsulosin in Subjects with Hepatic Insufficiency.

Investigator:

Objectives: The objectives of this study were to determine the effect of hepatic insufficiency on the pharmacokinetics of a single oral 0.4 mg dose of tamsulosin in subjects with hepatic insufficiency as compared to the subjects with normal hepatic function.

Study Design: This study was designed as an open label, single-dose pharmacokinetic study of oral tamsulosin in 8 subjects with hepatic insufficiency and 8 subjects with normal hepatic function. Normal subjects were matched to hepatic subjects on the basis of age (± 4 years) and smoking status.

Subjects: Sixteen (16) volunteers were enrolled into the study. Eight (8) subjects had hepatic insufficiency and 8 were normal healthy subjects.

Formulation: The drug was formulated in a modified release formulation and was supplied as tamsulosin 0.4 mg capsules (Lot No. 92-A44AA) the to be marketed formulation.

Dosage and administration: A single 0.4 mg oral dose (one 0.4 mg capsule) of tamsulosin was administered with 200 mL of water at approximately 8:00 a.m. on the day of dosing. The dose was administrated after overnight fast.

Blood Sampling: Venous blood samples (10 mL) for the determination of plasma tamsulosin concentrations were obtained prior to (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, and 72 hours post dosing for all subjects. Additional samples were drawn at 96, 120, 144, and 168 hours post dosing for the hepatically impaired subjects.

Plasma Protein Binding: A venous blood sample (10 mL) for *in vitro* determination of percentage of protein unbound tamsulosin was obtained prior to (0 hour) the administration of tamsulosin.

Urine Specimens: Urine samples for the determination of tamsulosin and its metabolites' concentrations were collected prior to (0 hour) and at 0-12 hr, 12-24 hr, 24-48 hr, and 48-72 hr following tamsulosin administration for all subjects. Additional urine was collected at 72-96 hr, 96-120 hr, 120-144 hr, and 144-168 hr for the hepatically impaired subjects.

Analytical Procedures: Determination of tamsulosin concentrations in plasma was conducted using high performance liquid chromatography (HPLC) at Determination of percentage of protein unbound tamsulosin was conducted at Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan. Determination of tamsulosin and its metabolites' concentrations in urine samples was conducted using liquid chromatography/tandem mass spectrometry (LC-MS/MS) or gas chromatography/tandem mass spectrometry (GC-MS/MS) at Complete assay/validation reports for the determination of plasma and urine concentrations were performed.

Results: Mean tamsulosin plasma-concentration time curve for all subjects (hepatic insufficiency and normal) is shown in Figure 23.

Figure 23. Mean Tamsulosin concentration-time curve.

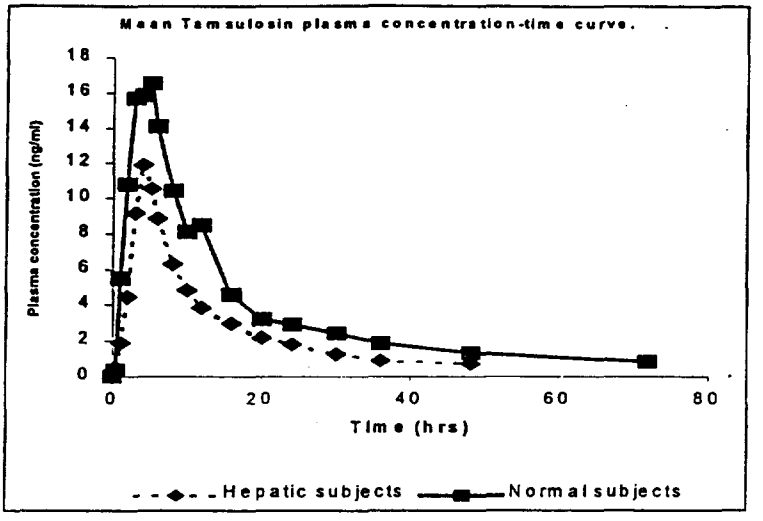


Table 57 Individual and mean % excretion of tamsulosin, M-1, M-2, M-3, M-4, and AM-1

	Tamsulosin	M-1	M-2	M-3	M-4	AM-1
Group I (Hepatic Subjects)						
Mean	20.08	0.02	0.80	3.18	1.65	6.70
S.D.	5.29	0.03	0.60	2.43	1.18	3.83
%C.V.	26.35		75.61	76.52	71.35	57.26
Group II (Normal Subjects)						
Mean	10.06	0.02	0.98	2.92	1.13	7.29
S.D.	3.61	0.04	0.38	1.72	0.69	3.37
%C.V.	35.89		38.75	58.95	61.15	46.18

Individual and mean ICG clearance (ICG CL) values and tamsulosin pharmacokinetic parameters Cmax, Tmax, $t_{1/2}$, AUC_{0-inf}, Vdarea/F, CL/F, CLr, % excreted, CLint/F, fu, and Cb/Cu for hepatic and normal subjects are listed in Table 58.

Table 58 Individual and mean tamsulosin pharmacokinetic parameters

	ICG CL (L/h)	Cmax (ng/mL)	Tmax (h)	t½ (h)	AUC_{0-inf} (mcg.h/L)	Vdarea/F (L/kg)	CL/F (L/h)	CL/F (L/h/kg)	CLr (L/h)	% excr	CLint/F (L/h/kg)	Cb/Cu —	fu
Group I (Hepatic Subjects)													
Median	18.11	10.90	4.00	11.95	126.70	0.73	3.16	0.0423	0.4995	19.55	1.384	45.10	0.022
Mean	25.47	12.45	4.43	13.63	144.02	0.75	3.26	0.0407	0.6629	20.11	1.752	58.63	0.025
S.D.	17.35	6.10	0.53	5.46	61.32	0.24	1.41	0.0157	0.3882	5.30	0.905	37.07	0.019
%C.V.	68.1	49.0	12.1	40.1	42.6	31.3	43.3	38.6	58.6	26.4	51.7	63.2	76.6
Minimum	11.02	6.37	4.00	10.04	70.16	0.44	1.71	0.0247	0.2703	13.80	0.826	13.78	0.009
Maximum	62.32	20.00	5.00	25.67	234.27	1.06	5.70	0.0713	1.2349	29.50	3.094	116.61	0.068
Group II (Normal Subjects)													
Median	35.94	16.65	4.50	14.61	255.41	0.45	1.62	0.0185	0.1744	9.25	1.946	121.50	0.008
Mean	40.96	18.82	4.25	16.07	246.30	0.56	2.38	0.0282	0.2338	10.06	2.587	110.42	0.010
S.D.	10.35	10.24	0.89	4.89	145.77	0.25	1.73	0.0209	0.1811	3.61	1.592	25.06	0.003
%C.V.	25.3	54.4	20.9	30.4	59.2	44.4	72.6	74.1	77.5	35.9	61.5	22.7	31.5
Minimum	31.92	7.43	3.00	10.34	68.71	0.37	0.77	0.0125	0.0975	6.70	1.305	60.00	0.007
Maximum	62.66	40.00	5.00	23.10	521.99	1.10	5.82	0.0737	0.6496	16.20	5.848	139.69	0.016

There were no significant differences in tamsulosin Cmax (p=0.175), Tmax (p=0.651), $t_{1/2}$ (p=0.377), AUC_{0-} (p=0.109), Vdarea/F (p=0.140), CL/F (p=0.304, 0.218), and CLint/F (p=0.243) between the hepatic and normal subjects. Hepatic impairment did not influence the rate of tamsulosin absorption since Tmax was similar between the two groups. There was a significant increase in fu (p=0.041) for the hepatic subjects. This 150% increase in fu for hepatic subjects can be explained by the significant reduction in α_1 acid glycoprotein values (p=0.002) and 47% reduction in binding capacity (p=0.006) for hepatic subjects, as the binding capacity of tamsulosin for α_1 acid glycoprotein is significantly dependent upon the concentration of α_1 acid glycoprotein (r=0.910, p<0.001)

There was a significant difference in CLr (p=0.015) and % excretion of tamsulosin (p=0.001) between the hepatic and normal subjects. Hepatic subjects had an almost 3-fold increase in CLr and 2-fold increase in % excretion of tamsulosin compared to normal subjects. Since CLcr was not significantly different between hepatic and normal subjects (p=0.880), the increase in CLr was attributed to the 150% increase in fu. The slight decrease in CLint/F (32%) would result in a moderate increase in free tamsulosin steady-state concentration. Since the rate of excretion depends on the unbound concentration of tamsulosin in plasma, the increased free tamsulosin level would be responsible for the significant increase in % excretion of tamsulosin.

Despite a statistically significant lower ICG CL in the hepatic versus normal subjects, there was no significant correlation between ICG CL and tamsulosin CL/F (r=-0.358, p=0.190). Significant correlation was observed between tamsulosin CL/F and α_1 acid glycoprotein (r=-0.632, p=0.011). Stepwise multiple linear regression analysis

revealed age and α_1 acid glycoprotein as the best predictors of tamsulosin CL/F (r=-0.806, p=0.002). Tamsulosin CL/F significantly correlated with fu (r=0.645, p=0.009). There was no significant correlation between CLint/F and fu (r=-0.422, p=0.117) supporting their independence of each other in determining CL/F. For highly protein bound drugs such as tamsulosin, CL/F is dependent upon fu and CLint/F. Therefore, although the attenuation in protein binding would decrease total tamsulosin concentrations, unbound tamsulosin concentrations might increase conversely because of the slight decrease in CLint/F in patients with hepatic insufficiency.

Sponsors Conclusions: The results of this study indicate that patients with a similar range of hepatic insufficiency would not require an adjustment in tamsulosin dosing.

Reviewer comments: The conclusions are consistent with the results.

PHASE II DOSE FINDING

Study Number: US90-01A

Study Title: A Phase II dose-finding placebo-controlled study of four dose levels of tamsulosin in patients with the signs and symptoms of benign prostatic hyperplasia.

Principal Investigator:

Objectives: The primary objectives of this study were to establish the effective dose of tamsulosin in patients with the signs and symptoms of benign prostatic hyperplasia (BPH) and to demonstrate the safety of tamsulosin in a clinical setting. The pharmacokinetic objectives of this study were to 1) study the pharmacokinetics of tamsulosin in the target population under multiple dose conditions, and 2) to study the linearity in kinetics between 0.1 mg and 0.2 mg doses of tamsulosin under a.m. and b.i.d. dosing conditions.

Study Design: This was a 14-week, multi-center, parallel-group, placebo-controlled Phase II trial in male patients between the ages of 40-75 years with the signs and symptoms of BPH. This study consisted of a three-week single-blind placebo evaluation period, an eight-week double-blind fixed dose treatment period, and a three-week single-blind placebo washout period. There were five treatment groups: placebo, tamsulosin 0.1 mg a.m., tamsulosin 0.1 mg b.i.d., tamsulosin 0.2 mg a.m., and tamsulosin 0.2 mg b.i.d.

Subjects: Of the 366 patients who completed the double-blind portion of the study, 39 patients completed the pharmacokinetic portion (9 patients on 0.1mg a.m., 9 patients on 0.1 mg b.i.d., 5 patients on 0.2 mg a.m. and 10 patients on 0.2 mg b.i.d. tamsulosin, and 6 patients on placebo).

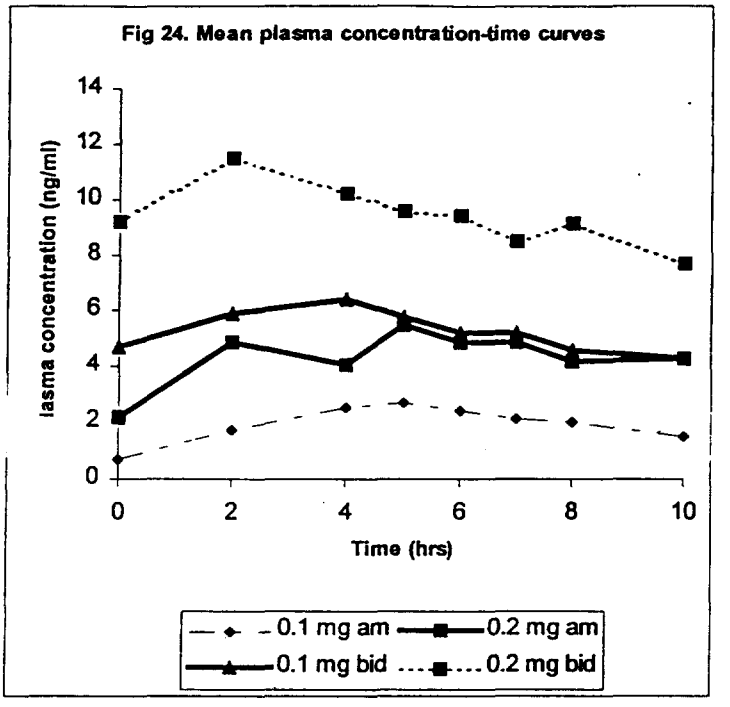
Formulation: Study medications were capsules filled with either modified release granules of tamsulosin (to be marketed product) or placebo granules. The lot numbers were LA617DP (placebo capsules), LA6175A (0.1 mg tamsulosin capsules) and LA617FB (0.2 mg tamsulosin capsules).

Dosage and administration: During the single-blind placebo evaluation period, all patients received placebo b.i.d. During the double-blind treatment period, patients received one of five treatments: either one placebo capsule b.i.d., tamsulosin 0.1 mg a.m. and identical placebo capsule p.m., tamsulosin 0.1 mg b.i.d., tamsulosin 0.2 mg a.m. and identical placebo capsules p.m., or tamsulosin 0.2 mg b.i.d.. During the single-blind placebo washout period, all patients received a placebo capsule b.i.d.

Blood Sampling: On the morning of Visit 8, patients who consented to participate in the pharmacokinetic study had blood drawn prior to dosing (hour 0), and at 2, 4, 5, 6, 7, 8 and 10h following dosing.

Analytical Procedures: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-20 ng/mL); mean recovery (91.1%, 66.9%, 86.0%, 71.1%, and 65.8% at concentrations of 2, 5, 10, 15, and 20 ng/mL, respectively; n=5 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 28.3%, 7.1%, 6.9%, and 5.0%, and accuracy of 100%, 100%, 108%, and 105% at concentrations of 0.5, 3.1, 11.4, and 17.5 ng/mL, respectively).

Results: Mean plasma concentrations for tamsulosin (linear and semi-log) for the a.m. and b.i.d. dosing regimens are plotted in Figure 24.



The plasma profiles are broad and flat following all treatments, indicating that tamsulosin formulation was functioning as a sustained release preparation. Summary statistics (n, mean, standard deviation, median, minimum and maximum) for these parameters are presented in Table 59.

TABLE 59: Mean (Standard Deviation) Steady-State Pharmacokinetic Parameters for Tamsulosin Following Administration of Four Different Dosing Regimens (Extracted from Study US90-01A)

	0.1 mg q.d. (A)	0.2 mg[1] q.d. (B)	0.1 mg b.i.d. (C)	0.2 mg[1] b.i.d. (D)	Ratio (90% CI)[2,4] B/A	Ratio (90% CI)[2,4] D/C
$AUC_{(0-10)}$ (ng*h/mL)	18.9 (11.5)	20.7 (6.2)	51.6 (12.1)	46.5 (25.7)	123 (79,190)	80 (56,113)
C_{max} (ng/mL)	2.7 (1.6)	3.3 (1.3)	6.6 (1.9)	5.6 (2.5)	128 (84,196)	80 (56,115)
T_{max} (h)[3]	5.0 (4.0,10.0)	5.0 (2.0,6.8)	4.0 (2.0,10.0)	3.0 (2.0,7.9)	-	-

1 Normalized to a 0.1 mg dose.
2 90% confidence interval on geometric least squares mean ratio (%).
3 Median (range).
4 Based on dose-normalized values.
Note: Subjects were fed prior to dosing.

While regression analysis was unable to reject the hypothesis of dose proportionality for either the a.m. or b.i.d. dosing regimens, the results of this study appear to indicate a greater than proportional change in C_{max} and $AUC_{(0-10)}$ for the 0.1 mg a.m. vs 0.2 mg a.m. treatment and a less than proportional change in C_{max} and $AUC_{(0-10)}$ for the 0.1 mg b.i.d. vs 0.2 mg b.i.d. treatment. Sample sizes for each treatment group were small, resulting in a fair degree of

variability being associated with parameter estimates. This is evident in the wide 90% confidence intervals associated with the least squares mean ratios for C_{max} and $AUC_{(0-10)}$ for the a.m. and b.i.d. dosing regimens. As a result, conclusions about dose proportionality are somewhat uncertain.

All five treatment groups generally had mean improvement from baseline in total symptom score (decrease) and in peak urine flow rate (increase) throughout the double-blind period of the study. The two tamsulosin b.i.d. treatment groups showed higher mean improvement in total symptom score and peak urine flow rate than the placebo treatment group during this period. At the end-point of the double-blind period, the percentages of patients with at least a 3 ml/sec improvement from baseline were 21% (15/70), 9% (6/64), 33% (21/64), 27% (19/71), and 36% (25/70) for the placebo, 0.1 mg a.m., 0.1 mg b.i.d., 0.2 mg a.m., and 0.2 mg b.i.d. treatment groups, respectively. A higher percentages of patients achieving at least a 3ml/sec improvement in peak urine flow rate was observed in the two tamsulosin b.i.d. treatment groups compared to placebo. Statistical significance was consistently observed only in the comparison of the placebo and 0.2 mg b.i.d. treatment groups for total symptom score. The 0.2 mg b.i.d. treatment group showed a statistically significant improvement over placebo in the investigator's global symptom assessment.

Sponsor's Conclusions: While regression analysis was unable to reject the hypothesis of dose proportionality, there appears to be a greater than proportional change in C_{max} and $AUC_{(0-10)}$ for the 0.1 mg a.m. vs 0.2 mg a.m. treatment. While regression analysis was unable to reject the hypothesis of dose proportionality, there appears to be a less than proportional change in C_{max} and $AUC_{(0-10)}$ for the 0.1 mg b.i.d. vs 0.2 mg b.i.d. treatment. While no significant changes were observed in t_{max} between any treatments, t_{max} appears to occur at an earlier time, following b.i.d. dosing. The peak/trough ratios for the 0.2 mg a.m. and 0.1 mg b.i.d. treatments indicated a larger range in plasma concentrations following a.m. dosing than b.i.d. dosing.

This study demonstrated the clinical efficacy of tamsulosin when compared to placebo, although it did not unequivocally establish an optimal dosing regimen. The active treatment groups generally provided similar results relative to the placebo treatment group. However, there was some evidence of the b.i.d. and the higher dose regimens being more efficacious than the a.m. regimens.

Reviewer's Comments: Dose proportionality does not appear to be a problem. The differences in t_{max} between once daily and twice daily dosing are to be expected. A dose of 0.4 mg tamsulosin daily appears to be well tolerated.

CONTROLLED CLINICAL TRIALS - PK/PD STUDIES

Study Number: 90-HAR-02

Study Title: Report on a study in elderly patients with benign prostatic hyperplasia to measure the pharmacokinetics of ym617 (tamsulosin) and its effects upon urinary flow when given as single and multiple oral doses.

Investigator:

Objectives: To investigate primarily the pharmacokinetics of tamsulosin following a single dose and seven days treatment with 0.4 mg modified release capsule once daily in patients with symptomatic BPH, and to determine whether repeated dosing alters the pharmacokinetics of the drug.

Study Design: A single centre, open study in which all eligible patients were to receive a once daily oral dose of 0.4 mg tamsulosin for 8 days.

Subjects: A total of 14 patients were selected for the study. One patient was rejected before study drug administration for not meeting the inclusion criteria. Another patient withdrew after the first study day for family reasons. Twelve patients completed the study.

Formulation: Study medication was a capsule filled with modified release granules of tamsulosin (to be marketed product). The lot number was KA6172D (0.4 mg tamsulosin capsules).

Dosage and administration: All patients received a once daily oral dose of 0.4 mg tamsulosin for 8 days.

Blood Sampling: Bood samples were taken on Days 1 and 8, at 0, 1, 2, 4, 6, 8, 9, 14, 24, 28 and 32 hours after dosing for estimation of tamsulosin blood levels. Urine was collected on Days 1 and 8 over the following periods: 0-6, 6-12 and 12 to 24 hours.

Analytical Procedures: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-20 ng/mL); mean recovery (91.1%, 66.9%, 86.0%, 71.1%, and 65.8% at concentrations of 2, 5, 10, 15, and 20 ng/mL, respectively; n=5 at each concentration level); sensitivity (LOQ) of 0.5

ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); validation quality control samples (CV% of 5.3%, 4.3%, 5.5%, and 3.3%, and accuracy of 94.4%, 96.3%, 97.5%, and 98.6% at concentrations of approximately 0.5, 2, 10, and 20 ng/mL, respectively).

A validated HPLC assay with fluorescence detection was used for tamsulosin urine samples; Standard curve (4.9-510.1 ng/mL); mean recovery (53.6%, 63.8%, 70.0%, 91.4% and 67.6% at concentrations of approximately 20, 50, 100, 240 and 510 ng/mL, respectively; n=5 at each concentration level); sensitivity (LOQ) of 4.9 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); intra- and inter-batch validation quality control samples (CV% of <12%, and accuracy of within ±5% at concentrations of 5.0, 39.8, 119.0 and 392.3 ng/mL, respectively). Tamsulosin was determined in plasma and urine by validated reverse phase HPLC with fluorescence detection at Simbec Research Limited.

Results: Mean values of pharmacokinetic parameters on Days 1 and 8 are presented in Table 60.

TABLE 60: Mean (Standard Deviation) Pharmacokinetic Parameters for Tamsulosin Following Administration of 0.4 mg Modified Release Formulation to Elderly Male BPH Patients (n=13) for Eight Days (0.4-02)

	Day 1	Day 8	Ratio (90% CI)[2,5] Day 8:Day 1
C_{max} (ng/mL)	9.9 (3.7) [8.4 (5.9,17.9)][3]	17.4 (12.4) [13.1 (5.7,47.5)][3]	157 (131,188)[6]
T_{max} (h)	9 (6,28)[3]	9 (4,28)[3]	-
AUC[1] (ng*h/mL)	255 (151) [206 (139,625)][3]	290 (179) [247 (111,672)][3]	92 (68,124)[7]
$t_{½}$ (h)	14.1 (8.2) [10 (8.6,34)][3]	13.1 (4.1)[4] [12 (9.8,20)][3]	-
fe (%)[2]	5 (5) [3 (2,6)]	10 (9) [7(1,28)]	-
CL_R (L/h)	0.15 (0.12) [0.10 (0.04,0.40)]	0.12 (0.06) [0.15 (0.05,0.20)]	-

1 AUC_{∞} for Day 1 and $AUC_{(0-24)}$ for Day 8.
2 Based on supplementary analyses done during preparation of the NDA.
3 Median (range).
4 Estimable for only five patients on Day 8.
5 90% confidence interval on least squares mean ratio (%).
6 The theoretical accumulation ratio was calculated as 150 (50) percent based on the estimate of $t_{½}$ on Day 1.
7 $AUC_{(0-24)}$:AUC_{∞}.

The mean AUC_{0-inf} after a single oral dose (Day 1) of 0.4mg tamsulosin was 255 ng/ml h (s.d. 151, n = 9) and on Day 8, the AUC_{0-24} was 290 ng/ml h (s.d. 179, n = 12). There was no significant difference in the AUC_{0-inf} on Day 1 and the AUC_{0-24} in steady-state on Day 8; the ratio of these AUC values amounted to 1.00 (s.d. 0.41, n = 8). Plasma levels after the first dose proved to be within the range observed after the first dose of 0.4 mg in healthy caucasian males, however, T_{max} proved to be later, compared with the 4-5 hour range in the healthy volunteer study. Also AUC's tended to be higher than those in healthy males, AUC_{0-inf} in that population ranging from ng.h/ml. Apparent elimination half-lives in the elderly patient population tended to be higher than the hour range in healthy subjects. These tendencies in kinetic parameters may indicate a reduced release/absorption rate and/or a reduced intrinsic clearance of tamsulosin in elderly patients.

Sponsor's Conclusions: Oral dosing of the 0.4 mg modified release capsule of tamsulosin demonstrated variable kinetics of tamsulosin in elderly BPH patients. There were no indications for a change in kinetics on multiple dosing.

Compared with healthy subjects, tamsulosin levels tended to be higher in the elderly. Haemodynamic or clinically important adverse events were not observed, suggesting a favourable safety profile of the drug in the target population. Efficacy data indicated a clinical benefit, warranting further, more extensive and placebo controlled evaluation.

Reviewer's Comments: This study supports linear kinetics of tamsulosin.

Study Number: US92-03A

Study Title: Phase III Multicenter Placebo-Controlled Study of Two Dosages (0.4 mg q.d. and 0.8 mg q.d.) of Modified Release Tamsulosin in Patients with the Signs and Symptoms of Benign Prostatic Hyperplasia

Investigator: Multiple

Objectives: The pharmacokinetic objective of this study was to investigate the population pharmacokinetics of tamsulosin in patients with BPH.

Study Design: This was a 13-week, randomized, multicenter, parallel, double-blind Phase III trial in male patients between the ages of 45-83 years with the signs and symptoms of BPH.

Subjects: A total of 374 patients who received tamsulosin were included in the population pharmacokinetic analysis and in modeling of peak flow rates. A total of 579 patients (374 on tamsulosin and 205 on placebo) were included in modeling of American Urological Association (AUA) Symptom Scores. The mean (± standard error) age of patients in the pharmacokinetic sub-group was 58 (± 0) years and the mean weight was 87.4 (± 0.7) kg.

Formulation: The 0.4 mg capsules of tamsulosin were from a to be marketed clinically tested batch (Lot. No. SC6174C).

Dosage and administration: The study consisted of a four-week single-blind placebo evaluation period and a thirteen-week double-blind treatment period. Treatments consisted of placebo, 0.4 mg q.d. tamsulosin (one 0.4 mg capsule of the modified release formulation of tamsulosin HCl) or 0.8 mg q.d. tamsulosin (two 0.4 mg capsules of the modified release formulation of tamsulosin HCl). Patients on 0.4 mg q.d. tamsulosin received 0.4 mg q.d. during the entire double-blind period, while patients on 0.8 mg q.d. received 0.4 mg q.d. for 1 week and 0.8 mg q.d. for the remaining 12 weeks. Dosing was scheduled a half-hour after breakfast. Clinic visits were scheduled at 1, 2, 4, 7, 10, and 13 weeks during the double-blind period.

Blood Sampling: Venous blood samples (10 mL each) were collected for determination of tamsulosin plasma concentrations in a subset of patients at selected visits (one sample at 4-8 hours post-dose during weeks 1 and 2; and two samples, one upon arrival and one before discharge from the visit, during week 13 of the double-blind period.

Analytical Procedures: A validated HPLC assay with fluorescence detection was used for tamsulosin (plasma samples); Standard curve (0.5-60 ng/mL); mean recovery (74.7%, 79.7%, and 79.8% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively; n=3 at each concentration level); sensitivity (LOQ) of 0.5 ng/mL; specificity (no interfering peaks for tamsulosin or internal standard); in-process quality control samples (CV% of 5.2%, 5.4%, and 8.3%, and accuracy of 101%, 97%, and 101% at concentrations of 50.0, 8.0, and 1.0 ng/mL, respectively).

Results: Fitted pharmacokinetic parameters (Table 61) were in agreement with fitted estimates of these parameters in healthy young volunteers (US93-08 and US93-09). None of the covariates tested (demographics, laboratory values, concomitant drugs or diseases) exerted a clinically significant effect on the pharmacokinetics of tamsulosin. Peak urine flow rate exhibited a very steep concentration-effect relationship (sigmoidicity factor >20), with no significant changes in flow rate observed at or above tamsulosin concentrations of 10 ng/mL. At these concentrations, the model predicted that 70% of the population would experience at least 15% improvement in flow and 15% of the population would experience at least 33% improvement in flow. Further, the model predicted that only modest improvement in peak flow would be observed at doses above 0.4 mg q.d. (11, 20, 24, and 24% of patients would experience at least 30% improvement in flow at 0.2, 0.4, 0.6, and 0.8 mg q.d., respectively) (See figure 25). None of the covariates tested exerted a clinically significant effect on peak urine flow rate. Modeling of AUA symptom scores predicted that at tamsulosin concentrations of 20 ng/mL and above, 45% of the population would show a drug-related improvement in scores up to 10%, 25% of the population would show at least a 25% improvement, and 15% of the population would show at least a 50% improvement. Unlike the predictions for peak flow rates, the model predicted modest improvements in symptom scores above doses of 0.4 mg q.d(See figure 26). None of the covariates tested exerted a clinically significant effect on symptom scores.

TABLE 61: Mean (Standard Deviation) Model-Fitted Pharmacokinetic Parameters for Tamsulosin Following Administration of 0.4 mg q.d. and 0.8 mg q.d. to BPH Patients (Extracted from Study US92-03A)

	Mean (SD)
V_c/F (L)	12.1 (6.6)
V_{SS}/F (L)	36.2 (10.1)
CL/F (L/h)	2.17 (0.98)
$t_{½}$ (h)	32.8 (5.3)

Note: Parameters generated using population pharmacokinetic methods. Data from 374 patients were included.

Sponsor's Conclusions: Based on population pharmacokinetic and pharmacodynamic modeling, the pharmacokinetics of tamsulosin in middle-aged to elderly patients with BPH were comparable to healthy, young volunteers. Maximal improvement in peak urine flow rate was predicted with 0.4 mg q.d. tamsulosin (at least a 30% improvement in 20% of the population), with minimal improvements above this dose. In contrast to flow rates, the model predicted modest improvements in AUA symptom scores above doses of 0.4 mg q.d. None of the covariates tested (demographics, laboratory values, concomitant drugs or diseases) were found to exert a clinically significant effect on the pharmacokinetics or pharmacodynamics of tamsulosin.

Reviewer's Comments: The dose of 0.4 mg q.d. provides optimal efficacy and tolerance with very little improvement in peak flow with higher doses. A slight improvement in symptom score may occur in some patients with higher doses. Doses greater than 0.8 mg q.d. are unlikely to be of any benefit.

Figure 25

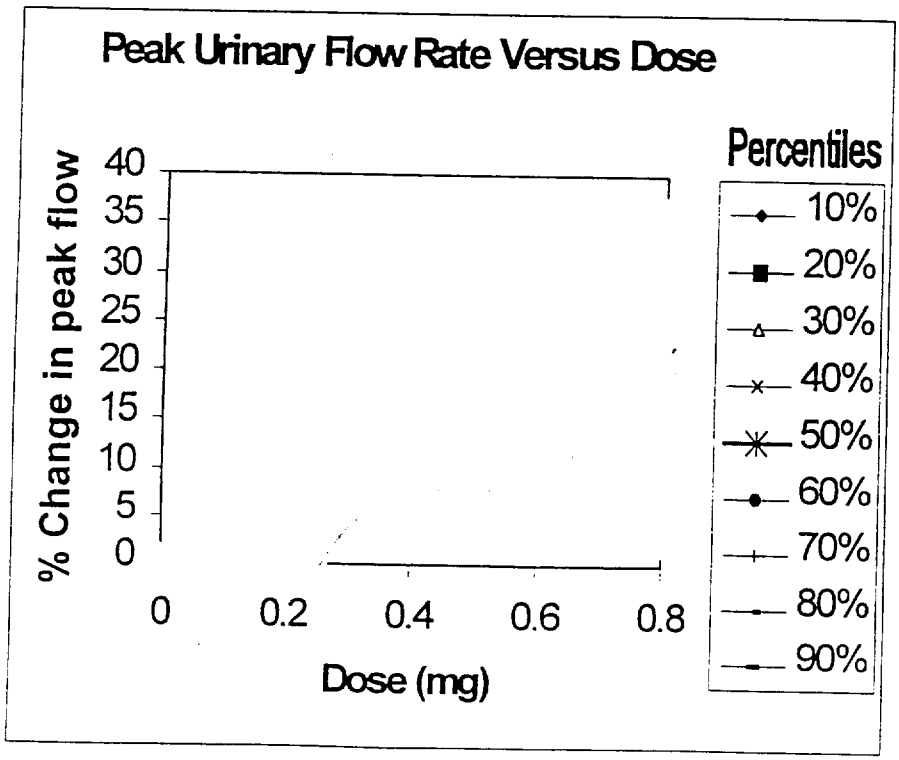
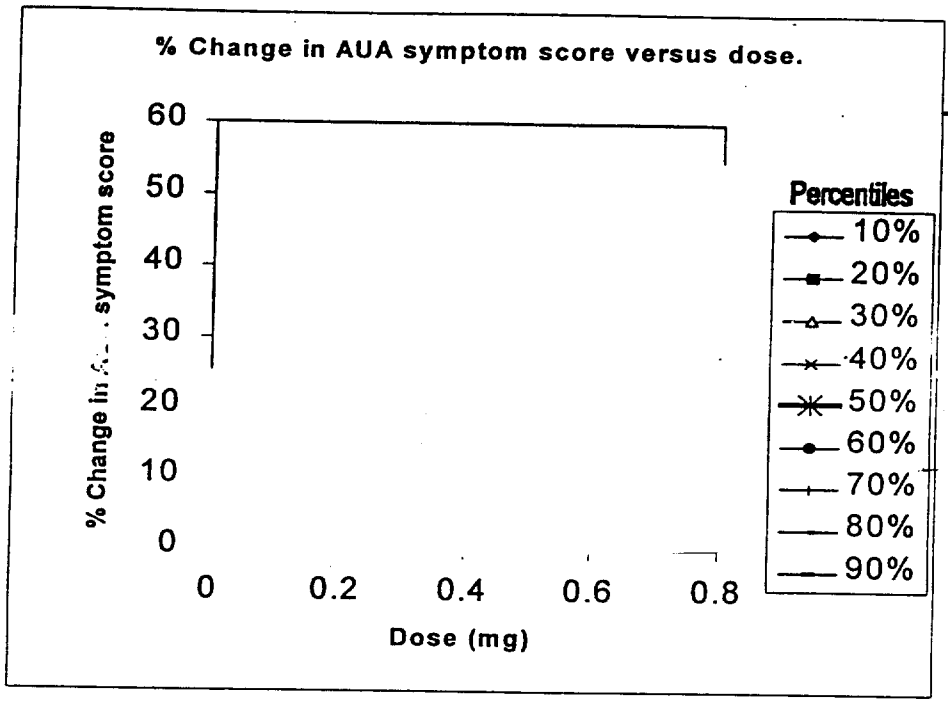


Figure 26


% Change in AUA symptom score versus dose.
% Change in AUA symptom score
60
50
40
30
20
10
0
0
0.2
0.4
0.6
0.8
Dose (mg)
Percentiles
10%
20%
30%
40%
50%
60%
70%
80%
90%

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MAR 7 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

IND:	30,365 (Serial No. 140)
NDA:	20-579 (consultation)
Compound:	Flomax™ (tamsulosin hydrochloride 0.4 mg capsules)
Submission Dates:	2/14/97 4/15/96
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Type of Submission:	Amendment to IND: *In Vitro* Drug Metabolism Original NDA
Reviewer:	K. Gary Barnette, Ph.D.

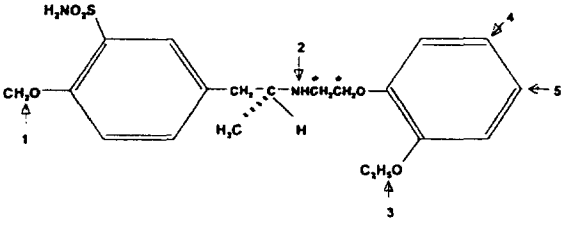
NDA 20-579, Flomax™ (tamsulosin hydrochloride), was submitted by Boehringer Ingelheim Pharmaceuticals on April 15, 1996 for the indication of treatment of signs and symptoms of benign prostatic hyperplasia (BPH). Tamsulosin is a new molecular entity and the primary review is being conducted by Drs. Raymond Miller and Ene Ette, Pharmacometrics, Office of Clinical Pharmacology and Biopharmaceutics.

The submission to NDA 20-579 (Original NDA), dated April 15, 1996, contains one *in vitro* metabolism study (US95-3365) that assesses possible interactions between tamsulosin and amitriptyline, diclofenac, salbutamol, glibenclamide, finasteride, warfarin and SKF 525-A. Additionally, on February 14, 1997 the sponsor submitted an amendment to IND that contained an additional *in vitro* metabolism and binding study (U95-3371) assessing the interaction of tamsulosin and radiolabeled diclofenac and warfarin.

This document is the review (consultation) of the *in vitro* drug metabolism studies submitted to support the approval of NDA 20-579, Flomax™ (tamsulosin hydrochloride).

The structure of tamsulosin is included below (MW = 445);

Figure 1.



The positions of the ^{14}C label used in the studies reviewed herein are indicated by *.

The proposed points of metabolism of tamsulosin are identified and numbered. The following is the nomenclature used by the sponsor to identify each metabolite and the Phase II metabolism that is possible.

1. M-4 (O-demethylation) → glucuronidation
2. The acid that results from cleavage at this nitrogen is identified as AM-1.
3. M-1 (O-deethylation) → glucuronidation and sulfation
4. M-3 (hydroxylation) → glucuronidation and sulfation
5. M-2 (hydroxylation) → glucuronidation

Study Number: US95-3365

Title: YM617 (tamsulosin hydrochloride) effects of six potential interacting drugs on the *in vitro* metabolism by human liver microsomal fraction.

Objectives:

1. To assess possible drug interactions between tamsulosin and amitriptyline, diclofenac, salbutamol, glibenclamide, finasteride, warfarin and SKF 525-A.
2. To assess the enzyme primarily responsible for the metabolism of tamsulosin.

Tissue:

Objective #1--- Pooled human liver microsomes from 5 individual donors (Subject #s
Objective #2--- Human liver microsomes from 10 individual donors (Subject #s

Study Design:

Reaction mixtures

NADP*	0.4 mM
Glucose 6-phosphate	5 mM
Magnesium Chloride	1.85 mM
Glucose 6-phosphate dehydrogenase	0.75 U/ml
Microsomal protein	0.5 mg/ml
Phosphate buffer	0.1 M, pH 7.4
Volume	3 ml
Tamsulosin hydrochloride	64-2400 ng/ml

Additionally, to satisfy Objective #1, 30 µl of one of the following DMSO (1% v/v), Diclofenac (200 µg/ml), Amitriptyline (5 µg/ml), salbutamol (0.5 µg/ml), glibenclamide (20 µg/ml), finasteride (2 µg/ml), warfarin (100 µg/ml), or SKF 525-A (1 mM) was also added.

Assay:

The assay used to estimate tamsulosin and metabolites is an HPLC with UV/vis detector at 275 nm. Tamsulosin and metabolites were identified by comparing the elution of radioactivity with the elution of standards containing non-radiolabeled tamsulosin and metabolites. However, proper validation of the assay is not presented.

Additionally, the methodology used to estimate the metabolism of the marker substrates (Objective and validation of these assays is not presented.

Results:

Metabolism of Tamsulosin

Table 1 contains the rates of formation of various metabolites (see Figure 1) from 10 individual donors. It should be noted that five additional metabolites were measured from the HPLC that have not been identified structurally. The unidentified metabolites are A, B, C, D and E.

Table 1. Rate of Formation of the Metabolites from 10 Individual Donors (pmoles metabolite formed/minute/mg microsomal protein).

Individual Donor #	Metabolite									
	AM-1	M-1	M-2	M-3	M-4	A	B	C	D	E
									—	
									—	—

ND = not detected (<0.75 pmoles/min/mg microsomal protein)

Determinations of Km and Vmax were made from the disappearance of tamsulosin ng/ml) in incubations with pooled human liver microsomes (10 minute) plotted against initial substrate concentrations (Lineweaver-Burk plot). The Vmax and Km were determined to be 635.3 pmoles tamsulosin metabolized/minute/mg pooled human liver protein and 6.3 µg/ml (14.2 µM), respectively.

Interaction Studies

The results of a 10 minute incubation of the various potentially interactive compounds and tamsulosin with pooled human liver microsomes are included in Table 2.

Table 2.

Potential interacting compound	± DMSO (1% v/v)	Quantity of tamsulosin metabolized	
		%	nmoles
NONE	-	21	1.42
Amitriptyline.HCl (5 µg/ml)	-	15	1.01
Diclofenac (200 µg/ml)	-	**89**	**6.00**
Salbutamol (0.5 µg/ml)	-	21	1.42
SKF 525-A (1mM)	-	4	0.27
NONE	+	13	0.88
Glibenclamide (20 µg/ml)	+	12	0.81
Finasteride (2 µg/ml)	+	15	1.01
Warfarin (100 µg/ml)	+	95	6.40

Determinations of Primary Metabolizing

The sponsor incubated tamsulosin with the human liver microsomes from 10 individual donors (NOT POOLED). Microsomes from the same 10 donors were incubated with various marker substrates for specific enzymes. The rate of disappearance of tamsulosin was plotted against the rate of metabolism of the marker substrates and a Pearson correlation coefficient was generated (Table 3).

Table 3.

Enzymatic Reaction	Related cytochrome P450	Pearson correlation coefficient
7-ethoxyresorufin O-dealkylation	1A	0.242
Caffeine N3-demethylation	1A	0.349
Coumarin 7-hydroxylation	2A	0.305
Tolbutamide methyl-hydroxylation	2C	0.725
S-mephenytoin 4'-hydroxylation	2C	-0.087
Dextromethorphan O-demethylation	2D	-0.105
Chlorzoxazone 6-hydroxylation	2E	0.555
Testosterone 6β-hydroxylation	3A	0.971
Lauric acid 12-hydroxylation	4A	0.519

Sponsor's Conclusions:

1. Diclofenac and Warfarin activated the metabolism of tamsulosin by pooled human liver microsomes in a concentration dependent manner.

2. There was no evidence of an effect of amitriptyline, salbutamol, glibenclamide or finasteride on the metabolism of tamsulosin.

3. Because the correlation coefficient with testosterone 6β-hydroxylation, a marker for P-450 3A4, was 0.971, the sponsor has concluded that the primary metabolism of tamsulosin is catalyzed by 3A4.

General Reviewer Comments:

1. The raw data from these studies were not submitted for review. Therefore, reanalysis of these data are not possible.

2. The assay used to estimate the levels of each analyte (tamsulosin and metabolites and marker substrate metabolites) in this *in vitro* drug metabolism study was not properly validated. Therefore, the confidence one can have in any of the conclusions herein, is considerably limited.

3. The concentration of tamsulosin used in these *in vitro* drug metabolism studies (64 to 2400 ng/ml) is 2-80 times the Cmax at steady state from a 0.8 mg dose of the to-be-marketed formulation of tamsulosin (≈30 ng/ml).

4. Only ^{14}C-tamsulosin was used in the *in vitro* drug metabolism studies reviewed herein. It is unknown if an isotope effect on the metabolism may exist.

5. The formation of unidentified metabolites C, D and E appeared to be substantial in some individual donors and metabolite B was measurably formed in all donor tissues tested.

Reviewer Comments on Interaction Evaluations:

1. Diclofenac and Warfarin appear to activate the metabolism of tamsulosin in pooled liver microsomes. The mechanism of activation is not addressed by the sponsor. It should be noted that Diclofenac and Warfarin are primarily metabolized by and are not reported to induce metabolism by any mechanism.

2. Amitriptyline, primarily metabolized by appears to have little effect on tamsulosin

metabolism.

3. In the interaction studies, it is reported that 3-9% of the tamsulosin does not elute with the parent compound in the absence of microsomes (data not shown). The mechanism of the "non-enzymatic" transformation is unclear.

Reviewer Comments on Primary Enzyme Identification:

1. The rationale the sponsor uses to identify as the primary catalyzing enzyme of tamsulosin is inappropriate and probably incorrect since interaction studies with glibenclamide (Drug Saf. 1995, 13: 105-122) and finasteride (Drug Metab Dispos. 1995, 23: 1126-1135) both reportedly metabolized by showed no interaction with tamsulosin metabolism.

2. Since the metabolism of tamsulosin is complex, with at least five possible metabolic pathways primarily catalyzed by the sponsor should identify the enzyme responsible for each metabolic pathway by appropriate *in vitro* metabolism and validated assay methodologies.

Study Number: U95-3371

Study Title: Binding to human liver microsomes and effects on the *in vitro* metabolism of ^{14}C-diclofenac and ^{14}C-warfarin by a pooled human liver microsomal fraction.

Objectives:

1. To determine the effect of diclofenac and warfarin on the binding of tamsulosin to microsomal protein.
2. To determine the effect of tamsulosin on the metabolism of ^{14}C-diclofenac and ^{14}C-warfarin.

Study Design:

Objective #1---- Centrifree™ Micropartition System was used to assess the binding of radiolabeled tamsulosin incubated with pooled human liver microsomal fraction, without added NADP+, in the presence and absence of diclofenac and warfarin for 10 minutes at 37°C.

Objective #2---- ^{14}C-diclofenac and ^{14}C-warfarin were incubated with pooled human liver microsomal fraction in the absence and presence of tamsulosin (1 µg/ml) for 10 minutes at 37°C.

