CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Labeling Memo

NDA	21,269
NDA Submission Date	December 17, 2003
Label Submission Date	February 16, 2005
Brand Name	Cardura XL
Generic Name	Doxazosin mesylate
Reviewer	Stephan R. Ortiz, R.Ph., Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Pfizer
Submission Type; Code	Re-submission
Dosing regimen	Once daily
Indication	Benign Prostatic [redacted] (BPH)

This labeling memo serves to replace the labeling memo dated 2/17/05. Specifically, according to the sponsor, CYP2C9 was identified as a minor metabolic pathway, not CYP2C19 as was stated in the earlier labeling memo.

A teleconference was held with the sponsor on February 1, 2005 regarding the in vitro and in vivo metabolism of Cardura XL. In response to this teleconference, the sponsor faxed the Agency results of several in vitro metabolism studies involving Cardura XL on February 3, 2005. The study summaries are attached to this memo (pages 2-16).

Analysis of these in vitro studies suggests that the primary metabolic pathway for elimination is via CYP3A4; however, CYP2D6 and CYP2C9 metabolic pathways also exist to a lesser extent. No in vivo drug interaction studies have been performed with CARDURA XL.

RECOMMENDATION

Based on the results of these studies, appropriate changes have been made to the sponsor-proposed label. Specifically, changes have been made to the Metabolism section and PRECAUTIONS; Drug Interactions sections of the label. Following is the OCPB-proposed language for these sections:

Metabolism

Doxazosin is extensively metabolized in the liver. In vitro studies suggest that the primary pathway for elimination is via CYP3A4; however, CYP2D6 and CYP2C9 metabolic pathways also exist to a lesser extent. No in vivo drug interaction studies have been performed with CARDURA XL. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites have not been characterized. (See PRECAUTIONS; Drug Interactions).

PRECAUTIONS

***Drug Interactions**: No in vivo drug interaction studies were conducted with CARDURA XL (see CLINICAL PHARMACOLOGY; Drug-Drug Interactions). In vitro studies suggest that doxazosin*

is a substrate of CYP3A4. Caution should be exercised when concomitantly administering a potent 3A4 inhibitor, such as atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole with CARDURA XL. Pharmacodynamic interactions between CARDURA XL and anti-hypertensive medications or other vasodilating agents have also not been determined.

As of February 22, 2005, the sponsor has verbally agreed to the revised labeling language. The sponsor intends to submit a formal report of these studies. At that time, in lieu of a re-review of the studies, this memo will be referenced.

Stephan R. Ortiz, R.Ph., Ph.D.
Clinical Pharmacologist, HFD-870
2/22/05

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✓ Draft Labeling

_____ Deliberative Process

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/s/

Stephan Ortiz
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BIOPHARMACEUTICS

Myong-Jin Kim
2/22/05 03:13:14 PM
PHARMACOLOGIST

Clinical Pharmacology and Biopharmaceutics Review

NDA	21,269
Submission Date	December 17, 2003
Brand Name	Cardura XL
Generic Name	Doxazosin mesylate
Reviewer	Stephan R. Ortiz, R.Ph., Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Pfizer
Submission Type; Code	Re-submission
Dosing regimen	Once daily
Indication	Benign Prostatic [redacted] (BPH)

The OCPB briefing was held June 1, 2004 and was attended by the following: Hank Malinowski, John Hunt, Ameeta Parekh, Mark Hirsch, Jerry Willet, Myong Jin Kim, Leslie Kenna, Sandhya Apparaju, Rajiv Agarwal and Martin Kaufman.

Executive Summary

[redacted]

This review will focus on the sponsor's resubmission of data in an attempt to address these comments, namely intra-subject variability, dissolution specifications and labeling. Previous labeling recommendations will be reconsidered in light of the newly submitted data and current label standards.

A. Recommendation

The submission of NDA 21269 for Cardura XL is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective given that the sponsor incorporates the recommended labeling changes.

B. Phase IV Commitments

None

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

- ***PK Highlights***

This resubmission addressed two specific PK-related issues. First, the intra-subject variability in studies DAZ-NY-96-007 (4 and 8 mg GITS) and DAZ-NY-96-009 (4 mg GITS) was reported. In study DAZ-NY-96-007, the intra-subject CV%'s ranged from 7-23% with the highest CV% seen in the 8mg GITS group while in study DAZ-NY-96-009, the intra subject CV%'s ranged from 11-24% with young female subjects experiencing the greatest intra-subject variability.