Results

Tamsulosin Binding Interaction

Since warfarin and diclofenac appeared to activate tamsulosin metabolism in Study US95-3365, the sponsor assessed the effect of these compounds on the binding of tamsulosin to microsomal protein. Table 4 contains the results of this evaluation.

Table 4.

Compound	± microsomes	Radioactivity in incubation medium	Radioactivity in Centrifree™ filtrate	% bound radioactivity
water	-	16777	15796	7.2
	+	17481	16620	4.7
DMSO (1%, v/v)	-	20445	18944	6.0
	+	18657	18236	3.1
Diclofenac	+	16700	15132	7.9
Warfarin	+	19741	18534	5.0

Interaction Studies

Tables 5 and 6 contain information about the effect of tamsulosin on the metabolism of diclofenac and warfarin.

Table 5. *In Vitro* Interaction Between Tamsulosin and Diclofenac.

Diclofenac (µg/ml)	± tamsulosin (1 µg/ml)	Quantity of ^{14}C not eluting with parent diclofenac			
		Without microsomes		With microsomes	
		%	nmoles	%	nmoles
200 (627.9 µM)	-	7.0	131.9	23.8	448.4
	+	nm	nm	6.8	79.1
20 (62.8 µM)	-	1.0	1.9	23.4	24.9
	+	nm	nm	12.6	23.8

nm = not measured

Table 6: *In Vitro* Interaction Between Tamsulosin and Warfarin

Warfarin (µg/ml)	± tamsulosin (1 µg/ml)	Quantity of ^{14}C not eluting with parent warfarin			
		Without microsomes		With microsomes	
		%	nmoles	%	nmoles
100 (324.7 µM)	-	0.4	3.9	1.9	18.5
	+	nm	nm	2.7	25.8
10 (32.5 µM)	-	1.3	1.3	1.8	1.8
	+	nm	nm	0.7	0.7

nm = not measured

Conclusions:

1. The extent of binding of radiolabeled tamsulosin to human liver microsomal protein is not substantially affected by the presence of either diclofenac and warfarin.

2. Tamsulosin appears to inhibit the metabolism of ^{14}C-diclofenac in pooled liver microsomes.

3. Tamsulosin does not appear to significantly activate the metabolism of ^{14}C-warfarin in pooled liver microsomes, but the low levels of warfarin metabolism preclude any conclusions on the possible inhibitory effects of tamsulosin.

Reviewer Comments:

1. The raw data from these studies were not submitted for review.

2. The assays used to estimate the levels of each analyte (tamsulosin, warfarin, diclofenac and/or metabolites) were not properly validated.

3. Under the conditions tested in this study, it appears that tamsulosin inhibits diclofenac metabolism.

4. The cause of limited metabolism of warfarin by the pooled liver microsomes used in this study is unknown.

RECOMMENDATION

Study U95-3371 included in the amendment to IND and Study U95-3365 *(in vitro* drug metabolism testing) included in NDA 20-579 submitted on April 15, 1996, have been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the sponsor has not adequately assessed the enzyme(s) primarily or secondarily responsible for the metabolism of tamsulosin.

The sponsor should conduct appropriate *in vitro* drug metabolism studies to characterize the that catalyze the metabolism of tamsulosin. If the Division of Reproductive and Urologic Drug Products (HFD-580) deems that the sponsor has provided sufficient efficacy and safety information for approval of NDA 20-579, Flomax™ (tamsulosin hydrochloride), the *in vitro* testing can be performed post-approval and the label updated, as appropriate.

The sponsor should submit the proposed protocol(s) for the *in vitro* drug metabolism studies to OCPB/DPEII for comment prior to initiation of the studies.

The sponsor's proposed *Metabolism/Excretion* portion of the **CLINICAL PHARMACOLOGY, Pharmacokinetics** section is included below;

> *Metabolism/Excretion*
> Tamsulosin is extensively metabolized by enzymes (in the liver, followed by extensive of metabolites. On administration of a radiolabeled dose of tamsulosin to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours. Less than 10% of the dose was recovered as unchanged (parent) compound in the urine.
>
> Metabolites of tamsulosin do not contribute significantly to tamsulosin adrenoceptor antagonist activity. Furthermore, there is no enantiomeric bioconversion from tamsulosin [R(-) isomer] to the S(+) isomer in studies with mice, rats, dogs, and humans.
>
> Tamsulosin undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h). Tamsulosin exhibits linear pharmacokinetics following single or multiple dosing resulting in a proportional increase in C_{max} and AUC at therapeutic doses. Intrinsic clearance is independent of tamsulosin binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.
>
> Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin in plasma ranged from five to seven hours. Because of absorption rate-controlled pharmacokinetics with the FLOMAX™ modified release formulation, the apparent half-life of tamsulosin increases to approximately 9 to 13 hours in healthy volunteers and to 14 to 15 hours in the target population.
>
> Incubations with human liver microsomes showed no evidence of clinically significant interactions between tamsulosin and drugs which are known to interact or be metabolized by hepatic enzymes, such as amitriptyline, diclofenac, albuterol (beta agonist), glyburide (glibenclamide), finasteride (5alpha-reductase inhibitor for treatment of BPH), and warfarin.

It is the recommendation of this reviewer that the above excerpt of the proposed label be changed to the following text;

> *Metabolism*
> There is no enantiomeric bioconversion from tamsulosin [R(-) isomer] to the S(+) isomer in humans.
>
> Tamsulosin is extensively metabolized by enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Additionally, the enzymes that primarily catalyze the Phase I

metabolism of tamsulosin have NOT been identified. Therefore, possible interactions with other metabolized compounds can not be discerned with current information. The metabolites of tamsulosin undergo extensive Phase II prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor for treatment of BPH). However, *in vitro* testing of the tamsulosin interaction with diclofenac and warfarin were equivocal.

Excretion
On administration of a radiolabeled dose of tamsulosin to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin in plasma ranged from five to seven hours. Because of absorption rate-controlled pharmacokinetics with the FLOMAX™ modified release formulation, the apparent half-life of tamsulosin is approximately 9 to 13 hours in healthy volunteers and to 14 to 15 hours in the target population. Tamsulosin undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

The Recommendation and Comments should be communicated to the sponsor as appropriate.

K. Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes,Ph.D., Team Leader AD 3/6/97
FT signed by Angelica Dorantes, Ph.D., Team Leader 3/7/97

cc: NDA 20-579, HFD-580 (Fourcroy, Rumble), HFD-870 (M.Chen 13B-17, Dorantes, Miller 13B-17, Barnette), Drug file (CDR, Barber Murphy).

Kumor

FEB 25 1997

NDA 20-579

Drug: Flomax (Tamsulosin)

Sponsor: Boerhinger Ingleheim Pharmaceuticals
Ridgefield, Connecticut

RECOMMENDATION- The Pharmacology and Toxicology data submitted are adequate to support the safety of Flomax. The NDA is Approvable.

Labeling Comments- pages 34-36

Jeri El-Hage 2/21/97
Jeri El-Hage, Ph.D.

2/25

cc: NDA 20-579, HFD-580 NDA
HFD-580/ A Jordan/ J El-Hage
20579.nda

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NDA 20-579
Division of Reproductive and Urologic Drug Products
HFD-580
Reviewer: Jeri El-Hage, Ph.D.

Sponsor: Boehringer Ingleheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

Submission Date: April 15, 1996

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

Drug Name: Tamsulosin, LY 253351, YM-12617-1

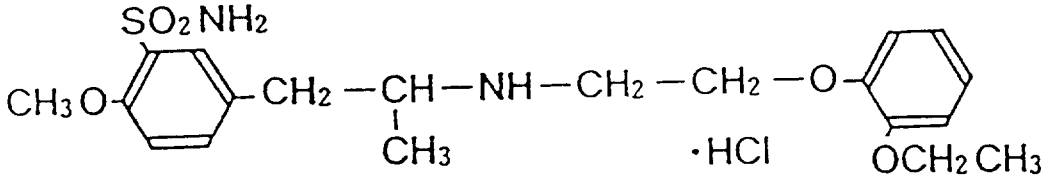
Chemical Name: (R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride

CAS No: 106463-17-6

Proprietary names: Flomax™ (U.S.), Harnal (Japan), Omnic (Europe)

USAN Name: Tamsulosin hydrochloride

Structure:



M.W. = 444.98 M.F. $C_{20}H_{23}N_2O_5S$ Hcl

Formulation: 0.4 mg tamsulosin hydrochloride modified release capsule

Inactive ingredients	mg/capsule
✓Microcrystalline cellulose	
✓Triacetin	
✓Calcium stearate	
✓Talc	
✓Gelatin (capsule)	

Category: Alphal-Adrenergic Receptor Antagonist

Indication: Benign Prostatic Hyperplasia (BPH)

Related NDAs: 20-223 Hytrin (Terazosin) for BPH
20-371 Cardura (Doxazosin) for BPH

Dates of Previous Pharmacology Reviews of IND

PHARMACOLOGY

The potency of Tamsulosin, Prazosin, phentolamine, and yohimbine as postsynaptic α1-antagonists were assessed in rabbit aorta (Table 1). The presynaptic α_2-antagonist activity of the same compounds were assessed in rat vas deferens (Table 2). Tamsulosin and prazosin were determined to be approximately 5,000 times more selective for α_1-adrenergic receptors than for α_2-receptors. Phentolamine has equal affinity for the α_1 and α_2 subtypes. Yohimbine has higher affinity for α_2-adrenergic receptors.

Comparative Blocking Effects of Tamsulosin and Other Adrenoceptor Blocking Agents on α_1- and α_2- Receptors

Antagonist	α_1-adrenoceptor (rabbit aorta)[a] pA_2	α_2-adrenoceptor (rat vas deferens)[b] pA_2	α_1-/α_2-[c]
tamsulosin	10.11±0.04	6.41±0.02	5000
Prazosin	8.85±0.03	5.16±0.02	4900
Phentolamine	8.04±0.04	8.17±0.03	0.74
Yohimbine	6.35±0.01	7.83±0.04	0.03

[a] Determined as potency in antagonizing norepinephrine-induced contraction in 16 to 18 replicates per drug.

[b] Determined as potency in antagonizing clonidine-induced contraction in 12 to 18 replicates per drug.

[c] Antilog of difference between pA_2 values in rabbit aorta and rat vas deferens

Table 2 Inhibition of α_1- and α_2-adrenoceptor binding by YM-12617 and other α-adrenoceptor blocking agents in rat brain membrane preparations

Antagonist	α_1-Adrenoceptor (^{3}H-WB4101 binding)			α_2-Adrenoceptor (^{3}H-clonidine)			α_1/α_2 ratio[c]
	n	pKi[a]	Slope[b]	n	pKi[a]	Slope[b]	
YM-12617	30	9.64 ± 0.06	0.91 (0.84-0.99)	21	6.03 ± 0.03	0.73 (0.70-0.76)	4,100
Prazosin	17	9.39 ± 0.08	0.74 (0.63-0.85)	24	5.53 ± 0.10	0.48 (0.37-0.60)	7,200
Phentolamine	29	8.07 ± 0.06	0.85 (0.76-0.93)	18	8.12 ± 0.07	0.75 (0.67-0.83)	0.89
Yohimbine	18	6.41 ± 0.04	0.96 (0.89-1.03)	18	7.27 ± 0.13	0.80 (0.68-0.92)	0.14

a): pKi values (mean ± SEM) were calculated from negative logarithm of Ki values which were derived from IC_{50} values estimated from logic-log plots of the displacement data shown in Fig. 3.
b): Hill coefficients (means with 95% confidence limits) were calculated by logit-log method as shown in Fig. 3.
c): Antilogarithm of the difference between pKi values obtained in ^{3}H-WB4101 binding and ^{3}H-clonidine binding assays.
n = No. of specimens

The ability of several α-antagonists to inhibit phenylephrine-induced increases in intraurethral pressure (IUP) and diastolic blood pressure (DBP) was assessed in anesthetized dogs (study U93-1087). The relative antagonist potency in this model were:
R(-)YM 12617 (Tamsulosin) > (±) YM-12617 > Prazosin > phentolamine > S(+) YM-12617 > yohimbine.

SAFETY PHARMACOLOGY

The general pharmacology of Tamsulosin was assessed in numerous standard models. Tamsulosin (1 mg/kg, po) had no effect on glucose tolerance in rats. Tamsulosin (10^{-6} to 10^{-4}M) had no effect on platelet aggregation induced by ADP and collagen.

Cardiovascular Effects: Tamsulosin (0.3-3 mg/kg, po) and prazosin (1-10 mg/kg, po) produced large, dose-dependent reductions in mean blood pressure (30-45%) in conscious normotensive rats, conscious spontaneously hypertensive rats, and conscious normotensive dogs. The hypotensive effect of Tamsulosin was 3 times as potent as prazosin. Tamsulosin also produced a dose-dependent inhibition of contractile force at concentrations > 10^{-9} M (maximum inhibition of 35% with 10^{-5}M). The effect of Tamsulosin (0.3-30 ug/kg, iv) on blood pressure and blood pressure responses to head-tilt were compared with prazosin(3-300 ug/kg, iv) in the conscious normotensive rabbit. The potency of these compounds to produce postural hypotension in this model was: Tamsulosin > (±) YM-12617 > prazosin > S(+) YM-12617.
The effect Tamsulosin controlled-release granules on postural blood pressure changes was also assessed in conscious normotensive rabbits.

Data are summarized in the following table. The bulk powder produced maximal reductions in blood pressure at 1-2 hours after dosing which were maintained for 2 to 6 hours. The controlled-release granules also reduced baseline blood pressure for 8 hours.
Postural hypotensive effects were assessed one hour after dosing. Bulk powder produced further postural hypotension with head tilt of 11 mmHg at 0.3 mg/kg and 17 mmHg at 1 mg/kg (in addition to the 14 and 22 mmHg reduction in baseline BP). The controlled release granules produced 6-7 mmHg postural changes with head tilt.

Drug	Dose (mg/kg,po)	Baseline BP (mmHG)	Reduction in Mean BP (mmHg)
Control		102	- 2
Bulk Powder	0.3	98	-14
	1.0	100	-22
	3.0		-34
Controlled release granule	0.3	100	-10
	1.0		-18
	3.0	101	-26

CNS Effects: An Irwin Test was used to assess CNS effects of 0.1, 1, 10, and 100 mg/kg,po Tamsulosin in mice. Tamsulosin had no effect on convulsion threshold or motor co-ordination.
Results: Miosis and blepharoptosis ≥ 1 mg/kg
Decreased motor activity and respiration at 100 mg/kg
Increased hexobarbital sleeping time at 100 mg/kg
Dose-related decrease in body temp ≥ 10 mg/kg
Mild analgesic activity ≥ 10 mg/kg

Doses from 0.1 to 10 mg/kg,po had no effect on EEG activity in the cat. Tamsulosin (10^{-9} to 10^{-5}M) had no effect on acetylcholine or histamine-induced contraction of isolated guinea pig ileum.
Tamsulosin (10^{-5}M) inhibited nicotine-induced (-35%) and serotonin-induced (-65%) contraction in guinea pig ileum.
Tamsulosin (0.1 to 1.0%) produced dose-dependent surface and infiltrative anesthetic effects. The potency of the anesthetic action of Tamsulosin was comparable to lidocaine.

Gastrointestinal Effects: Tamsulosin (0.1-100 mg/kg,po) had no effect on GI transit time in the mouse. Doses from 0.1 to 10 mg/kg,po had no effect on gastric acid secretion in the rat stomach and no effect on gastric mucosa. Tamsulosin at 100 mg/kg,po, the highest dose tested, significantly increased acid secretion in rat stomach and caused ulceration of the mucosa in 2/8 rats. Tamsulosin (0.1-100 mg/kg,po) had no effect on bile secretion in the rat.

Urogenital Effects: Tamsulosin (≥ 10^{-10}M) elicited concentration-dependent inhibition of norepinephrine-induced contraction of rat vas deferens (80% inhibition at 10^{-8}M). Tamsulosin at doses from 0.1 to 10 mg/kg,po had no effect on urinary excretion in the rat.

The pharmacology of the five major metabolites of Tamsulosin namely AM-1 and M-1 through M-4 were studied (see Table 3 below). Metabolite M-4 and impurity R-4 were essentially equipotent with tamsulosin in their ability to inhibit phenylephrine-induced contraction in rabbit aortic and prostatic smooth muscle. The other metabolites were 1/10 to 1/20 as potent as the parent compound.

Table 3 Antagonistic effects of YM-12617-1 and its analogues on the phenylephrine-induced contraction in in isolated rabbit aortic and prostatic smooth muscle

	Aorta		Prostate	
	pA_2 values	Efficacy ratio	pA_2 values	Efficacy ratio
YM-12617-1	9.71 ± 0.09	1.0	9.87 ± 0.13	1.0
AM-1	< 6	<1/5100	< 6	<1/7400
M-1	8.75 ± 0.04	1/9.1	8.96 ± 0.10	1/8.1
M-2	8.44 ± 0.02	1/19	8.70 ± 0.12	1/15
M-3	8.54 ± 0.03	1/15	8.83 ± 0.03	1/11
M-4	9.59 ± 0.06	1/1.3	9.64 ± 0.07	1/1.7
R-4	9.58 ± 0.03	1/1.3	9.66 ± 0.04	1/1.6

Values represent the mean ± S.E. (aorta: N=12-17, prostate: N=3-6)
Efficacy ratios represent values obtained based on a YM-12617-1 value of 1.0.

Tamsulosin (0.5 to 50 mg/kg, ip) produces dose-related increases in plasma prolactin concentrations in male rats.

PHARMACOKINETICS/TOXICOKINETICS

The absorption, metabolism, distribution and excretion studies were performed at the Drug Metabolism Dept., Yamanouchi Pharmaceuticals Co, Ltd., Tokyo, Japan.

Pharmacokinetics in Rats

Male Fischer 344 rats were administered single intravenous and single and multiple oral doses of Tamsulosin and pharmacokinetics parameters were determined. Data are summarized in the table below.

After intravenous dosing in male rats, the plasma clearance rate was 7.88 L/hr.kg and the volume of distribution was 2.86 L/kg.

Pharmacokinetics of Tamsulosin in the Male Rat

Dose, mg/kg	Tmax (min)	Cmax ng/ml	AUC 0-∞ ng.hr/ml	T ½	Bioavail-ability, %
Single dose					
1 mg/kg, iv			127	19 min	100%
1 mg/kg, po	7 min	7	9	1 hr	7%
3 mg/kg,po	"	56	55	1 hr	14%
10 mg/kg,po	"	284	290	1 hr	23%
3 mg/kg,po **15 days**	8-10	28	53	1-2 hrs	

Pharmacokinetics in Dogs

Male beagle dogs were administered single intravenous and single and multiple oral doses of Tamsulosin and pharmacokinetics parameters were calculated. The data are summarized in the table below. After intravenous dosing in male dogs, the plasma clearance = 1.16 L/hr.kg and the volume of distribution = 1.7 L/kg.

Pharmacokinetics of Tamsulosin in Male Beagle Dogs

Dose, mg/kg	Tmax	Cmax ng/ml	AUC 0-∞ ng.hr/ml	T ½, hrs	Bioavail-ability, %
Single dose					
1 mg/kg, iv			87.3	1	100%
0.3 mg/kg,po	30 min	37	78	1-1.5	30%
1 mg/kg, po	"	116	223	"	27%
3 mg/kg, po	"	445	1109	"	42%
Multiple dose					
1 mkd,po, Day 1	1-1.5hr	84	390	2	
1 mkd, Day 8-15	1 hr	132	476	1.5	

Metabolism

Tamsulosin (1, 10, 30 mg/kg,po for 7 days) had no effect on the levels of hepatic drug metabolizing enzymes in rats. Tamsulosin is extensively absorbed from all sections of the rat intestines ~~but~~ not from the stomach. In the rat, there is 100% absorption but only 7-23% bioavailability indicative of extensive first pass metabolism in the liver. The metabolic pathways of Tamsulosin and the metabolite profiles in the urine, bile and plasma of rats and dogs are depicted in Figures 5, 6, 7 and 9 taken directly from the submission (see Appendix 2).

^{14}C-Tamsulosin [(-)isomer] was administered orally to rats, dogs and humans, unchanged drug was isolated from the urine, and the two enantiomers were isolated by HPLC. The (-) isomer represented > 99% of radioactivity in all 3 species, suggesting no enantiomeric inversion occurred in these species.

Excretion

Male Fischer rats and beagle dogs were administered a single oral dose of 1 mg/kg ^{14}C-Tamsulosin and the excretion of radioactivity was monitored in the urine and feces for 72 hours. The excretion data are summarized in the table below. Radioactivity was excreted primarily in the bile (feces) of rats and equally in the urine and bile (feces) of dogs.

Per cent Radioactivity Excreted

Species	Urine	Bile	Feces
Male Rat	17%		80%
Bile-duct cannulated rat	21%	84%	0.4%
Dog (both sexes)	47%		63%
Bile-duct cannulated dog	42%	46%	5%

Distribution

Tissue concentrations of radioactivity were measured in male Fischer rats after single and multiple (21 days) doses of ^{14}C-Tamsulosin (see Appendix II). Steady state concentrations in tissues were reached in approximately 7-10 days. The distribution of radioactivity was as follows:

Liver (25X)> Intestine, stomach, kidney (5-7X) > Prostate, pancreas, lung, salivary gland (1.5X) > Plasma, heart, skin, spleen, adrenal, pituitary > Muscle, fat, bone, testes, brain (0.5X), where multiples represent concentrations relative to plasma drug concentrations.

Plasma Protein Binding

In vitro binding of Tamsulosin ng/ml) to plasma proteins of Fischer rats, beagle dogs and men were measured using the ultrafiltration method.

Per cent Plasma Protein Binding

Species	In vitro Binding	In vivo Binding
Rats, Fischer	80-82%	—
Dogs, Beagle	90-93%	
Human	94-95%	96-98%

Kinetics of Tamsulosin After In Diet Dosing to Rats and Mice
Fischer rats (n = 5/sex/dose) and B6C3F$_1$ mice (n= 5/sex/dose) were administered 0.01, 0.03 and 0.1% Tamsulosin in the diet for 2 weeks. These dose levels represent the 3 highest dose levels utilized in the 2 year carcinogenicity studies. The concentrations of unchanged drug were measured in the plasma for 24 hours from the 15-16th day of dosing. Toxicokinetics data are summarized in the table below taken directly from the submission.

Animal	Sex	Drug Conc. in Diet (%)	Drug Intake (mg/kg/day)	Plasma Conc. of Unchanged Drug	
				Cmax (ng/ml)	AUC 0-24 (ng·hr/ml)
Rats	Male	0.01	8.4	4.6	64.2
		0.03	25.9	11.5	199.8
		0.1	86.6	111.8	1411.7
	Female	0.01	8.2	6.2	99.5
		0.03	25.2	17.0	268.5
		0.1	87.0	141.2	1845.5
Mice	Male	0.01	16.1	5.2	15.6
		0.03	49.8	47.9	576.2
		0.1	173.7	330.0	3593.9
	Female	0.01	19.0	9.0	95.7
		0.03	59.7	54.7	841.5
		0.1	192.2	313.4	4139.1

Single Dose Oral Gavage Toxicokinetic Study with YM 617 in Rats(Study U95-3130 lot W001)

The study was conducted according to GLP at from 7-12-94 to 3-8-95. The study was conducted to provide toxicokinetics data for the dose levels utilized in the reproductive toxicity studies.

Male and female Fischer 344 rats were administered a 10 or 300 mg/kg single dose of Tamsulosin orally by gavage (n=24/sex/dose). Blood samples were collected from 3 animals at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours postdose. The kinetics data are summarized below.

Single Dose Toxicokinetics of Tamsulosin in Rats

Dose level (Mg/kg)	Cmax (ng/ml)	Tmax (hrs)	AUC 0-24 (Ng.hr/ml)	Multiple of Human AUC
10	46	0.5	96	1/5
300	2,773	0.5	24,984	50

Summary and Conclusions- This study provides the only toxicokinetics data for gavage dosing in the rat. The study suggests that AUC exposures in rats administered 300 mg/kg, the highest dose utilized in the reproductive toxicity studies are fold higher than those in elderly men receiving the highest therapeutic dose (AUC in men on 0.8 mg/day = 500 ng.hr/ml). This data is somewhat flawed because this study was performed using the drug product (- isomer) Tamsulosin while most of the reproductive toxicity studies were conducted with the racemate. The exception is the highly relevant male fertility study which was repeated using Tamsulosin.

Although this data is not perfect, it probably provides the most useful data available for exposure comparisons. The reproductive toxicity studies have been conducted with single daily doses of the pure drug which has a very short half-life (1-2 hours). The drug product Flomax is given twice daily in a modified release preparation with a 9-13 hour half-life resulting in sustained exposures to drug in men. Utilization of mg/kg or mg/M^2 comparisons provides grossly exaggerated exposure comparisons due to both the different formulations and interspecies differences in metabolism. (EG., On a mg/kg basis 300 mg/kg/day represents times the clinical dose of 0.01-0.12 mg/kg, while AUC data demonstrates an actual exposure multiple of times human AUC).

Single Oral Dose Toxicokinetics of YM617 in Dogs (study U95-3126, lot # W001

The study was conducted at — from 8-9-94 through 10-14-94.

Male beagle dogs (n = 3/dose) were adminsitered a single dose of 2 or 200 mg/kg YM617 orally by capsule. Blood samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours postdose. The toxicokinetics data are summarized below.

Single Dose Toxicokinetics of Tamsulosin in Dogs

Dose, mg/kg	Cmax Ng/ml	Tmax Hrs	AUC 0-24 Ng.hr/ml	Half-life Hrs	Multiple of Human AUC
2	183	1.83	487	1.24	1 X —
200	8,393	6.67	100,831	2.65	200 X

TOXICOLOGY

Acute Toxicity
Acute toxicity studies for Tamsulosin were previously reviewed in IND

Toxicology Studies Completed
Racemate
Oral toxicity studies conducted with the racemate include acute toxicity studies in mice, rats and dogs, three month oral toxicity studies in rats and dogs, a one year oral toxicity study in rats, and fertility studies in male and female rats. Ocular and dermal toxicity studies were also performed with the racemate. These data were all previously reviewed for IND
Teratology studies in rats and rabbits and a Peri/Postnatal toxicity study in rats were conducted with the racemate and are reviewed for IND

Tamsulosin
Oral toxicity studies with the drug product Tamsulosin (R-isomer) include acute toxicity in mice, rats and dogs, and three month in-diet dose-finding studies in mice and rats, and one year oral toxicity studies in rats and dogs. Genotoxicity and male fertility studies were also conducted with Tamsulosin. These studies were reviewed for IND The data from the oral dose finding studies and the two year oral carcinogenicity studies are reviewed below.

One Year Oral Toxicity in Rats (Study R04987 and R05087, lot H-2)
This study was previously reviewed under IND
The study was conducted according to GLP at
for March 20, 1987 through Jan 5, 1989.

Fischer 344 rats (n= 20/sex/dose) were administered 0, 0.03, 0.1 and 0.3 % LY 253351 in diet for one year.
Additional findings not noted in the previous review include:
Organ weights
Increased adrenal weights(35%) in HD males
Increased liver weights in all treated females
Increased spleen weights in MD, HD females
Marked (>60%) decrease in uterine weights in MD, HD females
Increased pituitary weights in MD, HD females

Histopathology
Kidney - increased frequency of glomerulonephrosis in treated males
2/20 C, 7/20 LD, 6/20 MD, 6/20 HD males
Testes- bilateral atrophy of seminiferous tubules in 5/20 HD males
Mammary gland- dose-related increase in the incidence and severity of mammary gland hyperplasia in treated females (slight in LD, MD; moderate in HD) 0/20 C, 3/20 LD, 16/20 MD, 20/20 HD females

CARCINOGENICITY

Three Month Oral Dose-Finding/Toxicity Study in Fischer Rats (study R10986, lot #H-1)

The study was conducted according to GLP at
from July 2, 1986 to October 3, 1986.

Fischer 344 rats (n = 20/sex/dose) were administered 0, 0.1, 0.3 and 0.5% LY 253351 orally in diet for 3 months.

Compound was stable and diets were within 8% of nominal concentrations in all diet samples analyzed. Mean daily intake of LY 253351 was 67.5, 200 and 327 mg/kg/day in males and 80, 228 and 378 mg/kg/day in females.

Mortality - unremarkable (1 LD male died while on study)

Clinical signs - The incidence and duration of chromodacryorrhea was increased in mid and high dose males and in females at all dose levels
Incidence: Males- 0 C, 1 LD, 8 MD, 5 HD
Females- 5 C, 13 LD, 13 MD, 19 HD
Duration: 1-2 weeks in males and LD females, 2-4 weeks in MD females and 9-11 weeks in HD females

Body weight -statistically significant dose-related decreases in mean body wt and body wt gain in MD, HD males and HD females. Body weight gain was reduced 13% in MD and 35% in HD males and 30% in HD females.

Food consumption- dose-related decreases in average daily food consumption in mid and high dose males and females.
Males - decreased 9% MD, 24% HD
Females - decreased 9% MD, 23% HD

Hematology -
RBC,Hgb,PCV- significantly decreased in MD, HD of both sexes
MCV, MCH, MCHC- mildly increased in MD, HD animals of both sexes.
Mean reticulocyte counts- increased in MD, HD both sexes, indicative of increased bone marrow activity.
Total leukocyte counts - dose-dependent decreases at all dose levels in treated males.

Clinical chemistry-
AST- increased 2-fold in HD females

Urinalysis-
Specific gravity - mildly increased in HD females

Hepatic Enzyme Induction: P-Nitroanisole O-demethylase activity was slightly increased in males and females receiving the 2 highest dose levels.

Plasma Drug Concentrations-C_{ss} measured from 3 samples/sex/dose obtained between 8 and 10 am on days 15, 45, and 89.

Ng LY 253351/ml

Sampling Day		15	45	89	Multiple of Human Cmin[a]
Males,	0.1%	45	38	36	2.5 X
	0.3%	621	544	512	38 X
	0.5%	944	1918	2354	
Females,	0.1%	69	140	65	5 X
	0.3%	1119	1076	1465	80-100 X
	0.5%	1490	2087	1456	100 X

a. Cmin after multiple dosing with 0.8 mg/day in volunteers the same age as the target population (elderly males) = 13 ng/ml. Cmax in this population = 29 ng/ml.

Organ Weights
Adrenal- dose-related increase in absolute and rel wts at all dose levels in males and in HD females
Spleen- increase in absolute and relative weights in LD, MD males and at all dose levels in females.
Liver- increased absolute and relative weights all doses males and females.
Kidneys - decreased absolute wts MD, HD males; HD females
Ovaries- increased absolute/ relative wts. LD, MD females

Histopathology-
Mammary glands- dose-related increase in the incidence and severity of mammary gland hyperplasia in treated females; mild in LD, moderate in MD, severe in HD . 0/20 C, 2/20 LD, 17/20 MD, 18/20 HD females.

No other drug-related pathology.

Conclusions- No dose-limiting toxicity was observed at any dose level. Decreased body weight gain secondary to decreased food consumption (decreased palatability ?) was observed in MD, HD males and HD females. The sponsor states that 0.1% was the **no effect level.**

Based on this study the sponsor choose dose levels of 0.003, 0.01, 0.03 and 0.1% for the 2 year rat carcinogenicity study. These dose selections would not be supported by this dose-finding study. Body weight reductions > 10% were observed in MD, HD males and HD females but these were secondary to decreased food consumption. No data is available regarding body wt/food consumption with gavage dosing at dose levels > 100 mg/kg. No other dose-limiting toxicity was observed. The oral LD_{50} for Tamsulosin in Fischer rats is 650 mg/kg in males and 750 mg/kg in females.

Tamsulosin was not genotoxic in an extensive battery (Ames, CHO Chromosome Aberrations, Mouse lymphoma/TK, Unscheduled DNA Synthesis, Sister Chromatid Exchange, Mouse Micronucleus Test). AUC data were not available from this study to allow dose selections to be based on AUC ratios. Comparison of Css data from rats and humans suggests the high dose of 0.1% LY 253351 in rats produces plasma levels 2 to 5 times those in men receiving a 0.8 mg/day dose. Clearly, this does not meet the 25-30 times human exposure requirement.

Two Year Carcinogenicity Study with LY 253351 Administered in Diet to Fischer 344 Rats (Study 07187 and 07287, lot # DPD-11101 and 12151)

The study was conducted according to GLP at
from June 23, 1987 to June 23, 1989.
The test article was stable throughout the duration of the studies. Mean dietary concentrations were within 10% of nominal concentrations in all samples. Lot DPD 11101 was 99.5% R -enantiomer (drug product); lot DPD 12151 was 98.8% R enantiomer.

Fisher 344 rats (n = 60/sex/dose) were administered 0, 0.003, 0.01, 0.03, and 0.1% LY235531 orally in diet for 2 years.
These concentrations resulted in average daily doses of:
1.3, 4.3, 13.1 and 43.3 mg/kg/day for males
1.6, 5.4, 16.0 and 51.6 mg/kg/day in females

Mortality-
Two year **survival** rates were as follows:
Males - 57%, 42%, 53%, 40%, and 32% for control, LD, LMD, HMD, and HD
Females-67%, 67%, 48%, 60%, and 43% for control, LD, LMD, HMD, and HD.

The apparent dose-related mortality was statistically significant for both sexes(See biostatistics review page 8). Therefore, the 2 year rat carcinogenicity study was conducted at adequate dose levels despite the inadequacy of the dose-finding data.

Clinical signs- no treatment-related signs

Body weight/food consumption- food consumption was increased in MD, HD females and HD males from study month 6-7. Slight increases in body weight gain were observed in these dose groups during months 4 to 15 but body weight and wt gain were similar to control values in all groups at the end of the study.

Hematology-no treatment-related changes

Clinical chemistry- changes observed were consistent with impairments in kidney and liver function.
BUN- increased in both sexes at all dose levels.(50 to 100%)
Creatinine- increased in both sexes at all dose levels
Cholesterol- increased in both sexes at doses ≥ 0.01% (5 mg/kg/day)
Triglycerides - increased in treated males at all dose levels.

Plasma Drug Concentrations- Samples were collected from 3 rats/sex/dose between 8 and 10 am on days 93 and 640. Levels were below quantifiable levels (20 ng/ml) for the 3 lowest dose levels. Plasma levels in the high dose group are shown in the table below. These plasma concentrations in male rats are 1-3 times therapeutic C_{ss}.

Plasma Concentrations (ng/ml) of LY 253351

	Day 93	Day 640
Males , 0.1%	28 ± 14	39 ± 12
Females, 0.1%	119 ± 22	59 ± 7

A separate TK study was conducted according to GLP by Yamanouchi Pharmaceuticals, Ltd, Japan (study 389323, 1990). The study provides Cmax and AUC data after 2 weeks of dosing with 0.01, 0.03 and 0.1% LY 253351 in diet in Fischer 344 rats and B6C3F1 mice. Data for rats are summarized below.

Plasma Concentration of LY 253351

Rat, Fischer	Drug Conc(%)	Drug Intake mg/kg/day	Cmax (ng/ml)	AUC 0-24 (ng.hr/ml)	Multiple of Human AUC with 0.8 mg/day*
Male		8.4	4.6	64.2	1/9
		25.9	11.5	199.8	2/5
		86.6	111.8	1411.7	3 X
Females		8.2	6.2	99.5	
		25.2	17	268.5	
		87.0	141.2	1845.5	

* AUC_{0-24} in elderly men dosed with 0.8 mg/day = 450 ng.hr/ml (fed) and 550 ng.hr/ml (fasted).

Organ weights- absolute and relative organ wts changes included
Kidney - increased in both sexes at all dose levels
Liver- increased in LMD, HMD and HD males; HMD and HD females
Heart- increased in both sexes at doses ≥ 0.01% (5 mg/kg/day)
Spleen - increased in HMD and HD males
Prostate- increased in males at all dose levels
Uterus- decreased wts in females at all dose levels.
Adrenal- wts increased in HD males
Thyroid- decreased wts in males at doses ≥ 0.01% (5 mg/kg/day)

The increased kidney weights were secondary to increased severity of glomerulonephrosis. The increased liver wts were considered to be secondary to mild induction of microsomal enzymes. Weight changes in the prostate, uterus, adrenals and thyroid were small and not associated with histopathologic alterations.

Histopathology
Data tables for non-neoplastic findings, benign neoplastic findings, and malignant neoplastic findings are summarized in Tables 38, 39, and 40 in Appendix III of this review. Also see the Biostatistics Review.

Non-neoplastic findings
Tissues with dose-related non-neoplastic findings are summarized in the table below. In the liver, centrilobular degeneration and necrosis were observed with increased frequency in high dose males. Thrombosis in the left atrium was observed with increased frequency in male rats receiving 16 and 51 mg/kg/day (high dose gives C_{ss} exposure 2.5 times human; high middle dose exposure ≤ human therapeutic exposure). Stomach ulcers were more prevalent in male rats at all dose levels and in high dose females. Moderate to severe mammary gland hyperplasia was observed with increased frequency in drug-treated females. This finding has been observed in all other rat toxicity studies and is secondary to elevations in serum prolactin levels. Pituitary gland hyperplasia was observed with increased frequency in high dose female rats. This may also be related to drug-induced prolactin secretion.

Organ/ Finding	Sex	control	0.003%/ 1.5 mkd	0.01%/ 5 mkd	0.03%/ 15 mkd	0.1%/ 45 mkd
Liver-Centilobular	M	5	6	5	7	14
degeneration	F	6	7	10	2	3
Centrilob. Necrosis	M	0	2	1	1	2
	F	0	0	0	1	2
Heart -Thrombosis	M	3	3	4	10	12
Left Atrium	F	3	5	3	3	2
Spleen - Infarct	M	0	1	3	1	3
	F	0	1	0	0	1
Stomach- Ulcer	M	1	6	7	10	8
	F	3	2	3	4	6
Mammary gland	M	1	0	2	1	0
hyperplasia (gd 3-4)	F	10	13	15	21	16
Pituitary	M	0	0	0	0	0
hyperplasia	F	0	0	0	0	12

n = 60/sex/dose.

Neoplastic Findings-

Benign- The following benign neoplasms were observed with dose-related incidence

Lung- Adenomas were observed in 1 C, 2 LD, 0 LM, 0 HM, 4 HD males (P< 0.02). Historical incidence rates for this tumor are 1.3% (NTP) and 2.3% (Charles River, 1990 data). Therefore, lung adenomas are common tumors and the P value does not meet the CDER requirement of p< 0.005 for significance.

Uterus -Leiomyoma was observed in 0 C, 0 LD, O LM, 0 HM and 2 HD females (P< 0.022, sponsor; P< 0.018, biostat review pg 49). Leiomyoma are rare tumors in females rats with historical incidence rates of 0.2% (NTP) and 0.5% (Charles River). Therefore, the P values of < 0.022 (0.018) meet CDERs requirement of P< 0.025 for significance of a rare tumor.

Skin-Adnexal gland adenoma was observed with increased frequency in treated males 0 C, 0 LD, 1 LM, 1 HD and 1 HD male. The historical incidence rate is 0.1% (NTP 1 tumor/948 male rats). The biostat review calculates a P value of < 0.15 to 0.17 obviously not statistically significant.

Brain- Numerous rare brain tumors (astrocytoma, glioma, oligodendroma, ependymoma) were observed in the study but the incidence of the individual tumor types did not reach statistical significance (see biostat review pg 24) except in males with oligodendroglioma. The historical incidence rate of oligodendroglioma is 0.5% (NTP) and 0.2% (Charles River, 1990).

Oligodendroglioma
Males - 0 C, 0 LD, 0 LM, 0 HM, 1 HD P< 0.019-0.027 (biostat,pg 24)
Females - 0 C, 0 LD, 0 LM, 0 HM, 1 HD P< 0.06 (biostat, pg 39)

Mammary gland

The incidence of mammary gland fibroadenomas was increased in females at dose levels ≥ 0.01% (5 mg/kg/day).

Incidence = 9 C, 13 LD, 17 LMD, 14 HMD, 16 HD(P< 0.015).

Mammary gland fibroadenomas are common tumors in female Fischer rats occurring in 2.6% (range %, NTP) and 12% (range = %,Charles River, 1990) of control females in 2 year carcinogenicity studies. Therefore, the P value of < 0.015 is not adequate to meet CDER requirements of P< 0.005 for significance of common tumors. However, it is clear that these tumors are drug-related since tamsulosin has been demonstrated to increase plasma prolactin levels in rodents, produce dose-related mammary gland hyperplasia in female mice and rats, and increase the incidence of mammary gland fibroadenomas and adenocarcinomas in female mice.

Malignant neoplasms

Mononuclear Cell Leukemia(MCL)-The frequency of MCL as the cause of death and the severity of the cancer (degree of metastases) displayed a dose-related increase in drug treated males. The frequency of MCL as cause of death are presented below.

	Number of Rats Dying from Mononuclear Leukemia				
	Control	**0.003%**	**0.01%**	**0.03%**	**0.1%**
Males	12	17	16	24	21
Females	8	9	13	9	12

According to the sponsors analysis, the incidence of MCL displayed a dose-related increase in frequency in male rats ($P< 0.014$). MCL is a common tumor with a historical control frequency of 33.6% (NTP) and 16.5% (Charles River, 1990 data for approximately 950 male Fischer rats). Therefore, the P value of < 0.014 is not adequate to meet FDAs requirement of $P< 0.005$ for common tumors.

Conclusion- The rat carcinogenicity study is adequate in that the doses clearly exceed the MTD as evidence by a statistically significant increase in mortality in high dose rats of both sexes. Survival was adequate in all dose groups , except high dose males, to permit evaluation of 25 surviving rats/dose group ($\geq$ 40% survival x 60 rats/sex/dose).

Treatment with Tamsulosin increased the frequency of leiomyomas in the uterus of HD female rats. Drug treatment increased the incidence of mammary gland hyperplasia and fibroadenomas in drug-treated females. An increase in frequency of mononuclear cell leukemia was observed in male rats.

The biologic significance of the tumor findings was discussed in a meeting of the Executive Carcinogenicity Assessment committee on January 21, 1997. The increased frequency of leiomyoma in females was not deemed biologically significant because it was observed in only 2 rats in the highest dose group where the dose level clearly exceeded the MTD. In addition, this finding is not a major concern since the drug is indicated for use in males only. The increase in mononuclear cell leukemia was not deemed biologically significant since the P value did not meet the requirement of $P< 0.005$ for common tumors. Although the mammary gland findings did not reach significance according to CDER guidelines, it was concluded that the finding should be discussed in the labeling in association with the mammary tumor findings in mice.

Three Month Oral Dose-Finding Study in Mice (study M02986, lot

The study was conducted according to GLP at from August 15, 1986 through Nov 19, 1986.

B6C3F$_1$ mice (n = 15/sex/dose) were administered LY253351 in diet at concentrations of 0, 0.1, 0.35 and 0.7% (150, 525, and 1050 mg/kg/day) for 3 months. The test drug was stable for the duration of the study and was within 7% of nominal concentrations in all diet samples. A satellite experiment(M03086) was conducted with the same dose groups (12/sex/dose) sampled between 8 and 10 am on days 2, 45 and 90 for determination of plasma concentrations of LY 253351.

Mortality- Deaths in 3 M, 1 F in the high dose group of the main study. In the TK satellite study 2 LD and 1 HD male rats died. Deaths in the LD males were attributed to a defective water nipple. Two HD males from the main study (#3002, 3007) had distended urinary bladders at necropsy. Cause of death in other animals could not be determined.

Clinical signs-
Alopecia- 0 C, 3 LD, 4 MD, 8 HD

Body weight- decreased body weight gain (33%) in HD males. Body weight gain was increased from control values in females at all dose levels (30% LD, 50% MD, 40% HD). Note: Historical control data for body weight gain in females was not provided.

Food consumption data was not provided. There is no indication in the methods that this data was collected during the experiment so it is unclear how dosing was calculated or confirmed. Animals were group caged (3/cage). Obviously it is impossible to assess if decreased body wt gain in HD males was secondary to decreased food consumption.

Hematology -(analyzed at 3 months)
RBC, HGB, PCV- slightly decreased in HD females
Leukocyte counts.- decreased MD, HD males; HD females
Lymphocyte counts -decreased (27%) in HD males
Neutrophil counts - increased (50%) in HD males

Clinical chemistry-
Alkaline phosphatase - mildly increased (25%) in HD males
ALT- mildly increased (50%) in HD males; 2-fold increase in HD females
AST - 2-fold increase in HD males and HD females

Hepatic Enzyme Induction-
Administration of LY 253351 to mice for 3 months had no effect on hepatic p-Nitroanisole O-Demethylase activity in males and produced slight(30%) increases in activity in MD, HD females.

Plasma drug concentrations -plasma samples for 4 animals were pooled for measurement. Plasma concentrations are summarized in the following table. There were no sex differences in metabolism and no accumulation with multiple dosing. The reason for the discrepant values on day 44 is unknown.

Plasma LY 253351 Levels in Mice (ng/ml)

Diet Conc.	0.1%	0.1%	0.35%	0.35%	0.7%	0.7%
	Males	Females	Males	Females	Males	Females
Day 1	267	164	1199	1050	2349	2272
Day 44	85	49	156	186	890	411
Day 90	250	189	1629	1558	2422	2556

Organ weight
Males - There were no differences in absolute organ weights between treatment groups. Increases in relative liver, testes and brain weights were observed in high dose males but were probably secondary to the decreased body weight in this group.
Females-Increased absolute weights for kidneys, liver, spleen, and pituitary were observed in females at all dose levels (weight increases were not dose-related). Relative weights were also increased in the liver, spleen and pituitary suggesting these observations were real. Uterine weights (absolute and relative) were decreased in a dose-related fashion in all females.

Histopathology -
Two high dose males had renal tubular casts, severe urinary bladder distension and lung congestion. (These were animals that died on study).
The only other drug-related histopathologic finding was mammary gland hyperplasia in female mice. Most treated animals were affected with incidence rates of 0 C, 13/14 LD, 12/13 MD, 13/14 HD . The lesions were dose-related in severity being minimal in LD, slight in MD and moderate in severity in HD female mice.

Summary and Conclusion- Administration of LY253351 to B6C3F1 mice for 3 months was generally well-tolerated. Administration of 0.7% (1050 mg/kg/day) produced deaths in 4/15 in the main study and 1/15 in the TK satellite study. This dose level also caused decreased body weight gain in males (33%), decreases in hematology parameters and increases in liver enzymes. Evidence of renal damage was observed in 2 HD males which died during study. Data from the 2 year rat study also suggested toxic effects on the kidney as the severity of glomerulonephropathy(GN) and number of deaths due to GN increased in a dose-related fashion. No significant pathology was observed in other organs with the exception of mammary gland hyperplasia in mice treated females.

Again, there is not adequate toxicokinetics data to base dose selection on multiples of human therapeutic AUC exposure.
Data from the study suggest 0.7% is too high a dose (deaths, elevated liver enzymes). The sponsor chose the same dose levels for the mouse carcinogenicity study as those used in the rat study, namely 0.003, 0.01, 0.03 and 0.1%. Data from the 3 month dose-finding study suggest the 0.35% dose would be tolerated.

Two Year Oral (In diet) Carcinogenicity Study with LY 253351 in B6C3F1 Mice (Study M01487, M01587, lot #DPD-11101, DPD12151)

The study was conducted according to GLP at
from July 22, 1987 to August 2, 1989.
The lots used were 99.4% and 98.8% R isomer (drug product) and 0.2 and 0.4% S isomer. Absence of enantiomeric inversion in vivo has been demonstrated in mice, rats, dogs and man.

$B6C3F_1$ mice (n = 60/sex/dose) were administered 0, 0.003, 0.01, 0.03, and 0.1% LY 253351 in diet for 2 years.
These concentrations in diet provided mean drug concentrations as follows: 3.7, 12.6, 39.1, 126.8 mg/kg/day in males
3.3, 14.5, 45.2, 158.1 mg/kg/day in females
The test article was stable throughout the studies and assayed concentrations of LY253351 were within 10% of nominal for all samples analyzed.

Mortality- Survival rates are summarized in the table below.

Per cent Survival at Two Years

Dose	Control	0.003%	0.01%	0.03%	0.1%
MALES	92%	73%	73%	67%	73%
FEMALES	73%	72%	70%	60%	50%

A statistically significant increase in mortality was observed in all treated male groups compared to controls. However, this effect is equivocal because the survival in the control group is unusually high and the survival in the treated groups is comparable to historical control data.
The increased mortality in females is statistically significant ($P< 0.003$) and displays a dose-related pattern.
Historical control rates for mean survival rates in control female B6C3F1 mice in 2 year CA studies at Lilly (1985-86, n= 8) was 77%. The range of survival in these studies was 65% to 86%.

Clinical signs-
Signs observed with a treatment-related increase in frequency are summarized below.
Penile swelling- 5 C, 4 LD, 10 LMD, 10 HMD, 8 HD males
Distended abdomen - 3 C, 10 LD, 6 LMD, 10 HMD, 9 HD males
Labored/shallow respiration - 0 C, 2 LD, 1 LMD, 4 HMD, 3 HD (M and F)
Nodule - 8 C, 6 LD, 4 LMD, 16 HMD, 25 HD females

Body weight-no significant effects on mean body weight or body weight gain were observed in LY253351 treated mice.
Food consumption- mean food consumption was slightly increased in HD females throughout the study.

Hematology-
RBC, Hgb, PCV- mild non dose-related increases in treated females.
Leukocytes, lymphocytes, neutrophils - increased (50%) HD both sexes
Bands - increased 10-fold in HD males
Monocytes- dose-related decrease in all groups; significant in HMD and HD males (decreased 65% in these groups)

Clinical chemistry- unremarkable

Plasma drug concentrations- Samples were collected from 8 to 10 am on days 7, 90, 365 and 630 of dosing. Plasma concentrations were below the limit of quantitation for most timepoints and did not display a dose relationship. The plasma concentrations could not confirm dosing. Therefore, the sponsor measured urinary excretion of drug which confirmed systemic exposure to LY253351.
The best available toxicokinetics data in the mouse is from the 2 Week study conducted by Yamanouchi, Japan (study U93-1084). B6C3F1 mice were administered 0.01, 0.03, and 0.1% LY 253351 orally in diet for 2 weeks and Cmax and AUC values were determined. Data are summarized in the table below.

Mice, B6C3F1	Drug Conc %	Drug Intake (mg/kg/day)	Cmax (Ng/ml)	AUC 0-24 (ng.hr/ml)	Multiple of Human AUC*
Males	0.01	16.1	5.2	15.6 ??	
	0.03	49.8	47.9	576.2	1 X
	0.1	173.7	330.0	3593.9	7 X
Females	0.01	19.0	9.0	95.7	
	0.03	59.7	54.7	841.5	
	0.1	192.2	313.4	4139.1	

* AUC_{0-24} in elderly men dosed with 0.8 mg/day = 450 ng.hr/ml(fed) and 550 ng.hr/ml (fasted).
?? The accuracy of this value is questioned as the AUC value for females is considerably higher than for males and no sex differences in kinetics are observed at any of the other dose levels (or in rats).
Organ weights-
Kidney- increased abs wts in HD mice of both sexes
Increased relative wts in males at all dose levels
Liver- increased absolute/rel. wt in HD females
Spleen - decreased abs/rel wts in all treated males;
increased abs/rel wt in HD females
Uterus- decreased abs/rel wts in HMD (30%) and HD (60%) females

Histopathology
Data for non-neoplastic findings, benign neoplastic findings, and malignant neoplastic findings are summarized in Tables 47, 48 and 49 in Appendix III of this review.

Frequency of Non-Neoplastic Findings

Tissue/Finding	**Control**	0.003% 3.5 mkd	0.01% 13 mkd	0.03% 40 mkd	0.1% 127 mkd
Bladder,					
Distension, Males	4	14	3	13	10
Inflammation, Males	1	2	1	4	
Lung, Congestion Males	3	2	5	6	8
Spleen,					
Hyperplasia, Females	13	22	18	17	22
Uterus, Hyperplasia	31	25	28	14	8
Seminal vesicles					
Distension	1	4	7	28	35
Inflammation	0	3	3	9	9
Penis,					
Prepuce Inflammation	0	5	1	2	0
Mammary gland					
Hyperplasia, Females	4	3	6	5	40

Drug treatment was also associated with an increase incidence of death due to mouse urologic syndrome in males- 0 C, 6 LD, 0 LMD, 8 HMD, 7 HD

Benign Neoplastic Lesions- The following lesions were increased in Tamsulosin treated mice.

Benign Neoplastic Lesions

Tissue/Benign Neoplasm	**Control**	**0.003**	**0.01%**	**0.03%**	**0.1**	**P * Value**
Liver, Hemangioma (Males)	0	0	0	0	1	<0.026
Spleen, Hemangioma(Female)	0	0	1	1	4	<0.0011
Testis, Interstitial Tumor	0	0	2	1	2	<0.085
Skin, Hemangioma (Females)	0	0	0	0	3	<0.0005
Mammary gland (Females)						
Adenoma	1	1	0	2	2	
Fibroadenoma	0	0	2	7	16	<0.0000

* P values are taken from FDA Biostatistical Review ,page 18.

Spontaneous tumor rates in B6C3F$_1$ mice (Charles River,1989 data for 1360 mice/sex) are as follows:

Liver hemangioma in males 9/1257 = 0.7% (range)
Spleen hemangioma in females 10/1269 = 0.8% (range %)
Skin hemangioma in females 4/1286 = 0.3% (range %)

Hemangiomas are uncommon tumors (< 1%)in B6C3F1 mice. The single finding in a HD male is close to statistically significant for a rare tumor, but clearly falls within the historical control range. The sponsor's "whole animal analysis" for hemangioma/hemangiosarcoma findings demonstrated a statistically significant increase ($P< 0.007$) in the incidence of these tumors in high dose female mice. Hemangioma are rare tumors (<1%) in control female B6C3F1 mice studied during the same time period at NTP or Charles River. The historical control incidence of hemangiomas in female B6C3F1 mice in carcinogenicity studies conducted at were 0/60 in 5 studies, 1/60 in 5 studies and 2/60 in one study. These data suggest the increased frequency of hemangioma in female mice at the highest dose level is biologically significant. However, the high dose in females exceeded the MTD as evidenced by the increased mortality at this dose.

The increased incidence of mammary gland fibroadenomas in females at dose levels ≥ 0.03% is also highly significant.
The sponsor's analysis found no significant increase in the incidence of benign neoplasms in male mice.

Malignant Neoplasms
The following malignant neoplasms were observed with increased frequency in Tamsulosin treated mice.

Malignant Neoplasms in Mice

Tissue/Neoplasm	Control	0.003%	0.01%	0.03%	0.1%	P Value
Liver						
Lymphosarcoma (Male)	1	0	0	0	4	P<0.0008
Hemangiosarcoma(male)	0	0	0	1	0	
Mammary gland(Female)						
Adenocarcinoma	1	0	1	4	4	P<0.0075

Both the sponsor's (see Appendix III) and FDA's analyses (Appendix I) revealed a statistically significant increase in the frequency of mammary gland adenocarcinoma in female mice at dose levels ≥ 0.03%. The FDA biostatistics review also concluded that there was a highly statistically significant dose-related increase in the frequency of lymphosarcoma in the liver of male mice. The sponsor performed a whole animal analysis on the frequency of lymphosarcoma which was not significant for either sex of mice. Lymphosarcomas are common tumors in B6C3F mice with incidences of 6% in males (range %) and 12% in females (range %).

Conclusion -
The hemangioma and mammary tumor findings in female mice are both statistically and biologically significant and will be discussed in the labeling. There were no biologically significant tumor findings in male mice treated with Tamsulosin for 2 years.

IMMUNOTOXICITY

Studies to evaluate the effects of Tamsulosin on immune responses in mice (IgE production) and the induction of anaphylaxis in guinea pigs were previously reviewed (see Appendix I). Arthus reaction and delayed skin reaction tests were also conducted in guinea pigs using the racemate YM 12617 at doses of 0.05 or 2.5 mg/animal (study # 391858). YM 12617 did not produce Arthus or delayed skin reactions in guinea pigs.

REPRODUCTIVE TOXICITY
The effects of YM-12617 (racemate) on male and female fertility in rats was evaluated in study 85104 performed at Yamanouchi Pharmaceuticals. These studies were previously reviewed under IND . The effects of the racemate on reproduction were also evaluated in teratology studies in rats and rabbits, a peri/postnatal toxicity study in rats and a two generation reproductive toxicity study in rats. These studies are reviewed under IND . Studies submitted under the NDA which were not previously reviewed are reviewed below and include a male fertility study with Tamsulosin, a rat teratology study with Tamsulosin and investigative studies into the cause of YM12617-induced reductions in fertility in male and female rats.

Twenty-Three Week Male Fertility Study in Rats with Tamsulosin (Study R15087, lot H2 = DPD-11101)

The study was conducted according to GLP at from August 4, 1987 through January 16, 1988.

Male Sprague Dawley Crl:CD rats (n = 20/dose) were administered 0, 10, 100 or 300 mg/kg Tamsulosin (LY 253351) orally by gavage for 14 weeks; 10 weeks pre-mating and 4 weeks during the first mating trial with untreated females. Fertility was assessed in males in 4 additional mating trials of 1 week duration beginning 18 days after cessation of drug treatment to evaluate reversibility.
Mortality/signs-
2 HD males died - one of gavage error , one cause unknown.
Ptosis was observed in all treatment groups and a high incidence of urogential soiling was observed in HD males.

Body weight/food consumption - A dose-related reduction in food consumption was observed in treated males. This resulted in decreased

body weight gain (18%) and mean body weight (11%) after 18 weeks of dosing in HD males.

Mating Performance and Fertility- Mating and fertility indices were significantly reduced in males dosed with 300 mg/kg/day Tamsulosin. Mating occurred in only 13/18 HD males and only 8 of the 13 that mated were fertile during the initial 4 week mating period. During the 4 one week mating periods (4, 5, 6, and 7 weeks after drug withdrawal) to assess reversibility, the mating index was normal but the fertility index remained low in HD males.

Mating index(4 weeks on drug)- 100% C, 100% LD, 100% MD, 72% HD
Mating decrement in HD males was reversible after a 4 week drug-free interval.
Fertility index-
during drug treatment - 100% C, 100% LD, 85% MD, 62 % HD
The decrease in the fertility index in HD males was maintained 4, 5, 6, and 7 weeks after drug withdrawal.
Reproductive parameters - the number of corpora lutea, implantation, and live fetuses, fetal weights, and fetal sex ratio were all normal in untreated females mated with treated males.

Conclusions- Significant reductions in the mating and fertility indices of male rats were observed at 300 mg/kg and marginally reduced fertility was observed at 100 mg/kg/day. It is unclear if the negative effects on mating and fertility were secondary to hyperprolactinemia or alpha 1 inhibition of smooth muscle contraction in the vas deferens and epididymes. The no effect level in the study was 10 mg/kg/day.

Oral Teratology Study of YM617 (-)Isomer in Rats (Study 87104, lot H-1)

The study was conducted according to GLP by Yamanouchi Pharmaceuticals Co., Tokyo, Japan. The study was conducted from Feb 6, 1987 through April 27, 1989.

Female Sprague Dawley rats (n=32/dose) were administered 0, 10, 100 and 300 mg/kg/day Tamsulosin orally by gavage in % methylcellulose on days 7 through 17 of pregnancy. Twenty dams/group were subjected to cesarean section on day 20 of pregnancy. The 12 remaining dams/dose were allowed to deliver spontaneously and nurse their offspring for 22 days postpartum. Developmental, behavioral and reproductive assessments were performed on the F1 pups.

Mortality/clinical signs- There was no mortality attributable to the test drug. Ptosis was observed at all dose levels. Decreased motor activity for 1-6 hours after dosing was observed in HD dams.

Body weight/food consumption- food consumption and mean body weight were significantly decreased % in HD dams during late parturition.

Reproductive Parameters
Cesarean section- The number of corpora lutea were reduced in MD, HD dams. (19.9 C, 20 LD, 17.5 MD, 17.2 HD. The number of dead fetuses also increased in HD dams (11 C, 11 LD, 10 MD, 22 HD). The number of live fetuses, sex ratio, fetal weight, placental weight and external anomalies were unaffected by treatment.
The length of gestation, birth rate, survival rate, and weaning rate were unaffected by treatment.

Fetal parameters-
Visceral defects were observed in 0/96 C, 2/108 LD, 2/98 MD and 3/91 HD fetuses

LD- 1 dilation of the ureter; 1 dilation of the renal pelvis
MD- 2 dilation of the ureter
HD- 2 dilation of the ureter; 1 absence of aortic arch, and retroesophageal subclavian artery

Skeletal defects
Variation of 13th rib- 2C, 1 LD, 7 MD, 10 HD
Shift of lumbrosacral vertebral border - 1 C, 1 LD, 2 MD, 5 HD
Wavy ribs -3 HD

Full-term Evaluations- no differences in the number of live offspring, sex ratio or delivery rate in Tamsulosin-treated dams. There were no differences in the survival rate of offspring at day 4 and weaning between control and treated groups. There were no significant increases in skeletal or visceral anomalies in the full-term pups of Tamsulosin-treated dams. There were no differences in the postnatal development of pups (i.e., hair growth, pinna unfolding, eruption of incisors, eyelids opening, descent of testes, vaginal opening). Pinna reflex, pain response and righting reflex were also normal in pups of all groups.

Behavioral Assessment of Offspring (F1)
There were no treatment related effects on pups evaluated in the open field test and rotorod test. In the water-filled maze test there were no differences in the male offspring of Tamsulosin-treated dams. The female pups of HD dams (300 mkd) had significantly more errors on the repeat runs (2nd, 3rd, 4th run on second testing day). Dilation of the ureters and variation of the 13 rib and lumbar sacral vertebral border were observed in F1 pups but only the variation in the 13th rib reached statistical significance.

Reproductive Assessment of Offspring (F1)
F1 offspring from the same dose level were mated with each other (no specifications with regards to litter mates). There were no differences in mating and pregnancy rates, maternal body weights, parturition, number of implantation sites, or number of live pups/gross anomalies in the F2 generation.

Summary
Administration of Tamsulosin to pregnant rats during the period of organogenesis had no effect on reproductive outcome (length of gestation, parturition, number of live fetuses, sex ratio, fetal wts). The only statistically significant anomaly was absence/shortening of the 13th rib. Since 8 of 10 cases occurred in one litter in the HD group and the finding was observed in controls the sponsor contends it is unlikely to be attributable to drug treatment.
Administration of Tamsulosin during gestation produced no developmental or reproductive effects in F1 offspring. The only impairment noted in the behavioral assessments was mild decrements in learning ability (maze test) observed in the female pups of HD dams.

Conclusion- Tamsulosin administered to pregnant rats at dose levels up to 300 mg/kg/day (50 times human therapeutic exposures) during organogenesis had no lethal, growth retardation, or teratogenic effects. Postnatal development, behavioral and reproductive functions of the offspring were normal.

Oral Teratology Study with Tamsulosin in Rabbits (Study 87107, lot # H-1)

The study was conducted by Yamanouchi Pharmaceuticals Co, Ltd, Tokyo, Japan from 5-8-87 through 10-28-97.

Pregnant female New Zealand White rabbits (n=20/dose) were administered 0.1, 1, 5, 15 and 50 mg/kg/day Tamsulosin orally by gavage from days 6 to 18 of gestation.
(Dose-finding study established 50 mg/kg/day as maximum tolerated dose as deaths occurred in 1/3 at 100 mkd and 5/5 pregnant rabbits at 200 mkd).

No deaths or signs at the 3 lower doses (0.1, 1, 5 mkd). At 15 mg/kg/day, one rabbit aborted on day 29 after 2 weeks of decreased food consumption and one rabbit was killed in extremis secondary to a gavage error. There were no deaths or abortions in the 50 mkd group. Drug treatment had no effect on body weight or food consumption.

Reproductive parameters- Treatment with dose levels up to 50 mg/kg/day had no effect on the number of implants, live/dead fetuses, fetal body weight or placental weight. Rabbits treated with the highest dose level had significantly fewer corpora lutea, an effect also observed in pregnant rats and female dogs.

Fetal evaluations- The were no drug-related effects on the incidence of external variations and visceral or skeletal anomalies in the fetuses of Tamsulosin-treated dams.

Conclusion- Administration of Tamsulosin to pregnant rabbits at dose levels up to 50 mg/kg/day during organogenesis produced no fetotoxic or teratogenic effects in rabbit fetuses.

Investigation of Reduced Fertility in Male Rats Treated with YM12617 (study 391108, lot H-7)

The study was conducted by Yamanouchi Pharmaceuticals, Ltd. Tokyo, Japan from Feb 8, 1991 through June 6, 1991.

Male rats were administered a single oral dose of 300 mg/kg YM 12617 and mated with untreated females in proestrus on the day of dosing and for 3 days thereafter. Drug treatment had no effect on mating behavior but significantly decreased the copulation index, fertility index, and vaginal plug formation rate (see table below).. The drug-induced deficits were reversible by post-treatment day 3. Although not examined in this study, no histologic changes in the reproductive organs of males were observed in a previous male fertility studies with YM 12617. Effects of treatment on sperm counts or motility have not been assessed in animals or man. The copulation and fertility indices are also reduced in male rats treated with phenoxybenzamine, prazosin and urapidil.

Table 1. Effects of YM617 on mating behavior, copulation index, vaginal plug formation rate, and fertility index

	Day 0 (after administration)		Day 1		Day 2		Day 3	
	Control	YM617	Control	YM617	Control	YM617	Control	YM617
Mating behavior (%)	100.0	80.0	90.0	100.0	100.0	100.0	100.0	100.0
Copulation index (%)	100.0	40.0**	90.0	40.0**	100.0	100.0	100.0	100.0
Vaginal plug formation rate (%)	100.0	0.0**	100.0	25.0**	100.0	10.0**	100.0	100.0
Fertility index (%)	100.0	25.0**	88.9	0.0**	80.0	30.0	88.9	70.0

Investigation of Reduced Fertility in Female Rats Treated with YM12617 (study 391117, lot H-7)

The study was conducted by Yamanouchi Pharmaceuticals, Tokyo from Dec, 1991 to February 1992.

A marked decrease in the fertility index was observed in female rats administered 300 mg/kg YM 12617 in a Segment I oral fertility study. The present study was conducted to determine the effects of administration of a single dose of YM 12617 before mating on fertility and to try to determine if the effects of drug treatment are on ovulation or fertilization.

Female Sprague Dawley rats were administered a single oral dose of 300 mg/kg YM12617 on proestrus and mated with untreated males. The fertility index was 50%, reproducing the results of the previous study. It was determined that ovulation occurred in all animals but cleavage of the ova was observed in only 4 of 10 drug-treated rats. It was concluded that the impairment in fertility was due to a fertilization disorder but the nature of the fertilization disorder could not be determined from the present study.

GENOTOXICITY

Genotoxicity assays conducted with Tamsulosin include the Ames Test, Unscheduled DNA Repair Synthesis, Mouse Lymphoma/Thymidine Kinase Assay, Sister Chromatid Exchange in Chinese Hamsters, and a Mouse Micronucleus Assay. The studies were conducted with adequate dose levels and no evidence of genotoxicity was demonstrated in any of the studies. The studies were previously reviewed under IND

Cytogenetics Study in Cultured Human Lymphocytes (study U95-0672, lot # H7)

The study was conducted according to GLP by
from April 3, 1995 through June 6, 1995.

Cytogenic testing was performed in two tests as follows:
Test 1:
21 hr sampling time without S-9: 25, 50, 100, 150, 200, 250 ug/ml
With S-9 mix: 250, 500, 1000, 1200, 1400,1600, 1800 ug/ml
45 hr sampling time without S-9: 100, 150, 200, 250 ug/ml
With S-9: 800, 900, 1000, 1100, 1150, 1200, 1250, 1300 ug/ml
Test 2:
21 hr sampling only: Without S-9: 100, 150, 200, 250, 300 ug/ml
With S-9: 250, 500, 1000, 1100, 1150, 1200, 1250, 1300 ug/ml.

Preliminary cytotoxicity assays were conducted to permit dose selections. Concentrations of tamsulosin ug/ml without S9 or ug/ml with S-9 produced % reductions in the mitotic index. There were no tamsulosin-induced increases in chromosomal aberrations in samples incubated without S-9 in either test.
In tests with tamsulosin plus S-9 mix, there were no increases in aberrations at concentrations up to ug/ml. Increases in the frequency of chromatid and chromosome gaps and breaks were observed in lymphocytes treated with 1200 ug/ml with S-9. Although this concentration produced only % reductions in the mititic index, concentrations ug/ml with S-9 produced % cytotoxicity.

Conclusion: Tamsulosin showed weak evidence of clastogenic activity but only at a concentration associated with cytotoxicity.

OVERALL SUMMARY

Flomax (tamsulosin hydrochloride) is an α_1-adrenergic receptor antagonist proposed for use in the treatment of urinary obstruction associated with benign prostatic hyperplasia (BPH). *In vivo* and *in vitro* experiments in mammalian models have demonstrated that tamsulosin antagonizes phenylephrine-induced contraction of prostatic smooth muscle and elevation of urinary bladder pressure. Tamsulosin is specific for α_1-adrenergic receptors (K_i = 0.09-0.11 nM) but also has weak antagonist activity at D_2-dopamine, μ-opioid, α_2-adrenergic and β-adrenergic receptors (K_i = 50, 300, 1300, 800 nM, respectively).

The sponsor contends that tamsulosin displays a specificity for urogenital α_1-adrenoreceptors. However, the available data do not support this contention. Tamsulosin(0.3-3 mg/kg,po) produces sustained dose-related hypotension in normotensive rats, rabbits, dogs, and in hypertensive rats. In these animal models, tamsulosin is three times as potent as prazosin. Tamsulosin was equipotent in inhibiting phenylephrine-induced prostate and blood pressure responses in dogs as demonstrated in the table below. Tamsulsosin was fold more potent than the α_1-antagonists doxazosin, terazosin or alfuzosin.

Effect of α_1-Adrenoceptor Antagonists on Phenylephrine Induced Prostate and Blood Pressure Responses in Anesthetized Dogs

Test Compound	n	Derived "pseudo pA2" Values	
		Prostate Pressure	Blood Pressure
Doxazosin	4	7.47±0.01	7.49±0.02
Terazosin	3	7.59±0.09	7.78±0.10
Alfuzosin	3	7.38±0.16	7.20±0.28
Tamsulosin	3	8.94±0.06	8.75±0.20
5-Methyl-urapidil	3	8.72±0.08	7.22±0.16

Tamsulosin produced miosis, ptosis, and decreased body temperature, and had analgesic activity in mice administered oral doses of 1-10 mg/kg, which produce systemic exposures in the therapeutic range. Large doses of tamsulosin (≥ 100 mg/kg, po) increase acid secretion and the incidence of gastric ulcers in rats. There is no evidence of an increased frequency of ulcers in men treated with tamsulosin.

The pharmacokinetics of tamsulosin have been studied in mice, rats and dogs. Tamsulosin is stable in the GI tract and is rapidly absorbed from all sections of the intestines. Little absorption occurs in the stomach. Maximum plasma concentrations(Cmax) are observed within 15 to 30 minutes after oral dosing in animals. Steady state kinetics are acheived within one week of dosing. Drug exposures (AUC) remain unchanged with multiple dosing displaying no accumulation. Tamsulosin

does not induce liver metabolizing enzymes in rats. The plasma half-life of parent drug after oral dosing is approximately 1½ hours in rats and dogs. Plasma protein binding is extensive (>80%) in rats, dogs, and humans. Orally administered tamsulosin is rapidly and widely distributed although little reaches the CNS. Tamsulosin is rapidly metabolized in the liver. The major metabolic pathways in rats are O-deethylation, O-demethylation, glucoronidation and sulfation. In dogs, the major pathway is O-deethylation with sulfonation and oxidative deamination. Elimination in rats is 80% fecal (biliary) and 17% urinary, while in the dog these routes each account for approximately 50%.

The oral LD_{50} values for tamsulosin are > 1000 mg/kg in mice, > 650 mg/kg in rats, > 1000 mg/kg in dogs, and > 1500 mg/kg in rhesus monkeys. Thirteen week subchronic toxicity studies with tamsulosin were conducted in mice and rats (in-diet dosing) and dogs (bolus dosing in capsules). Studies in mice and rats established the uterus and female mammary glands as target organs of high doses of tamsulosin. Decreased uterine weights and mammary gland hyperplasia were observed in both species of rodent and are probably secondary to the drug-induced hyperprolactinemia observed in rodents (observed in both sexes). Drug treatment decreased ovarian and uterine weights in female rats and dogs.

Chronic toxicity of tamsulosin was assessed in one year oral toxicity studies in rats and dogs. Chronically administered tamsulosin produced testicular atrophy in male rats and uterine atrophy and mammary gland hyperplasia in female rats. In rats, a dietary concentration of 0.1% (50 mg/kg/day = 2 times human exposure) was the no effect level in males and 0.01% (5 mg/kg/day = 1/5 human exposure) was the no effect level in females. The one year dog study was conducted with doses of 2, 20 and 200 mg/kg/day (1, 10, 200 times human AUC exposures). Salivation, intermittent tremors, hypoactivity, reduced heart rates, and electrocardiographic changes were observed in high dose dogs. No toxicologically important changes in organ weights or histopathology were observed. The only microscopic change was small follicles and no corpora lutea in the ovaries of HD female dogs, evidence that ovulation had not occurred in these animals. Decreased numbers of corpora lutea were also observed in the rats and rabbits in the reproductive studies with tamsulosin. The ovarian and mammary gland effects in female animals are not a major concern since tamsulosin is indicated for the treatment of benign prostatic hyperplasia in males only. Serious signs of toxicity in dogs including cardiac toxicity, decrements in body weight gain, tremors, and hypoactivity were only observed at the highest dose level which produces AUC exposures fold higher than therapeutic exposures.

Two year carcinogenicity studies were conducted in Fischer rats and B6C3F$_1$ mice with doses of 0.003, 0.01, 0.03, 0.1% tamsulosin administered in the diet. The high dose of 0.1% produced AUC exposures in rats 3 times human therapeutic exposures and AUC exposures in mice 8 times therapeutic exposures. Treatment with

tamsulosin increased the incidence of mammary gland neoplasms in female rats and mice at doses ≥ 0.03% (AUC exposures comparable to therapeutic exposures). This effect is thought to be secondary to drug-related increases in circulating prolactin in rodents. There were no other biologically significant tumor finding in the carcinogenicity studies. The drug-induced increase in mammary tumors in female rodents are not a major concern since the drug is indicated for use only in men. The effects of tamsulosin on plasma prolactin levels in humans has not been evaluated, but gynecomastia has not been observed in men treated with tamsulosin.

Tamsulosin produced no evidence of mutagenic potential in an extensive battery of *in vitro* and *in vivo* genotoxicity assays including the Ames Test, Mouse Lymphoma Assay, Unscheduled DNA Synthesis Assay, Chromosomal Aberrations Assay in Human Lymphocytes, Sister Chromatid Exchange and Mouse Micronucleus Assays.

Fertility studies in male and female rats revealed that single and multiple doses of 300 mg/kg (AUC 50 times human therapeutic exposure) reduced fertility in rats of both sexes. The impairments in fertility were reversible. The data suggest the impairment in fertility in males is secondary to impaired ejaculation, as has been observed with other α_1-antagonists. Multiple doses of 10 or 100 mg/kg/day tamsulosin (1/5 and 16 times human AUC exposures) had no effect on fertility in male or female rats. Ejaculation disorders are observed with increased frequency observed in men treated with tamsulosin. Effects of tamsulosin on sperm number or function have not been assessed clinically. In the rat and rabbit teratology studies, tamsulosin produced no evidence of fetotoxicity or teratogenicity even at dose levels associated with mild maternal toxicity.

LABELING REVIEW

The Pharmacology/Toxicology sections of the labeling require major revisions. Suggested revisions are listed below by subsection.

Pregnancy (currently lines 483-487) should be revised as follows-

Comments: The sponsor had suggested a Pregnancy Category C. However, the CFR states that Pregnancy Category C indicates reproductive studies in animals have demonstrated an adverse effect on the fetus. Administation of Tamsulosin to rats or rabbits during organogenesis was not fetoxic or teratogenic. Both categories imply there are no data from adequate well-controlled studies in humans.

In the current labeling, exposure comparisons between doses utilized in the preclinical studies and human therapeutic doses were made on a mg/kg basis. This method greatly over estimates the actual exposure comparisons. In the reproductive toxicity studies, a single gavage dose of pure drug was given ($T_{½}$ = 1-2 hours). The clinical formulation is modified release granules with a $T_{½}$ of 9-13 hours. The clinical formulation results in sustained exposures in men. Due to the differences in the formulation and metabolism in animals and man only AUC or C_{ss} values provide accurate exposure comparison across species. Both mg/kg and mg/M^2 provide greatly exaggerated exposure ratios. There are no toxicokinetics data available for rabbits. I think is is preferable to provide no exposure comparison for rabbits rather than provide a calculated value which is deceptive.

Examples-
Toxicokinetics data generated in rats after gavage dosing with 300 mg/kg, the highest dose utilized in the rat reproductive studies, are compared with human therapeutic exposures in the table below. Rat data is from study U95-3130. Human data is from elderly men dosed with 0.8 mg/day for 7 days.

Species	Dose	Cmax ng/ml	Cmax Multiple	AUC 0-24 Ng.hr/ml	AUC Multiple	Mg/kg Multiple
Rat	300 mg/kg	2,773	90 X	24,984	50 X	25,000 X
Man	0.8 mg/d = 0.012 mg/kg	30		500		

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis section (lines 494-504) should be revised as follows-

Comments: As discussed above, the labeling must be changed to express rodent/human exposure comparisons on the basis of AUC since exposures are greatly exaggerated by mg/kg comparisons. The rodent AUC data for the carcinogenicity study comparisons was obtained from a 2 week in-diet toxicokinetics study # U93-1084 (see page 8 of this review).

Mutagenesis section (lines 506-515) should be revised as follows-

Impairment of Fertility Section (lines 517-524) should be revised as follows-

Comments:
As stated above, mg/kg dose comparisons greatly exaggerate relative drug exposures. AUC data in rats are available for the 10 and 300 mg/kg/day gavage doses utilized in the reproductive toxicity studies (study U95-3130). There are no data for the 100 mg/kg/day dose. The multiple expressed is extrapolated from the high dose level since data suggest that drug metabolism pathways in the rat are saturated at doses ≥ 50 mg/kg.

The sponsor includes a statement about deaths and body weight reductions in male rats treated with 300 mg/kg/day, implying the reduction in fertility is secondary to systemic toxicity. Deaths occurred in 2/20 high dose males in the male fertility study- one due to gavage error, the cause of death in the second rat was unknown. The reduction in mean body weight was 11% after 18 weeks of treatment with 300 mg/kg/day tamsulosin and would not be expected to be severe enough to impact on fertility. The observation of reduced fertility after a single 300 mg/kg doses suggests systemic toxicity was not the primary factor. Ptosis was the only clinical sign, and is an expected pharmacologic effect. No other signs of toxicity commonly associated with high doses of α-antagonists (decreased motor activity, decreased respiration, tremors) were observed. Based on the data, I feel the second sentence is misleading and should not be included.
Although the effects on fertility in females are not relevant to the present indication, they are included for completeness since drugs are often utilized for indications other than those originally proposed.

NDA 20-579

DRUG: FLOMAX (Tamsulosin)

APPENDIX II

Metabolite Profiles

Tissue Distribution in Rats

Appendix 2

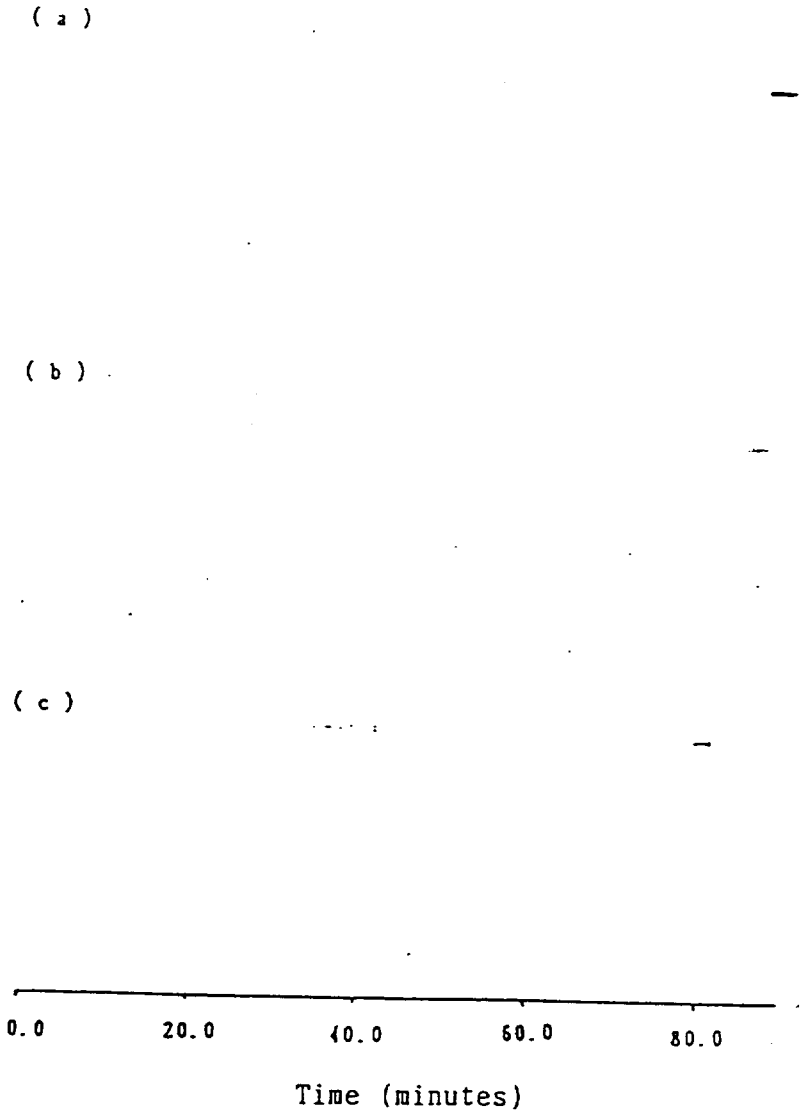


Fig. 5 UV-detected HPLC chromatogram of YM-12617-1 and the authentic compounds of its metabolites, and radioactivity-detected HPLC chromatograms of the 0-24 hr urine specimens from rats and dogs orally given ^{14}C-YM-12167-1 1 mg/kg

(a) UV (275 nm)-detected HPLC chromatogram of the mixture of authentic YM-12617-1, M-1, M-2, M-3, M-4 and AM-1.
(b) Radioactivity-detected chromatogram of rat urine specimen
(c) Radioactivity-detected chromatogram of dog urine specimen
Glu: glucuronide Sul: sulfate

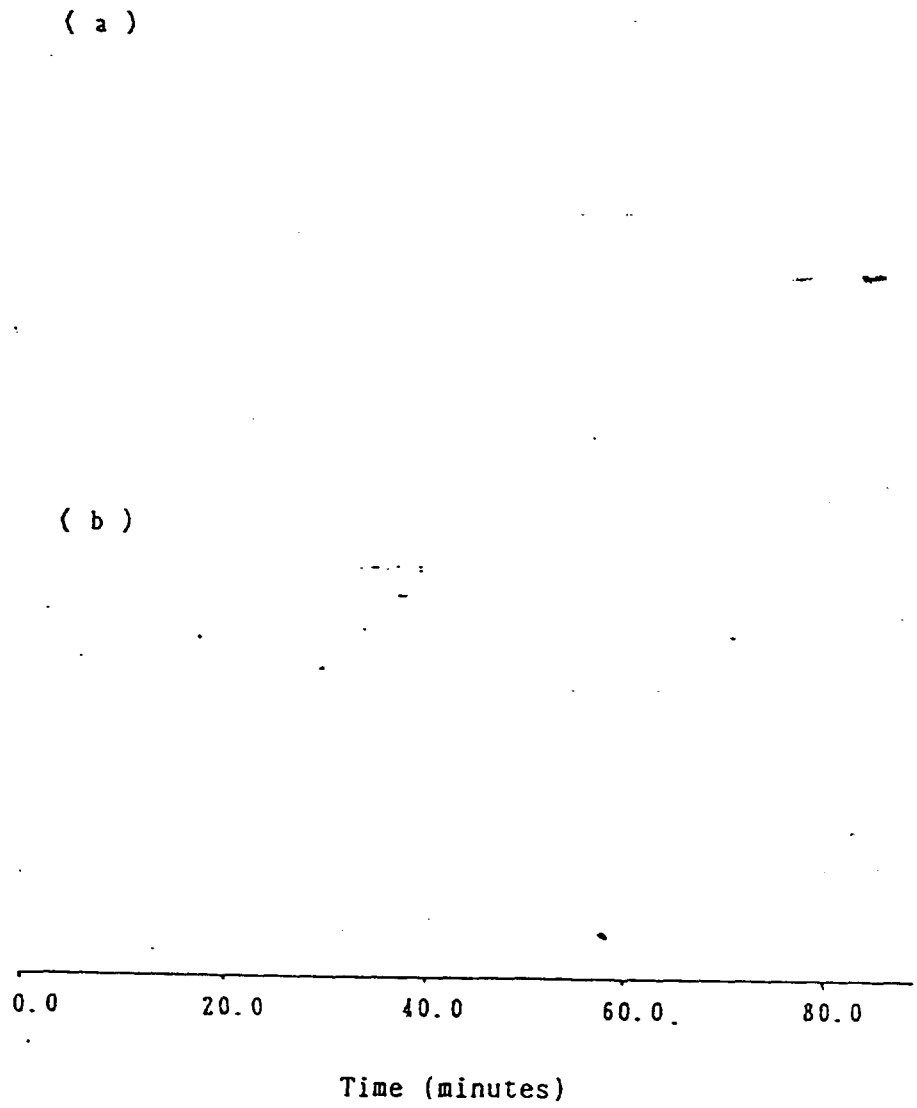


Fig. 6 Radioactivity-detected HPLC chromatograms of 0-24 hr bile specimens taken from rats and dogs given oral ^{14}C-YM-12617-1 1 mg/kg

(a) Rats (b) Dogs
Glu: glucuronide Sul: sulfate

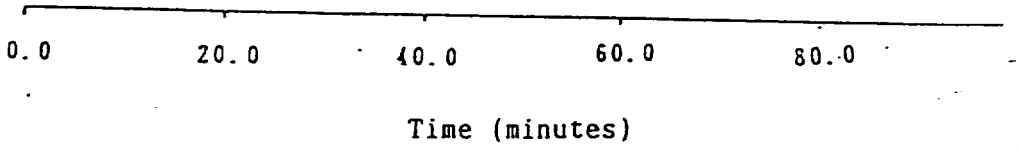


Fig. 7 Radioactivity-detected HPLC chromatogram of plasma extract taken 30 min after oral administration of ^{14}C-YM-126127-1 to rats

Glu: glucuronide Sul: sulfate

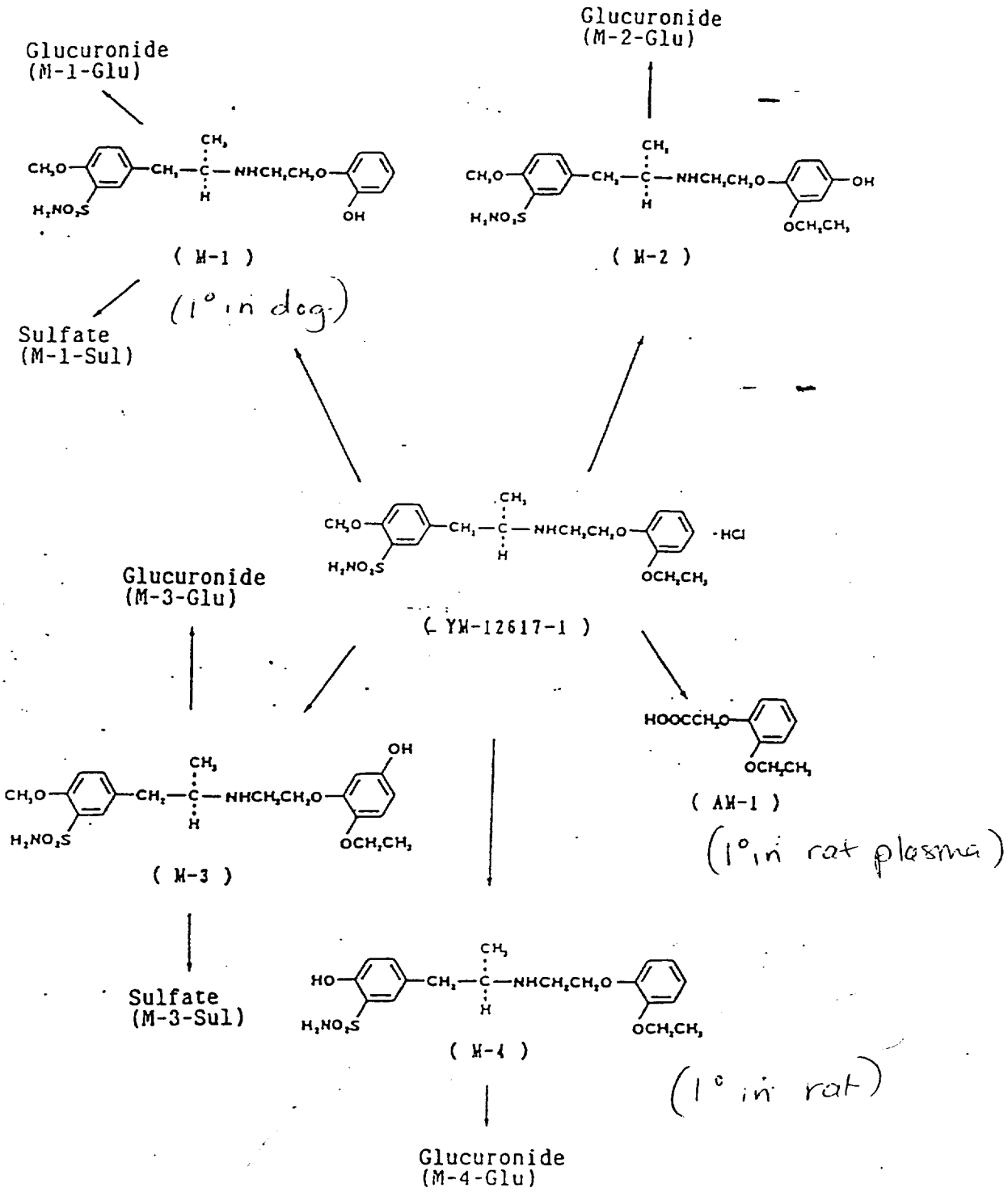


Fig. 9 Possible metabolic pathways of YM-12617-1

Table 2 Tissue concentrations of unchanged drug and radioactivity after administration of ^{14}C-amsulosin hydrochloride to rats at a dose of 1 mg/kg. (Mean ± SE, n = 3)

Tissue	Intravenous administration						Oral administration		
	5 minutes			1 hour			1 hour		
	Concentration of unchanged drug (ng/g or ml)	Concentration of radioactivity (ng/g or ml)	Unchanged drug percent of radioactivity (%)	Concentration of unchanged drug (ng/g or ml)	Concentration of radioactivity (ng/g or ml)	Unchanged drug percent of radioactivity (%)	Concentration of unchanged drug (ng/g or ml)	Concentration of radioactivity (ng/g or ml)	Unchanged drug percent of radioactivity (%)
Plasma	156 ±	233 ±	66.7 ±	21 ±	67 ±	31.8 ±	4 ±	63 ±	6.3 ±
Liver	198 ±	2069 ±	9.7 ±	48 ±	1902 ±	2.5 ±	146 ±	1588 ±	8.5 ±
Kidney	2482 ±	2995 ±	82.4 ±	242 ±	546 ±	44.2 ±	38 ±	255 ±	14.6 ±
Heart	850 ±	980 ±	88.3 ±	125 ±	157 ±	80.0 ±	22 ±	40 ±	56.7 ±
Lung	1404 ±	1606 ±	87.3 ±	336 ±	419 ±	80.2 ±	29 ±	60 ±	47.7 ±
Adrenal [1]	1095	1396	78.5	135	171	79.0	17	36	46.5

[1] : Tissues of 3 rats were used together

Table 3 Tissue concentrations of unchanged drug and radioactivity at 1 hour after oral administration of ^{14}C-amsulosin hydrochloride to dogs at a dose of 1 mg/kg (Mean ± range, n = 2)

Tissue		Concentration of unchanged drug (ng/g or ml)	Concentration of radioactivity (ng/g or ml)	Unchanged drug percent of radioactivity (%)
Plasma		76 ±	518 ±	14.7 ±
Liver		1170 ±	5719 ±	20.5 ±
Kidney		430 ±	3377 ±	12.9 ±
Heart		256 ±	522 ±	48.7 ±
Lung		462 ±	758 ±	61.1 ±
Adrenal		418 ±	881 ±	49.7 ±
Prostate	Medulla	230 ±	640 ±	38.0 ±
	Intermediate	266 ±	534 ±	49.9 ±
	Cortex	356 ±	880 ±	46.8 ± 1
Urinary bladder		61 ±	481 ±	12.6 ±
Urethra		70 ±	673 ±	11.2 ±
Aorta		152 ±	333 ±	46.4 ±

STATISTICAL REVIEW AND EVALUATION
CLINICAL

Date: FEB 28 1997

NDA#: 20-~~664~~ 579

Applicant: Boehringer Ingelheim Pharmaceuticals Inc

Name of Drug: Flomax (Tamsulosin HCl Capsules)

Indication: Treatment of Benign Prostatic Hyperplasia

Documents Reviewed: 1.001, 1.188 - 192, 1.220 -223, 1.231, 1.341 - 343, 1.370, of this NDA, dated April 15, 1996. Data submitted on external hard-drive as CANDA and supplementary data on floppies.