Overall, considerable variability was observed throughout all the clinical trials. The inter-subject CV% ranges were between 33.6 and 67.7% throughout all studies using the 8mg GITS formulation. The 4mg GITS formulation yielded CV% ranges between 47.2 and 74%.

Second, differences in T_{max} were noted between single-dose and multiple-dose administration. The T_{max} reported for SD and MD were 14-15 hours and 8-9 hours, respectively. This is a cross-study comparison and the clinical relevance of this difference is not considered significant. Note that the clinical safety and efficacy studies were conducted with multiple dosing.

Upon conducting a food-effect study, the sponsor noted an increase of 32% and 18% in C_{max} and AUC, respectively, in the fed vs. fasted states. These differences may be clinically significant, particularly considering the safety issues associated with this class of drug (syncope, hypotension). As the clinical trials instructed the subjects to take the drug with breakfast, the following food-related dosing recommendation will be made in the label: *In order to provide the most consistent exposure, CARDURA XL should be administered with breakfast* [redacted] *(see DOSAGE and ADMINISTRATION).*

Upon conducting an age-effect study, the sponsor noted an increase of 27% and 34% in C_{max} and AUC, respectively, in the elderly (>65 years of age) vs. young subjects.

- ***Drug-Drug Interactions***

No formal *in-vivo* or *in-vitro* drug-drug interaction studies were performed with Cardura XL. However, based on the hypotensive effects of Cardura XL, concurrent administration with other antihypertensives or vasodilating agents should be considered carefully. Additionally, the food- and age-effect studies suggest that decreased GI motility may be leading to increased doxazosin exposure. A statement will be added to the Drug-Drug Interactions section of the label as to the potential for altered exposures when concomitantly administered with drugs that alter GI motility (e.g., anticholinergics).

- ***QT Prolongation***

The sponsor did not perform a prospectively designed QT study. OCPB and the clinical division agree that no formal QT study is necessary based on the following reasons:

1. Database of over 92,000 patients over 220 controlled, clinical studies with no evidence of QT prolongation or Torsades.
2. Over 1.4 million patient-years of use of Doxazosin IR with virtually no reports of QT prolongation or Torsades (3 cases; 2 cases involved subject concomitantly receiving therapy with known QT prolonging medication).
3. Over 4 years marketing Cardura XL in Europe with no sign of QT-related issues.

- ***Dissolution***

The dissolution method proposed by the sponsor (i.e., USP Apparatus 2, 75 rpm, 900 ml of SGF without enzymes at 37° C), is adequate and acceptable. The sponsor initially suggested the following dissolution specifications:

Cumulative
16 hrs Q is not less then [redacted] of label claim

Average
4-8 hrs (R1) [redacted] of label claim per hour
8-12 hrs (R2) [redacted] of label claim per hour

These specifications were unacceptable and after considerable communication with the sponsor, the following specifications have been agreed upon:

Cumulative
4 hrs: [redacted]
8 hrs: [redacted]
16 hrs: NLT [redacted]

3 Question Based Review

A. General Clinical Pharmacology

1. Pharmacokinetics/Bioavailability

This resubmission addresses 2 PK-related issues from the original submission.

Intra-subject Variability

Re-analysis of studies DAZ-NY-96-007 (4 and 8 mg GITS) and DAZ-NY-96-009 (4 mg GITS) was performed in order to assess the individual clinical predictability for the control release 4 and 8 mg GITS tablets with respect to the immediate release product. A brief description of each study is provided with subsequent intra-individual variability estimates.

For study DAZ-NY-96-007, an open, randomized two-way crossover study to evaluate the multiple dose pharmacokinetics of 4 and 8 mg doxazosin GITS and 4 and 8 mg doxazosin standard it was only possible to assess intra-subject variability for C_{min}, since this was the only PK parameter for which multiple measurements were reported by subject. C_{min} was assessed using the 24-hour plasma concentration data after 5, 6 and 7 days of once daily doses for both formulations at the 4 and 8 mg levels. ANOVA by dose/formulation with terms for subject and day were performed with the following results. The residual error term from the ANOVA model estimates the intra-subject variability.