Statistical Reviewer: Ananda V. Gubbi, Ph.D. (HFD-715)

Medical Input: Dr. Jean Fourcroy M.D., HFD-580, has been consulted during the process of this review.

0.1 Introduction:

This review focuses primarily on the results of two placebo-controlled, double-blind, randomized, Phase III multicenter studies conducted in the USA, to show the efficacy and safety of Flomax for the treatment of benign prostatic hyperplasia (BPH). Characteristics of the two efficacy studies are summarized in the table below:

STUDY	START DATE	TREATMENT ARM	NUMBER OF PATIENTS	DURATION OF STUDY
US92-03A (10 CENTERS)	11/92	placebo Flomax .4 mg Flomax .8 mg	254 254 248	13 weeks
US93-01 (14 CENTERS)	04/93	placebo Flomax .4 mg Flomax .8 mg	239 248 244	13 weeks

Both studies had a four-week orientation period and the baseline measurements on the efficacy parameters were obtained in the third visit, which occurred in the fourth week.

0.2 Timing Schedules and Visit Numbers: Randomization was done in the fifth week, which was Visit 4. Dosing was started immediately after randomization. During the first week of treatment, both .4 mg and .8 mg arms received the same dose of .4 mg in order to acclimatize the patients to the new drug. Thereafter, a full complement of .8 mg was administered to the higher dose group. The placebo group was given the placebo tablets during the first week and throughout the experiment. A unique feature of these two studies was that all measurements were obtained and summarized by visit number, as defined in the protocol. In general visit n occurred in week n+1 after the subject's enlisting into the trial and after dosing was started. Since the study was scheduled for 13 weeks from the start of dosing, it was important that the endpoint measurements for the four efficacy parameters were obtained immediately following the 13 weeks. This reviewer went through the submitted documents and noticed discrepancies ranging up to 40 days in Study US92-03A and up to 30 days in Study US93-01.

0.3 Reviewer's Order of Presentation:

The two studies will be discussed in their chronological order. This review will focus, as suggested by the reviewing medical officer Dr. Jean Fourcroy, on the four primary efficacy parameters measured at week 13, Total American Urology Association Scores(TAUAS), Qmax, which measures the peak urine flow rate, AUA-Responders and Qmax-Responders. See the next paragraph for a brief description of these terms. In addition, a combined response analysis, as suggested by Dr. Heidi Jolson will be discussed for the two studies.

0.4 The Patient Population: Both studies included men aged between the years 45 and 84, suffering from symptoms of benign prostatic hyperplasia. The inclusion criteria listed specific conditions on the four primary efficacy parameters, in addition to other criteria regarding the general health conditions of the patients.

Total AUA scores had to be at least 13 on a scale of 0 to 35 for a patient to be included in the study. Qmax rate (measures the peak urine flow rate) had to be between 4 and 15 ml/sec. An AUA-Responder was one who showed at least 25% improvement in the Total AUA score from his baseline value. A Qmax-Responder was one who showed at least 30% improvement in the Qmax value from baseline. These are defined in greater detail in the sponsor's submissions.

For each study, tables showing the number of patients on study and the reasons for dropouts are provided by this reviewer. These tables were created using the sponsor's data in Table 1 - 1.4, Vol 1.189 and 7.1:2, Vol 220. The number of patients on study are the number of patients who completed the study week and entered the next week.

Data integrity and consistency checks between the hard-copy and data submission on hard-drive and floppy diskettes were conducted by this reviewer and were found to be satisfactory.

0.5 A Brief Discussion of Statistical Procedures Used by the Sponsor:

Basically the same statistical procedures were used by the sponsor for both studies. Data from the intent-to-treat sample were analyzed and results for the last-observation-carried - forward (LOCF) were presented.

The distributions of categorical variables were described with frequency tables; treatment group comparisons were done using Mantel-Hanszel tests with centers as strata. For categorical variables with ordinal outcomes, the Kruskal-Wallis test was used. The distribution of continuous variables were described with means, standard errors, medians, and minimum and maximum values; treatment group comparisons were done using the Analysis of Variance tests with treatment and centers effects. McNamer's test, Wilcoxon Signed Rank test and the matched pair t-test were used to assess changes from baseline within each treatment group in nominal, ordinal and continuous efficacy variables, respectively.

0.6 Sponsor's Statistical Procedures for Analyzing the Primary Efficacy Parameters:

The primary efficacy parameters, viz., Total AUA Scores and Qmax Rates were analyzed as follows: Changes in AUA scores and Qmax values from baseline at the end of 13 weeks were computed and pairwise comparisons of mean changes among the three pairs were made using the t-test. Adjustments for multiple comparisons were done using the Bonferroni-Holmes correction. For analyzing the QUA-Responses and the Qmax-Responses data, the Logistic Regression was used, adjusting for baseline differences, if any.

0.9 Followup Study:

Patients that completed the study US92-03A were given the

option of continued therapy for an additional 40 weeks. This study bears the reference number US92-03B. Study US93-01 did not have a followup.

0.10 Demographics:

These were independently studied by this reviewer. Overall, the demographics across both studies were consistent. Statistically significant differences specific to each study, if any, will be discussed in the appropriate study.

SECTION 1: STUDY US92-03A:

1.1 Study Dates: This study was conducted between November 1992 and October 1993, which includes four weeks of patient orientation and collection of baseline values of the patients, the 13-week study and the 40-week followup study.

1.2 Disposition of Patients:

TABLE 1: PATIENTS ON STUDY US92-03A:

WEEK NUMBER (VISIT NO.) FROM DAY OF ORIENTATION	PLACEBO (NUMBER LOST) [% REMAINING]	0.4 MG ARM (NUMBER LOST) [%REMAINING]	0.8 MG ARM (NO. LOST) [%REMAINING]
4 (3)*	254	254	248
5 (4)**	254	254	248
6 (5)	241 (-13) [95%]	243 (-11) [96%]	233 (-15) [94%]
7 (6)	235 (-6) [93%]	234 (-9) [92%]	227 (-6) [92%]
9 (7)	225 (-10) [89%]	226 (-8) [89%]	215 (-12) [87%]
12 (8)	213 (-12) [84%]	219 (-7) [86%]	208 (-7) [84%]
15 (9)	208 (-5) [82%]	213 (-6) [84%]	201 (-6) [81%]
18 (10)	207 (-1) [82%]	213 (0) [84%]	198 (-3) [80%]
TOTAL LOSS AND %REMAINING	(-47) [82%]	(-41) [84%]	(-49) [80%]

* Baseline Values Obtained for the Primary Efficacy Parameters.
** Patients Were Randomized and Dosing Was Started.

More than 80% of the patients completed the study in each treatment group (Table 1). The attrition is maximum in the .8 mg arm, reflecting more adverse effects as discussed below. Adverse Events that accounted for maximum attrition were: Low blood pressure - 9, 7 and 13 percents in the placebo, .4 mg and .8 mg arms respectively. See Table 2.

There were respectively 151 (59%), 165 (65%) and 180 (73%) cases of Adverse Effect reported in the placebo, 0.4 mg and 0.8 mg arms. The differences in the number cases were statistically significant between the placebo and the 0.8 mg, with a p-value of 0.006. The p-values for placebo vs 0.4mg and the arms 0.4 vs 0.8 mg arms were respectively, 0.201 and 0.066. These tests were conducted by the reviewer.

A dose-related AE that showed a very highly statistically significant trend that was reported by the sponsor, is abnormal ejaculation: 0/254 in the placebo group, 15/254 (6%) in the 0.4 mg group and 44/248 (18%) in the 0.8 mg group. An exact test was performed to test for the differences (Cochran-Armitage exact trend test) and the p-value was <0.0001. Rhinitis tested at 0.0543 and dizziness at 0.1675. These tests were performed by the reviewer.

The sponsor excluded data of patients from the efficacy analyzable population if they discontinued within four weeks of double-blind treatment. The numbers of patients not included for this reason were: 26 (10%), 26 (10%) and 28 (11%) in the placebo, .4 mg arm and .8 mg arm respectively (Vol 1.189).

TABLE 2: REASONS FOR DROPOUTS --- STUDY US92-03A

REASON FOR DROPOUT	PLACEBO	0.4 MG	0.8 MG
LACK OF EFFICACY	1 (<1%)	1 (<1%)	0
ADVERSE EXPERIENCE	22 (9%)	18 (7%)	31 (13%)
LOST-TO-FOLLOWUP	0	2 (<1%)	1 (<1%)
OTHER	25 (10%)	23 (9%)	19 (8%)

1.3 Results Communicated by Sponsor:

The mean ages in years for the three groups were 59.5, 57.3 and 59.0, for the placebo, 0.4 mg arm and 0.8 mg arm, respectively. The p-value, based on the Analysis of Variance

with treatment and investigator-site effects was 0.00, indicating a statistically significant difference in age among the three treatment arms. [**Reviewer's comments**: The maximum difference in mean age between the groups is 2.2 years. The statistical significance is essentially due to the large size of nearly 250 in each arm -- the power to detect differences. We can safely ignore this small demographic difference in our analysis. In fact, results which were obtained by this reviewer after adjusting for Age for the entire ITT population, as well as for the completers (those that stayed on till the end of the study) do, indeed, show that a mean Age difference of 2 years did not matter).]

1.4 Primary Efficacy Results Communicated by Sponsor (ITT):

The following tables 3A through 3D describe the results of pairwise comparisons of the three arms on each of the four primary endpoints. The sponsor conducted t-tests to compare the pairs and applied corrections for multiple comparisons using the Bonferroni-Holm procedure. The intent to treat population includes all patients that were randomized and had at least one measurement available. For patients who discontinued before 13 weeks the last available observation was carried forward (LOCF). All patients who discontinued were treated as nonresponders and have been assigned a zero value , for the variables AUA-Responder and Qmax-Responder, provided LOCF were available. Whenever LOCF values were available, the definitions for responders were followed.

Table 3A describes the results of analysis for AUA Scores.

TABLE 3A: TOTAL AUA SCORE
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
	Mean Baseline Score		
	19.9	19.8	19.6
Number in the Arm	254	254	247
Mean Change in 13 wks	-5.5	-8.3	-9.6
Number in the Arm	246	246	237
p-values:			
Vs Placebo		<.001*	<.001*
Vs 0.4 mg			0.020*

*Statistically significant using the Bonferroni-Holm procedure.

Remarks on Table 3A: All the three pairwise comparisons showed statistically significant differences even after correcting for multiple comparisons.

Table 3B displays the results of analysis on AUA-Responders. The two treatment arms differed significantly from the placebo, while there were no significant differences between the 0.4 mg and 0.8 mg treatment arms.

TABLE 3B: AUA-RESPONDER
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders in 13 wks	126(51%)	171(70%)	175(74%)
p-values:			
Vs Placebo		<.001*	<.001*
Vs 0.4 mg			0.297

*Statistically significant using the Bonferroni-Holm procedure.

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Reviewer's Remarks: Table 3C displays the results of analysis on Qmax, the peak flow rate. The results are similar to those of AUA scores in Table 3A. There are no significant differences between the 0.4 mg and 0.8 mg arms, while each of the tratment arms differs differs significantly from the placebo.

TABLE 3C: Qmax (ML/SEC)
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	9.75	9.46	9.57
Number in the Arm	254	254	247
Mean Change in 13 wks	0.52	1.75	1.78
Number in the Arm	253	254	247
p-value:			
Vs placebo		<0.001*	<.001*
Vs 0.4 mg			0.887

*Statistically significant using the Bonferroni-Holm procedure.

==========

Results for Qmax-Responders (Table 3D) are similar to those for AUA-Responders.

TABLE 3D: Qmax RESPONDERS
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders in 13 wks	54(21%)	79(31%)	88(36%)
Number in the Arm	253	254	247
p-value:			
Vs placebo		<.001*	<.012*
Vs 0.4 mg			0.251

*Statistically significant using the Bonferroni-Holm Procedure.

1.5 Reviewer's Comments:

1. The results clearly indicate that both doses of Flomax are doing significantly better than placebo, on all the four efficacy parameters.

2. There are no statistically significant differences between the .4 mg and .8 mg treatment arms, as far as the four efficacy parameters are concerned. Indeed, in terms of benefit to Adverse Effects, the .4 mg arm had fewer dropouts due to adverse events. A study of the group of patients who discontinued revealed the following: The asymptotic p-value for a dose-related trend of AEs was .076, showing a marginal trend, if not a significant one (Cochran-Armitage Trend test).

3. The results reported here are for the ITT population.

1.6 Reviewer's Analyses:

In keeping with the suggestion of Dr. Fourcroy and Dr. Jolson, this reviewer tried to replicate the above results for the four efficacy parameters in the ITT and completers population (results are presented for the completers). An analysis for both

AUA- and Qmax- Responders was also done. A completer is one who underwent the full course of treatment of 13 weeks. At least 81% of patients were completers in each of the three arms, while the maximum percentage of 84% was in the 0.4 mg arm.

The following tables (Tables 4A-D) are the analogues of Tables 3 A-D: Comments on the results are presented after the tables.

TABLE 4A: TOTAL AUA SCORE
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	19.65	19.94	20.00
Number in the Arm	208	214	203
Mean Change in 13 wks	-5.96	-8.47	-10.00
Number in the Arm	208	214	202
p-values:			
Vs Placebo		<.001*	<.001*
Vs 0.4 mg			0.019*

*Statistically significant using the Bonferroni-Holm procedure.

TABLE 4B: AUA-RESPONDER
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders in 13 wks	116(56%)	151(71%)	153(75%)
p-values:			
Vs Placebo		<.001*	<.001*
Vs 0.4 mg			0.117

*Statistically significant using the Bonferroni-Holm procedure.

TABLE 4C: Qmax (ML/SEC)
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	9.71	9.40	9.52
Number in the Arm	208	251	203
Mean Change in 13 wks	0.64	1.93	1.90
Number in the Arm	208	214	203
p-value:			
Vs placebo		<0.001*	<.001*
Vs 0.4 mg			0.919

*Statistically significant using the Bonferroni-Holm procedure.

TABLE 4D: Qmax RESPONDERS
(COMPLETEERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders in 13 wks	46(22%)	69(32%)	78(38%)
Number in the Arm	208	214	203
p-value:			
Vs placebo		<.010*	<.001*
Vs 0.4 mg			0.094

*Statistically significant using the Bonferroni-Holm Procedure.

1.7 Comments on the Tables 4 A - D:

1. The above results are consistent with those reported by the sponsor for the ITT population.

2. The point estimates are tending to favor the treatment arms in the completers analysis more so than for the ITT population.

3. The 0.8 mg arm is doing just as well as the 0.4 mg arm, in terms of the four primary efficacy parameters, indicating thereby that even after 3 months of treatment, no statistically significant benefits are perceivable. The point estimates are approximately the same.

1.8 Analysis of Responders to both AUA and Qmax:

1. This reviewer first tested all the three arms simultaneously for overall linear trend using the Jonckheere-Terepstra test for two orderable variables. Note that both parameters, treatment arms and responders (see Table 5) have a natural order (dosage and response have both a natural order; an appropriate test that will take advantage of this is the J-T test). The p-value was less than 0.0001 (in fact, a Monte-Carlo estimate of the exact 99% confidence interval for the p-value was (0.0000, 0.0005)). This indicates a very significant linear trend in the responses as dosage increases.

2. Next, the pairwise comparisons, Placebo vs 0.4 mg arm; placebo vs 0.8 mg arm; 0.4 mg arm vs 0.8 mg arm were tested, using the Wilcoxon test for two independent groups. The respective two-sided p-values were 0.0013, <0.0000 and 0.1248 respectively.

3. The descriptive statistics of the double-responders and the non-responders(nonresponse on both AUA and Qmax) are given below. Note: The Population studied here is that of the completers (size 625).

TABLE 5: DISTRIBUTION OF PATIENTS BY TYPE OF RESPONSE

Responder to:	Placebo	0.4 mg	0.8 mg
BOTH AUA & QMAX	26 (12.5%)	53 (24.8%)	65 (32.2%)
AUA ONLY	90 (43.3%)	98 (45.8%)	88 (43.6%)
QMAX ONLY	20 (09.6%)	16 (07.5%)	13 (06.4%)
NONE	72 (34.6%)	47 (22.0%)	36 (17.8%)
TOTAL	208 (100%)	214 (100%)	202 (100%)

1.9 Results by center:

Ten centers were involved in this study. Sample sizes for the three treatment groups ranged between 33 and 88 with a mean size of 25 in each treatment arm. The 95% confidence intervals

for the difference between the treatment arm and placebo for each of the efficacy parameters Total AUA scores and Qmax values are presented in the Appendix. It can be seen that the results were generally consistent across the centers.

1.10 Efficacy Charts:

Bar charts showing the comparative efficacies of the three treatment arms for Total AUA scores and Qmax values measured at 4 time points are presented in the Appendix.

1.11 Conclusions on US92-03A:

1. This reviewer was able to replicate all results of the sponsor for the four efficacy parameters. Although results presented here are for the completers of the study, the reviewer carried out independent analyses for the entire ITT population and the results obtained confirm the results presented by the sponsor.

2. On the whole, there are no significant differences between the .4 mg and .8 mg arms as far as the four efficacy parameters are concerned, on the basis of pairwise comparisons. For the four efficacy parameters each treatment arm is significantly different from the placebo arm.

3. The combined responders to both Total AUA Scores and Qmax variables in both treatment arms show significant improvements over the placebo. Simultaneous comparison of the three arms also show significant dose-related improvements. This analysis however is not stipulated in the protocol.

SECTION 2: STUDY US93-01:

2.1 Study Dates: This study was conducted between April 1993 and December 1993.

2.2 Disposition of Patients:

TABLE 6: PATIENTS ON STUDY US93-01:

WEEK NUMBER (VISIT NO.) FROM DAY OF ORIENTATION	PLACEBO (NUMBER LOST) [% REMAINING]	0.4 MG ARM (NUMBER LOST) [%REMAINING]	0.8 MG ARM (NO. LOST) [%REMAINING]
4 (3)*	239	248	244
5 (4)**	232 (-7) [97%]	240 (-8) [97%]	234 (-10) [96%]
6 (5)	227 (-5) [95%]	233 (-7) [94%]	225 (-9) [92%]
9 (6)	217 (-10) [91%]	225 (-8) [91%]	215 (-10) [88%]
13 (7)	212 (-5) [89%]	219 (-6) [88%]	210 (-5) [86%]
17 (8)	209 (-3) [87%]	216 (-3) [87%]	206 (-4) [84%]
TOTAL LOSS AND %REMAINING	(-30) [87%]	(-32) [87%]	(-38) [84%]

* Baseline Values Obtained for the Primary Efficacy Parameters.
** Patients Were Randomized and Dosing Was Started.

==========

More than 84% of the patients completed the study in each treatment group (Table 7). The attrition was maximum in the 0.8 mg arm, with more AEs. Adverse Events accounting for maximum attrition were: Symptomatic Adverse Events 4%, 4% and 7% in the placebo, 0.4 mg and 0.8 mg arm respectively. Corresponding percentages for Abnormal EKG-Findings-Adverse-Event were 3, 5 and 6, respectively.

TABLE 7: REASONS FOR DROPOUTS --- STUDY US93-01

REASON FOR DROPOUT	PLACEBO	0.4 MG	0.8 MG
LACK OF EFFICACY	1 (<1%)	0	1 (<1%)
ADVERSE EXPERIENCE	20 (8%)	22 (9%)	30 (12%)
LOST-TO-FOLLOWUP	2 (<1%)	2 (1%)	1 (<1%)
OTHER	0	1 (<1%)	1 (<1%)

2.3 Results Communicated by the Sponsor:

The mean ages in years for the three groups were 58.6, 58.9 and 58.5, for the placebo, 0.4 mg and 0.8 mg arms respectively. These differences were not tested.

Tables 8A-8D on pages 14 and 15 are analogous to Tables 3A-3D; these are presented by the sponsor as 'panels' in the submission. In particular, Table 8A displays the results of analysis for AUA scores, while B, C, and D display the corresponding results of analyses for AUA-Responders, Qmax, and Qmax-Responders, respectively. Recall (paragraph **0.4**, page 2) that an AUA-Responder is one who showed at least 25% improvement from baseline and a Qmax-Responder is one who showed at-least 30% improvement from baseline.

The following quotation is from the synopsis submitted by the sponsor, vol 220, page 25: 'Dizziness, somnolence, rhinitis, and abnormal ejaculation were reported more frequently (statistically significant over placebo group) in the patients in the 0.8 mg group. The incidence of abnormal ejaculation in the 0.8 mg dose and the 0.4 dose group were statistically significantly higher than in the placebo group and appear to be dose-related. The incidence was lower in the 0.4 mg group and was not reported in the placebo group.'

TABLE 8A: TOTAL AUA SCORE
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	18.2	17.9	19.6
Number in the Arm	244	248	239
Baseline-Dif. p-value		0.022[1]*	0.084
Vs 0.4 mg arm			0.578
Mean Dif at 13 wks	-3.6	-5.1	-5.8
Number in the Arm	235	244	238
p-values:			
Vs Placebo		<.001*	<.009*
Vs 0.4 mg			0.231

[1] No correction for multiple comparison communicated by sponsor.
*Statistically significant using the Bonferroni-Holm procedure.

Remarks on Table 8A: Baseline differences are significant after B-H correction is applied. The adjusted critical level of significance (alpha value), after the Bonferroni-Holm correction is 0.044. (See Section 2.5. below for further discussion). The sponsors did not communicate in their NDA submission any correction for multiple comparisons when testing for baseline differences. This reviewer's analysis shows statistically significant differences, even after correction.

TABLE 8B: AUA-RESPONDER
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders at 13 wks	95(40%)	133(55%)	134(56%)
p-values:			
Vs Placebo		<.001*	<.001*
Vs 0.4 mg			0.694

*Statistically significant using the Bonferroni-Holm procedure.

Reviewer's Remarks: The B-H adjusted p-values are statistically significant for the treatment arms compared to the placebo arm.

TABLE 8C: QMAX (ML/SEC)
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	9.95	9.94	9.96
Number in the Arm	239	248	244
Mean Dif at 13 wks.	0.93	1.52	1.79
Number in the Arm	235	244	237
p-value:			
Vs placebo		<0.064	<.007*
Vs 0.4 mg			0.376

*Statistically significant using the Bonferroni-Holm procedure.

Table 8D displays the results of analysis on Qmax-Responders. Note the similarity of results to those of Study US92-03A.

TABLE 8D: QMAX RESPONDERS
(ITT POPULATION)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders at 13 wks	56(24%)	82(34%)	78(33%)
Number in the Arm	235	244	237
p-value:			
Vs placebo		<.001*	<.012*
Vs 0.4 mg			0.251

*Statistically significant using the Bonferroni-Holm Procedure.

Remarks: The results are similar to those of the first study.

2.5 Reviewer's Comments:

The two tamsulosin arms compared to the placebo individually, are doing significantly better. The differences between the 0.4 mg and the 0.8 mg arms are not significant on any of the four efficacy parameters. The emerging picture is very much similar to the study US92-03A. Although there are statistically significant baseline differences in the AUA scores, since the subjects are acting as their own control, this difference need not be viewed seriously. In fact, a one-way ANOVA test was performed by this reviewer, adjusting for baseline differences in AUA scores yielded results that were highly significant among the three groups ($p < 0.001$).

2.6 Reviewer's Analyses:

As in the earlier study, in keeping with the suggestions of Drs. Fourcroy and Jolson, this reviewer attempted to replicate the results of the sponsor for both the ITT and the completers populations and studied the double-responders data as in Section 1. The analyses will be presented for completers.

TABLE 9A: TOTAL AUA SCORE
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	19.4	18.3	18.1
Number in the Arm	208	217	206
Baseline-Dif. p-value		0.071	0.027*
Vs 0.4 mg arm			0.673
Mean Change at 13 wks	-3.7	-5.2	-6.1
Number in the Arm	208	217	206
p-values:			
Vs Placebo		.012*	<.001*
Vs 0.4 mg			0.158

*Statistically significant using the Bonferroni-Holm procedure.

Remarks: While each of the tamsulosin arms differs significantly from the placebo, there are no significant differences between the two arms themselves.

Table 9B displays the results of the analysis on AUA-Responders. The differences in response to tamsulosin compared to the placebo are very highly significant even after correcting for multiple comparisons, whereas, as in the earlier situations, there are no significant differences between the tamsulosin arms themselves.

Similar comments apply to Tables 9C and D.

TABLE 9B: AUA-RESPONDER
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders at 13 wks	86(41%)	122(56%)	124(60%)
p-values:			
Vs Placebo		=.001*	<.001*
Vs 0.4 mg			0.204

*Statistically significant using the Bonferroni-Holm procedure.

TABLE 9C: QMAX (ML/SEC)
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Mean Baseline Score	9.90	9.93	10.01
Number in the Arm	208	217	206
Mean Change at 13 wks	0.91	1.44	1.74
Number in the Arm	208	217	206
p-value:			
Vs placebo		<0.012*	<.009*
Vs 0.4 mg			0.381

*Statistically significant using the Bonferroni-Holm procedure.

TABLE 9D: QMAX RESPONDERS
(COMPLETERS ONLY)

	TREATMENT ARM		
	Placebo	0.4 mg	0.8 mg
Responders at 13 wks	48(23%)	72(32%)	66(32%)
Number in the Arm	208	217	206
p-value:			
Vs placebo		<.020*	<.012*
Vs 0.4 mg			0.481

*Statistically significant using the Bonferroni-Holm Procedure.

2.7 Comments on the above Analyses:

Results obtained here were similar to those of study US92-03A. However, there were a few exceptions:

1. Table 9A allows one to conclude that there was a statistically significant baseline difference in the mean baseline scores between the placebo and the 0.8 mg arms (even after the B-H correction with adjusted critical p-value of 0.027), while the differences were marginally significant between the placebo and the 0.4 mg arms (p = 0.071).

2. Overall, the results for the completers population corroborates the sponsor's results for the ITT population. The

treatment arms 0.4 mg and 0.8 mg arms are not significantly different on any of the four efficacy parameters.

2.8 Analysis of Responders to both AUA and QMAX:

1. As in Section 1, the Jonckheere-Terpstra test for overall differences testing simultaneously all the three groups yielded a highly significant p-value < 0.0001. This implies that the treatment responses are highly dose-dependent.

2. Among the pairwise comparisons, placebo vs 0.4 mg arm; placebo vs 0.8 mg arm; and 0.4 mg vs 0.8 mg arm, the first two comparisons yielded significant results -- 0.0101, .0021 (2-sided p-values); and the third comparison yielded a p-value of 0.6933.

TABLE 10: DISTRIBUTION OF PATIENTS BY TYPE OF RESPONSE

Responder to:	Placebo	0.4 mg	0.8 mg
BOTH AUA & QMAX	22 (10.6%)	43 (19.8%)	45 (21.8%)
AUA ONLY	64 (30.8%)	79 (36.4%)	79 (38.3%)
QMAX ONLY	26 (12.5%)	27 (13.0%)	21 (10.2%)
NONE	96 (46.2%)	68 (31.3%)	61 (29.6%)
TOTAL	208 (100%)	217 (100%)	206 (100%)

2.9 Results by Center:

Fourteen centers participated in this study. Sample sizes for the three treatment groups ranged from 6 to 33, with a mean size of 18 in each treatment arm. The 95% confidence intervals for the difference between the treatment arm and placebo for each of the efficacy parameteres Total AUA scores and Qmax values are presented in the Appendix. The results were generally consistent across the centers, although there was more variation in sample sizes from center to center.

2.10 Efficacy Charts:

Bar charts showing the comparative efficacies of the three treatment arms for Total AUA scores and Qmax values measured at 4 time points are presents in the Appendix.

2.11 Concluding Remarks on US93-01:

1. This reviewer was able to replicate the results of the sponsor for the four efficacy parameters. The results were analyzed by this reviewer for both the ITT population and the completers data (of size 631). However, results are presented for the completers.

2. There were statistically significant differences between the pairs placebo and the treatment arm 0.4 mg, as well as the pair placebo and the 0.8 mg arm. However, there are no significant differences between the 0.4 mg and .8 mg arms, as far as the four efficacy parameters are concerned. These results reconfirm in their entirety, those of the first study.

3. The combined responders to both Total AUA Scores and Qmax variables in the treatment arms show significant improvements over the placebo. Comparing the three groups simultaneously, one obtains highly significant dose-related improvements. These analyses were not specified in the protocol.

SECTION 3: THIS REVIEWER'S CONCLUDING REMARKS ON TAMSULOSIN:

Based on independent analyses of the studies US92-03A and US93-01 this reviewer concludes that:

1. This reviewer agrees that the sponsor has successfully established the superiority of the 0.4 mg arm of tamsulosin over placebo with respect to the four primary efficacy parameters.

2. The superiority of the 0.8 mg arm of tamsulosin over placebo has also been established with respect to the four efficacy parameters.

3. There are no statistically significant differences on any of the four primary efficacy parameters between the 0.4 mg and 0.8 mg arms. On the other hand, adverse effects such as abnormal ejaculation is statistically significantly higher in the 0.8 mg group compared to the placebo in both studies.

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Mathematical Statistician

Concur: Dr. Lisa Kammerman 2/22/97

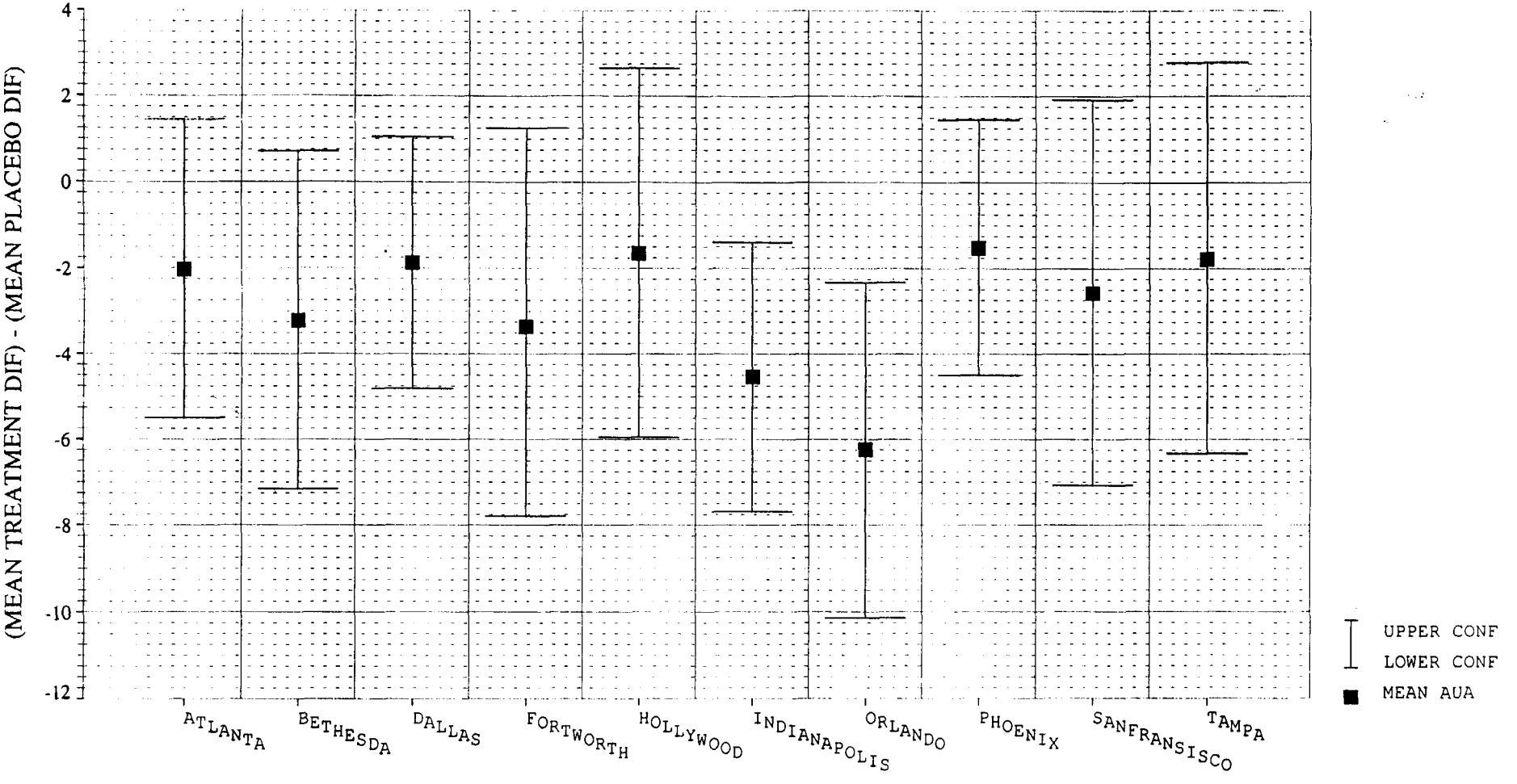
Dr. Nevius 2/28/97
Director, Division II

cc:
Archival NDA 20-~~564~~ 579
HFD-580/TRumble, HJolson, JFourcroy
HFD-715/Division file, ENevius LKammerman, AGubbi, Chron

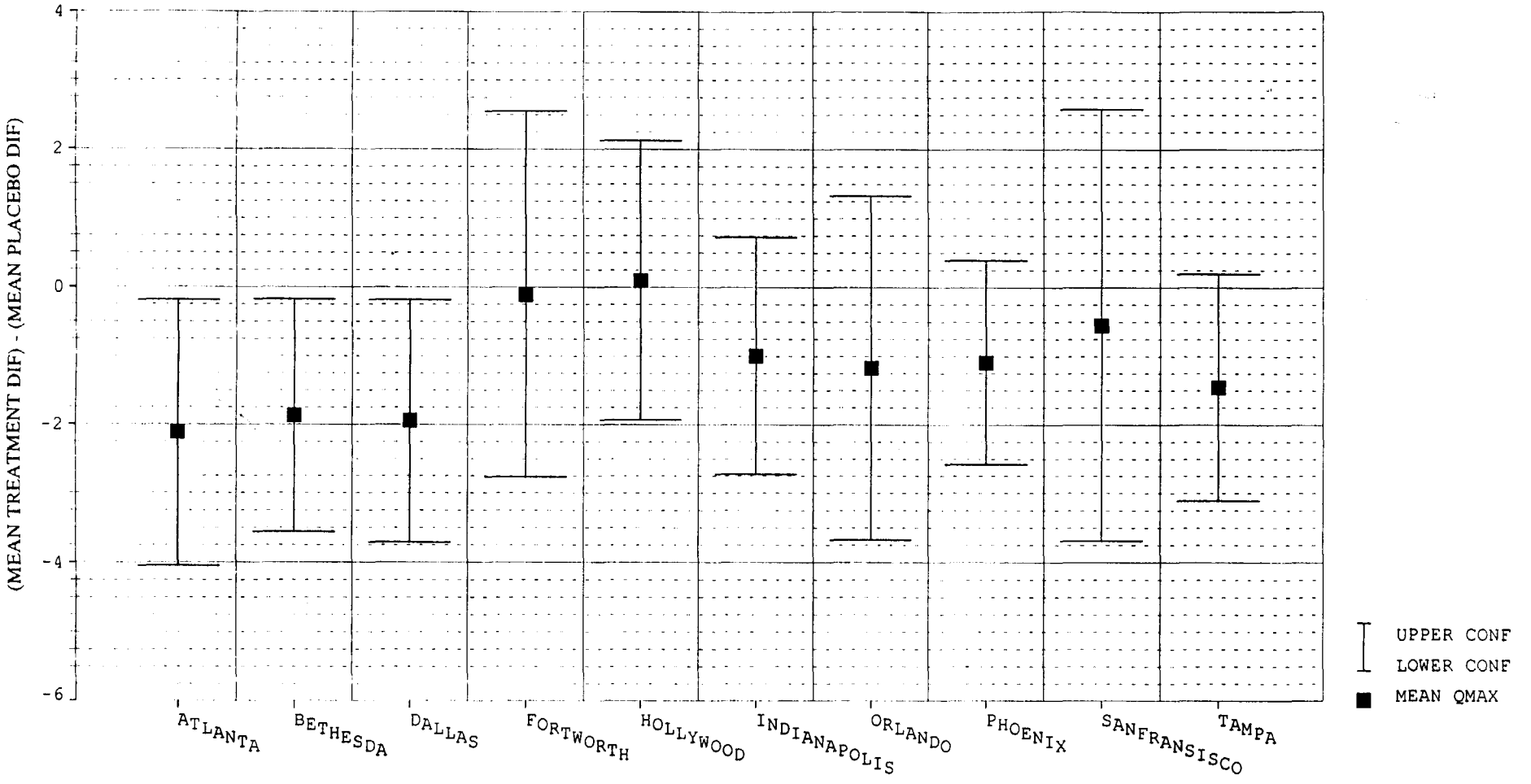
This review consists of 21 pages of text and 13 pages of appendix.