Intra-Subject variability by Dose/Formulation for Cmin
Study DAZ-NY-96-007

Dose/Formulation	Residual error	Cmin Mean	Coefficient of variation
4 MG GITS	1.2740	6.905652	18.44897
4 MG STD	0.579944	7.516989	7.715107
8 MG GITS	3.815002	16.38258	23.28694
8 MG STD	1.239654	17.52747	7.072637

Higher intra-subject variability was observed for the GITS versus the standard formulation for both 4 and 8 mg doses. The intra-subject CV%'s ranged from 7-23% with the highest CV% seen in the 8mg GITS group.

For study DAZ-NY-96-009, an open, randomized, parallel study to evaluate the steady-state bioavailability and pharmacokinetics of 4 mg doxazosin GITS tablets in young and elderly male and females volunteers it was also only possible to assess intra-subject variability for C_{min}. This is the only PK parameter for which multiple measurements were reported by subject. C_{min} was assessed using the 24-hour plasma concentration data after 19, 20 and 21 days of once daily doses for. ANOVA for total subject, young males, young females, elderly males and elderly females with terms for subject and day were performed with the following results

Intra-Subject variability for 4 mg GITS by Age and Sex for Cmin
Study DAZ-NY-96-009

Dose/Formulation	Residual Error	Cmin Mean	Coefficient of Variation
Total Subjects	2.2900	13.96344	16.39971
Young Males	2.0516	11.33949	18.09236
Young Females	3.1107	12.86675	24.17641
Elderly Males	1.8639	15.80103	11.79607
Elderly Females	1.8154	16.03389	11.32234

Higher intra-subject variability was seen in the younger subjects compared to the elderly subjects. The CV%'s ranged from 11-24% with young female subjects experiencing the greatest intra-subject variability in the study.

Overall, considerable variability was observed throughout all the clinical trials. The inter-subject CV% ranges were between 33.6 and 67.7% throughout all studies using the 8mg GITS formulation. The 4mg GITS formulation yielded CV% ranges between 47.2 and 74%.

T_{max} Differences between Single Dose and Multiple Dose
Analysis of Study DAZ-NY-96-007 shows that the steady state administration of Cardura XL yields a T_{max} between 8-9 hours. Analysis of Study A0351061 shows that upon single dose

administration of Cardura XL, the associated T_{max} is 14-15 hours. This difference in single- and multiple-dose related T_{max} is not expected to impact upon efficacy or safety, given that the clinical trials were conducted with multiple dosing.

B. General Biopharmaceutics

1. *In Vitro* Dissolution

The dissolution method proposed by the sponsor (i.e., USP Apparatus 2, 75 rpm, 900 ml of SGF without enzymes at 37 ° C), is adequate and acceptable.

The sponsor proposed the following dissolution specifications:

4 hrs: Q [redacted] label claim
8 hrs: Q [redacted] of label claim
16 hrs: Q > [redacted] of label Claim

These specifications were considered unacceptable as the ranges were too wide. The sponsor's contention that these were based on IVIVC is not acceptable since the proposed IVIVC could not be validated. After considerable negotiations, the following dissolution release specifications were agreed upon:

Cumulative

4 hrs: [redacted] of label claim
8 hrs: [redacted] of label claim
16 hrs: Q NLT [redacted] of label claim

These dissolution specifications are considered reasonable and are acceptable.

4 Draft Label (as of 6/17/04)

1. CARDURA®XL

(doxazosin mesylate extended release tablets)

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On Original

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✓ Draft Labeling

_____ Deliberative Process

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[redacted]

[redacted]

[redacted]

5 Appendices

A. Original Review Comments

DISSOLUTION

1. The dissolution method proposed by the sponsor (i.e., USP Apparatus 2, 75 rpm, 900 ml of SGF without enzymes at 37o C, sampling times; 4, 8, and 16 hours), is adequate and acceptable.

2. The provided IVIVC information (submission dated January 4th, 2002) is incomplete and is not acceptable. The following IVIVC deficiencies were identified:
   - The percent error [redacted] therefore, verification of a correlation between in vitro data and in vivo results was not established.
   - [redacted]
   - No raw data was submitted with the report, thus, it was not possible to verify the conclusions and calculations made by the sponsor.

3. It should be noted that the proposed dissolution specifications (i.e., 4 hrs: Q [redacted] of Label Claim, 8 hrs: Q= [redacted] of Label claim, and 16 hrs: Q [redacted] of Label Claim), were based on IVIVC, therefore, are not acceptable. In the absence of an acceptable IVIVC, the maximum width allowed, as per guidance is ± 10%. Therefore, the following dissolution release specifications are recommended:

   4 hours: [redacted] of Label Claim
   8 hours: [redacted] of Label Claim

16 hours: Q ≥ [redacted] of Label Claim

4. The sponsor should be informed that OCPB would revise the above recommended dissolution specifications (as appropriate) as soon as complete and acceptable IVIVC data are provided.

CLINICAL

In order to better assess the individual clinical predictability from day to day for the control release 4 and 8 mg GITS tablets with respect to the immediate release product, the intrasubject pharmacokinetic variability is needed. In this submission the intrasubject variability values were not reported in any of the PK studies. Therefore, it is recommended that the sponsor reanalyze the pharmacokinetic data from studies DAZ-NY-96-007 (4 and 8 mg GITS) and DAZ-NY-96-009 (4 mg GITS) and provide the intraindividual variability information.

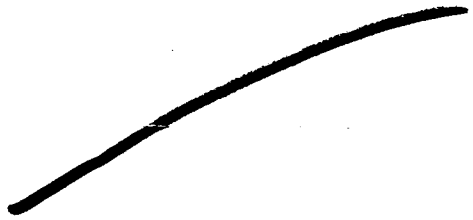
LABELING

1. [redacted]

2. On February 11, 2002, the sponsor submitted an amendment to NDA 21-269 [redacted] for CARDURA XL providing a revised labeling for the benign prostatic hyperplasia (BPH) indication. A copy of the revised BPH-labeling is included in Appendix I. It should be noted that OCPB/DCRDP is reviewing the revised BPH labeling, due to the fact that OCPB/DCRDP reviewed the original submission for CARDURÃXL.

3. It is recommended that the "Pharmacokinetics and Precautions" section of the proposed labeling for CARDURÃXL dated February 11, 2002, be modified as follows:

[redacted]



B. Cover Sheet and OCPB Filing/Review Form

3. Office of Clinical Pharmacology and Biopharmaceutics **2.** *New Drug Application Filing and Review Form*
General Information About the Submission

	Information		Information
NDA Number	21,269	Brand Name	Cardura XL
OCPB Division (I, II, III)	DPE II (HFD 870)	Generic Name	Doxazosin mesylate
Medical Division	DRUDP (HFD 580)	Drug Class	Alpha 1 antagonist
OCPB Reviewer	Stephan R. Ortiz, R.Ph., Ph.D.	Indication(s)	Benign Prostatic [redacted]
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Extended release tablets
		Dosing Regimen	Once daily
Date of Submission	December 17, 2003	Route of Administration	Oral
Estimated Due Date of OCPB Review	May 16, 2004	Sponsor	Pfizer
PDUFA Due Date	June 17, 2004	Priority Classification	3S
Division Due Date	May 16, 2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
A. Healthy Volunteers-				
single dose:				
multiple dose:				
1. Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• **Acceptability of average dissolution rate specifications** • **Intraindividual variability from assorted PK studies**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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/s/

Stephan Ortiz
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BIOPHARMACEUTICS

Ameeta Parekh
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Concur

Clinical Pharmacology and Biopharmaceutics
Memo To File
(Final Version February 4, 2002)

NDA: 21-269 Submission Date
April 20, 2001

Compound:	Cardora XL **(Doxazosin mesylate**
Formulation (s):	Extended Release Tablets (4 and 8 mg)
Sponsor:	Pfizer
Type of Submission:	NDA
Indications:	Benign Prostate Hyperplasia (BPH)
Reviewer:	Sayed Al Habet, Ph.D.
Memo Date:	February 4, 2002

Background:

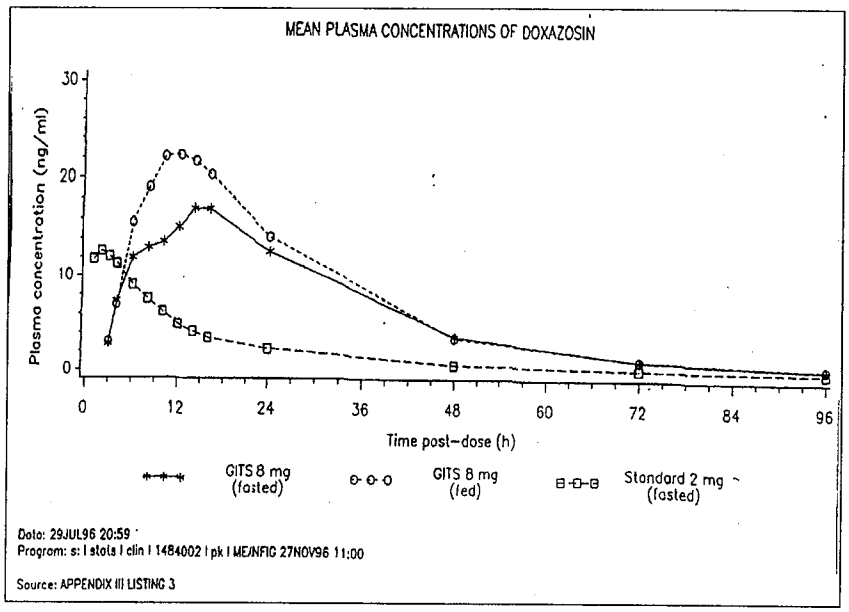
Cardura XL® NDA was submitted on April 20, 2001 to [redacted] Divisions: HFD-580 for BPH indication as NDA # 21-269 [redacted] The clinical pharmacology and pharmacokinetic studies were reviewed by the office of clinical pharmacology and biopharmaceutics cardio-renal review team. Dr. Lydia Kieffer is the primary reviewer and Dr. Patrick Marroum is the Team Leader.

Cardura XL® contains the active ingredient doxazosin mesylate, an alpha-antagonist agent previously approved as immediate release formulation known as Cardura®. The currently approved indications for Cardura are for the treatment of hypertension and BPH. Cardura XL is a modified released tablet formulation of 4 and 8 mg strengths utilizes a patented controlled rate delivery technology known as GITS (Gastrointestinal Therapeutic System). [redacted] The drug is administered initially as 1 mg dose of Cardura® (IR formulation) in patients with hypertension and/or BPH. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with Cardura®. The recommended dose of Cardura XL for BPH is 4 to 8 mg once daily. [redacted] The maximum dose of Cardura XL is 8 mg daily. The focus of this review and comments is on BPH.

Summary:

Doxazosin undergoes extensive metabolism in the liver through O-demethylation. The drug is highly bound to plasma protein (98%). The elimination half-life of doxazosin is approximately 15 hours. Food appears to increase the C_{max} and the $AUC_{0-\infty}$ by approximately 30% and 20%, respectively (**Figure 1**). The T_{max} of dozazosin occurred slightly earlier when Cardura XL was given with food (11 hours) than when given on fasting stomach (14 hours).

Figure 1 : Effect of Food of Cardura XL and Cardura Standard Tablets (study # 96-008)



It should be noted that the maximum plasma concentration of doxazosin achieved following 4 mg Cardura XL® appeared to be approximately equivalent to 2 mg IR Cardura. At steady-state, the relative bioavailability of doxazosin from Cardura XL® compared with Cardura was approximately 55% at the 4 mg daily doses and 60% at the 8 mg daily doses (**Figure 2**). This suggests that the two formulations are not bioequivalent to one another. However, the two strengths of Cardura XL® (4 and 8 mg) are bioequivalent to each other based on a single dose study of 2 X 4 mg and 1 X 8 mg GITS tablets (**Figure 3**).

Figure 2: Relative Bioavaliability of GITS and Cardura For 4 mg and 8 mg Tablets (study # 96-008)