APPENDIX PAGES

STUDY US92-03A: AUA SCORES -- PLACEBO VERSUS 0.4 MG ARM



STUDY US92-03A: QMAX VALUES - PLACEBO VERSUS 0.4 MG ARM



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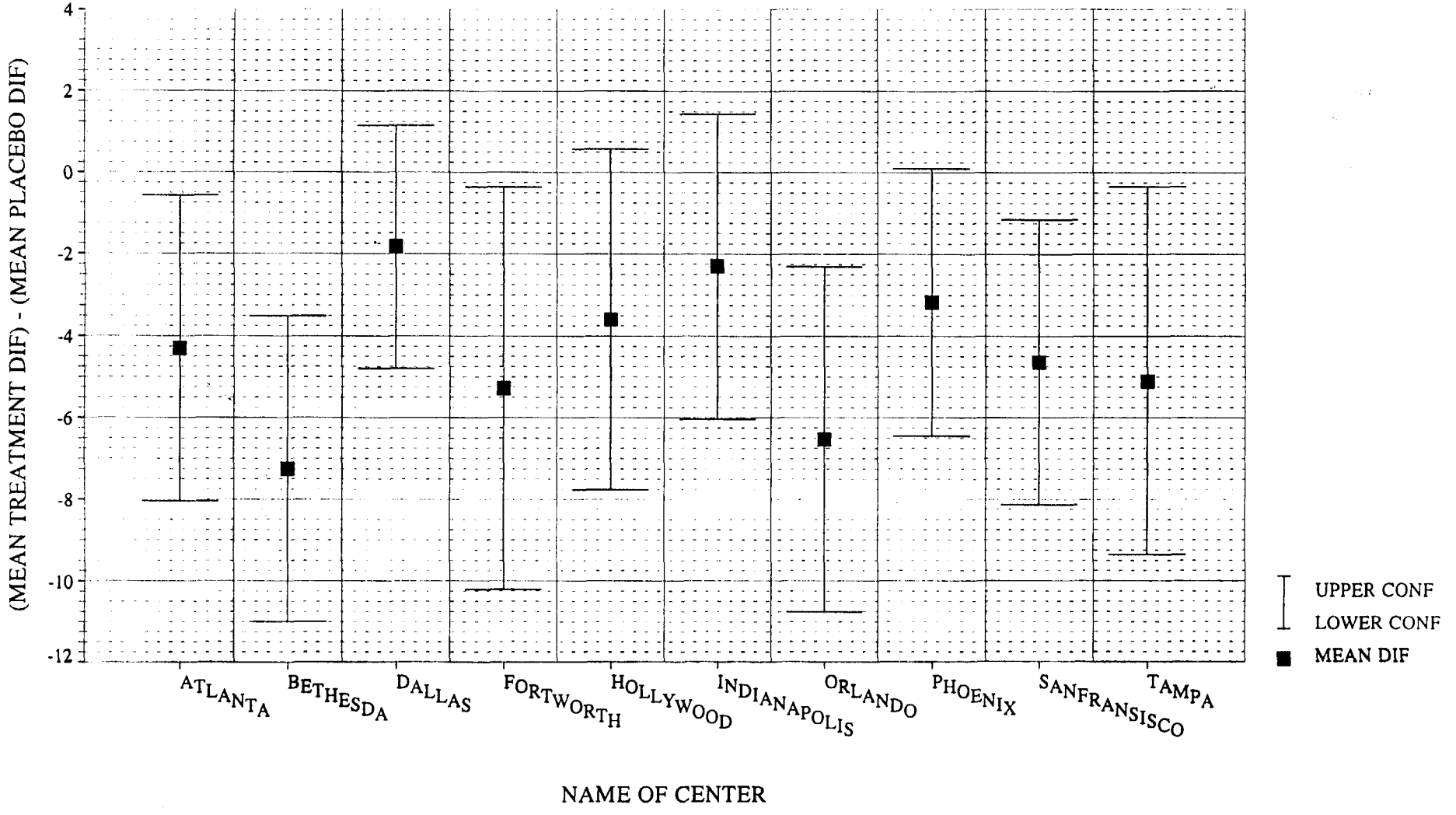
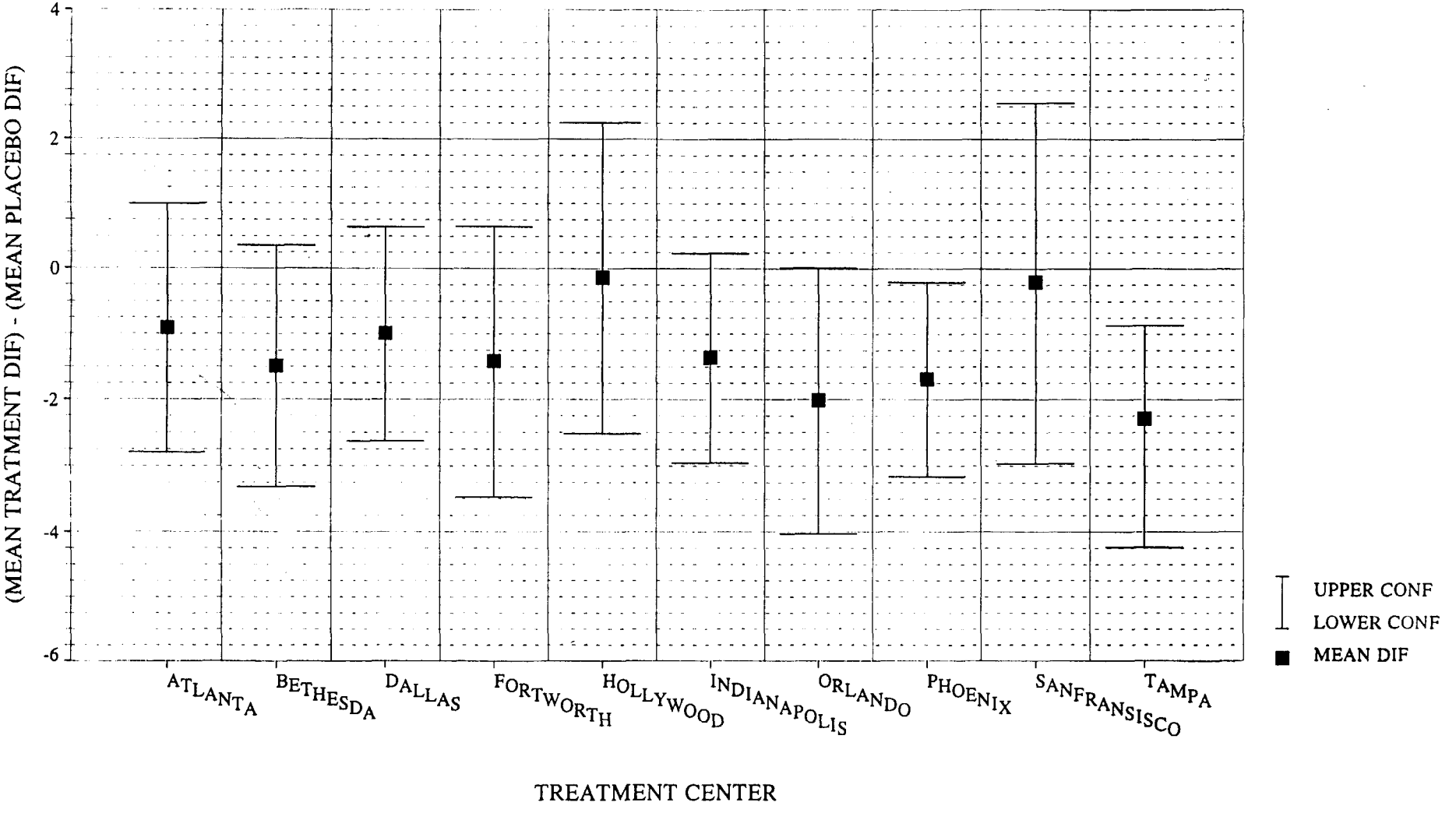
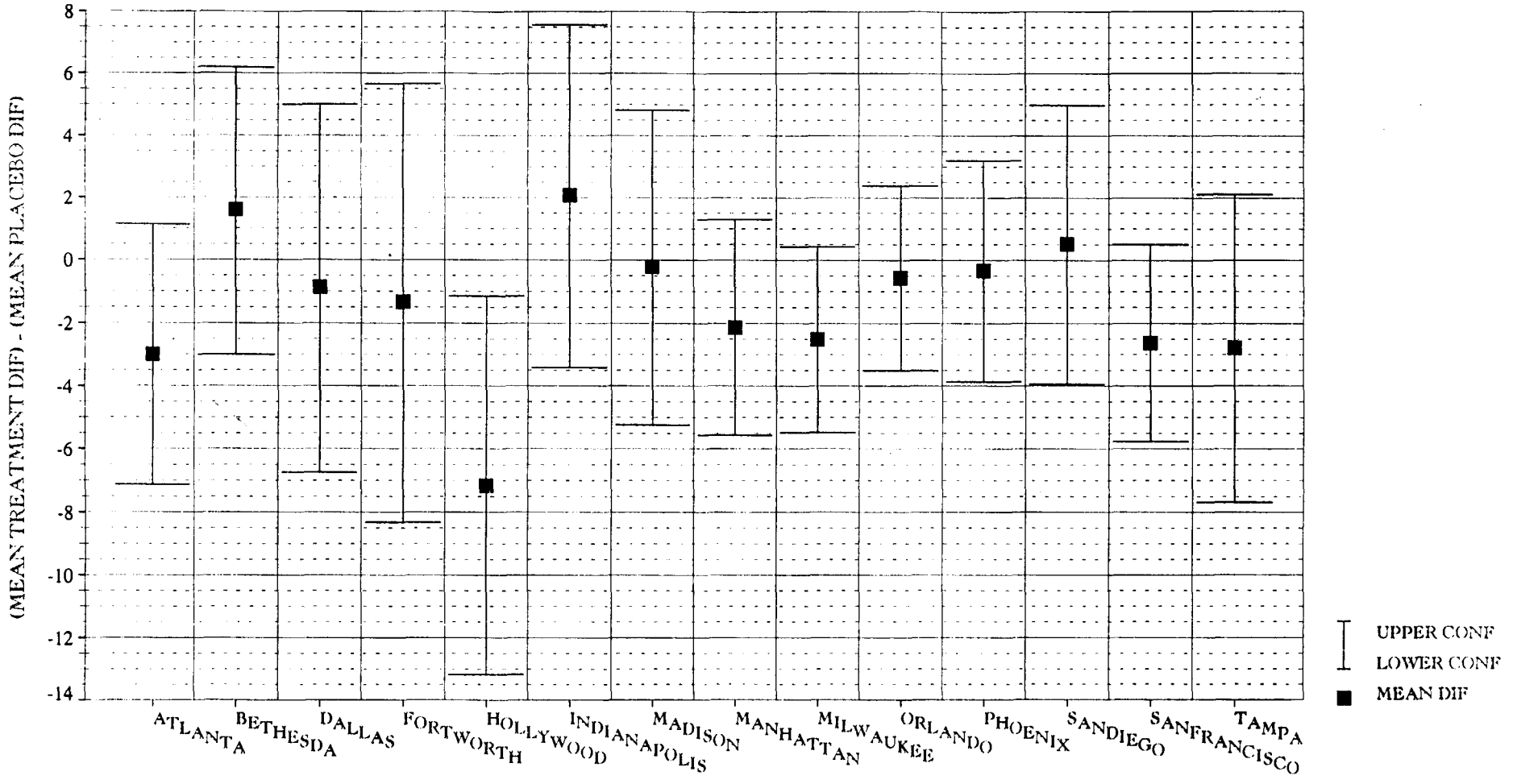
STUDY US92 - 03A: AUA SCORE - PLACEBO VS 0.8 MG ARM



STUDY US92 - 03A: QMAX VALUES -- PLACEBO VS 0.8 MG ARM



STUDY US93-01: AUA SCORES -- PLACEBO VERSUS 0.4 MG ARM



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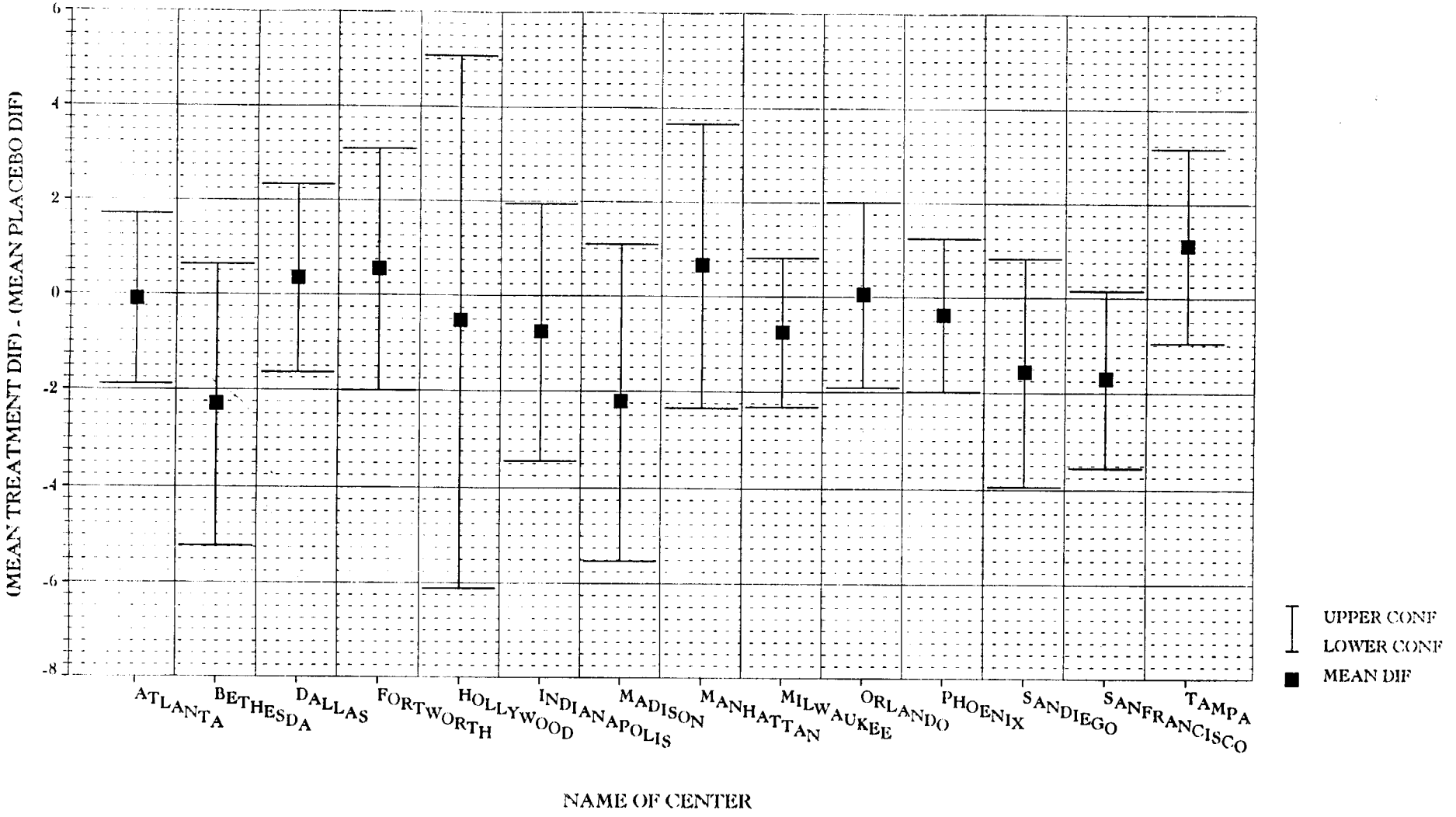

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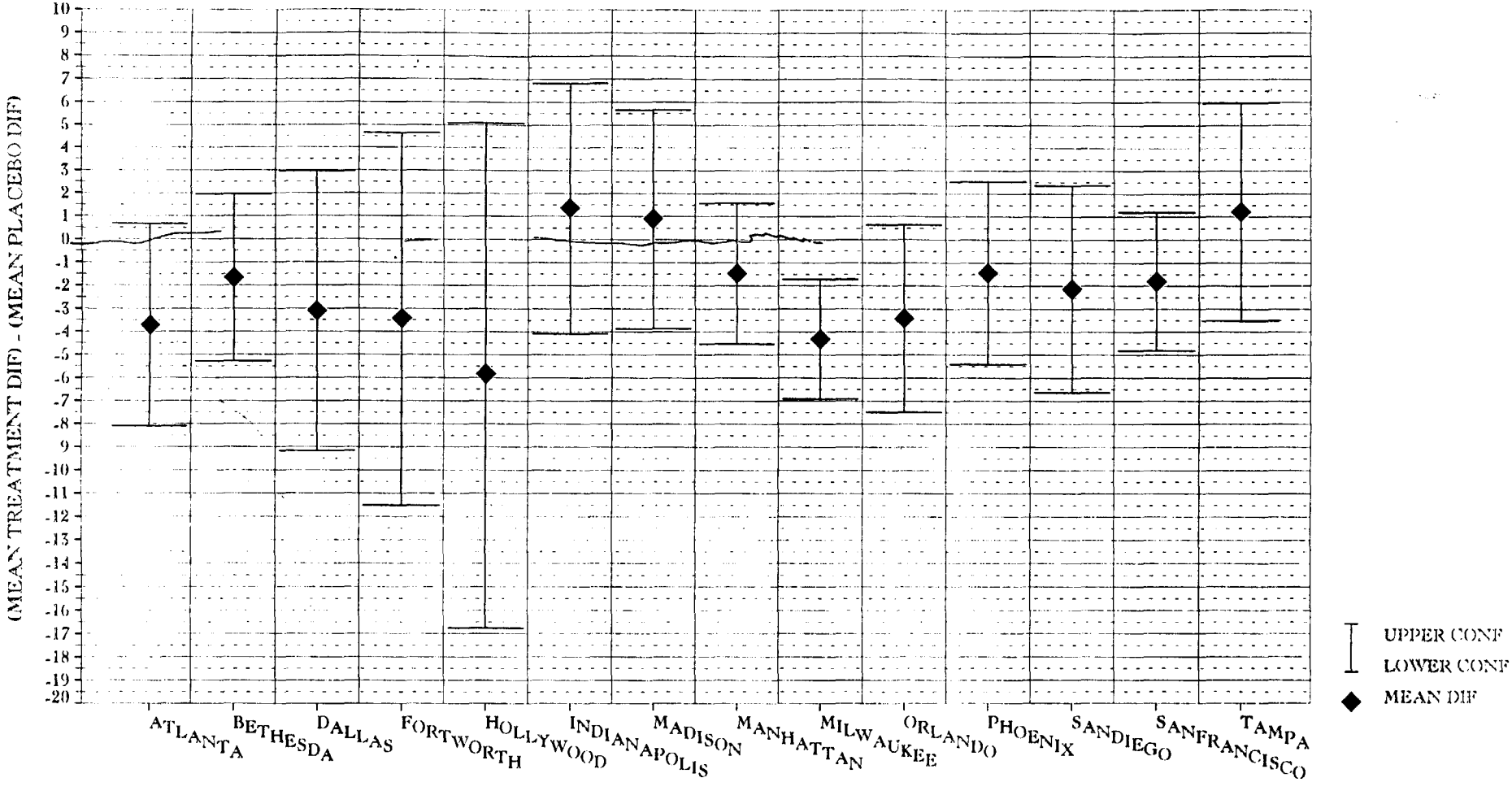

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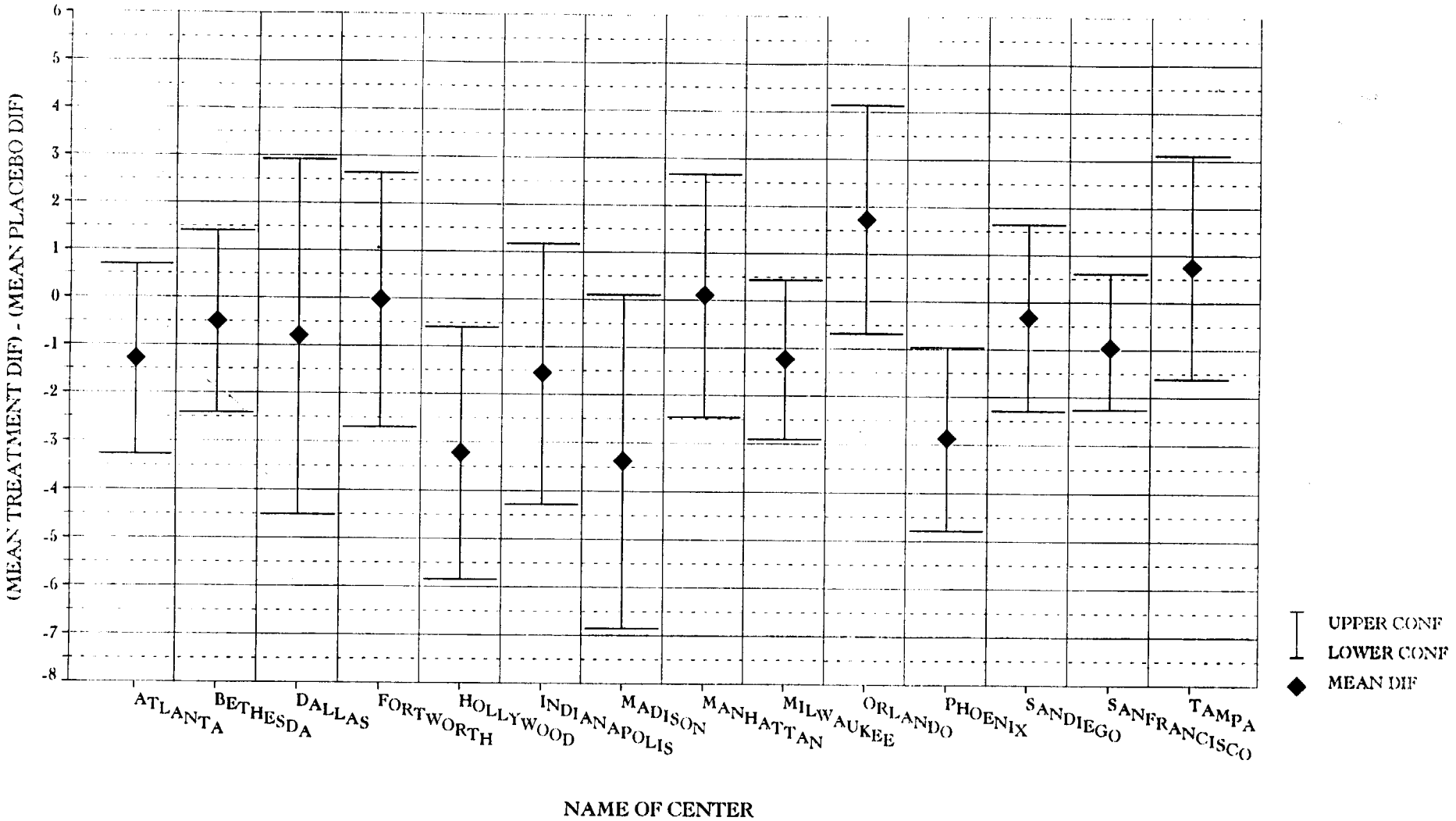
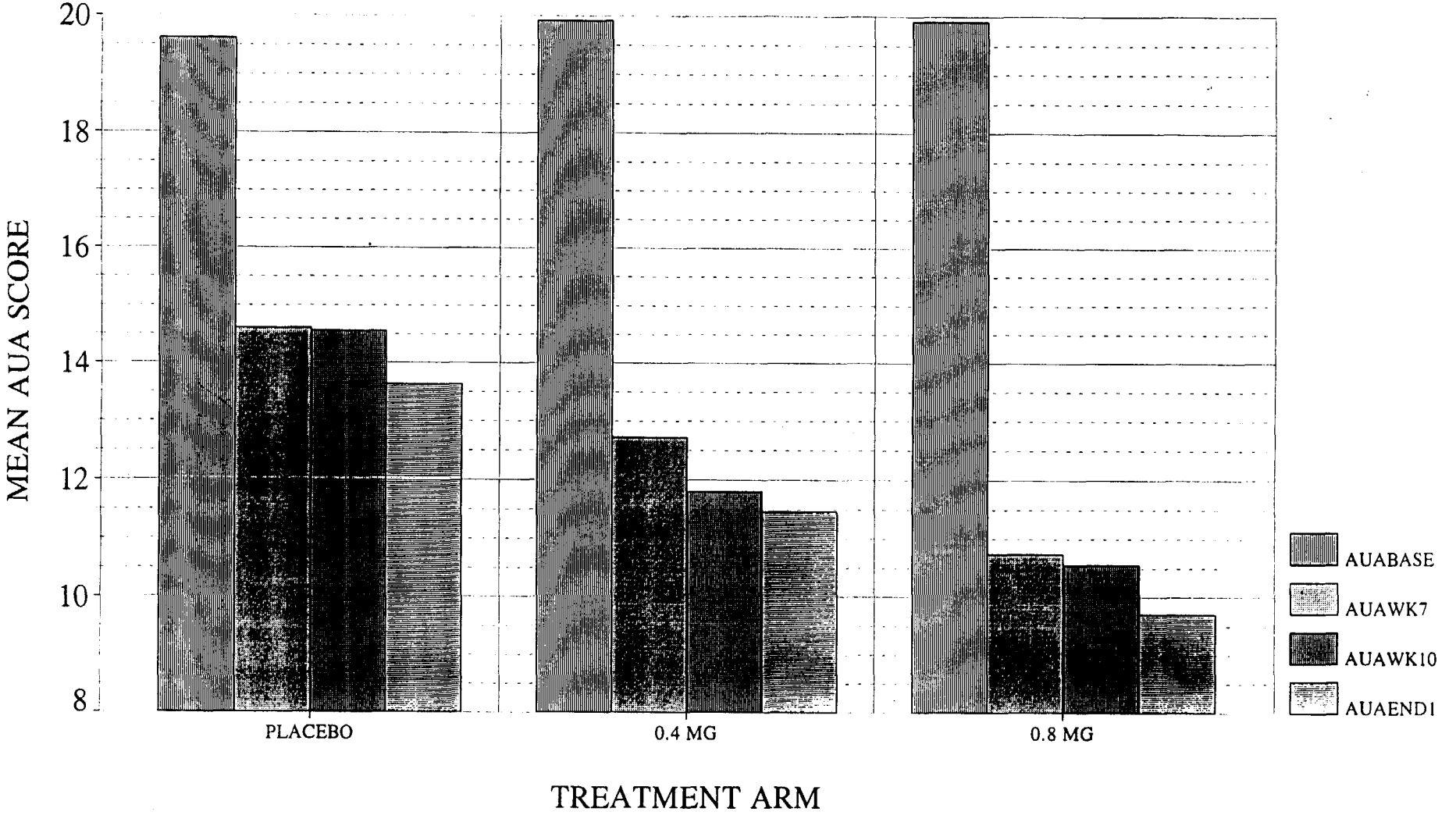
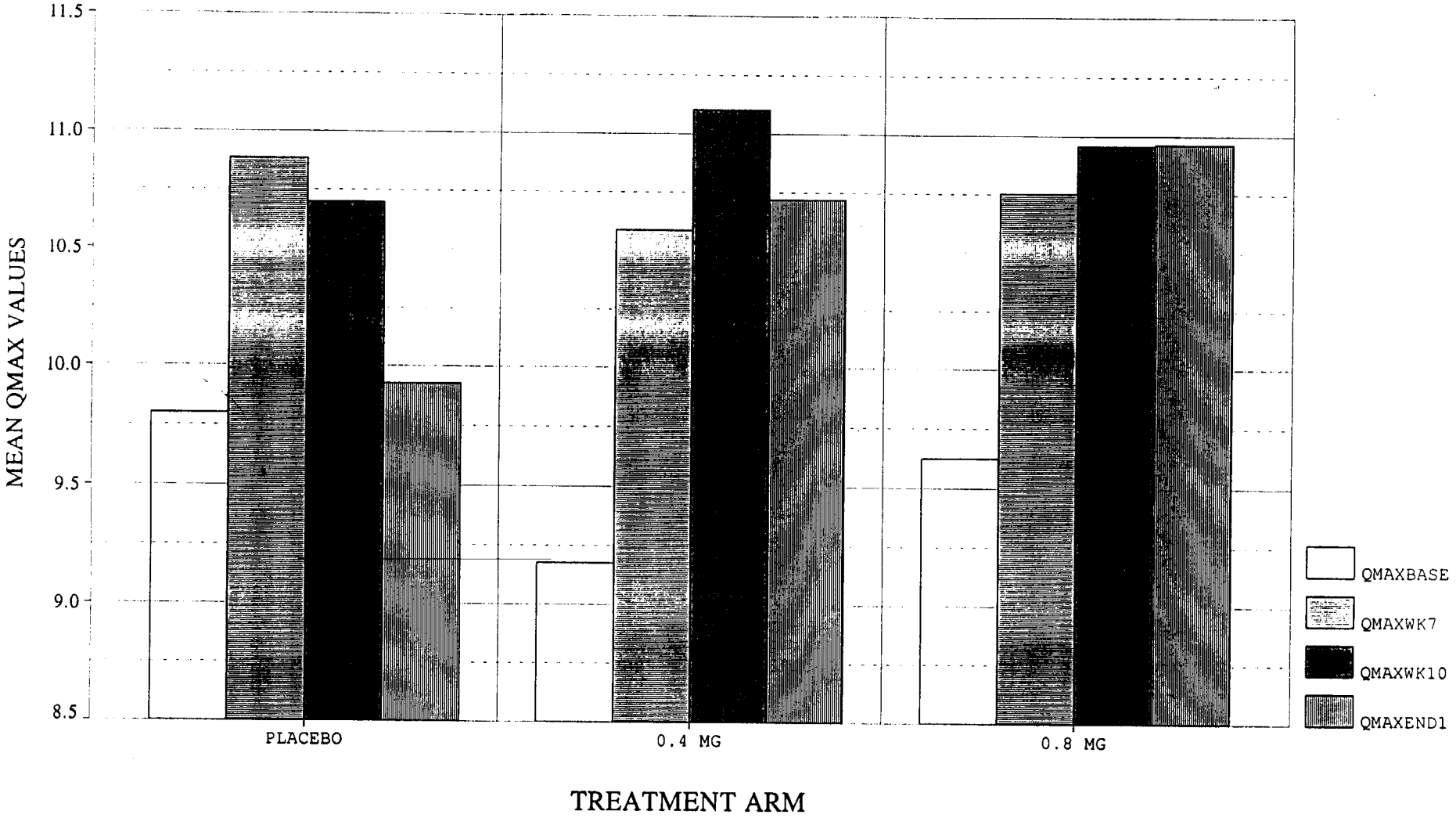


STUDY 92-03A: EFFICACY OF FLOMAX---TOTAL AUA SCORES



STUDY 92-03A: EFFICACY OF FLOMAX---MEAN QMAX VALUES



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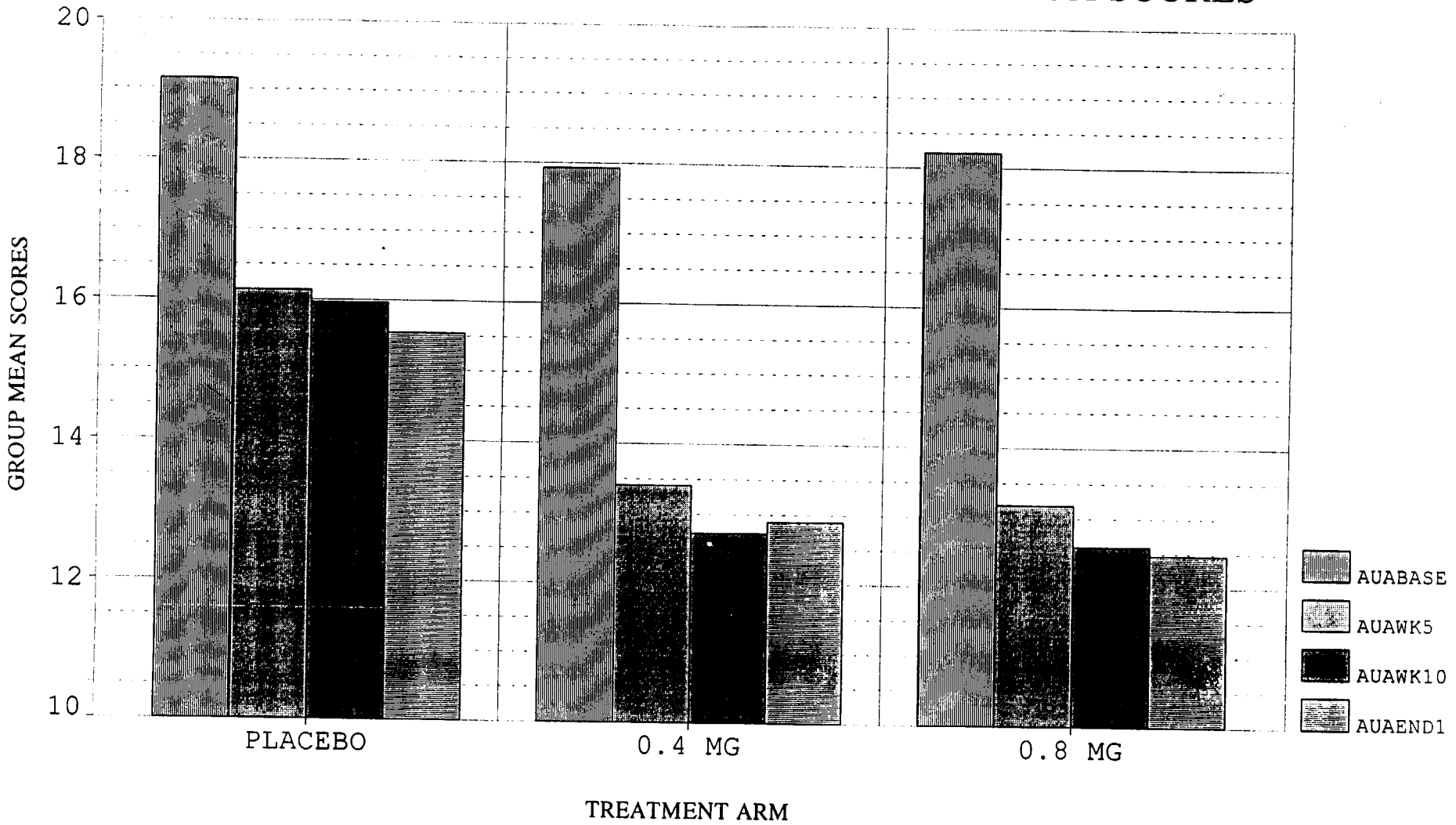
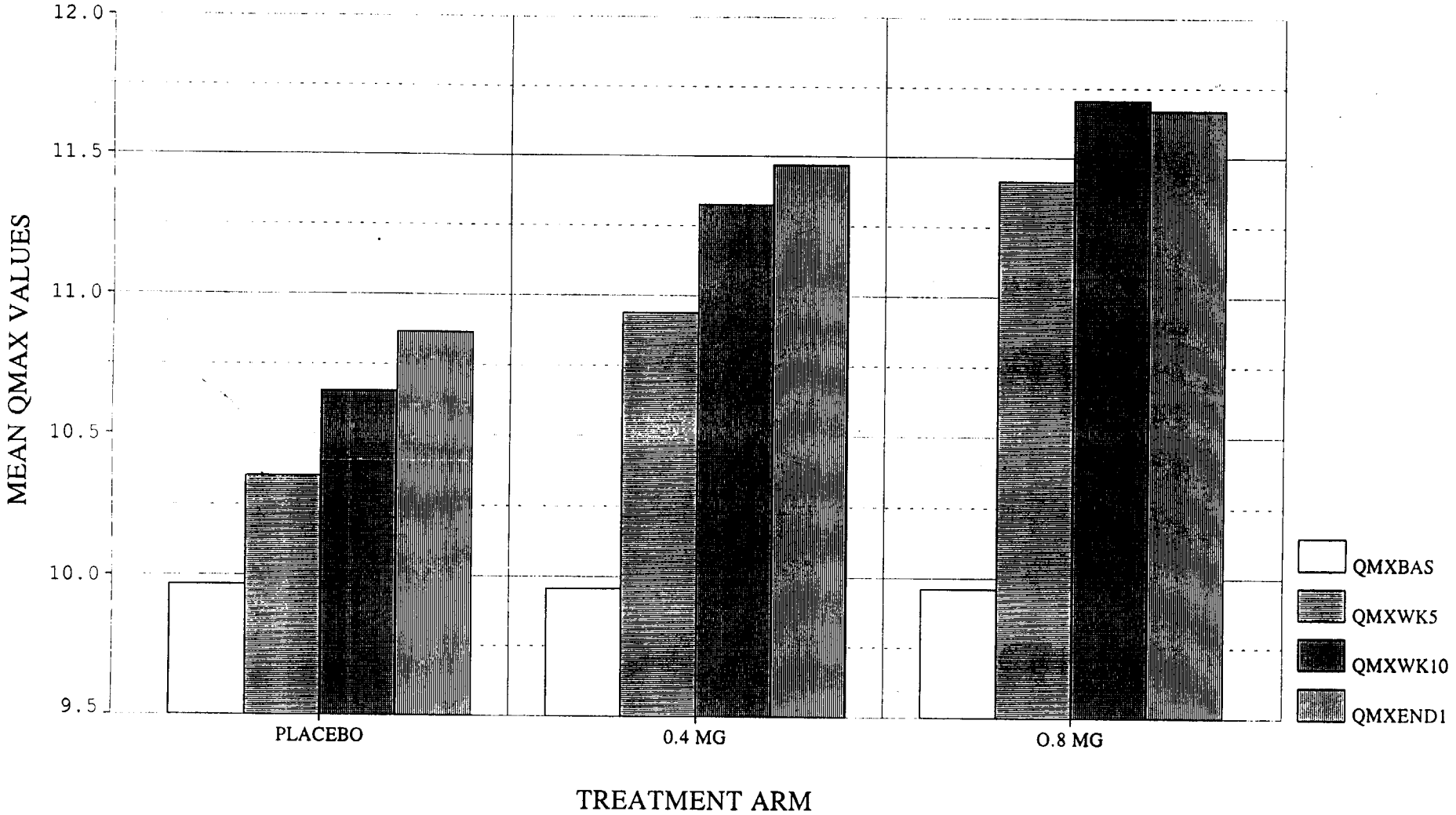


STUDY 93-01: EFFICACY OF FLOMAX---MEAN QMAX VALUES



DEC 4 1996

STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY

Date:
IND#:
NDA#: NDA 20-579
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Name of Drug: Flomax (Tamsulosin Hydrochloride) Capsules, 0.4 mg

Documents Reviewed:

- Letter: Applicant to Dr. Lisa Rarich, Division of Reproductive and Urologic Drug Products, HFD-580, July 11, 1996
- U93-1035: A 2-year chronic/oncogenic study of LY253351 (YM-12617-1) administered in the diet to Fischer 344 rats, unpublished report D9100302, July 1990, Volumes 1.017-1.021
- U93-1061: A 2-year chronic/oncogenic study of LY253351 (YM-12617-1) administered in the diet to B6C3F1 mice, unpublished report D9100300, July 1990, Volumes 1.029-1.031

Statistical Reviewer: Ted (Jiyang) Guo, Ph.D., DOBII/OEB, HFD-715
Pharmacologist: Jerid El Hage, ODE II, HFD-580

TABLE OF CONTENTS

1. Introduction

The purpose of this review is to evaluate the study of carcinogenic potential of chemical compound named LY253351 to selected rats and mice, reported in July, 1990 by the The rat study comprises two replications (using the same animal strain): studies R07187 and R07287, which were conducted during 6/23/87-6/22/89 and 7/9/87-7/13/89, respectively. The mouse study consists of two replications (using the same animal strain): studies M01487 and M01587, which were conducted during 7/22/87-7/28/89 and 8/6/87-8/6/89, respectively. This statistical review, as a response to the request for consultation from Jerid El Hage (ODE II, HFD-580), is based upon the data supplied by the sponsor. To examine the dose-response (tumor) relationship, the survival data analysis and the dose-response trend test were performed. The validity of the study design were examined as well. The entire review was done by species and sex.

2. The Rat Study

The Sponsor's Analyses

2.1 Study Design

The sponsor used a total of 600 Fischer 344 rats with equal number in each sex, supplied by These rats were about 5-6 weeks of age at the beginning of the study. The rats were treated by dietary administration. The males were assigned randomly to five treatment groups: 0.0 (control), 1.3, 4.3, 13.1, and 43.3 mg/kg/day; the females were assigned to five treatment groups with a different dosing: 0.0 (control), 1.6, 5.4, 16.0, and 51.6 mg/kg/day. According to the sponsor, these doses were equivalent to daily dietary concentrations of 0.0%, 0.003%, 0.01%, 0.03%, and 0.1%. Table 1 describes the numbers of rats included in studies R07187 and R07287 by dose and sex.

Table 1. Studies R07187 and R07287: Number of Rats

	Dose Level (% in diet)					Total
	Ctrl 0	Low 0.003	Med 0.01	High 0.03	Max 0.1	
Male	60	60	60	60	60	300
Female	60	60	60	60	60	300
Total	120	120	120	120	120	600

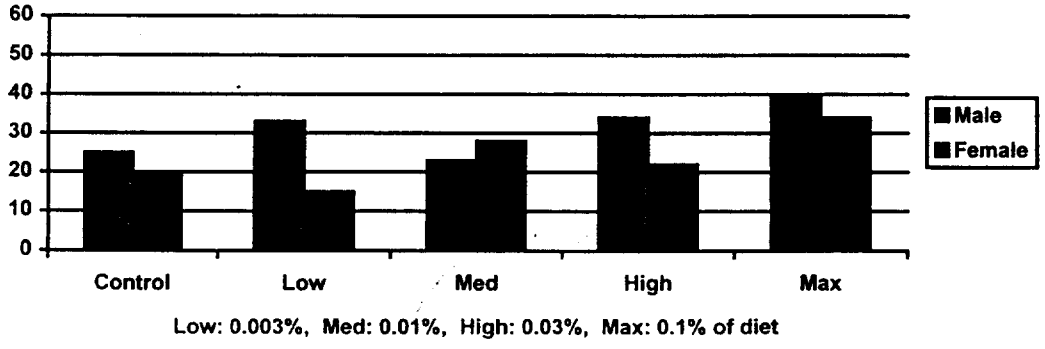
General physical conditions and behaviors of the rats were inspected at least once daily, and detailed physical examinations were made weekly for the presence of external lesions. The surviving rats were necropsied and microscopically examined on or after week 104.

2.2 Survival Data Analysis

In the Summary of report #U93-1035: A 2-Year Chronic/Oncogenic Study of LY253351 (YM-12617-1) Administered in the Diet of Fischer 344 Rats, page 16, Volume 1.017, the sponsor concluded that "the mortality rate in both control and treated rats was remarkably low through 18 months of the 24-month study." "Mortality at the end of the study was increased in males and females of the 0.1% group [the highest dose], primarily due to the increased severity of progressive glomerulonephrosis in males and females and to mononuclear cell leukemia in males."

Figure 1 depicts the number of rats died prior to the terminal sacrifice, by dose and by sex. For either sex, there were more rats died in the 0.1% dose group than in the other groups.

Figure 1. Number of Rats Died before Terminal Sacrifice



2.3 Tumor Data Analysis

In Summary (page 17, vol. 1.017) the sponsor concluded that "there was a slight, though statistically significant, increase in mammary gland fibroadenoma in females of the 0.01%, 0.03% and 0.1% groups and moderate to severe mammary gland hyperplasia in some of the females of the 0.03% and 0.1% groups. Some of the females of the 0.1% had hyperplasia of the pituitary gland." In Discussion and Conclusions (page 22, vol. 1.017) then sponsor said, "There was a statistically significant increase in the incidence of mononuclear cell leukemia (MCL) in males of the 0.03% and 0.1% groups and in females of the 0.1% group. However, this finding was not considered to indicate oncogenic potential since: MCL is a common neoplasm in aged Fischer 344 rats and rats dying before month 18 of this study had a very low incidence of the neoplasm that was unaffected by the LY253351 treatment. The incidence of MCL in this study, with the exception of a mid-dose (0.03%) group was within the range of historical control values for this laboratory." The sponsor said in the Summary (page 17, vol. 1.017) that "It may be concluded that this compound has not demonstrated any primary oncogenic activity in the rat."

The Reviewer's Analyses

The purposes of the survival data analysis were: (1) to examine the significance of the differences in survival among the treatment groups (i.e., homogeneity test), and (2) to determine the significance of positive or negative dose-mortality trend (i.e., dose-mortality trend test). The theoretic background for these tests is referred to Lin et al[1] and Thomas et al[2].

In the tumor data analysis, the tumors were classified as either fatal (lethal) or non-fatal (non-lethal) type. In the analysis for a selected tumor, the significance of dose-tumor positive linear trend was of our primary interest. According to Peto et al[3], the reviewer applied the death-rate method to fatal tumors and the prevalence method to non-fatal tumors. For tumors that caused deaths for some, but not all rats, a combined test was performed. The combined test used the Z-statistic which was assumed to follow a standard normal distribution. This test was referred to as the asymptotic test.

2.4 Survival Data Analysis

The numbers of male rats that died during the study are shown in Table 2 below. There were deaths in the control, 0.01% and 0.03%

dose groups for the first 52 weeks. There was only 1 death in each of the 0.003%(low) and 0.1%(max) dose groups for the first 52 weeks.

Table 2. Numbers of Male Rats Died by Time and Dose

		Dose					
		CTL	LOW	MED	HIGH	MAX	Total
Time							
0-52	No.	.	1	.	.	1	2
	Pct.	.	1.7	.	.	1.7	0.7
53-78	No.	2	5	3	6	5	21
	Pct.	3.3	8.3	5.0	10.0	8.3	7.0
79-91	No.	11	9	9	6	11	46
	Pct.	18.3	15.0	15.0	10.0	18.3	15.3
92-103	No.	12	18	11	22	22	85
	Pct.	20.0	30.0	18.3	36.7	36.7	28.3
Terminal	No.	35	27	37	26	21	146
	Pct.	58.3	45.0	61.7	43.3	35.0	48.7
Total	No.	60	60	60	60	60	300
	Pct.	100.0	100.0	100.0	100.0	100.0	100.0

The numbers of female rats that died during the study are shown in Table 3. Note that were no deaths during the first 52 weeks.

Table 3. Numbers of Female Rats Died by Time and Dose

		Dose					
		CTL	LOW	MED	HIGH	MAX	Total
Time							
53-78	No.	3	4	7	5	5	24
	Pct.	5.0	6.7	11.7	8.3	8.3	8.0
79-91	No.	8	5	6	5	9	33
	Pct.	13.3	8.3	10.0	8.3	15.0	11.0
92-103	No.	8	6	15	12	20	61
	Pct.	13.3	10.0	25.0	20.0	33.3	20.3
Terminal	No.	41	45	32	38	26	182
	Pct.	68.3	75.0	53.3	63.3	43.3	60.7
Total	No.	60	60	60	60	60	300
	Pct.	100.0	100.0	100.0	100.0	100.0	100.0

Table 4, which is more informative, shows the intercurrent mortality rates for the males. The differences in cumulative percentages of death among the groups appeared to be small. Before the terminal sacrifice, the percentage (65%) in the 0.1% (max) dose group was the highest among all groups.