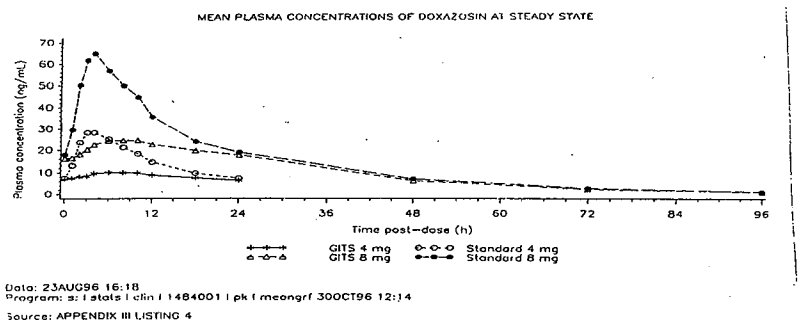


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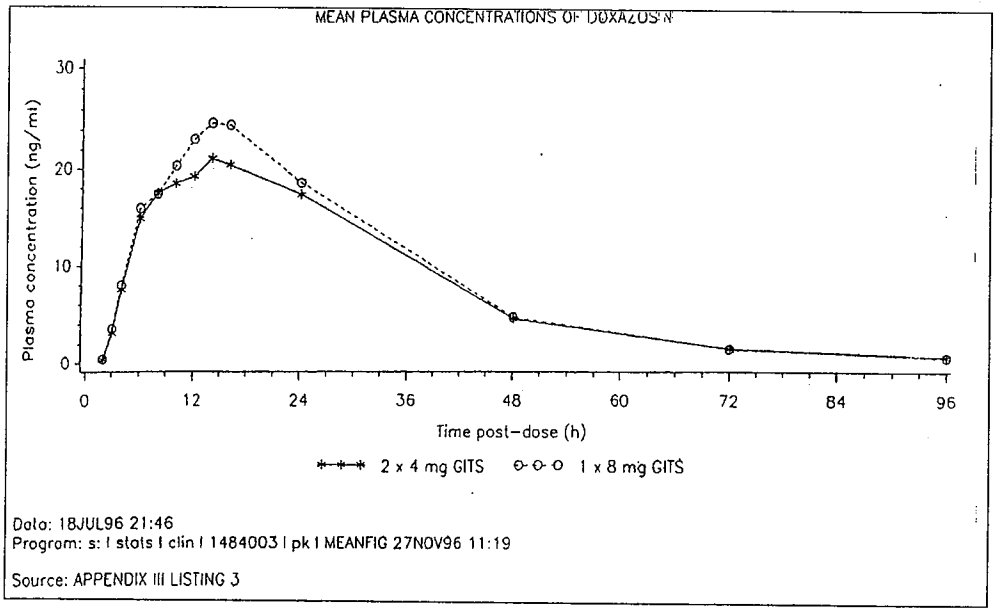
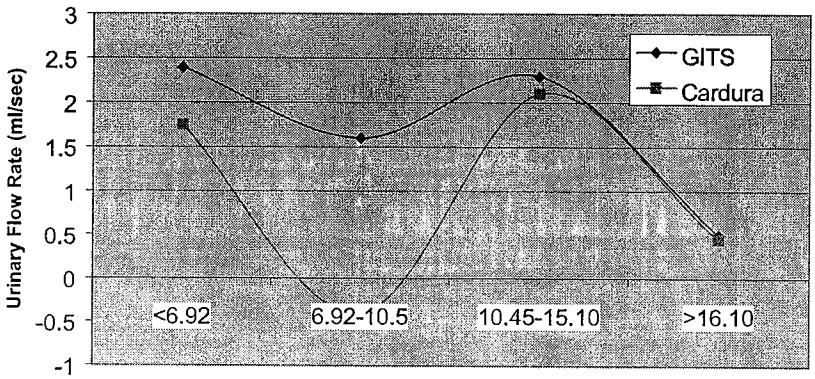
Figure 3: Relative Bioavaliability of 2 X 4 and 1 X 8 mg GITS Tablets (study # 96-008)