Table 4. Intercurrent Mortality Rates among Male Rats

	Dose														
	CTL			LOW			MED			HIGH			MAX		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)															
0-52	.	.	.	1	60	1.7	.	.	.	.	.	.	1	60	1.7
53-78	2	60	3.3	5	59	10.0	3	60	5.0	6	60	10.0	5	59	10.0
79-91	11	58	21.7	9	54	25.0	9	57	20.0	6	54	20.0	11	54	28.3
92-103	12	47	41.7	18	45	55.0	11	48	38.3	22	48	56.7	22	43	65.0
Termin. Sacrifice	35	60	58.3	27	60	45.0	37	60	61.7	26	60	43.3	21	60	35.0

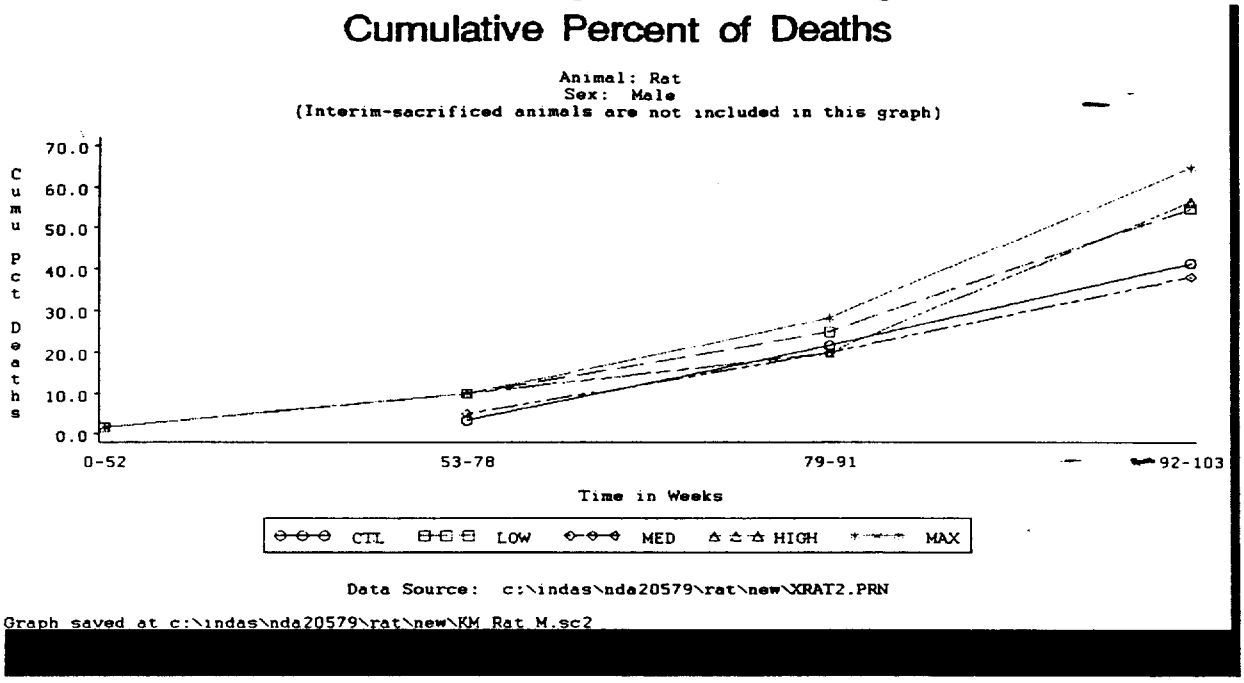
Table 5 shows the intercurrent mortality rats for the females. The difference in cumulative percentage of death among the groups appeared to be small. Before the terminal sacrifice, the percentages (57%) in the 0.1% (max) dose group was the highest among all groups.

Table 5. Intercurrent Mortality Rates among Female Rats

	Dose														
	CTL			LOW			MED			HIGH			MAX		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)															
53-78	3	60	5.0	4	60	6.7	7	60	11.7	5	60	8.3	5	60	8.3
79-91	8	57	18.3	5	56	15.0	6	53	21.7	5	55	16.7	9	55	23.3
92-103	8	49	31.7	6	51	25.0	15	47	46.7	12	50	36.7	20	46	56.7
Termin. Sacrifice	41	60	68.3	45	60	75.0	32	60	53.3	38	60	63.3	26	60	43.3

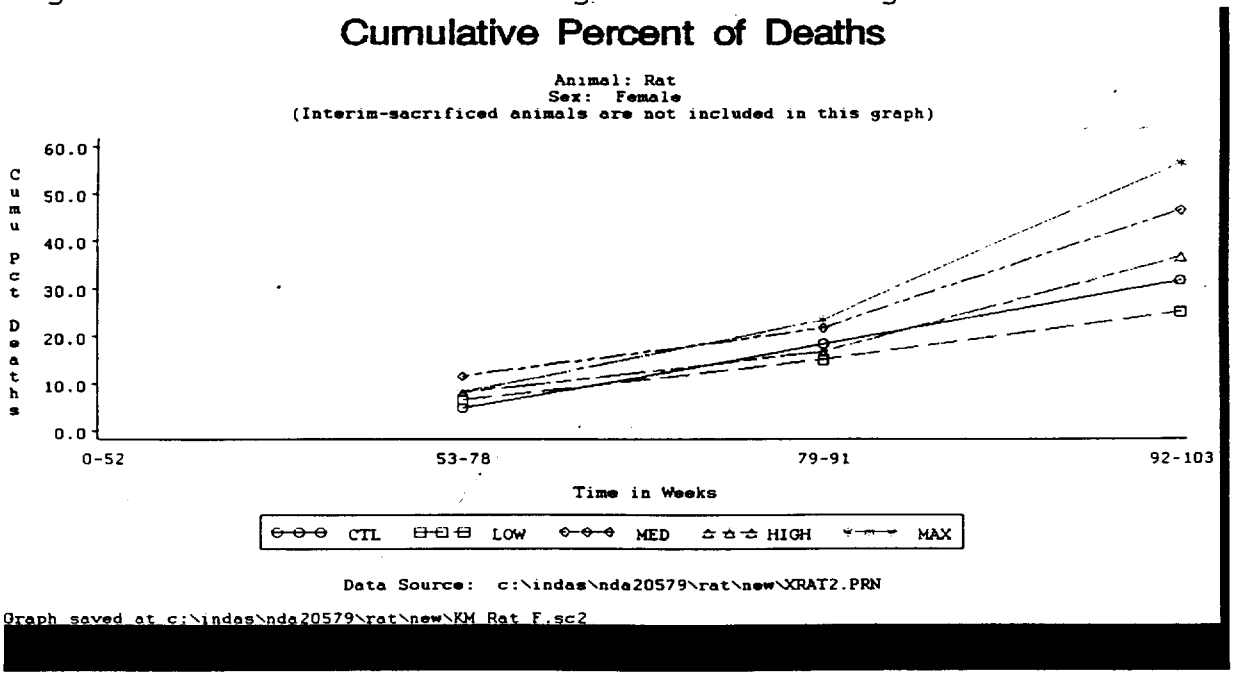
A graphical representation of the cumulative percentages of death for the males is shown in Figure 2. The mean cumulative percentage of death did not show a large difference among the treatment groups, even though the gap widened with time. The highest dose group had an highest cumulative percentage of death of all groups.

Figure 2. Cumulative Percentage of Death Among Male Rats



The following figure (Figure 3) shows the cumulative percentage of death for the females. The difference in cumulative percentage of death was small before week 92, and the gap widened prior to the terminal sacrifice. The highest dose group had the highest cumulative percentage of death of all groups.

Figure 3. Cumulative Percentage of Death Among Female Rats



Figures 4 and 5 depict the by-dose Kaplan-Meier survival functions, for the males and the females, respectively. For either sex, the difference in survival rate among the treatment groups seemed to be small. The numbers of death were low before through 60 weeks of the study.

Figure 4. Kaplan-Meier Survival Functions for Male Rats

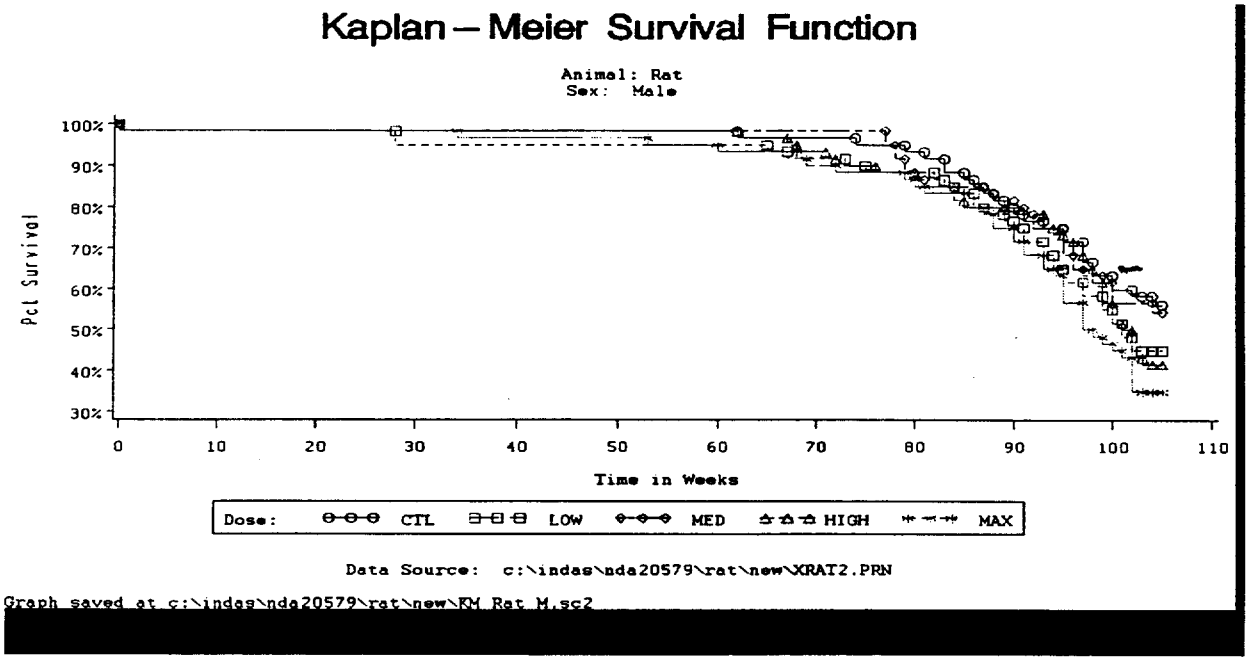
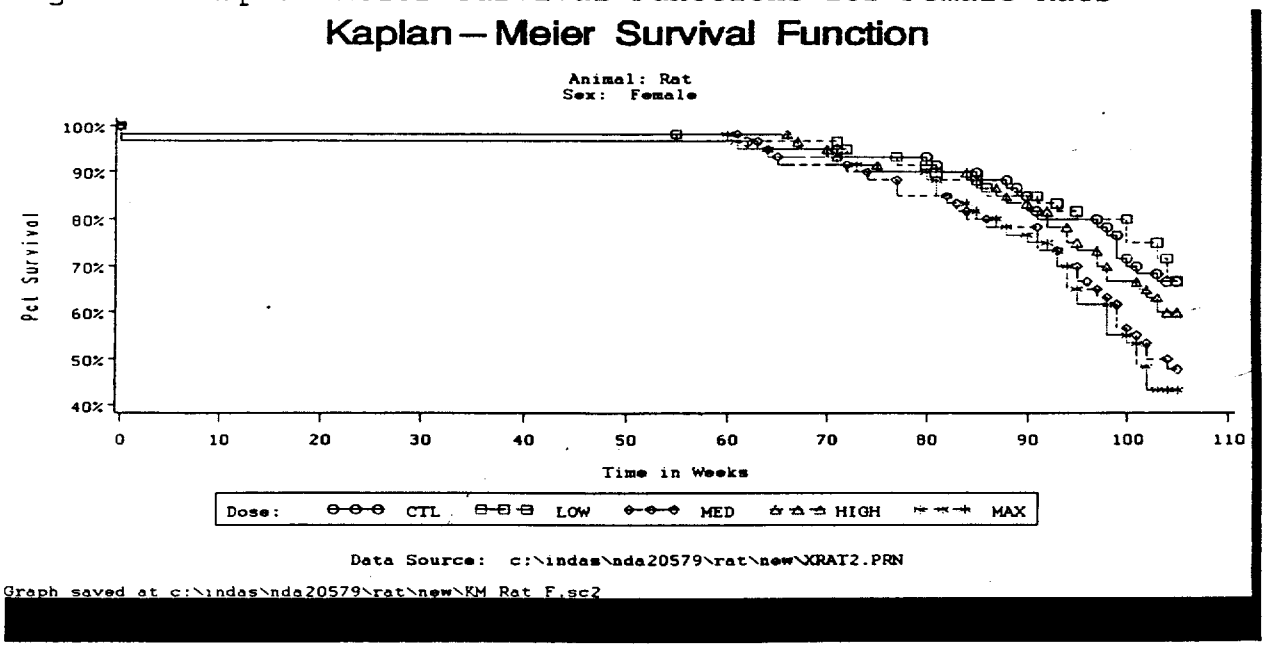


Figure 5. Kaplan-Meier Survival Functions for Female Rats



To test the homogeneity in survival among the treatment groups, and the significance of the positive dose-mortality trend, the time-adjusted tests were performed using the Cox and the Kruskal-Wallis tests. Table 6 summarizes these tests for the males and females. For either sex, the positive dose-mortality trend was shown to be significant. The mortality increased as the dose increased.

Table 6. Homogeneity Test for Dose-Mortality Trend for Males

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1, by Donald G. Thomas, National Cancer Institute

Males:

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	6.12	0.0133
	Depart from Trend	3.47	0.3244
	Homogeneity	9.60	0.0478
Kruskal-Wallis	Dose-Mortality Trend	4.96	0.0259
	Depart from Trend	2.72	0.4372
	Homogeneity	7.68	0.1040

Females:

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	9.51	0.0020
	Depart from Trend	5.32	0.1497
	Homogeneity	14.83	0.0051
Kruskal-Wallis	Dose-Mortality Trend	8.05	0.0046
	Depart from Trend	5.22	0.1566
	Homogeneity	13.26	0.0101

Reviewer's Comments

In conclusion, the positive dose-mortality trend was statistically significant, based on the time-adjusted tests. This trend was not clearly seen from Figures 2-5. The sponsor pointed out the increase in mortality in the 0.1% group, but did not address the association between dosing and mortality.

2.5 Tumor Data Analysis

The reviewer performed the dose-response (tumor) positive linear trend tests using both the exact permutation test and the asymptotic test. In this review, for tumors found either fatal or non-fatal to all the rats included in the study, the statistical interpretation is based on the exact test; for tumors found fatal to some, but not all rats, the statistical interpretation is based on the asymptotic tests, also known as the combined test. The asymptotic test used the Z-statistic, which follows a standard normal distribution. The detailed statistical results can be found in the Appendix.

To adjust for the effect of multiple testings, one can use a rule proposed by Haseman[1]. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is used in the review. This rule states that in order to keep the overall type-I error at the level of about 0.1, tumor types with a spontaneous tumor rate of 1% or less should be tested at a 0.025 significance level, otherwise, a 0.005 significance level should be considered.

The reviewer's test for positive dose-response linear trend in the females showed that the following tumor was significant:

ORGAN	TUMOR	P VALUE
STOMACH (ST)	MONONUCLEAR CELL LEUKEMIA (941)	0.0130

The tumor incidences from the control to the highest dose group were 0, 1, 0, 0, and 2. According to the FDA's rule, this tumor was decided to be a rare tumor (the observed spontaneous tumor rate in the control group was 0%). This tumor was considered to be significant, because the p-value, 0.013 was less than 0.025, a cut-off p-value used for rare tumors.

No other tumors tested were determined to show a positive dose-response linear trend, according to the FDA's rule.

Reviewer's Comments

The sponsor concluded that there was a statistically significant increase in incidence in mammary gland neoplasms (fibroadenoma and hyperplasia) in the females of the 0.01%, 0.03% and 0.1% groups. However, the reviewer's trend test showed that fibroadenoma was not significant. For this tumor, the p-value was 0.0629 from the trend test, and the tumor incidences from the control to the highest dose group were 9, 13, 17, 14, and 16, respectively. The The sponsor concluded that there was a moderate to severe mammary gland hyperplasia in some of the females of the 0.03% and 0.1% groups. But hyperplasia never appear in the sponsor's file, TAM_R.TXT, containing individual animal records.

2.6 Evaluation of Validity of Design

The evaluation of the validity of design addresses the following issues:

- Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor?
- Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There has been no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with 50 animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by the experts in this field.

Haseman[1] investigated the first issue. Based on the data from twenty one studies using Fischer 344 rats and B6C3F1 mice conducted at the , he found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. In a personal communication with Dr. Karl Lin, Division of Biometrics II, CDER, FDA, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, after 80-90 weeks, would be consider as a sufficient number and adequate exposure. However, the percent could be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there would be 20-30 animals still alive after the above weeks. In addition, Chu, Cueto and Ward[1] suggested that "[in order for the number of animals] to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year." It appears that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and the number of animals at risk.

As far as the adequacy of dose level is concerned, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In a 1981 article by Chu, Cueto and Ward, the following criteria are mentioned for the dose adequacy.

- "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

If one of the above applies, then the doses are considered to be properly selected. Based on the above guidelines, this reviewer examined the validity of design for the rats.

Thirty five percent of the males in the highest dose group survived until the terminal sacrifice. Forty three percent of the

females in the highest dose group survived until the terminal sacrifice. This reviewer concluded that there were sufficient number of animals who had enough exposure to the test drug.

The mean body-weights for the males and the females are depicted on Figures 4.1, 4.2, 5.1, and 5.2 (pages 51-54 of vol. 1.017). Copies of these images are included in Figures A-5-1, A-5-2, A-6-1, and A-6-2, Appendix.

Overall, the mean body-weight of changes in either sex were similar among all groups. At the time of terminal sacrifice, the male-rat body weight in the highest dose group dropped more than the other groups.

According to the mean weight gains reported by the sponsor (page 81, vol. 1.017), for the males, the body-weight gains ranged grams among the treated groups. On the other hand, the body-weight gain was 383 grams for the control group. The differences in body-weight gain between the control group and the treated groups were in the range of %.

For the females, the body-weight gains ranged grams among the treated groups. On the other hand, the body-weight gain was 209 grams for the control group. The differences in body-weight gain between the control group and the treated groups were in the range of %.

Based on the death rates and mean body weights, this reviewer did not find any anomaly in the study design. However, information about clinical signs or severe histopathological toxic effects exhibited in dosed animals should also be considered in the final evaluation of the appropriateness of the selected doses.

3. The Mouse Study

The Sponsor's Analyses

3.1 Study Design

The sponsor used a total of 600 B6C3F1 mice with equal number in each sex, supplied by
These mice were about 5-6 weeks of age at the beginning of the study. The mice were treated by dietary administration. The males were randomly assigned to five treatment groups: 0, 3.7, 12.6, 39.1 and 126.8 mg/kg/day; the females were assigned to five treatment groups: 0, 3.3, 14.5, 45.2, and 158.1 mg/kg/day. According to the sponsor, these doses were equivalent to daily

dietary concentrations of 0.0%, 0.003%, 0.01%, 0.03%, and 0.1%. The following table (Table 7) describes the number of the mice included in studies M01487 and M01587 by dose and sex.

Table 7. Studies M01487 and M01587: Numbers of Mice

	Dose Level (% in diet)					Total
	Ctrl 0	Low 0.003	Med 0.01	High 0.03	Max 0.1	
Male	60	60	60	60	60	300
Female	60	60	60	60	60	300
Total	120	120	120	120	120	600

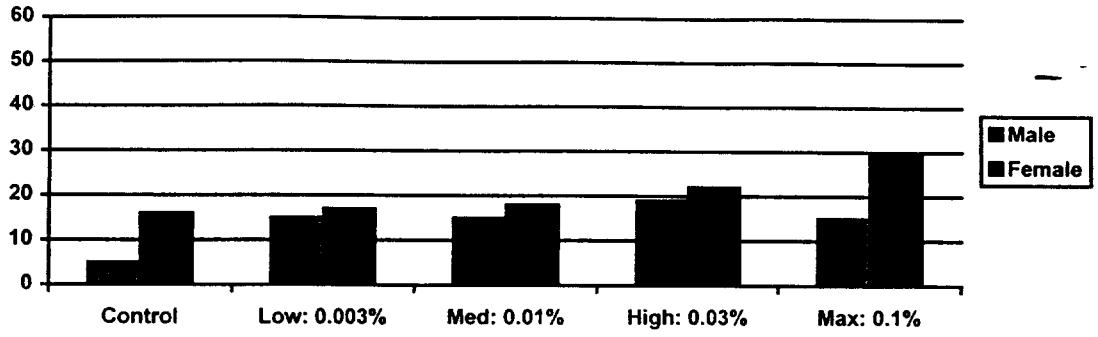
General physical conditions and behaviors of the rats were inspected at least once daily, and detailed physical examinations were made weekly for the presence of external lesions. The surviving mice were necropsied and microscopically examined on or after week 105.

3.2 Survival Data Analysis

In the report #U93-1061: A 2-Year Chronic/Oncogenic Study of LY253351 (YM-12617-1) Administered in the Diet of B6C3F1 Mice, page 18, Volume 29, the sponsor concluded that "survival was decreased in males of all LY253351 treatment groups, but the effect was equivocal because there was not dose response and the survival of control males was unusually high." "In females, survival was unaffected in study M01487, while in study M01587 it was decreased in a dose-related manner in animals of the 0.03% and 0.1% groups. This difference in survival across replicate studies suggests that factors other than the LY253351 treatment were contributing to the mortality." In other words, these was no noticeable dose-mortality relationship.

Figure 6 depicts the numbers of mice died before the terminal sacrifice, by dose and by sex. In females, the numbers of females died appeared to increase as dose increased. This observation seems to deviate from the sponsor's conclusion quoted above. The deaths were somewhat related to the doses in the males. There was not such a clear relation seen in the females.

Figure 6. Numbers of Mice Died before Terminal Sacrifice



3.3 Tumor Data Analysis

The sponsor concluded (page 36, Vol. 1.029) that "There was a statistically significant increase in mammary gland fibroadenoma and adenocarcinoma occurred in females of the 0.03% and 0.1% groups and an increased in the incidence and severity of mammary gland hyperplasia in females of the 0.1% group." "All of these effects can be attributed to one of the physiological effects of the compound; LY253351 increases circulating prolactin levels in the mouse." Also "there was a slight, though statistically significant, increase in hemangiomas of the spleen and skin in females of the 0.1% group." The sponsor did not report any statistically significant increase in tumor incidences in the males.

The Reviewer's Analyses

3.4 Survival Data Analysis

The numbers of males died during the study are shown in Table 8 below. The differences in the numbers of death among the groups appeared to be small. The overall number of death prior to the terminal sacrifice was low.

Table 8. Numbers of Male Mice Died by Time and Dose

		Dose					
		CTL	LOW	MED	HIGH	MAX	Total
Time							
0-90	No.	2	10	9	8	10	39
	Pct.	3.3	16.7	15.0	13.3	16.7	13.0
91-104	No.	3	5	6	11	5	30
	Pct.	5.0	8.3	10.0	18.3	8.3	10.0
Terminal	No.	55	45	45	41	45	231
	Pct.	91.7	75.0	75.0	68.3	75.0	77.0
Total	No.	60	60	60	60	60	300
	Pct.	100.0	100.0	100.0	100.0	100.0	100.0

The numbers of females died during the study are shown in Table 9. A similar trend seen in the male mice data was also observed here.

Table 9. Numbers of Female Mice Died by Time and Dose

		Dose					
		CTL	LOW	MED	HIGH	MAX	Total
Time							
0-52	No.	2	2	2	4	3	13
	Pct.	3.3	3.3	3.3	6.7	5.0	4.3
53-78	No.	1	1	2	3	3	10
	Pct.	1.7	1.7	3.3	5.0	5.0	3.3
79-91	No.	2	6	4	4	7	23
	Pct.	3.3	10.0	6.7	6.7	11.7	7.7
92-104	No.	11	8	10	11	17	57
	Pct.	18.3	13.3	16.7	18.3	28.3	19.0
Terminal	No.	44	43	42	38	30	197
	Pct.	73.3	71.7	70.0	63.3	50.0	65.7
Total	No.	60	60	60	60	60	300
	Pct.	100.0	100.0	100.0	100.0	100.0	100.0

Table 10 shows the intercurrent mortality rates for the males. Before the terminal sacrifice, the cumulative percentage of death showed an increase as dose increased, except for the highest dose in which the cumulative percentage of death was the same as in the low and medium dose groups. The dose-mortality trend was equivocal.

Table 10. Intercurrent Mortality Rates among Male Mice

	Dose														
	CTL			LOW			MED			HIGH			MAX		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)															
0-90	2	60	3.3	10	60	16.7	9	60	15.0	8	60	13.3	10	60	16.7
91-104	3	58	8.3	5	50	25.0	6	51	25.0	11	52	31.7	5	50	25.0
Terminal Sacrifice	55	60	91.7	45	60	75.0	45	60	75.0	41	60	68.3	45	60	75.0

Table 11 shows the intercurrent mortality rates for the females. Unlike the males, there was a clear trend that the cumulative percentage of death increased as dose increased.

Table 11. Intercurrent Mortality Rates among Female Mice

	Dose														
	CTL			LOW			MED			HIGH			MAX		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)															
0-52	2	60	3.3	2	60	3.3	2	60	3.3	4	60	6.7	3	60	5.0
53-78	1	58	5.0	1	58	5.0	2	58	6.7	3	56	11.7	3	57	10.0
79-91	2	57	8.3	6	57	15.0	4	56	13.3	4	53	18.3	7	54	21.7
92-104	11	55	26.7	8	51	28.3	10	52	30.0	11	49	36.7	17	47	50.0
Terminal Sacrifice	44	60	73.3	43	60	71.7	42	60	70.0	38	60	63.3	30	60	50.0

Figures 7 and 8 depict the by-dose Kaplan-Meier survival functions, for the males and the females, respectively. The male survival rates were higher in the control group than any other groups. From Figure 8, the female survival rates decreased as dose increased.

Figure 7. Kaplan-Meier Survival Functions for Male Mice

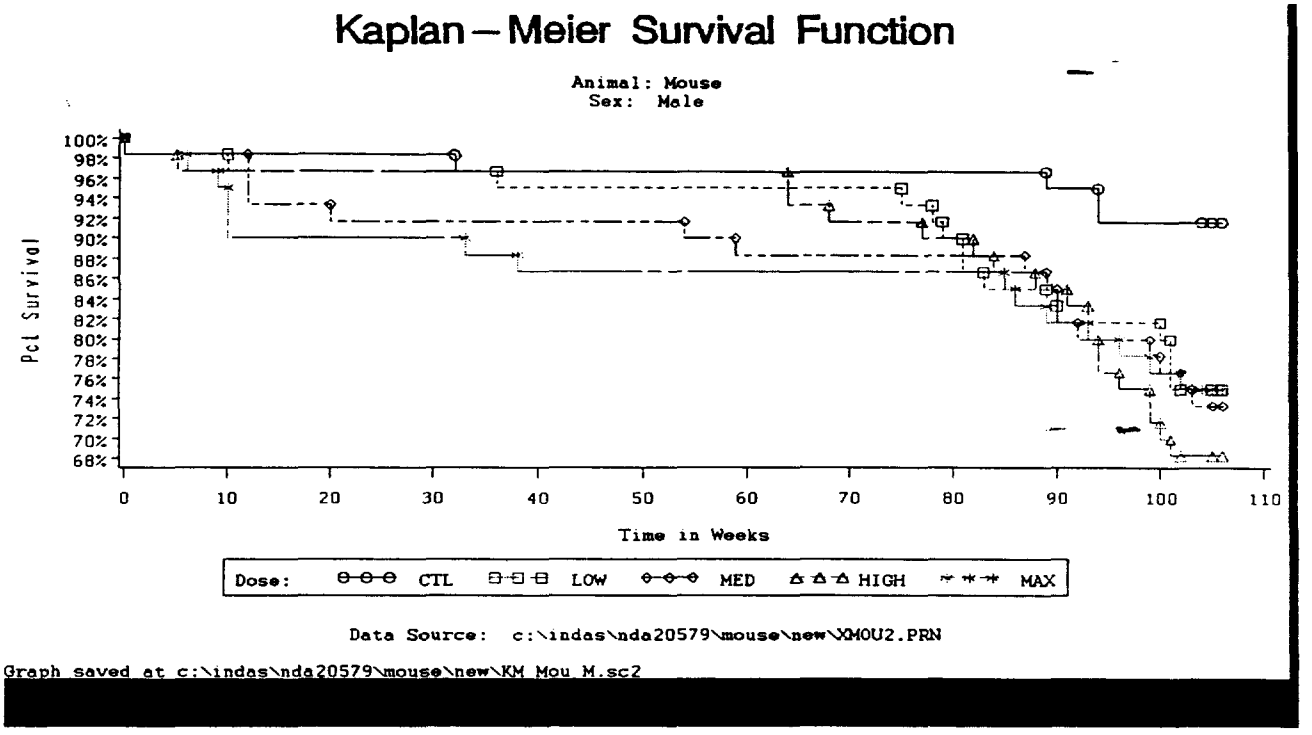
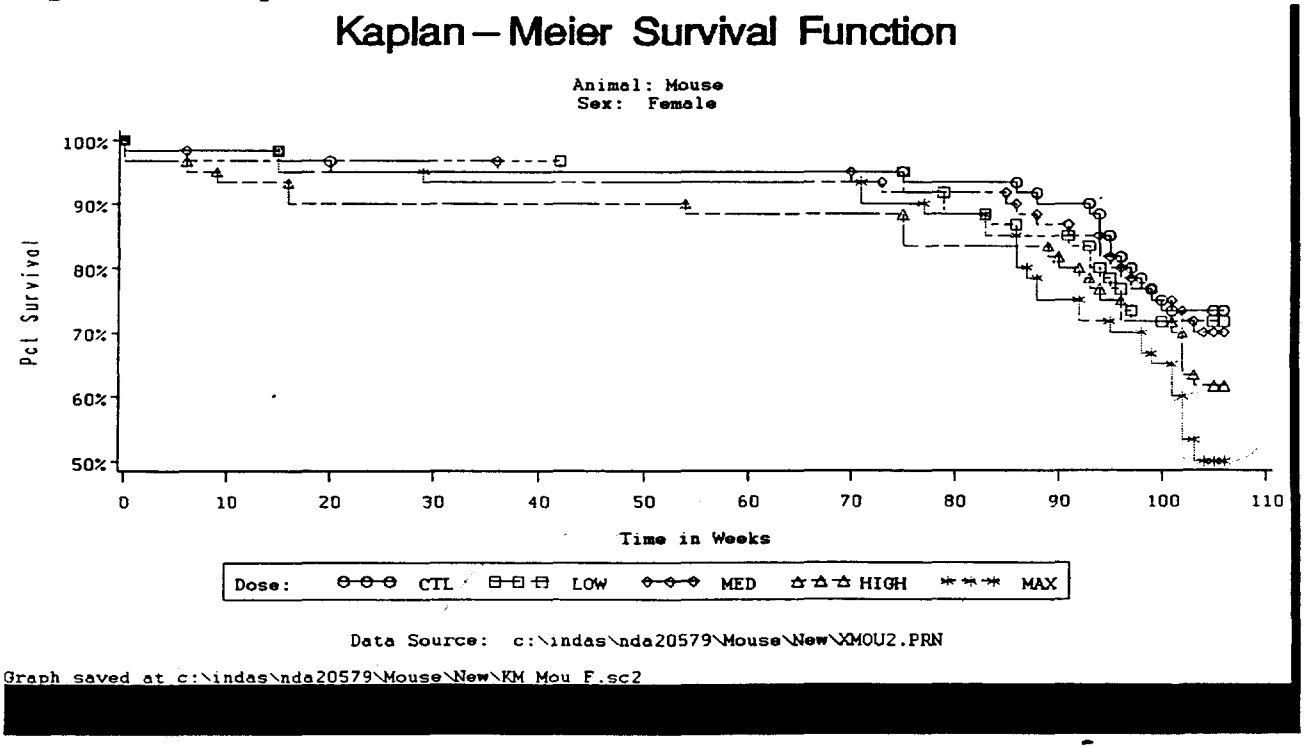


Figure 8. Kaplan-Meier Survival Functions for Female Mice



To test the homogeneity in survival among the treatment groups, and the significance of the positive dose-mortality trend, the time-adjusted tests were performed using the Cox and the Kruskal-Wallis tests. Table 12 summarizes these tests for the males. There was a significant positive dose-mortality trend in the females; while such a trend was not significant in the males.

Table 12. Homogeneity Test for Dose-Mortality Trend

Dose-Mortality Trend Tests
(For pairwise comparisons, see c:\indas\nda20579\mouse\new\SV_Mou_M.TXT.)

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1, by Donald G. Thomas, National Cancer Institute

Male Mice:

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.41	0.2343
	Depart from Trend	8.38	0.0387
	Homogeneity	9.80	0.0440
Kruskal-Wallis	Dose-Mortality Trend	1.63	0.2022
	Depart from Trend	8.22	0.0417
	Homogeneity	9.84	0.0431

Female Mice:

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	8.70	0.0032
	Depart from Trend	0.19	0.9794
	Homogeneity	8.88	0.0641
Kruskal-Wallis	Dose-Mortality Trend	7.55	0.0060
	Depart from Trend	0.30	0.9610
	Homogeneity	7.85	0.0974

Reviewer's Comments

There was a statistically significant positive dose-mortality trend in the females. this trend was not considered to be significant in the males.

3.5 Tumor Data Analysis

The reviewer's test for dose-response positive linear trend found significant results in the following tumors:

Table 13. Test for Dose-response (Tumor) Positive Linear Trend

Sex	Organ		Tumor		Type	Tumor incidence	P-value
M	Liver	LI	Hemangioma*	805*+	rare	0,0,0,0,1	0.0262
M	Liver	LI	Lymphosacoma	939+	common	1,0,0,0,4	0.0008
F	Mammary Gland	MG	Fibroadenoma	820	rare	0,0,2,7,16	0.0000
F	Mammary Gland	MG	Adenocarcinoma	902*	common	1,0,1,4,4	0.0075
F	Pituitary	PI	Lymphosacoma	939*	rare	0,0,0,0,1	0.0276
F	Skin	SK	Hemangioma	805	rare	0,0,0,0,3	0.0005
F	Spleen	SP	Hemangioma	805	rare	0,0,1,1,4	0.0011

Reviewer's Comments

Note that the cut-off p-values are 0.025 for rare tumors and 0.005 for common tumors. The tumors with symbol, "*" listed in above Table 13 were not statistically significant, according to the rules set by the Divisions of Biometrics, FDA. However, their p-values are close to the cut-off p-values that the incidences of these tumors might be highly associated with the test drug. The tumor codes with symbol, "+" indicate that tumors with significant results were not reported by the sponsor.

3.6 Evaluation of Validity of Design

Seventy five percent of the males in the highest dose group survived until the terminal sacrifice. Fifty percent of the females in the highest dose group survived until the terminal sacrifice. This reviewer concluded that there were sufficient number of animals living long enough to receive adequate exposure to the test drug.

The mean body-weights for the males and the females are depicted in Figures 4.1, 4.2, 5.1, and 5.2 (pages 47-50 of vol. 29). Copies of these images are included in Figures A-7-1, A-7-2, A-8-1, and A-8-2, in Appendix. Overall, the mean body-weight changes in either sex were similar among all groups.

According to the mean weight gains reported by the sponsor (page 63, vol. 29), for the males, the body-weight gains ranged grams among the treated groups. On the other hand, the body-weight gain was 18.5 grams for the control group. The differences in body-weight gain between the control group and the treated groups were in a range of %.

For the females, the body-weight gains ranged , grams among the treated groups. On the other hand, the body-weight gain was 16.7 grams for the control group. The differences in body-weight gain between the control group and the treated groups were in a range of %.

Based on the data of death rates and mean body weights, this reviewer did not find any anomaly in the study design. However, information about clinical signs or severe histopathological toxic effects exhibited in dosed animals should also be considered in the final evaluation of the appropriateness of the selected doses.

3.7 Conclusions

Conclusions for the Rat Study

The reviewer concluded that there was a statistically significant positive dose-mortality trend among the treatment groups in both sexes. According to the criteria set by the Divisions of Biometrics, FDA, this reviewer found that, among the **female rats**, for

- mononuclear cell leukemia (code: 941) in stomach (code: ST), (p=0.0130)

the dose-response (tumor) positive linear trend was statistically significant. None of the tumors tested in the **male rats** demonstrated a statistically significant dose-response trend.

Conclusions for the Mouse Study

The reviewer concluded that there was a statistically significant positive dose-mortality trend among treatment groups in the females; while the trend was not statistically significant in the males. The reviewer found that, in the **female mice**, there was a positive dose-response (tumor) linear trend in the following tumors:

- fibroadenoma in mammary gland (p<0.025),
- hemangioma in skin (p=0.0005) and
- hemangioma in spleen (p=0.0011).

In the **male mice**, there was a significant dose-response trend in the tumor of

- lymphosacoma in liver (p=0.0008).

It may be important to know that for the following tumors, the increasing tumor incidences might be highly related to the increasing of dose, though the trend tests were not statistically significant according to the rules set by the Divisions of Biometrics, FDA:

- hemangioma in liver in males,
- adenocarcinoma in mammary gland in females, and
- lymphosacoma in pituitary in females.

Ted (Jiyang) Guo, Ph.D., Ted Guo
Mathematical Statistician

Karl K. Lin 12/4/96

Concur: Dr. Karl K. Lin

cc:
Archival NDA 20-579
HFD-580/Division file
HFD-580/SSobel
HFD-580/JElhage
HFD-580/DMoore
HFD-715/Division file
HFD-715/Enevius
HFD-715/KLin
HFD-715/WSteve
HFD-715/Tguo
HFD-700/CAnello
TG/November 15, 1996
/November 27, 1996
/O:\DB2\Reviews\Guo\Carcinogenicity\NDA20579.Doc

Kumble

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

FEB 11 1997

NDA #: 20-579
CHEMISTRY REVIEW #: 3 **DATE REVIEWED:** Feb 6, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4-15-96	4-15-96	4-18-96
AMENDMENTS	12-13-96		

NAME & ADDRESS OF APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
P.O. Box 368
Ridgefield, Connecticut 06877

DRUG PRODUCT NAME

Proprietary: Flomax (temporary for USA), Harnal(Japan), Omnic (Europe), Omic (France)

Nonproprietary/Established/USAN: Tamsulosin Hydrochloride

Code Name/#: YM 617, YM-12617-1, (-)-YM-12617, LY253351, AB-250A

Chem.Type/Ther.Class: 1 S

PHARMACOLOGICAL CATEGORY/INDICATION: α_{1C}-adrenoceptor antagonist/BPH

DOSAGE FORM: Capsules (modified release formulation) in HDPE bottles containing 100 or 1000 capsules. Physicians samples are in HDPE bottles containing 7 capsules

STRENGTHS: 0.4mg/capsule

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride
$C_{20}H_{28}N_2O_5S.HCl$
MW = 444.98

CONCLUSIONS & RECOMMENDATIONS:
The responses to the deficiency letter are deemed satisfactory and the FONSI for EA was signed off on Jan 14, 1997. The only pending issue for the approval of this NDA is satisfactory EER. Summary of Chemistry Review is attached.

cc:
Org. NDA
HFD-510/Division File
HFD-510/MRhee/CSO

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader

filename: n20579.#3

Kish
OCT 10 9

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-579
CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 10-10-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4-15-96	4-15-96	4-18-96

AMENDMENTS

NAME & ADDRESS OF APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
P.O. Box 368
Ridgefield, Connecticut 06877

DRUG PRODUCT NAME
Proprietary: Flomax (temporary for USA), Harnal(Japan), Omnic (Europe), Omic (France)
Nonproprietary/Established/USAN: Tamsulosin Hydrochloride
Code Name/#: YM 617, YM-12617-1, (-)-YM-12617, LY253351, AB-250A
Chem.Type/Ther.Class: 1 S

PHARMACOLOGICAL CATEGORY/INDICATION: α_{1C}-adrenoceptor antagonist/BPH

DOSAGE FORM: Capsules (modified release formulation) in HDPE bottles containing 100 or 1000 capsules. Physicians samples are in HDPE bottles containing 7 capsules

STRENGTHS: 0.4mg/capsule

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride
$C_{20}H_{28}N_2O_5S.HCl$
MW = 444.98

CONCLUSIONS & RECOMMENDATIONS:
EA was reviewed by Nacy Sager (9-19-96, and the deficiencies described in the draft letter should be conveyed to the firm together with those described in Chem Rev #1 (10-4-96).

cc:
Org. NDA
HFD-510/Division File
HFD-510/MRhee/CSO
HFD-820/YChiu (NME only)

Moo-Jhong Rhee, Ph.D.
Acting Chemistry Team Leader

R/D Init by:

NL-1.210

K150

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-579 OCT 7 1996
CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** 10-4-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	4-15-96	4-15-96	4-18-96
AMENDMENTS	5-21-96	5-22-96	
	6-28-96	7-1-96	
	8-6-96	8-7-96	

NAME & ADDRESS OF APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
P.O. Box 368
Ridgefield, Connecticut 06877

DRUG PRODUCT NAME

Proprietary: Flomax (temporary for USA), Harnal(Japan), Omnic (Europe), Omic (France)

Nonproprietary/Established/USAN: Tamsulosin Hydrochloride

Code Name/#: YM 617, YM-12617-1, (-)-YM-12617, LY253351, AB-250A

Chem.Type/Ther.Class: 1 S

PHARMACOLOGICAL CATEGORY/INDICATION: α_{1C}-adrenoceptor antagonist/BPH

DOSAGE FORM: Capsules (modified release formulation) in HDPE bottles containing 100 or 1000 capsules. Physicians samples are in HDPE bottles containing 7 capsules

STRENGTHS: 0.4mg/capsule

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(R)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride
$C_{20}H_{28}N_2O_5S.HCl$
MW = 444.98

CONCLUSIONS & RECOMMENDATIONS:
This NDA is approvable from chemistry point of view pending satisfactory EER and EA. The deficiencies delineated in the draft letter should be conveyed to the firm and should be clarified/or corrected before approval.

cc:
Org. NDA
HFD-510/Division File
HFD-510/MRhee/CSO
HFD-820/YChiu (NME only)

R/D Init by:

10/7/96
Moo-Jhong Rhee, Ph.D.
Acting Chemistry Team Leader

filename: **NL. 210**

SUPPORTING DOCUMENTS:
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

Related Document:
IND

Consults: A consult review for EA was sent to Nancy Sager on 4-22-96 and to be completed by November.

REMARKS/COMMENTS:
This NDA describes a new drug product aimed at treating the symptom associated with benign prostate hyperplasia. The drug substance is a benzenesulfonamide derivative and is claimed to be a potent α_1-adrenoceptor antagonist, specifically, α_{1C}-adrenoceptor which is dominant in the hypertrophied human prostate. One chiral center in the structure results in two optical isomers and the (R)-stereoisomer is claimd to be pharmacologically active. The dosage form is a modified slow release formulation in capsules and its slow release is accomplished by coating the granules with enteric-soluble material. This matrial is mixed during the granulation procedure.

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-579

Flomax™ Capsules 0.4 mg

(tamsulosin hydrochloride)

REVIEW DIVISION: HFD-580

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

for

NDA 20-579

Flomax™ Capsules 0.4 mg

(tamsulosin hydrochloride)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for FLOMAX™, Boehringer Ingelheim Pharmaceuticals, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Tamsulosin hydrochloride is a chemically synthesized drug which is administered as a 0.4 mg capsule in the treatment of benign prostatic hyperplasia. The drug substance is manufactured by Yamanouchi Pharmaceutical Company Ltd., Japan. The packager of finished drug product is and the distributor of finished drug product is Boehringer Ingelheim Pharmaceuticals, Inc., Connecticut and Boehringer Ingelheim Pharmaceutical Distribution Center, Connecticut. The finished drug product will be used mainly in an outpatient setting throughout the United States..

Tamsulosin may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. Therefore, the applicant has submitted a tier 0 EA without format items 7, 8, 9, 10 and 11 in accordance with the *Guidance for Industry for the Assessment in Human Drug Applications and Supplements.*

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

01/13/97 P.G. Vincent
DATE

Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

1/14/97 Nancy B. Sager
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

3.4 ENVIRONMENTAL ASSESSMENT

The following environmental assessment has been prepared in accordance with the requirements of 21 CFR §25.31a(a) for *TAMSULOSIN HCl* modified release capsules, 0.4 mg. The current revision is formatted according to the requirements for Tier 0 outlined in the CDER "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements."

1. Date:

March 7, 1996 - original
May 20, 1996 - revision 1
October 29, 1996 - revision 2

2. Name of applicant:

Boehringer Ingelheim Pharmaceuticals, Inc.

3. Address:

900 Ridgebury Road
P. O. Box 368
Ridgefield, Connecticut 06877

4. Description of the proposed action:

a. Requested Approval

The requested action is for approval of a new drug application for *TAMSULOSIN HCl* modified release capsules, 0.4 mg. Tamsulosin hydrochloride 0.4 mg modified release capsules are packaged in high-density polyethylene bottles, containing 7, 100 or 1000 capsules per container. The composition of the drug product is shown in Appendix 7. This environmental assessment has been submitted pursuant to 21 CFR §25.31a(a), using the Tier 0 approach.

b. Need for Action

This action will make available an alternate product for use in the treatment of benign prostatic hyperplasia.

c. Production Locations

The firms which participate in manufacture of the product and descriptions of the manufacturing sites are as follows:

Yamanouchi Pharmaceutical Company Ltd, Takahagi Plant (supplier of active ingredient) - Address: 160-2 Akahama, Matsukubo, Takahagi-shi, Ibaraki-ken 318, Japan. The facility is located on a site of 136,682 square meters in Takahagi city, Ibaraki prefecture. The plant is within about 300 meters of national road Route 6 and is located about 150 kilometers northeast of Tokyo. The city of Takahagi has an approximate population of 35,500. The regional climate is mild, with an average temperature of about 14°C and annual precipitation of approximately 150 cm.

The plant is situated in the Matsukubo Industrial Area. The area also houses other secondary processing industry facilities, dealing with foods, car parts, and building materials. The land surrounding the plant site is flat and well developed. The mean elevation above sea level is about 30 meters. Residential and suburban communities are about 200 meters away from the plant. A map showing the facility location is provided in Appendix 3.

Four intermediates used in the synthesis are produced for Yamanouchi under contract. These compounds and their manufacturers are described in confidential Appendix 6.

Yamanouchi Pharmaceutical Company Ltd., Nishine Plant (manufacturer of drug product) - Address: 154-13, Dai 2 Chiwari, Obuke, Nishine-cho, Iwate 028-71, Japan. This facility is located on a site of 346,540 square meters in the outskirts of the town of Nishine about 25 kilometers north from the city of Morioka, Iwate prefecture. The plant site is at the east foot of Mt. Iwate facing Route 282 close to the Nishine interchange of Tohoku Highway. The town of Nishine has an approximate population of 19,300. The region lies 260 meters above sea level, and the seasons vary sharply. A relatively cool summer contrasts with a hard winter involving consecutive severe midwinter days. The average temperature is about 9°C and the annual precipitation is approximately 120 cm.

The plant is situated in the Northern Morioka Industrial Complex which encompasses a total of 12 enterprises such as auto parts manufacturing plants, watch parts factories and sewing factories. An area of 74,955 square meters of

the plant site is leveled and plant buildings are set back 50 meters from the boundary to the highway. The compound is surrounded by Japanese red pine woods. A map showing the facility location is provided in Appendix 3.

(packager of finished drug) -

The facility includes 349,250 sq. ft. of building floor area on a 221-acre parcel of land. The surrounding land is zoned for residential/industrial use. Domestic water is supplied by the City of Norman. The climatic zone is typical of that found in the plains states as described in *Climates of the States* (Appendix 5). Copies of the site survey for the facility and a map of the city of Norman showing the facility location are provided in Appendix 2.

Boehringer Ingelheim Pharmaceuticals, Inc (distributor of finished drug product) - Address: 900 Ridgebury Road, Ridgefield, Connecticut 06877. The facility is located on a 300-acre site which resides partially in the city of Danbury and partially in the town of Ridgefield. The site is within one-half mile of Interstate 84. The city of Danbury has an approximate population of 68,000. The climate is temperate with an average mean temperature of 50°F and annual precipitation of 58 inches. The plant is located in a suburban area of low hills. The surrounding area is zoned for residential/light industrial use.

Boehringer Ingelheim Pharmaceutical Distribution Center (distributor of finished drug product) - Address: 595 Federal Road, Brookfield, Connecticut 06804. The facility, which is a leased warehouse, resides in the town of Brookfield. The distribution center comprises 155,000 square feet on a site of 12.5 acres.

d. Locations of Use

The product will be used by patients suffering from benign prostatic hyperplasia throughout the United States. Its use will be limited to patients obtaining it upon written prescription of a physician. It will be used mainly in an outpatient setting. The administered drug and/or its metabolites will be excreted and will eventually pass through wastewater treatment facilities. Used packaging components will be disposed of by the patient in a variety of settings throughout the country, primarily via municipal waste disposal services. The components are comparable in composition and type to packaging components typically used for food products or other medications that already exist in widespread distribution.

e. Disposal Sites

Disposal of product or packaging components rejected during manufacture will be the responsibility of Yamanouchi Pharmaceuticals. Disposal of product or packaging components rejected during secondary (final) packaging of the product will be the responsibility of Shaklee Corporation. Disposal of returned product will be the responsibility of Boehringer Ingelheim Pharmaceuticals, Inc. These functions will be performed in accordance with procedures to be described in item 6.

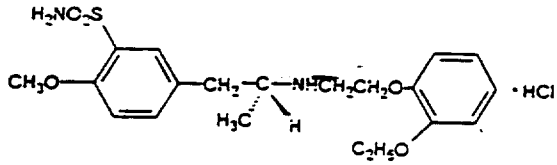
An analysis of the projected yearly market volume of the drug product is provided in Appendix 8.

5. Identification of chemical substances that are the subject of the proposed action:

a. Nomenclature

i. Established Name	Tamsulosin hydrochloride
ii. Brand/Proprietary Name	Flomax® (U.S.) Harnal® (Japan) Omnic® (Europe) Omic® (France)
iii. Chemical Names	(R)-5-[2-[[2-(2-Ethoxyphenoxy)-ethyl]-amino]propyl]-2-methoxybenzene-sulfonamide, monohydrochloride (-)-(*R*)-5-[2-[[2-(*o*-Ethoxyphenoxy)ethyl]-amino]propyl]-2-methoxybenzene-sulfonamide monohydrochloride
b. CAS Registry Number	106463-17-6 (hydrochloride) 80223-99-0 for racemic compound
c. Molecular Formula	$C_{20}H_{28}N_2O_5S \cdot HCl$
d. Molecular Weight	444.98

e. Structural Formula



f. Physical Description — White crystals; odorless

g. Additives — The substances that are used in the formulation of tamsulosin HCl modified release capsules are listed in item 6a.

h. Impurities — No impurities will be present in the drug at levels greater than 1%. Limits are included in the specifications for specific impurities that have been identified.

6. Introduction of substances into the environment:

a. Substances Expected to be Emitted

All manufacturing operations for tamsulosin hydrochloride drug substance and the modified release capsules take place in Japan, in facilities for which appropriate certification is provided in Appendix 3. The substances associated with the production of *TAMSULOSIN HCl* modified release 0.4 mg capsules that may be introduced into the environment during the manufacturing process are:

Substance	CAS Number
Tamsulosin hydrochloride	106463-17-6
Microcrystalline cellulose	9004-34-6
(composed of methacrylic acid copolymer,	
polysorbate 80,	9005-65-6
and sodium lauryl sulfate)	151-21-3
Triacetin	102-76-1
Calcium stearate	1592-23-0
Talc	14807-96-6
Purified water	7732-18-5
Gelatin	9000-70-8
FD&C Blue No. 2	860-22-0

Titanium dioxide	13463-67-7

b. Controls Exercised —

Controls are in place at each production facility to minimize the release of hazardous substances to the environment. These pertain to the discharge of solid, air-borne, and aqueous process wastes and the disposal of returned or rejected materials.

The operations of each facility involved in the production, packaging, and distribution of the product are in compliance with governmental regulations applicable at the federal, state, and local level. Yamanouchi has provided in Appendix 3 signed statements from the responsible governmental authorities in Japan, certifying that the operations at the two Yamanouchi manufacturing facilities (at Takahagi and Nishine) are in full compliance with applicable environmental regulations of Japan concerning emissions at the sites. Each of the four contract manufacturers that supply proprietary intermediates has provided certification that its operations are performed in compliance with all applicable governmental regulations.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

As indicated in item 6.b, statements of compliance with applicable environmental regulations in Japan are provided in Appendix 3 for the Yamanouchi manufacturing sites at Takagi and Nishine and for the four contract manufacturing facilities in Japan in Appendix 6. The following information pertains to operations that take place in the United States. A material safety data sheet is provided in Appendix 1.

The facility has obtained the following use permits:

Issuing Authority	Permit Type	Permit Number	Applicable Date
City of Norman	Certificate of Occupancy	10401 10402 10403	Issued 10/19/79 Issued 10/19/79 Issued 10/19/79
City of Norman	Industrial Discharge Permit	NID002	Expires 5/14/98 (renewable upon expiration)
State of Oklahoma	Department of Environmental Quality Permit	78-044 81-107 85-009 94-323-O	-
State of Oklahoma	Department of Health Industrial Waste Disposal Plan	Plan #14006	Approved 7/16/79
State of Oklahoma	Department of Health Establishment License	Establishment #140007793	Renewed on annual basis; current expiration 7/18/97
State of Oklahoma	Board of Pharmacy Manufacturer Permit	7-M-270	Renewed on annual basis; current expiration 6/30/97

The disposal of hazardous wastes is contracted to:

Wastes are disposed of by incineration. disposal site is located at:

The management and disposal of chemical wastes generated for packaging tamsulosin hydrochloride capsules are described in "Reject and Scrap Handling, Documentation and Disposal Procedure," and in Attachment of E of Natural Hazard Mitigation Study. Copies of all three documents are provided in Appendix 9. facility has a materials recycling plan for many of the large volume dietary supplement products produced there. However, the packaging of tamsulosin hydrochloride capsules is not expected to generate any materials which would be appropriate for recycling. A statement of compliance with all applicable environmental regulations is provided in Appendix 2.

The federal EPA ID generators number for the site is CTD097730709. Disposal of hazardous materials waste is performed by incineration under contract by:

or

A statement of Boehringer Ingelheim's compliance with all applicable environmental regulations is provided in Appendix 4.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Approval to manufacture this product will have no significant effect on compliance with current emission requirements. The product is similar in manufacturing process and packaging system to other products currently manufactured at the sites.

e. Expected Introduction Concentrations

The projected usage of tamsulosin hydrochloride 0.4 mg modified release capsules in the U.S. is outlined in Appendix 8 for the first five years following approval. The calculations show the quantity of tamsulosin hydrochloride that will be required to manufacture these amounts. The high therapeutic potency of the drug on a weight basis and the once a day dosing regimen keep the total production requirements to relatively low levels, in spite of the large patient population.

The introduction of tamsulosin hydrochloride into the environment will occur primarily following its use by patients and the excretion of the drug compound and/or its metabolites in urine and feces to waste-water treatment plants (WWTPs). The metabolites are compounds having similar structural features to the parent molecule (refer to Appendix 10 for an outline of the metabolic pathway in man). The patient population is distributed throughout the U.S. Based on the estimated highest year production volume, the expected introduction concentration has been calculated for the tamsulosin active moiety (refer to Appendix 8). The projected requirements result in a calculated EIC well below the level of 1 part per billion designated for applicability of the Tier 0 approach for environmental assessment.

The other potential source of environmental exposure is accidental release during manufacture or transportation of the product. A worst-case scenario would involve the spillage or rejection of a complete lot of either bulk drug substance (approximately 26 kg) or a full capsule batch (approximately capsules, equivalent to g).

Since both the drug substance and the dosage form are solids, the containment of a spill is relatively straightforward using simple clean-up procedures. The wastes generated in such a case would consist of solids that would be incinerated and liquid wastes such as waste water from cleaning up residues.

Rejected drug substance and capsules will be disposed by Yamanouchi (primarily by incineration). All aspects will be in accordance with the regulatory requirements of Japan, compliance with which has been documented in Appendix 3.

Disposal of rejected drug during packaging at or of returned product by BIPI will be accomplished by incineration.

7. **Fate of emitted substances in the environment:**

Not required under Tier 0 approach. However, a series of fate and effect tests were performed to investigate the behavior of tamsulosin. The compound is subject to photodegradation in aqueous solution and will be rapidly depleted by photolysis when introduced into natural aquatic systems. Tamsulosin itself showed minimal toxicity to aquatic organisms, only at concentrations many orders of magnitude above the EIC.

8. **Environmental effects of released substances:**

Not required under Tier 0 approach.

9. **Use of resources and energy:**

Not required under Tier 0 approach.

10. **Mitigation measures:**

Not required under Tier 0 approach.

11. **Alternatives to the proposed action:**

Not required under Tier 0 approach.

12. **List of preparers:**

Sandra C. Brown, Ph.D.
Pharmaceutical Consultant
4471 East Sunset Drive
Phoenix, AZ 85028

Summary of Qualifications:

Education: B.A., Chemistry, George Washington University
Ph.D., Physical Chemistry, University of South Carolina

Experience: 1985-present, Pharmaceutical Consultant
1981-1985, Project Officer, National Toxicology Program
1981-1983, Adjunct Assistant Professor of Pharmacology, Schools of Medicine and Dentistry, Georgetown University
1977-1981, Chemist, Bureau of Drugs, FDA
1976-1977, Analyst, Enviro Control
1974-1975, Health and Regulatory Affairs Chemist, Arapahoe Chemicals, Inc.

William F. Schaber
QA Manager, Regulatory Affairs
Shaklee Corporation
1992 Alpine Way
Hayward, CA 94545

Summary of Qualifications:

Education: B.A., Chemistry, University of California, San Diego
A.A., Engineering, Pasadena City College

Experience: 1992-present, Quality Assurance Manager, Regulatory Affairs/Audits, Shaklee Corporation
1988-1992, QA Manager, BestWater Products, Shaklee Corporation
1985-1987, Director of Technical Services, Vidal Sassoon Division of Richardson-Vicks, Inc.
1983-1985, Manager of Technical Regulatory Affairs, Shaklee Corporation
1981-1983, Quality Assurance Field Representative, Shaklee Corporation
1980-1981, Quality Assurance Supervisor, Shaklee Corporation

1978-1980, Quality Control Chemist, Shaklee Corporation
1976-1978, Research Technician, Salk Institute for Biological Sciences
1976-1976, Research Chemist, Terra-Marine Bioresearch

13. Certification:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

The undersigned official certifies that the EA summary document (pages 1-13) and Appendices 1-5 (pages 14-36) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR §1506.6.

Arthur E. Slesinger — Date: 11/22/96

Arthur E. Slesinger
Director, Environmental Affairs and Safety
Boehringer Ingelheim Pharmaceuticals, Inc.

14. References:

Climates of the States, National Ocean and Atmospheric Administration (Gale Research Company)

15. Appendices:

NON-CONFIDENTIAL APPENDICES

Appendix 1 - Material Safety Data Sheet
Appendix 2 - Site Survey and Location Map for Shaklee Corporation, Norman, OK, and Statement of Regulatory Compliance
Appendix 3 - Statements of Regulatory Compliance for Yamanouchi
Appendix 4 - BIPI's General Compliance Statement
Appendix 5 - Copies of References

CONFIDENTIAL APPENDICES

Appendix 6 - Manufacturers of Proprietary Intermediates
Appendix 7 - Quantitative Composition of Tamsulosin Hydrochloride 0.4 mg Capsules
Appendix 8 - Projected Market Volume of Tamsulosin hydrochloride 0.4 mg Capsules
Appendix 9 - Environmental Control Procedures
Appendix 10 - Metabolic Pathway for Tamsulosin Hydrochloride in Man

APPENDIX 1

Material Safety Data Sheet

01

SAFETY DATA SHEET: YM617 (TAMSULOSIN)

Hazardous ingredients/identity information
No hazardous components

All excipients are so safe that they can be taken orally. Active ingredient is encapsuled into microcapsule granule and hardly be released under usual condition.

Active ingredient (YM617) is a moderate eye irritant and slight skin irritant.

Physical/chemical characteristics

Boiling point	N.A.
Vapor pressure (mmHg)	N.A.
Vapor density (AIR·1)	N.A.
Specific gravity (H_2O·1)	N.A.
Melting point	232°C (decomposed)
Evaporation rate (butyl acetate)	N.A.
Solubility in water	(that of active ingredient) 1.2% W/V under room temperature (of active ingredient)
Appearance and odor	white solid, no odor

Fire and Explosion hazard data

Flash point	N.A.
Flammable units	N.A.
LEL	N.A.
UEL	N.A.
Extinguishing media	Water: dry chemical, CO_2, foam
Special fire fighting procedures	Cool fire - exposed containers with water.
Unusual fire and explosion hazards	No unusual fire or explosion hazards.

Reactivity Data

Stability: stable

Conditions to avoid: Exposure to extremely high humidity (more than 75% more than two months).

Incompatibility (materials to avoid): nothing particular.

Hazardous decomposition of byproducts: nothing particular.

Hazardous polymerization: will not occor.

Conditions to avoid: nothing particular.

Health Hazard Data

Routes of entry: skin, eye, ingestion

Health hazards (acute and chronic): nasal congestion, orthostatic hypotension; causes lowered blood pressure when one ingested more than two capsules and collapse may happen when he stands from a laying position.

Careinogenicity: NTP - No, IARC Monographs - No, OSHA Regulated - No

Signs and symptoms of exposure: direct exposure to eye may cause redness of eyes.

Medical conditions generally aggrevated by exposure: nothing particular.

Emergency and first aid procedures: keep in bed and call a doctor.

Precautions for safe handling and use

Steps to be taken in case material is released or spilled: remove the granules with a vacuumcleaner. Use gloves and wipe the powder by wet cotton with alcohol.

Waste disposal method: incinerate

Precautions to be taken in handling and storing: nothing particular.

Other precautions: nothing particular.

Control measures

Respiratory protection: not required
Ventilation: Local exhaust - not required, Special - not required, Other - not required
Protective clothes: not required
Eye protection: not required
Other protective clothing or equipment: not required
Work/hygienic practices: nothing particular

Compound: YM617 (Alpha-1 Antagonist)

Issue date: May, 1987

This document should not be used for registration purposes. The following data have been obtained from initial toxicology and mutagenicity studies and should be considered as preliminary. These data, and the resulting caution statement, are provided so that proper protective measures can be taken by persons who may be exposed to the compound during initial research and development activities.

Caution statement: YM617 is a moderate eye irritant and slight skin irritant. It may cause lowered blood pressure, and high doses may cause elevated prolactin levels. Exposure may cause allergic-type reactions, such as nasal and sinus congestion and redness of eyes.

Pharmacology: YM617 is an alpha-1 adrenergic antagonist, and may elicit effects common to this class of compounds (e.g. decreased blood pressure, dizziness, headache, drowsiness, weakness, palpitations, nausea).

PRELIMINARY TOXICOLOGY DATA

Acute ingestion: The median lethal dose of YM617 when administered orally to rats was 975 mg/kg for males and 550 mg/kg for females. Signs of toxicity included leg weakness, hypoactivity, lethargy, poor grooming, ptosis, ataxia, clear ocular discharge and coma. The median lethal dose in mice was 3750 mg/kg for males and 2917 mg/kg for females. Signs of toxicity were similar to those seen in rats. Two of four dogs died, and the remaining two were moribund, following a single oral dose of 1500 mg of YM617/kg. Signs of toxicity were increased lacrimation, relaxed nictitating membranes, miosis, ptosis, redness, hypoactivity, ataxia, tremors, increased salivation, emesis and increased frequency of clawing behaviors. One of four dogs died following a single oral dose of 500 mg/kg. Signs of toxicity were similar to those in dogs given 1500 mg/kg. Monkeys given an single oral dose of 1500 mg/kg exibited vomiting, ptosis, profuse salivation and hypoactivity. Monkeys given a single dose of 750 mg/kg exhibited hypoactivity, ptosis and vomiting. One monkey that did not vomit became moribund by 29 hours after dosing, but with supportive fluids and heat, appeared normal by the following day.

Dermal exposure: Single-doses of 200 mg of YM617 per kg of body weights, applied to the shaved backs of rabbits for 24 hours, caused no systemic toxicity and very slight irritation which cleared within 48 hours after exposure.

Ocular exposure: Single doses of YM617 were installed into rabbit eyes, caused corneal dullness, slight iritis, and slight to moderate conjunctivitis within one hour after exposure. Corneal and iridal irritation cleared within seven days after exposure.

Subchronic exposure: In a three month dietary study, rats received time weighted avarage daily doses of 50, 200, or 327 mg of YM617 per kg of body weight for males, and 80, 229 or 378 mg/kg for females. Treatment related effects included dose related decreases. In main body weight and weight gain, food consumption, and efficiency of food utilization, decreased mean erythrocyte count, hemoglobin, packed cell volume, leukocyte counts and neutrophil count, increased reticulocyte counts and lymphocyte counts, increased aspartate transaminase values and increased specific gravity of the urine. Hepatic enzyme activity was increased at the middle and high dose. Absolute and relative organ weights (organ weight to body weight and organ weight to brain weight) were increased for the liver, spleen, and adrenals (males only), and decreased for the uterus. Hyperplasia of the glandular tissue of the mammary gland in the middle and high dose was the only histopathologic finding. the low dose was considered to be a no-effect level. In a three month study in dogs, all animals survived daily oral doses of 2, 20 or 200 mg/kg. Signs of toxicity included relaxed nictitating membranes, miosis, excessive salivation, hypoactivity, redness of the eyes, exessive lacrimation, tremors, ataxia, lethargy and emesis. Preliminary results indicate that treatment related effects were increased erythrocyts, hemoglobin, packed cell volume, raticulocyte and leukocytes values and increased alanine transaminase and aspartate transaminase level. Ovarian and uterine weights were decreased at the high dose. The no effect level was considered to be 20 mg/kg.

Mutagenicity data: YM617 was negative in the Ames test, the DNA repair assay in primary rat hepatocytes and the mouse lymphoma assay.

Conclusion: YM617 is a moderate eye irritant and is slightly irritating to the skin. Observed major effects of exposure to YM617 in animals have been consistent with the phamracological activity of the compound. No YM617 related mutagenic effecs have been observed.

FIRST AID AND HANDLING

YM617 is an experimental material and no specific antidote is known. If systemic effects are suspected, consult a physician for supportive treatment as indicated.

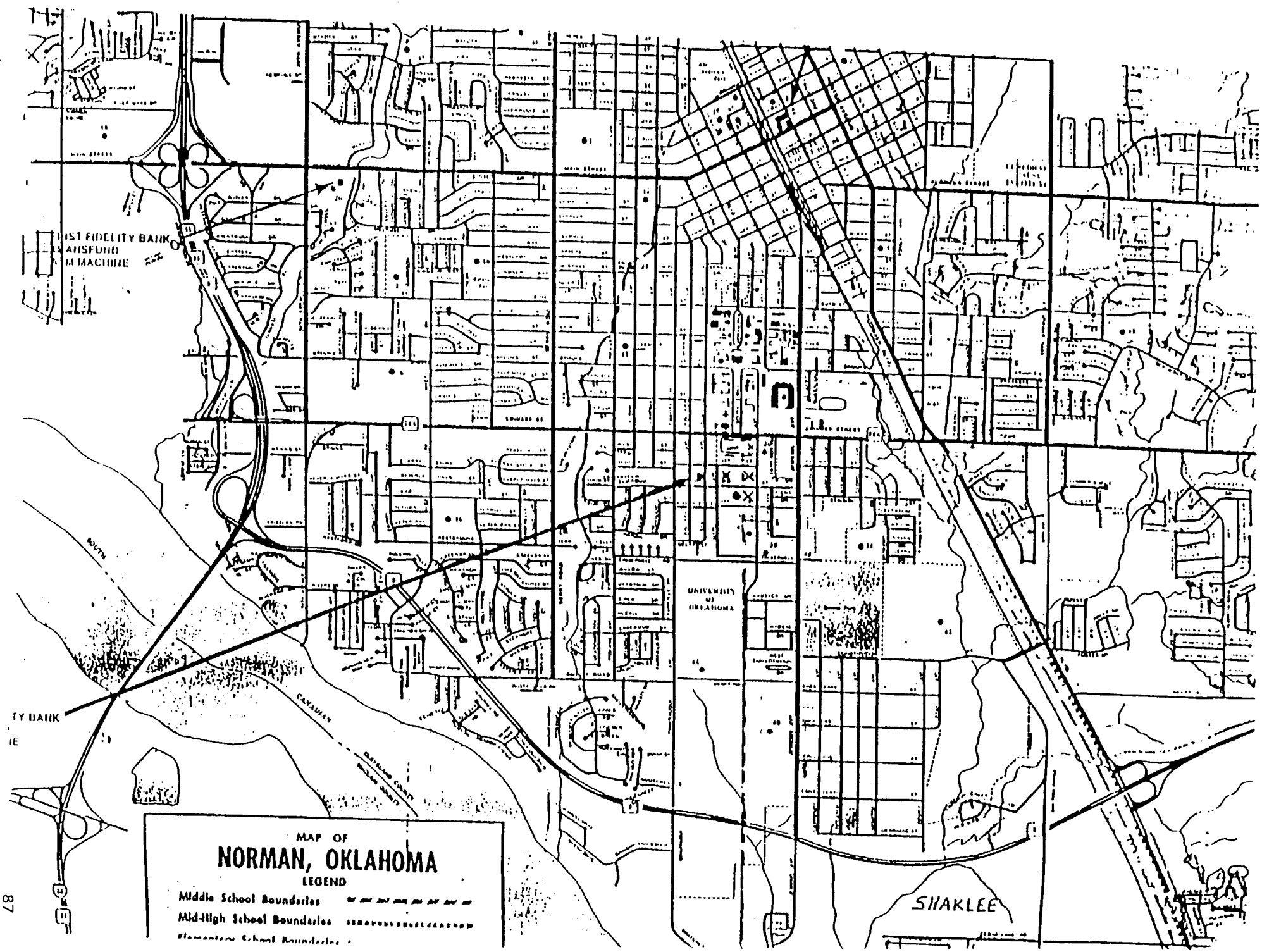
Eye:	Immediately flush with plenty of water, holding the eye open, if necessary seek medical attention.
Skin:	Immediately wash with plenty of water, using soap. Remove contaminated clothing and wash before re-use.
Inhalation:	Remove individual to fresh air. If breathing difficulty occurs, get medical attention. If not breathing give artificial resuscitation, preferable mouth-to-mouth.

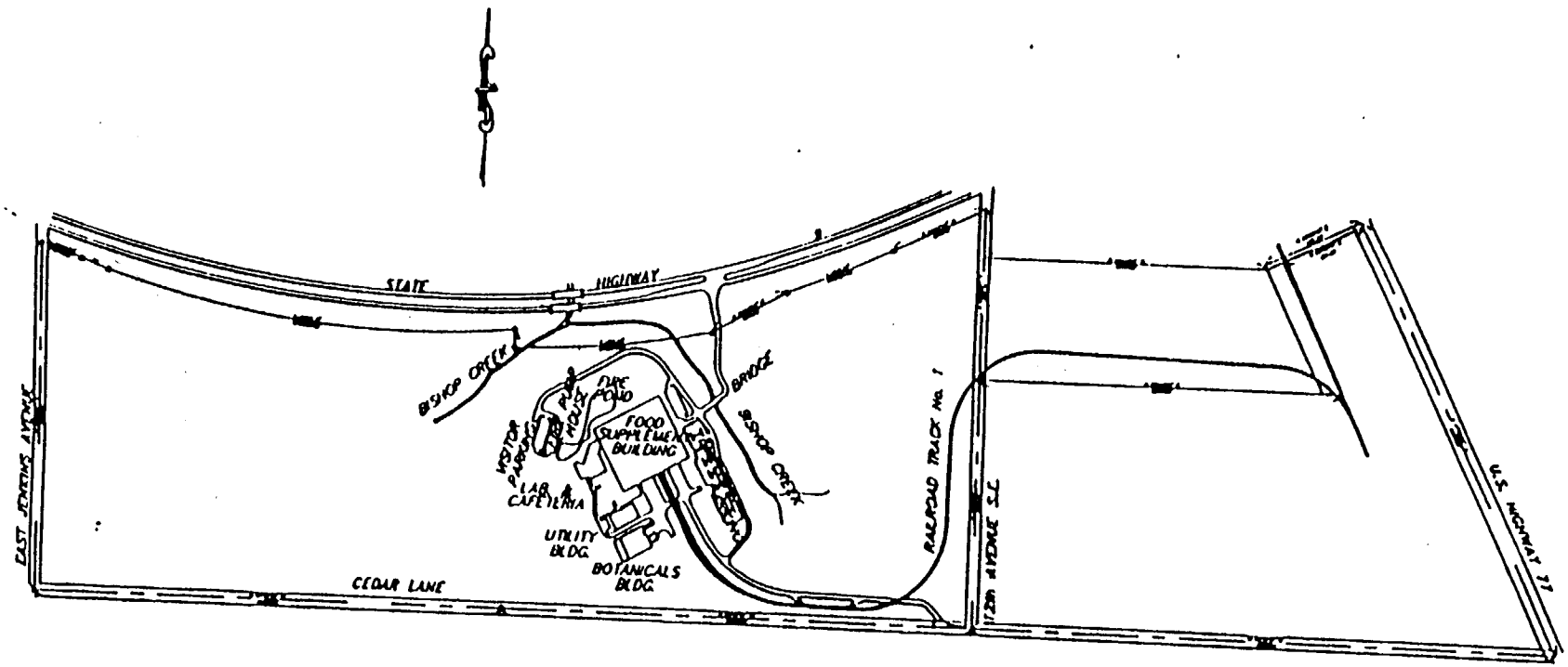
Ingestion:

Contact a physician immediately. If swallowed, induce vomiting by tickling the back of the throat with a finger or a blunt object. If necessary, give a syrup of Ipecac.

APPENDIX 2

Site Survey and Location Map for Shaklee Corporation, Norman, OK
and Statement of Regulatory Compliance


MAP OF
NORMAN, OKLAHOMA
LEGEND
Middle School Boundaries
Mid-High School Boundaries
SHAKLEE



LINE	DIRECTION	DISTANCE
L1	S 70°30'55" E	163.36'
L2	N 00°02'19" W	90.31'

SCALE

Shaklee

3300 MARSHALL AVENUE

NORMAN, OKLAHOMA

PLOT PLAN

GENERAL COMPLIANCE STATEMENT

Shaklee Corporation states that the packaging of capsules containing Tamsulosin Hydrochloride at its facility in Norman, Oklahoma, will be done in compliance with any applicable emissions requirements (including occupational) at the Federal, State and local level.

Lawrence N. Clark, Jr.
Vice President, Operations

2/10/95

APPENDIX 3

Statements of Regulatory Compliance for Yamanouchi.

Environmental Assessment

To whom it may concern:

This is to affirm that all drug substances including "Tamusulosin Hydrochloride" manufacturing in Takahagi plant of Yamanouchi Pharmaceutical Co., Ltd. complies with all applicable local Takahagi City, Ibaraki Prefecture and Japanese National Environmental Regulations.

Date: 1995 02 06

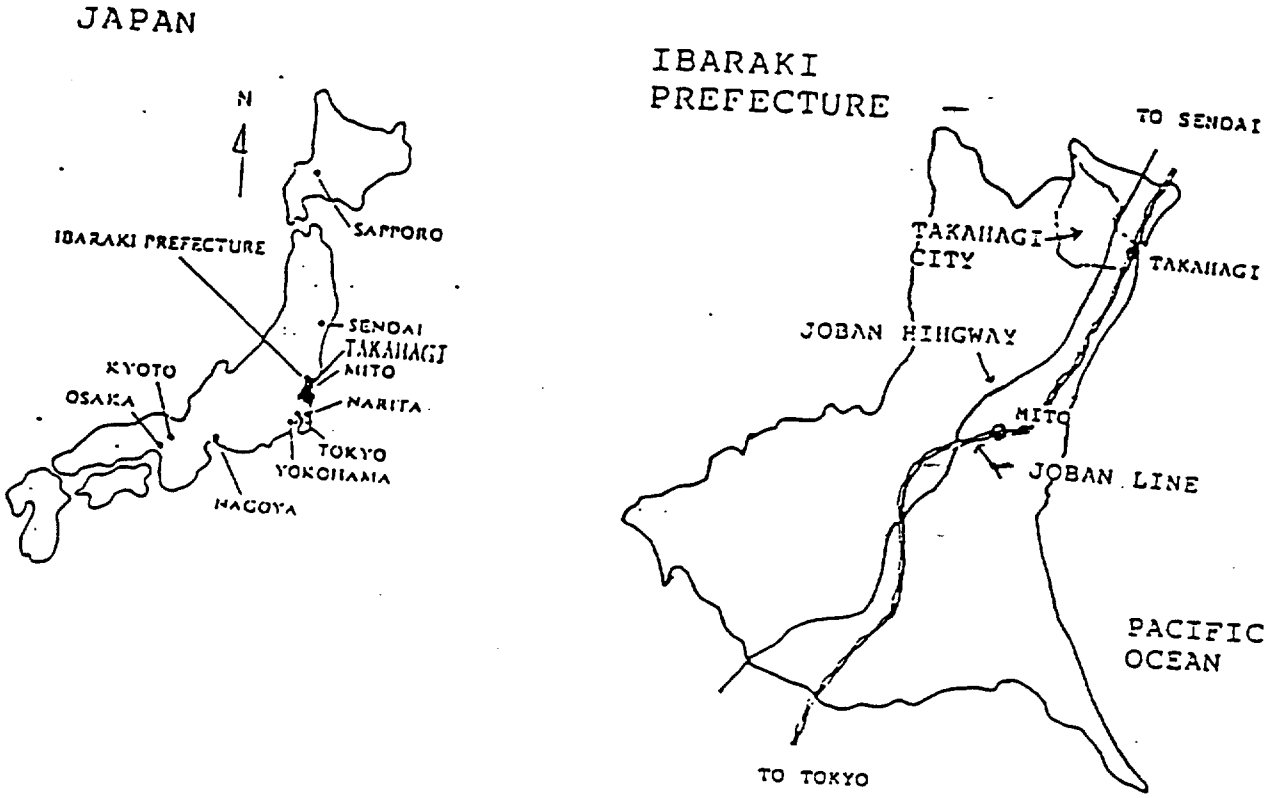
Signed by: Kiyoshi Ohkubo

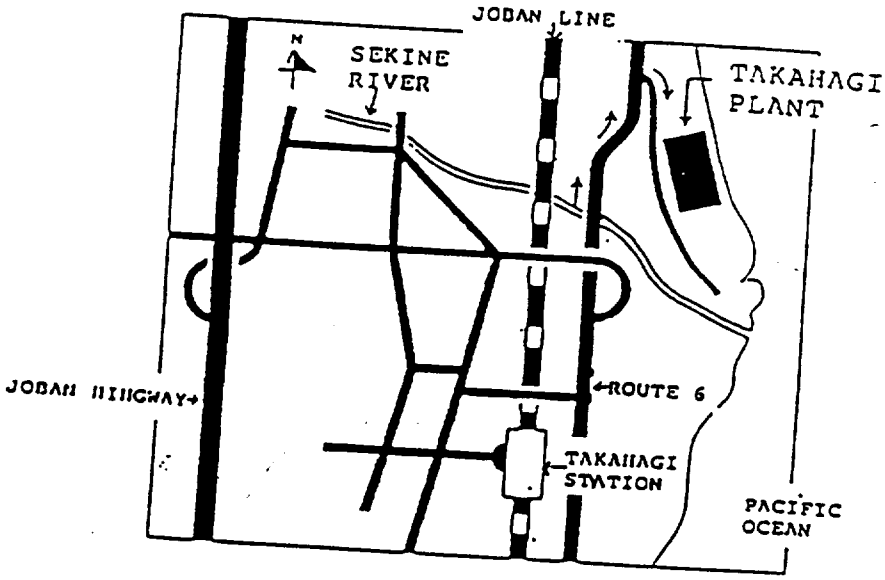
Kiyoshi Ohkubo

The Mayor of Takahagi City

Figure 1

Guide Map to TAKAHAGI PLANT





Environmental Assessment

To whom it may concern:

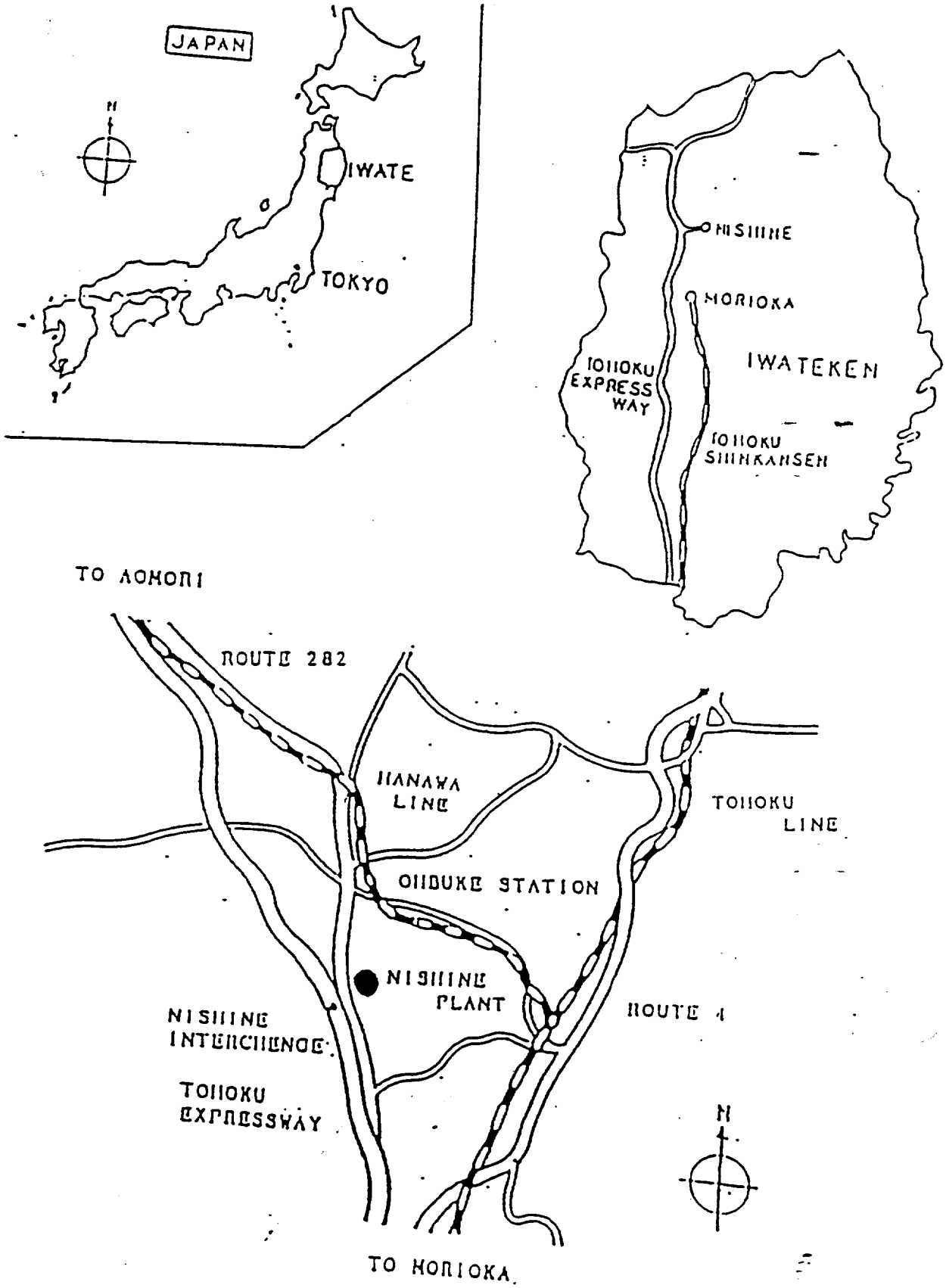
This is to affirm that the drug product of Harnal "Tamusulosin Hydrochloride" manufacturing in Nishine plant of Yamanouchi Pharmaceutical Co., Ltd. complies with all applicable local Nishine Town, Iwate Prefecture and Japanese National Environmental Regulations.

Date: 1995.01.27

Signed by: Katsuji Kudo
Katsuji Kudo

The Mayor of Nishine town

Location of the Nishine Plant



APPENDIX 4

BIPI's General Compliance Statement

Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

To Whom it May Concern,

Boehringer Ingelheim certifies by this letter, that the facilities operated by Boehringer Ingelheim Pharmaceuticals, Inc. at 175 Briar Ridge Road in Danbury, Connecticut and at 595 Federal Highway in Brookfield, Connecticut are in full and substantial compliance with all applicable Federal, State and local environmental regulations. The addition of the distribution of Tamsulosin tablets in no way alters the compliance posture of these operations.

In the event goods are returned to these facilities, they will be disposed of by incineration in a fully licensed hazardous waste incinerator, such as the one operated by Rollins International, in Bridgewater, New Jersey. While the returned goods are not hazardous substances under RCRA, it is the company's policy to incinerate all drug substances and dosage forms which are not normally sold.

Very truly yours,

Dr. Richard Charles
Vice President of Q.A. and Environmental Affairs

(203) 798-9988

APPENDIX 5

Copies of References

03

CLIMATES OF THE STATES

National Oceanic and Atmospheric Administration
Narrative Summaries, Tables, and Maps
for Each State

with

Current Tables of Normals, 1941-1970
Means and Extremes to 1975
Overview of State Climatologist Programs

New Material by
James A. Ruffner

Volume 2

Nebraska-Wyoming
Puerto Rico and U.S. Virgin Islands
Hurricane Data
The State Climatologist Program 1954-1973
Appendixes

Gale Research Company
BOOK TOWER • DETROIT, MICHIGAN 48226

CLIMATOGRAPHY OF THE UNITED STATES NO. 60-34

CLIMATES OF THE STATES

Oklahoma

(Normals, Means and Extremes tables revised 1970 and 1975. Basic report revised June 1970.)

Billy R. Curry, ESSA State Climatologist

Oklahoma is located in the southern Great Plains. Of the 50 states, it ranks 18th in size with an area of approximately 70,000 square miles, only 935 of which are covered by lakes and ponds. Its northern boundary is about 465 miles in length and its southern boundary 315 miles in length. Greatest depth is 222 miles.

The terrain is mostly rolling plains, sloping downward from west to east. The plains are broken by scattered hilly areas where most points are 600 feet or less above the adjacent countryside, and by a mountainous area in the southeast where some peaks rise more than 2000 feet above their base. The hilly areas consist of the Wichita Mountains, with some isolated peaks, in the southwest; the Arbuckle Mountains in the south-central; and, an extension of the Ozarks in the northeast. The Ouachita Mountains occupy much of the southeast. Elevations in the State range from 4,976 feet above sea level on Black Mesa in the northwestern corner of the Panhandle, to about 305 feet above sea level in the bed of the Red River where it leaves Oklahoma at the southeastern corner of the State.

Oklahoma lies entirely within the drainage basin of the Mississippi River. The two main rivers in the State are the Arkansas which drains the northern two-thirds of Oklahoma and the Red River which drains the southern third and forms the State's southern boundary. Principal tributaries of the Arkansas are the Verdigris, Grand (Neosho), Illinois, Cimarron, North Canadian, and Canadian Rivers. The Red draws largely from the North Fork of the Red, Washita, Boggy, and Little Rivers.

In western Oklahoma, rivers tend to be broad, shallow, sand choked, and dry or nearly dry much of the time. Basins are mostly long and narrow. In the east, rivers are fairly swift and clear and basins more oval in form. Most lakes are man-made and were built for flood control, irrigation, municipal water storage, recreational, and in a few cases hydro-electric power purposes. The largest lakes are Texoma on the Red River and Eufaula Reservoir on the Canadian.

Agriculture, mining, manufacturing, trade, and government are all important sectors of Oklahoma's economy. Leading agricultural crops and their main areas of production are: Wheat, western half of the State; cotton, southern two-thirds; corn, eastern half; peanuts, south; broomcorn, central and west; and milo, western half, especially in the Panhandle where a tremendous agricultural economy, based on irrigation from ground water, is being developed. The livestock industry is of great importance to all sections of the State. Minerals produced in the State include petroleum, natural gas, coal, lead, and zinc. Leading manufactured products include food products, transportation equipment, primary and fabricated metal products, machinery, and petroleum and coal products. Lumbering is important in the southeast.

The climate of Oklahoma is mostly continental in type, as in all of the central Great Plains. Warm,

moist air moving northward from the Gulf of Mexico exerts much influence at times, particularly over the southern and more eastern sections of the State where, as a result, humidities and cloudiness are generally greater and precipitation considerably heavier than in the western and northern sections. Summers are long and occasionally very hot. Winters are shorter and less rigorous than those of the more northern Plain States. Periods of extreme cold are infrequent.

The mean annual temperature over the State ranges from 64° along the southern border to about 60° along the northern border. It then decreases westward across the Panhandle to about 57° in Cimarron County. Temperatures of 90° or higher occur, on an average, about 85 days per year in the western Panhandle and in the northeast corner of the State. In the southwest, the average is about 120 days, and in the southeast from 95 to 100 days. Temperatures of 100° or higher are common over the State from May well into September. In the southwest part of the State the average number of 100° days is 20 to 25 per year. Other sections of the State will average somewhat less, but very seldom will any location in the State not reach a 100° temperature sometime during the summer months.

Low humidities and good southerly breezes usually accompany the high summer temperatures and somewhat lessen their discomforting effect. Occasionally strong, hot winds accompany the high daytime temperatures; this combination produces rapid evaporation and often injures crops. When these conditions persist for long periods of time, droughts develop and occasionally become severe. Nights are generally comfortable because the clear skies and dry air allows for rapid cooling after sunset.

The highest temperature ever recorded in the State was 120°. This reading was observed at Alva on July 18, at Altus on July 19 and August 12, and at Poteau on August 10--all during the extremely hot summer of 1936. Tishomingo also observed a 120° temperature on July 26, 1943.

Temperatures of 32° or less occur on an average of 55 to 65 days per year along the southern tier of counties and from 90 to 100 days per year along the Kansas border in the north-central and northeastern sections of the State. In the Panhandle, days with 32° or less occur, on an average, 125 to 140 days per year. The lowest temperature of record is -27° and was observed at Watts on January 18, 1930, and at Vinita on February 13, 1905.

The average length of the growing season, or freeze-free period, ranges from 168 days at Kenton, in the northwestern corner of the Panhandle, to about 225 days along the Red River in the south-central and southeastern sections of Oklahoma. Along the northern border of the State, the average date of the last spring freeze varies from April 5 in the northeast to April 27 in the western end of the Panhandle. Along the southern border, the average date varies from March 27 to April 5. The average date of the first fall freeze varies from October 12 to October 27 in the and from November 5 to November 30 alon southern border, the latest dates occurring south-central area. Freezing temperatures occurred as late as April 20 along the sou border and as late as May 15 in the ext northwest and in the Panhandle. Fall fre have occurred as early as September 2 the Panhandle and as early as October 9 a the southern border.