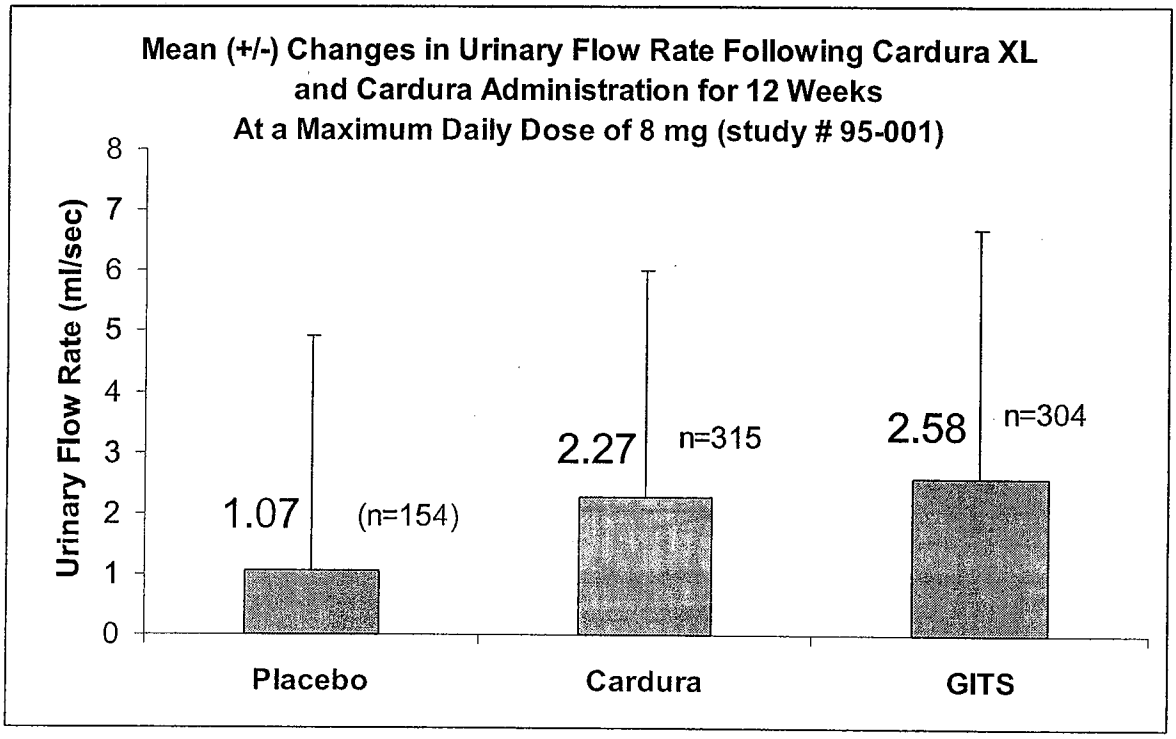
No clinically significant gender differences in the PK of doxazosin were observed at steady-state. The C_{max} and the AUC were approximately 20% higher in females compared to males. In contrast, after a single dose administration the C_{max} and the AUC_o in females were approximately 45% higher than males.

There was no correlation between dose, plasma levels of doxazosin for GITS formulation or Cardura standard tablet and response. **Figure 4** shows the relationship between the plasma concentration of doxazosin and mean maximum urinary flow rate. This data was based on a pilot study in BPH patients (n= 2-14) following 1, 2, 4, and 8 mg daily doses of standard Cardura and 4 or 8 mg doses of GITS for 13 weeks.

Figure 4. Relationship Between Doxazosin Plasma Concentration and Changes From Baseline Mean Maximum Urinary Flow Rate (Study # 95-001)



In the pivotal Phase III clinical trial in BPH patients the mean changes from baseline for maximum urinary flow rates was 2.27 and 2.58 following Cardura and Cardura XL, respectively (**Figure 4**, study # 96-001). Both formulations were titrated up to a maximum dose of 8 mg daily for approximately 12 weeks. Based on these data, the mean delta difference between Cardura and Cardura XL is 0.31 ml/sec and between placebo and Cardura XL is 1.51 ml/sec (**Figure 4**). In the extension study (#95-001B) in 289 BPH patients, the mean (± SD) change from baseline for maximum urinary flow rate was 2.70 ± 4.27 ml/sec following GITS treatment for 15 weeks at a maximum dose of 8 mg daily. These data were analyzed based on the draft review and the discussion with the medical officer, Dr. Gerald Willett. For more details, please see the medical officer review.



It is noteworthy that at the time of this memo, no decision has been made concerning the *in vitro* and *in vivo* correlation (IVIVC) and performance. Some additional *in vitro* dissolution data have been requested from the sponsor or awaiting further analysis.

Conclusions:

From the clinical pharmacology and biopharmaceutics point of view, Dr. Lydia Kieffer has provided a comprehensive review of this NDA. All the comments and conclusions made by Dr. Kieffer are valid and acceptable. The labeling comments provided by Dr. Kieffer are also acceptable.

Recommendation:

From the clinical pharmacology and biopharmaceutics perspective this NDA is acceptable. Dr. Kieffer's review should be incorporated as the official clinical pharmacology and biopharmaceutics review of this NDA. Therefore, no further review is necessary at this time.

Reviewer

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Ameeta Parekh, Ph.D. ----------

cc: HFD-580, HFD-870 (Al-Habet, Parekh, and Malinowski), Drug file (Biopharm File, Central Document Room).