Frozen soil is not a major problem, nor n of a deterrent to seasonal activities. Its oc rence is rather infrequent, of very limited ex and of brief duration. The average maximum d that frost penetrates the soil ranges from less 3 inches in the southeastern corner of the Stat more than 10 inches in the extreme northwest portion. Extreme frost penetration ranges fr 10 inches in the southeast corner to about inches in the northwest corner of the Panhand Factors having an important bearing on fr penetration are severity and duration of tempe ture below freezing; condition, character, moisture content of the soil; and amount character of protective cover of the soil includ snow cover.

The geographical distribution of rainfall d creases sharply from east to west. Avera annual precipitation ranges from about 56 inch in southern LeFlore County, in the southeaste corner of the State, to 15 inches in the extrem western Panhandle. The greatest annual precip tation recorded at an official reporting stati was 84.47 inches at Kiamichi Tower in southe LeFlore County in 1957. The least annual amou was 6.53 inches at Regnier in northweste Cimarron County in 1936.

Frequency of rainfall, as determined from th average number of days with 0.01 inch or more varies from 95 to 100 days a year in the extrem east to from 70 to 80 days a year over the weste third of the State.

Precipitation is usually adequate for successfu production of the State's principal crops. Spring and early summer rains are of more genera and abundant character. Late summer and early fall rainfall is more localized and less abundan as a rule. Fall precipitation, except in some western districts where occurrence at this season is uncertain, is usually adequate for putting soils in good workable condition and for giving fall-sown grains a good start. Average summer rainfall of less than 2 inches per month is unfavorable to crops normally maturing during that season of the year, and poor yields of such crops usually result even on good soils.

Excessively heavy rains occur at times. Amounts of 10 inches or more within a 24-hour period, have been recorded. The greatest official rainfall, within a 24-hour period, was 15.50 inches at Sapulpa on September 3-4, 1940. Larger unofficial amounts have been recorded and in a shorter period of time; for instance, 24 inches in a 10-hour period in the Hallett-Maramec area in southern Pawnee County, also on September 3-4, 1940, and 23 inches within a 12-hour period on

April 3-4, 1934, near Cheyenne in Roger Mills County.

Floods may occur during any season. They occur with greater frequency, however, from May to July and in September and October, representing periods when storms are of greater magnitude and rains of greatest intensities. In general, floods in other seasons are the result of more abnormal and persistent buildup of soil moisture plus a concurrent increase in streamflow due to prolonged rains. The number of lakes built in Oklahoma within the past 10 years has done much in reducing flood damage.

Some notable flood years in Oklahoma are as follows: Verdigris--1904, 1922, 1927, 1941, 1951, 1957, 1959; Cimarron--1926, 1932, 1943, 1945, 1949, 1955, 1957; Grand (Neosho)--1943, 1948, 1951; Illinois--1950, 1951; Canadian--1904, 1914, 1941, 1943; North Canadian--1923, 1927, 1945; Washita--1908, 1923, 1927, 1936, 1938, 1949, 1951, 1955, 1957; Arkansas--1943, 1945, 1957.

Relative humidity averages about 10 percent higher in the eastern portion of the State because of lower elevations and more frequent inflow of Gulf moisture. Summer afternoon and early evening relative humidities are considerably lower than those of winter.

The geographical distribution of annual snowfall is usually almost the reverse of the annual precipitation pattern and ranges, on an average, from approximately 2 inches in the southeastern corner of the State to approximately 20 inches in the western sections of the Panhandle. Snow rarely remains on the ground more than a few days. At times, strong winds with heavy snowfalls cause bad drifting and occasionally produce blizzard conditions which restrict highway traffic and endangers livestock. The greatest seasonal snowfall ever recorded in Oklahoma was 87.3 inches at Beaver, in Beaver County, during the season of 1911-12. The greatest daily snowfall was 22 inches at Beaver on December 19, 1911.

Oklahoma, along with other states in the southern Great Plains, has at times been subject to droughts of varying degree and duration, although drought years have been far less frequent than dry summers and falls. Most notable of the drought periods in Oklahoma were the dry years which occurred in the late 1890's, the drought of 1910 to 1919, the very severe drought of the 1930's, and the most recent drought which persisted from July 1951 to March 1957. While little can be done at this time to correct deficient rainfall, which is the major contributing cause of droughts, much has been done since the late 1930's in adapting land use and cultivation practices to climatic deficiencies. The tremendous increase in the past 20 years in irrigation farming has also played a major role in reducing drought conditions in Oklahoma. Since 1947, farmland under irrigation has increased from 50,000 acres to approximately 600,000 acres--a 12-fold increase. Most of the irrigation land is in the western third of the State.

Average annual lake evaporation varies from about 48 inches in the extreme eastern sections of the State to as high as 65 inches in the southwestern corner. In the western Panhandle approximately 58 inches of water is evaporated each year. The importance of these evaporative losses from reservoirs and other surface water supplies has prompted a good deal of research to find ways of retarding the evaporation process.

Prevailing winds are southerly although northerly winds predominate during the winter months. Average yearly wind speeds vary from 9 m.p.h. in the east to approximately 14 m.p.h. in the west. March and April are the windiest months, and July and August the calmest.

Thunderstorms occur, on an average, of 50 to 60 days per year in the eastern half of the State and from 40 to 50 days per year in the western half. Some of the more severe thunderstorms are accompanied by tornadoes and damaging hail, and approximately 75 percent of these occur during the spring season. Since 1875, over 1600 tornadoes have struck the State. One of the best known and most destructive moved out of the Texas Panhandle on the evening of April 9, 1947, striking Ellis, Woodward, and Woods Counties before moving into Kansas. One hundred and one people lost their lives in Oklahoma, 95 of these at Woodward, Woodward County. Property damage in the State was a little over $8 million. Since 1924, estimated damage from hailstorms has averaged a little over $3 million per year. The most destructive hailstorm known to have hit the State struck Oklahoma City during the night of May 23-24, 1968, causing over $20 million property damage.

Skies are preponderantly clear in western and central sections and about equally clear and cloudy in eastern sections. Sunshine records show an annual average of 68 percent of the possible amount of Oklahoma City and 63 percent at Tulsa. Summer is the period of greatest possible sunshine and winter the least.

The climate of Oklahoma is favorable for a long vacation season and a wide variety of recreational activities. The wooded and more watered and mountainous eastern sections of the State are particularly attractive to the vacationer, especially those who enjoy boating, water-skiing, camping, hiking, and fishing.

REFERENCES

(1) Holbrook, Stanley G., ESSA, Weather Bureau. Oklahoma's Severe Hail, 1924-1961, 1962 (unpublished).

(2) Klein, John J., et al, Department of Economics, Oklahoma State University, Stillwater, Oklahoma, The Oklahoma Economy, 1963.

(3) Kohler, M. A., et al, ESSA, Weather Bureau, Evaporation Maps for the United States, Weather Bureau Technical Paper No. 37, 1959.

(4) Lehrer, Hugo V., ESSA, Weather Bureau, "Climate of Oklahoma", published in Climates of the States, Oklahoma, Climatography of the United States No. 60-34, ESSA, Environmental Data Service, 1960.

(5) Bureau of Business Research, University of Oklahoma, Norman, Oklahoma, Oklahoma Data Book, 1968.

(6) ESSA, Weather Bureau Climatological Services Division, Mean Number of Thunderstorm Days in the United States, Weather Bureau Technical Paper No. 19, 1952.

(7) Oklahoma Almanac, Incorporated, Norman, Oklahoma, The Oklahoma Almanac, 1961 edition.

(8) Oklahoma Water Resources Board, Oklahoma City, Oklahoma, Reported Water Use in Oklahoma, 1968.

BIBLIOGRAPHY

(A) Climatic Summary of the United States (Bulletin W), 1930 edition, Sections 42 and 43. ESSA, Weather Bureau.

(B) Climatic Summary of the United States, Oklahoma - Supplement for 1931 through 1952 (Bulletin W Supplement), ESSA, Weather Bureau.

(C) Climatic Summary of the United States, Oklahoma - Supplement for 1931 through 1960 (Bulletin W Supplement), ESSA, Weather Bureau.

(D) Climatological Data - Oklahoma, ESSA, Environmental Data Service.

(E) Climatological Data - National Summary, ESSA, Environmental Data Service.

(F) Hourly Precipitation Data - Oklahoma, ESSA, Environmental Data Service.

(G) Local Climatological Data - Oklahoma City and Tulsa, Oklahoma, ESSA, Environmental Data Service.

(H) Selected Climatic Maps of the United States, ESSA, Environmental Data Service

(I) Storm Data, ESSA, Environmental Data Service.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 16 1996

NDA 20-579

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

Dear Mr. Fernandes:

Please refer to your pending April 15, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tamsulosin Hydrochloride capsules.

We also refer to your amendments dated May 21, June 28, and August 6, 1996.

We have completed our reviews of the Chemistry, Manufacturing and Control and the Environmental Assessment sections of your submission and have identified the following deficiencies:

Chemistry

1. Please provide information as to how each reaction was monitored for its completion of reaction.

2. The specifications for related substance should be tightened to % for individual impurity and to % for total impurities, otherwise these impurities should be qualified (all the batches used in the preclinical and clinical studies show that the individual impurities were less than % and total impurities were less than %).

3. The equation for the calculation of impurity content described on p.301, vol. 1002, is not clear (the equation seems to indicate that the standard solution has a concentration of %, while the actual concentration of the standard appears to be %). Please clarify.

4. Please clarify the following equations:

   a. In the equation for the calculation of content uniformity on p.157, vol. 1003, "Amount of tamsulosin hydrochloride RS×0.02×100", the factor : seems to be a typographical error of

   b. In the equation for assay (p.158, vol.1003), "0.4 mg Capsules (%) of the amount claimed on the label=Amount (mg) of tamsulosin hydrochloride RS×(Qt/Qs)×0.0025×(weight of contents of the 20 capsules/sample weight)×100." How is the factor derived?

   c. In the equation for the calculation of related substances (p.162, vol.1003), "The area of any individual peak (%)=[Amount (g) of tamsulosin hydrochloride RS/0.5]×(At/As)×5." How are the factors derived?

5. Although the provided stability data suggest that degradation products and s-isomer are negligible during the proposed shelf-life (24 months), the tests for degradation products and s-isomer should be included in the stability protocol, if the expiry date is to be extended beyond the proposed expiry date in the future.

6. In the DESCRIPTION section of package insert: a) The chemical name should be (-)-(R)-5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene sulfonamide, monohydrochloride as is written in USAN. b) The last phrase".. should be revised to read "..

7. NDC numbers should be specified in the HOW SUPPLIED section.

8. Please provide specifications and test methods for printing ink.

9. The proposed tradename, is not acceptable. However, upon reconsideration, we can agree to Flomax as an acceptable name or you may propose a new one.

Environmental Assessment (EA)

Please submit EA addendums, both confidential and nonconfidential if appropriate, to address the following deficiencies regarding the Tier 0 EA dated May 15, 1996:

1. Section 4.c., Description of the Proposed Action, Proprietary Intermediates:

   The EA contains no reference to proprietary intermediates. If no such substances are

used in the production of the drug substance, the EA should so state. If proprietary intermediates are used, the EA should identify the location of their manufacture and discuss the environmental settings of the facilities and manufacturing site information (format item 6) or, if locations are outside the United States, provide appropriate certifications of environmental compliance.

2. Section 4.e, Description of the Proposed Action, Disposal Locations:

Information provided for domestic disposal facilities should include the method of disposal (landfill, incineration), the license or permit number, the EPA or other issuing authority's identification number, (if any), the license or permit expiration dates, and the issuing agent. Specific information on contract disposal facilities may be included in a confidential appendix.

3. Section 6.c, Citation of a Statement of Compliance with Applicable Emission Requirements:

For the State of Oklahoma Department of Health Industrial Waste Disposal Plan #14006, the date provided is 6/21/79. It should be clarified if this is the date of issue. Two other permits issued by the state Department of Health and the Board of Pharmacy are identified as having expired in July and June 1996, respectively. It should be clarified whether these permits have been renewed, superseded by new permits, or whether a renewal request is pending before the government agency.

4. Section 7, Fate of Emitted Substances in the Environment:

The word in the last line of the summary of fate and effects tests raises a concern regarding the possible effect of the drug on aquatic organisms. It seems likely from the context that the author intended to say that the toxicity is exhibited only at concentration orders of magnitude the EIC. Please clarify this issue.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Terri F. Rumble, B.S.N.
Regulatory Health Project Manager
(301) 827-4260

Sincerely yours,

10-11-96

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-579
HFD-580/Div. Files
HFD-580/PM/TRumble/LPauls
HFD-580/MJRhee
HFD-357/RHassell/NBSager
HFD-820/Yuan Yuan Chiu (only for CMC related issues)

drafted: TRumble/October 11, 1996/20579.ir1
r/d Initials: Rumble/October 16, 1996/MRhee,10.16.96 \LPauls,10.15.96
final: Trumble/October 16, 1996/wpfiles/nda/letters/20570.ir1

INFORMATION REQUEST (IR)

NDA 20-579

APR 23 1996

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Mr. Peter P. Fernandes
900 Ridgebury Road
P.O. Box 368
RIDGEFIELD CT 06877

Dear Mr. Fernandes:

We have received your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product:	Flomax (tamsulosin hydrochloride) 0.4 mg Capsules
Therapeutic Classification:	Standard
Date of Application:	April 15, 1996
Date of Receipt:	April 15, 1996
Our Reference Number:	NDA 20-579

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 14, 1996, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Mr. Stephen Trostle
Consumer Safety Officer
301-443-3520

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Enid Galliers 4/23/96

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-579
HFD-510/Div. Files
DISTRICT OFFICE
HFD-510/STrostle/ft/stt/04/23/96 \N20579AC.000
ST 04/23/96
ACKNOWLEDGEMENT (AC)

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

April 15, 1997

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

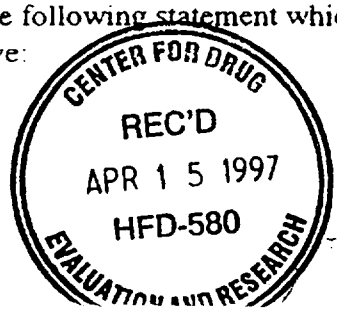
Re: FLOMAX™ Capsules, 0.4mg
(Tamsulosin Hydrochloride)
NDA 20-579

Dear Dr. Rarick:

This letter will serve to confirm our acceptance of all the changes telefaxed to us this morning with the following exceptions:

1. We consider it critically important to retain the word in the Clinical Studies Section. Therefore, we propose to include the following sentence beginning at line 246:

2. With deletion of most of the PRECAUTIONS section and moving of lines 365 - 377 regarding positive orthostatic test results to the ADVERSE REACTIONS section, we believe it is essential to provide the definition of what constitutes a positive orthostatic test result. Therefore, we propose to add midway through line 598 the following statement which will immediately precede the lines which you have requested we move:



Telephone: (203) 798-9988

3. With the changes to the ADVERSE REACTIONS section we believe it is important to provide the incidence of symptomatic postural hypotension, syncope and vertigo. Therefore, we are proposing to add the following text immediately following the footnotes to Table 3:

We are in the process of making all of these changes to the package insert and will be sending via FAX (and hard copy) a completely revised copy later this afternoon.

Sincerely,

Roger W. Croswell, Ph.D.,
Director
Drug Regulatory Affairs
(203) 798-4348
Fax (203) 791-6262

BOEHRINGER INGELHEIM

ORIGINAL

ORIG AMENDMENT

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Celebrating 25 YEARS in the U.S.

April 1, 1997

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Re: FLOMAX™ Capsules, 0.4 mg **Physicians Package Insert**
(Tamsulosin Hydrochloride)
NDA 20-579.

Dear Dr. Rarick:

This submission is in response to your facsimile dated March 26, 1996 containing your Division's comments to our Physicians Package Insert submitted to NDA 20-579. Attached is our copy of revised labeling, dated April 1, 1997. It contains FDA's and BIPI's proposed revisions, with a rationale for these newly proposed items.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Line 39-43: We have revised the nomenclature in the original insert to reflect the current nomenclature.

References are being attached to the package insert.

CLINICAL TRIALS

Line 64-75: As requested in FDA Enclosure 1, we have provided a concise and objective paragraph to describe the results in Table 1, with the necessary comments 1 to 4.

Line 76-98: For Table 1, we have made necessary changes to title and footnote; however, we have not included in the title as this measurement is made at Endpoint 1 and is explained in the footnote. Also in the footnote we have clarified that a statistically significant difference between the two treatment groups was seen in US92-03A.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 0 3 1997
HFD-580

Line 100-111: As requested in FDA Enclosure 1, we have provided a concise and objective paragraph to describe the results presented in Figures 1 A/B and 2 A/B and those figures from studies US92-03A and US93-01 incorporating FDA comments. However, please note that inclusion of SD instead of SE in the figures has made these figures difficult to interpret because of overlap of SD's. We request that we use SE for the final package insert.

Line 154-158: As requested by FDA we have inserted the pharmacokinetic/pharmacodynamic correlation analysis narrative and Figure 3.

Line 163: We have added in These studies were submitted in the NDA and in the safety updates 1 and 2.

Pharmacokinetics

Line 166-311: We have replaced the original text with FDA proposed text as provided in Enclosure 2. We have also included in this section the proposed Figure 4, with the revisions to Table 2 as proposed by FDA. However, we have not included data on clearance, as this was not done in studies US89-01 and US94-03.

INDICATION AND USAGE

Line 313-319: We request that we retain the statements as these statements appear in the Hytrin and Cardura package inserts and comparable supportive data have been generated for FLOMAX™.

WARNINGS

Line 326: We propose that we delete from the bold warning statement (from FDA fax line 344-35)

as we believe this more appropriately belongs in the PRECAUTION section under Drug-Drug Interactions.

Line 328-345: As requested in FDA comment (FDA fax line 347 to 352) we have provided the US data for Syncope and effect data for the FDA-specified duration and included the n/N (%). In contrast to those potentially serious adverse events we believe that the additional information requested by FDA regarding rates for postural hypotension in patients with either clinical symptoms or those who met one of the criteria is more appropriately placed in the PRECAUTIONS section under item 2) Orthostatic Hypotension.

PRECAUTION

Line 354-427: As discussed in the item above, and as requested by FDA (FDA fax line 378 to 385) we have included in this section the FDA requested information for symptomatic postural hypotension, dizziness and vertigo through 13 weeks, as well as the rates as n/N (%). Included in this section are the definition or criteria used for and However, we believe that the data on orthostatic testing does not provide useful additional clinical information to prescribers and thereby the impact of this precautionary section).

Line 429-449: We have included in the PRECAUTION section the FDA proposed text from Enclosure 1 page 6.

Laboratory Tests

Line 457-521: We have replaced the original text with the FDA proposed text from lines 420 to 486 of FDA fax. in line 481, is the figure obtained from males only.

Line 506-508: We have added the statement
as per FDA request (FDA fax line 487.)

ADVERSE REACTIONS

Line 523-607: We have revised the Table 3 and 4 (previously 4 and 5) as specified by FDA in the Fax Enclosure 3. However, on completing Table 4, we find it is extremely long and not clinically user friendly. We request FDA to consider reducing this listing to include only those with a higher incidence in FLOMAX™ compared to placebo, with lower incidences of AE's included in subsequent text.

Line 609-619: Added as per FDA request (FDA fax line 593 to 595).

HOW SUPPLIED

Line 698: We have added

Please contact the undersigned with any questions or comments pertaining to this submission.

Sincerely,

Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
Telephone (203) 798-5337
Facsimile (203) 791-6262

Desk Copy: Ms. T. Rumble

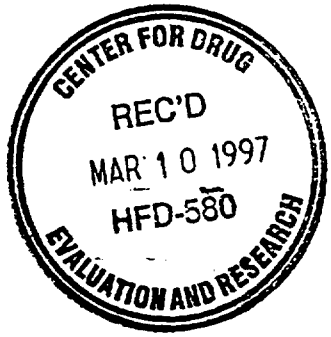
Boehringer Ingelheim

ORIGINAL

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

March 7, 1997

ORIG AMENDMENT



Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

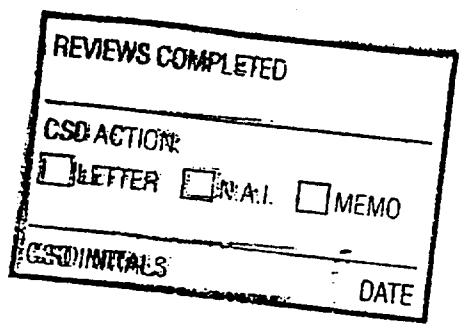
Re: FLOMAX® Capsules, 0.4 mg **Safety Update 3** (Goodwill Submission)
NDA 20-579.

Received Dear C
Copy
3/13/97

Dear Dr. Rarick:

Attached is the Section 9 update of the NDA No. 20-579, containing the third safety update report, with cut-off dates from September 1, 1996 to December 31, 1996. Based on data discussed in this submission, we do not propose any revisions to the labeling provided in the original NDA.

As previously discussed and agreed to with Dr. J. Fourcroy (see attached facsimile to Dr. J. Fourcroy dated September 4, 1996), this safety update only addresses critical safety information obtained during this four month reporting period. This submission is therefore limited to tabular listings and background information of all serious adverse events for US and non-US studies reported to the sponsor as of December 31, 1996 and concludes that there is no significant changes in the product safety profile.



(203) 798-9988

FLOMAX® Capsules, 0.4 mg
NDA 20-579
Safety Update 3 (Goodwill Submission)

Please contact the undersigned with any questions or comments pertaining to this submission.

Sincerely,

Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
Telephone (203) 798-5337
Facsimile (203) 791-6262

G:\DRA\Flomax\TA970305.doc

Boehringer Ingelheim

ORIGINAL

SUPPL NEW CORRESP

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

February 13, 1997

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

2-26-97

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Re: FLOMAX® Capsules, 0.4mg
NDA 20-579

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Rarick:

The following information is in response to Dr. Fourcroy's questions of February 10, 1997:

Question 1: Baseline characteristics of the patients responded to both Qmax and SS?

Please see attached.

Question 2: Trouble finding QOL data in the NDA.

The QOL validation report can be found from page 169 to 187, Volume 1.371 of NDA 20-579. Although the Table of Contents for this volume (page 9) refers to the publication, the NDA includes only a copy of the text sent to the publisher.

A copy of the QOL questionnaire actually used in the tamsulosin studies can be found on pages 177 of Volume 1.223 (Appendix F of the protocol for YM617US93-01). (copies from NDA attached)

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
FEB 14 1997
HFD-580

Telephone: (203) 798-9

Question 2: Trouble finding QOL data in the NDA. (continued)

The results of the QOL measurements in studies US92-03A. US93-01 and US92-03B can be found on the following pages:

US 92-03A	Volume 1.188,	p. 193 - 198
US93-01	Volume 1.220,	p. 107 - 110
US92-03B	Volume 1.231,	p. 190 - 194

(copies from NDA attached)

Question 3: Clarification on timing of uroflow measurements.

US92-03A:
The protocol requested that a uroflow measurement be performed 4-8 hours post dose at every visit.

US93-01:
The protocol requested that a uroflow measurement be performed 4-8 hours post dose at visits 4 and 5, and 24-27 hours post dose at visits 6,7 and 8.

US92-03B:
The protocol requested that uroflow be measured 24-27 hours post dose at L2 and L3. There were no particular scheduling requirements for visits L4 through L9.

Question 4: Peak urine flow rates at time of peak and trough plasma levels.

In study US93-01, the peak urine flow rates were measured around the expected time of peak plasma concentration at visits 4 and 5, and around the expected time of trough plasma concentration at visits 6,7 and 8. The results are available on pages 85-87 of volume 1.220 of the NDA. The changes from baseline in peak urine flow during trough times were smaller than those measured during peak plasma times.

Re: FLOMAX® Capsules, 0.4mg
NDA 20-579

RESPONSE TO FDA REQUEST
FOR INFORMATION

Question 4: Peak urine flow rates at time of peak and trough plasma levels (continued)

In study US92-03B, the double-blind extension study of US92-03A, the urine flow rates were measured around the expected time of trough plasma concentration at L2 and L3. The peak urine flow rates measured at these two visits were lower then those at prior visits during Study US92-03A where all the measurements were performed around the expected peak plasma concentration time. These results are included on page 261 of volume 1.233 and pages 123 - 125 of volume 1.232.(copies from NDA attached)

The above responses were sent via facsimile to Dr. Fourcroy on February 12, 1997.

If you have any further questions or comments, please do not hesitate to contact me at the number below.

Sincerely,

Peter P. Fernandes, M.Pharm.
DRA Associate Director
Drug Regulatory Affairs
Telephone (203) 798-5337
Facsimile (203) 791-6262

Desk Copy: Dr. J. Fourcroy

G:/DRA/Flomax/resp.doc

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, Connecticut 06877-0368

January 31, 1997

ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Re: FLOMAX® Capsules, 0.4 mg **Second Safety Update**
NDA 20-579.

Dear Dr. Rarick:

As per 21 CFR 314.50(d)(5)(vi)(b)(1), attached is the second safety update report in which the cut-off dates for all studies are August 31, 1996. On the basis of data discussed in this submission, we do not at this stage propose any revisions to the labeling provided in the original NDA. However, as of the cutoff date for Safety Update 2, and based on the results of the long term open label clinical BI report # U95-3261 (US 93-04) submitted to the NDA in December 1996, the mean treatment duration for the long-term exposure has been extended to 2 years, compared to 1.5 years in update 1, and 1 year in the original NDA labeling.

As discussed and agreed to with Dr. J. Fourcroy in September 1996 (see attached facsimile to Dr. J. Fourcroy dated September 4, 1996), this safety update does not contain specific items previously included in update 1 (see Table 1 and 2 of attached facsimile). We will also submit one additional safety update, namely update 3 (referred to as the "goodwill" submission). The "goodwill" submission proposed for filing in early March, 1997, however, will only address critical safety information of the drug available from September 1, 1996 to December 31, 1996. This submission will therefore be limited to tabular listings of all serious adverse events for US and non-US studies reported to the sponsor as of December 31, 1996, and will include an overall clinical assessment of any significant changes (if present) in the safety profile from that previously reported in updates 1 and 2.

Telephone: (203) 798-9988
Telex: 179153 Answer back: BIC

UT

FLOMAX® Capsules, 0.4 mg
NDA 20-579.
Second Safety Update

Please contact the undersigned with any questions or comments pertaining to this submission.

Sincerely,

Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
Telephone (203) 798-5337
Facsimile (203) 791-6262

G:\DRA\Flomax\secupdte.doc

Boehringer Ingelheim

NEW CORRESP

ORIGINAL

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

January 15, 1997

Faxed 1/28/97

Noted 1-28-97 JF

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 15 1997
HFD-580

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-45
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Re: Flomax® Capsules, 0.4mg Response to FDA Request for Information
NDA 20-579

Dear Dr. Rarick:

In reference to Dr. Fourcroy's request on 1/13/97, please find attached the following list of patients who met the following criteria in protocols 93-01/92-03A:

- A >30% response in Qmax.
- A >25% response on symptom scores.

If you need further assistance, please do not hesitate to contact me at the number listed below.

Sincerely,

Peter Fernandes, M. Pharm.
Associate Director
Drug Regulatory Affairs
(203) 798-5337
Fax (203) 791-6262

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

REQINFO.DOC

(203) 798-9988

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, Connecticut 06877-0368

ORIG AMENDMENT

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

December 13, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 16 1996
HFD-580

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-45
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Re: Flomax® Capsules, 0.4 mg
NDA 20-579

Response to FDA Letter (10/16/96)
Revisions to NDA (483 issues)

Dear Dr. Rarick:

We are herewith submitting responses to the Divisions letter dated October 16, 1996 regarding Chemistry, Manufacturing and Control and the Environmental Assessment sections deficiencies. Additional information is contained in the following appendices:

- Updated specifications for tamsulosin hydrochloride (Appendix #1)
- Updated package insert reflecting the requested changes (Appendix #2)
- Specifications for the printing ink (Appendix #3)
- Updated Environmental Assessment (Appendix #4)

Also provided in this submission are revisions to the NDA related to Form-483 issues. These are provided in the following appendices:

- Revisions of the NDA related to Form-483 issues (Appendix #5)
- Yamanouchi's responses to Form 483 (Appendix #6)

Telephone: (203) 798-9988
Telex: 179153 Answer back: BIC

UT

Thank you for your attention in this matter. If you should have any questions or comments concerning this submission, please contact the undersigned at (203) 798-5337.

Sincerely,

Peter P. Fernandes, M.Pharm.
Associate Director
Drug Regulatory Affairs
(203) 798-5337
Fax (203) 791-6262

Desk Copy: Dr. M. Rhee

G:DRA Flomax:961212.doc

ORIGINAL

Boehringer Ingelheim

ORIG AMENDMENT

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Celebrating 25 YEARS in the U.S.

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-580)
Document Control Room #17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

Re: FLOMAX® Capsules, 0.4 mg **4 Month Safety Update**
NDA 20-579.

Dear Dr. Rarick:

As per 21 CFR 314.50(d)(5)(vi)(b)(1), attached is Section 9 of the NDA No. 20-579, containing the first safety update report, dated October 23, 1996 (cut-off dates are August 31, 1995 for US studies and June 2, 1995 for European studies). Based on data discussed in this submission, we do not propose any revisions to the labeling provided in the original NDA.

As discussed and agreed to with Dr. J. Fourcroy in September 1996 (see attached facsimile to Dr. J. Fourcroy dated September 4, 1996), we will also submit two additional safety updates, namely update 2 and update 3 (referred to as the "goodwill" submission). Update 2 will have a cutoff date of August 31, 1996 for both US and European studies. The "goodwill" submission, however, will only address critical safety information of the drug available from September 1, 1996 to December 31, 1996. This submission will therefore be limited to tabular listings of all serious adverse events for US and non-US studies reported to the sponsor as of December 31, 1996, and will include an overall clinical assessment of significant change in the safety profile from that previously reported in updates 1 and 2.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

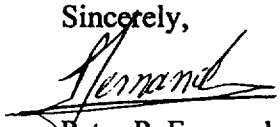
CSO INIT: DATE

(203) 798-9988

FLOMAX® Capsules, 0.4 mg
NDA 20-579.
4 Month Safety Update

Please contact the undersigned with any questions or comments pertaining to this submission.

Sincerely,



Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
Telephone (203) 798-5337
Facsimile (203) 791-6262

G:DRA:Flomax:NDA.Safup.doc

Attached: 90 volumes

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Celebrating 25 YEARS in the U.S.

August 16, 1996

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, 17B-45
Rockville, Maryland 20857

Attention: Lisa Rarick, M.D., Director (Room 17B-45)
Division of Reproductive and Urologic Drug Products (HFD 580)

Re: NDA 20-579 Tamsulosin Hydrochloride Capsules, 0.4 mg
Package for Dr. Albert Chen (Room 17B-31)

Dear Dr. Rarick:

This package is in reference to the request from Dr. Albert Chen regarding:

1. Electronic and hard copies on 21 pharmacokinetic study report data in specific table format. (Provided in this submission is 1 volume of text data and enclosed in this folder is the diskette for Dr. Chen only.)

2. Electronic files for report text and PK raw data. (Package containing 19 numbered diskettes and attached table listing contents within each diskette for Dr. Chen only.)

3. Electronic data files for NDA section 6. (Package containing 2 diskettees for Dr. Chen only.)

4. Electronic and hard copies on tamsulosin hydrochloride capsules 0.4 mg dissolution raw data. (Package containing 1 diskette for Dr. Chen only.)

The above package containing one copy of the text files and diskettes mentioned above are being mailed under separate cover to Dr. Albert Chen (room 17B-31).

I will call Dr. Chen some time next week to confirm receipt of the above packages and diskettes and his ability to successfully transfer these data to his computer.

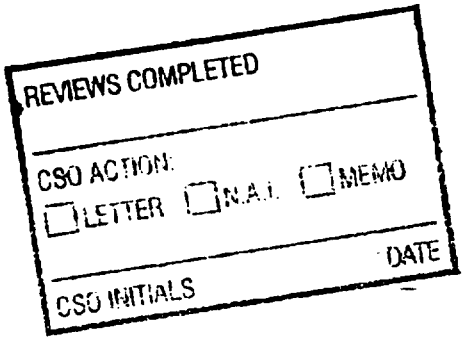
Thanking you,

Sincerely,

Pat Watson for Peter Fernandes

Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
(203) 798-5337
(203) 791-6262 (FAX)

Desk Copie containing diskettes: Dr. Albert Chen (17B-31)
Cover letter only: Ms. C. Kish (17B-45)



ORIGINAL

BC

ORIG AMENDMENT

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Celebrating 25 YEARS in the U.S.

August 6, 1996

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, 17B-45
Rockville, Maryland 20857

Attention: Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD 580)

Re: Tamsulosin Hydrochloride Capsules, 0.4 mg Trademark review.
NDA 20-579

m Rhee to fax
But accept fax 8-27-96

Dear Dr. Rarick:

We request your Division to reconsider the proposed tradename Dysutrol™ for Tamsulosin Hydrochloride Capsules, 0.4 mg.

See Chemley #1 dated 10/4/9
M Rhee 10/8/96

Based on our submission dated February 15, 1996, your Division conducted a trademark evaluation on 4 proposed proprietary names which included Flomax, Flostim, Stimflo and Dysutrol. Following this review, and subsequent discussions with Dr. M. Rhee, we were informed that, although Flomax was initially found acceptable by the Labeling and Nomenclature Committee, it was later determined by the medical reviewer to have clinical implications which make this name unacceptable. Dr. Rhee also requested that we not consider using the three other names proposed, as these also appeared to have some connotation with drug action.

It is our belief that a substantial majority of prescribing physicians will not associate Dysutrol with any special clinical efficacy claims for tamsulosin. At most, this name would be associated with a disease state classification rather than a drug action.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
10/25/96
CSO INITIALS DATE

printed on recycled paper

(203) 798-9988

As outlined in the attached list, the agency has permitted, on numerous occasions, proprietary names with some connotation to disease state and or drug action. We believe that agency acceptance of Dysutrol would be consistent with the policy allowing the use of those outlined proprietary names.

We appreciate your notifying us on your decision regarding the above request at your earliest convenience.

Sincerely,

Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
(203) 798-5337
(203) 791-6262 (FAX)

Desk Copies: Dr. M. Rhee (17B-45)
Ms. C. Kish (17B-45)

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ORIGINAL

Boehringer Ingelheim

July 11, 1996

Celebrating 25 YEARS in the U.S.

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-580
Rockville, Maryland 20857

Attention: Lisa Rarich, M.D., Acting Director
Division of Reproductive and Urologic Drug Products

Re: Tamsulosin Hydrochloride Capsules, 0.4mg FDA Request for Information
NDA 20-579

Dear Dr. Rarich:

During telephone conversations on June 5, 1996 and June 24, 1996, Dr. Ananda V. Gubbi (Biostatistician) requested carcinogenicity data files from studies in mice and rats for the Tamsulosin NDA review. On June 25, Dr. Gubbi sent via facsimile the proposed format for providing the above data. Enclosed is one unzipped diskette (provided only in Dr. Gubbi's desk copy) containing a complete set of the requested data files, and one hard copy of the document prepared as per Dr. Gubbi's proposed format.

A summary is also provided on how this information has been presented, along with Dr. Gubbi's fax on the proposed format.

If you or Dr. Gubbi have any further questions, please do not hesitate to contact me at the number listed below.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Sincerely,

Peter P. Fernandes, M. Pharm
DRA Associate Director
Drug Regulatory Affairs
(203) 798-5337
(203) 791-6262 (FAX)
Desk Copy: Dr. Gubbi

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 12 1996
HFD-510

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

June 28, 1996

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS 7/2/96 DATE

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D JUL 01 1996 HFD-510

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Document Control Room #14B-19
5600 Fishers Lane
Rockville, MD 20857

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Re: Tamsulosin Hydrochloride Capsules, 0.4 mg
NDA 20-579/Amendment No. 002

Dear Dr. Sobel:

Boehringer Ingelheim Pharmaceuticals, Inc. is amending this NDA to provide for replacement pages previously submitted to the New Drug Application dated April 15, 1996.

The reason for this replacement is due to our error in a listing of the HDPE resin supplier, previously reported as The correct supplier is

The following pages have been canceled and replaced:

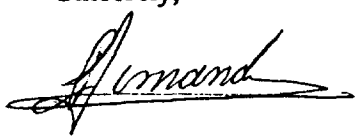
	Volume	Page	Corrected
Replacement 1	1.003	369	HDPE resin supplier (Table 3.3.9): , DMF #
Replacement 2	1.003	370-372	Specifications:
Replacement 3	1.003	390	Letter of Authorization:
Replacement 4	1.003	469-471	Stability Data

Telephone: (203) 798-9988

Re: Tamsulosin Hydrochloride Capsules, 0.4 mg
NDA 20-579/Amendment No. 002

Please incorporate this information into NDA 20-579 for Tamsulosin. We apologize for this error.

Sincerely,



Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
Phone: (203) 798-5337
Fax: (203) 791-6262

Enclosure

DESK COPY: Dr. H. Rhee

ORIGINAL

Boehringer Ingelheim

May 21, 1996

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

noted.
[See chem rev #1 (10-4-96)]
MMiller 10/8/96

Solomon Sobel, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products (HFD 510)
Document Control Room #14B-19
Rockville, Maryland 20852

Re: Flomax™ Capsules, 0.4 mg
(tamsulosin hydrochloride)

AMENDMENT TO NEW DRUG APPLICATION
NDA # 20-579

Dear Dr. Sobel:

This is in reference to the facsimile from Mr. Stephen Trostle, CSO, dated April 26, 1996 regarding your Division's preliminary review of the Environmental Assessment (EA) section of NDA 20-579 submitted on April 15, 1996. In Mr. Trostle's facsimile, we were advised that the Environmental Assessment (EA) for Flomax™ should be submitted in the Tier 0 format (shorter format.)

As requested, enclosed is a revised EA prepared according to a Tier 0 approach, in which format items 7, 8, 9, 10, 11 and 15 have been deleted. Pages 1-12 and appendices #1-5 (pages 1-36) are considered **non-confidential** material. Appendices 6-9 (pages 37-70) are considered **confidential** material.

Since the EA is part of Section 3.0, Chemistry, Manufacturing and Controls (CMC), of the Flomax™ NDA, copies of this amendment have also been submitted to FDA's inspectional district office, listed below , in compliance with 21 CFR 314.60(c).

REVIEWS COMPLETED
CSO ACTION: IR ltr to sponsor 10/10/96
☒ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

CENTER FOR DRUG
REC'D
MAY 22 1996
HFD-510
EVALUATION AND RESEARCH

EACOVLTR.DOC

(203) 798-9988

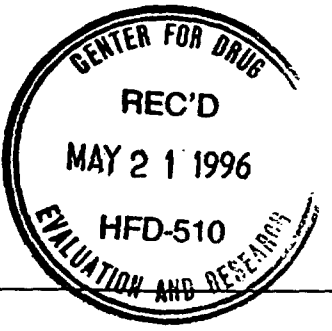
If there are any questions, please contact the undersigned at the phone number listed below.

Sincerely,

Peter P. Fernandes, M. Pharm.
DRA Associate Director
Drug Regulatory Affairs
(203) 798-5337
(203) 791-6262 (FAX)

Copy to: FDA Inspectional District for Applicant
Food and Drug Administration
One Montvale Avenue
Stoneham, Massachusetts 02180
Attention: Mr. Richard Penta

NEW CORRESPONDENCE ORIGINAL



Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

May 2, 1996

Dr. G. Turner
Pharmacologist, HFD 344
Food and Drug Administration
7520 Standish Place
Rockville, MD 20857

Noted 5-24-96 JL

Acted 5-23-96 G

Re: Tamsulosin Hydrochloride Capsules, 0.4 mg
NDA 20-579/Serial No.

RESPONSE TO FDA REQUEST FOR INFORMATION

Letter in DFL 5/24/96

Dear Dr. Turner:

As you requested in your telephone call on April 19, 1996, we are sending a listing of all U.S. investigators participating in the Tamsulosin clinical development program. This listing is followed by individual protocols with amendments for the two US phase III studies-US 92-03A and US 93-01 and the long term extension study -- US 92-03B. With each protocol is a separate list of the protocol investigators and number of patients at each study site. These documents are duplicate copies from relevant Clinical sections of the NDA. The NDA volume and page numbers are provided for each enclosure.

Sincerely yours,

Peter P. Fernandes, M.S.
DRA Associate Director
Drug Regulatory Affairs
Phone: (203) 798-5337
Fax: (203) 791-6262

REVIEWS COMPLETED
DSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
JL 9/19/96
DSO INITIALS DATE

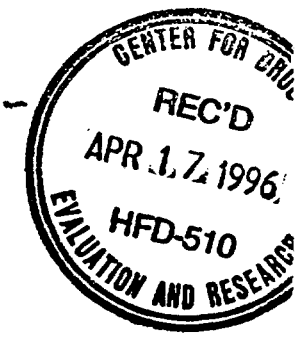
G:\DRA\FLOMAX\NDA\INFAMD1.DOC

Telephone: (203) 798-9988

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

April 15, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852



re: Flomax™ Capsules, 0.4 mg (tamsulosin hydrochloride) **ORIGINAL NEW DRUG APPLICATION NDA # 20-579, USER FEE # 2735**

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD 510)
Document Control Room #14B-19

Dear Dr. Sobel:

Pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.50, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is hereby submitting archival and review copies of New Drug Application (NDA) No. 20-579 for Flomax™ (tamsulosin hydrochloride) Capsules, 0.4 mg.

The proposed indication for Flomax ™ is for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The Clinical sections of the NDA provide data from 47 clinical and Phase I studies conducted in US, Europe and Japan. Two US Phase III, double blind, placebo-controlled studies, US92-03A (U95-3258) and US93-01 (U95-3259) are presented as the major studies that provide statutory evidence of efficacy and safety for the two doses (0.4 mg q.d. and 0.8 mg q.d.) of Flomax™ in the target population. In addition, a long-term, double-blind, placebo-controlled, extension study, with patients receiving up to 53 weeks of continual double-blind treatment US92-03B (U95-3260), is presented in support of the efficacy and safety of Flomax™. European and Japanese studies included in this submission provide additional supportive clinical evidence of the efficacy and safety of Flomax™.

The Nonclinical Pharmacology and Toxicology section of the NDA provides the results of *in vitro* and *in vivo* experimentation of the drug in animal models. It has been demonstrated that tamsulosin binds preferentially to the $alpha_{1C}$-adrenoceptor subtype found predominantly in the prostate. In comparison to other less subtype-selective $alpha_1$-adrenoceptor blockers currently in clinical use for the treatment of BPH and hypertension, Flomax™ decreases bladder neck smooth muscle tone while at the same time minimizing the risk from unwanted cardiovascular effects. The toxicologic profile of the drug predicts a wide margin of safety with the proposed therapeutic doses.

Tamsulosin hydrochloride is a benzenesulfonamide derivative with one chiral center, and is synthesized as the pure (R)-isomer. The dosage form is a modified release formulation (CR-M) supplied in a capsule. The same manufacturing process and formulations, as currently proposed for market introduction, were used for all key clinical studies supporting this NDA. Extensive stability data on both pilot and commercial production batches have shown the drug substance and dosage forms to be extremely stable.

The NDA comprises of 668 original volumes (volumes 1.001 to 1.667, plus 1 lettered volume). The NDA follows the format and content regulations as specified in 21 CFR 314.50 and applicable FDA guidelines. Following discussions in June 1995, Dr. J. Fourcroy accepted our proposal to provide case report form tabulation data (Section 11.0 of the NDA) for only the two Phase III US studies US92-03A and US93-01. Individual patient data on the other controlled studies however, will be accessible in the and in individual patient data listings provided in the clinical reports submitted with the NDA. In conformance with Section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 335a(k)(1), a certification statement is included in this NDA following the Form 356h.

One certified "true" copy of the Application Summary, Chemistry Manufacturing and Controls Section, and the Methods Validation Section, (volumes 1.001 to 1.008), containing batch records data as required under Section 314.50 (h)(3) is being submitted concurrently to the Stoneham Massachusetts District Office. Mr. Richard Penta, Pre-approval Inspections Manager, has been informed of this proposed submission via a phone call on April 1, 1996.

A for the clinical sections of the NDA is being submitted concurrently with this NDA. We will install this , using on Dr. J. Fourcroy's computer on April 15, 1996. An initial training session with Dr. J. Fourcroy is scheduled for April 22, 1996.

Please note that as of this date, BIPI is submitting under separate cover the required User Fee of to the Mellon Bank in Pittsburgh, PA. The user fee number assigned to this application is # 2735, issued on January 25, 1995.

We look forward to a close, collaborative working relationship with the Division during this NDA review process. Please contact the undersigned with any questions pertaining to this application. For questions regarding the CANDA, please contact Ms. Kristin O'Connor, Associate Director, Data Management, at 203-798-4244.

Sincerely,

Fernandes

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3 Desk Copies if the Application Summary volume 1.001 to Mr Stephen Trostle, CSO