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/s/

Sayed Al-Habet
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BIOPHARMACEUTICS

Ameeta Parekh
2/25/02 10:13:45 AM
BIOPHARMACEUTICS
I concur

6.1.1. Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	[redacted] 21-269	Brand Name	Cardura XL
OCPB Division (I, II, III)	DPE 1	Generic Name	Doxazosin GITS
Medical Division	HFD-110	Drug Class	Alpha-antagonist
OCPB Reviewer	Lydia Velazquez Kieffer	Indication(s)	[redacted] BPH
OCPB Team Leader	Patrick Marroum	Dosage Form	Oral Tablet
		Dosing Regimen	Once Daily
Date of Submission	April 20, 2001 January 4, 2002 February 11,, 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	February 11, 2002	Sponsor	Pfizer Pharmaceuticals
PDUFA Due Date	February 23, 2002	Priority Classification	4S
6.1.1.1. Divisi on Due Date	February 11, 2002		

CLIN. PHARM. AND BIOPHARM. INFORMATION

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
6.2 Healthy Volunteers-				
single dose:	X	2		
multiple dose:	X	2		
6.2.1. Patients-				
single dose:				
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	Same study as geriatric
pediatrics:				
geriatrics:	X	1	1	Same study as gender
renal impairment:				
hepatic impairment:	X	1	0	**Reviewed in Cardura NDA**
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:	x	1	1	Single-dose
replicate design; single / multi dose:	X	1	1	
Food-drug interaction studies:				
Dissolution:	**X**	**1**	**1**	
(IVIVC):	**X**	**1**	**1**	
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**	**7**	Hepatic Study previously reviewed in Cardura NDA

Filability and QBR comments

6.2.1.1.	**"X" if yes**	**COMMENTS**
6.2.1.2. Application filable ?	**X**	
6.2.1.3. Comments sent to firm ?	**X**	
6.2.1.4.		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Lydia Velazquez Kieffer 2/01/02**	
Secondary reviewer Signature and Date	**Patrick Marroum**	

CC: [redacted] 21-269, HFD-860, HFD-110(AllisD), HFD-860(Mehta, Marroum, Dorantes, VelazquezKieffer), CDR Central Document Room

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

[redacted]: 21-269 SUBMISSION DATES April 20, 2001
January 4, 2002
February 11, 2002

TYPE: 4-S

BRAND NAME: Cardura XL®
GENERIC NAME: Doxazosin Mesylate
DOSAGE STRENGTH: 4, 8 mg controlled release oral tablet
SPONSOR: Pfizer Pharmaceuticals, Inc.

PRIMARY REVIEWER: Lydia Velazquez Kieffer, Pharm.D.
TEAM LEADER: Patrick J. Marroum, Ph.D. and Angelica Dorantes, Ph.D.

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RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA [redacted] submitted on April 20, 2001 for Cardura XL and finds the clinical pharmacology and biopharmaceutics section acceptable provided the following dissolution, clinical, and labeling Reviewer Comments are addressed by the sponsor.

REVIEWER COMMENTS:

DISSOLUTION

1. The dissolution method proposed by the sponsor (i.e., USP Apparatus 2, 75 rpm, 900 ml of SGF without enzymes at 37 ° C, sampling times; 4, 8, and 16 hours), is adequate and acceptable.

2. The provided IVIVC information (submission dated January 4th, 2002) is incomplete and is not acceptable. The following IVIVC deficiencies were identified:
   - The percent error [redacted] therefore, verification of a correlation between in vitro data and in vivo results was not established.
   - [redacted]
   - No raw data was submitted with the report, thus, it was not possible to verify the conclusions and calculations made by the sponsor.

3. It should be noted that the proposed dissolution specifications (i.e., 4 hrs: Q [redacted] of Label Claim, 8 hrs: Q= [redacted] of Label claim, and 16 hrs: Q [redacted] of Label Claim), were based on IVIVC, therefore, are not acceptable. In the absence of an acceptable IVIVC, the maximum width allowed, as per guidance is ± 10%. Therefore, the following dissolution release specifications are recommended:

   4 hours: [redacted] of Label Claim
   8 hours: [redacted] of Label Claim
   16 hours: Q ≥ [redacted] of Label Claim

4. The sponsor should be informed that OCPB would revise the above recommended dissolution specifications (as appropriate) as soon as complete and acceptable IVIVC data are provided.

CLINICAL

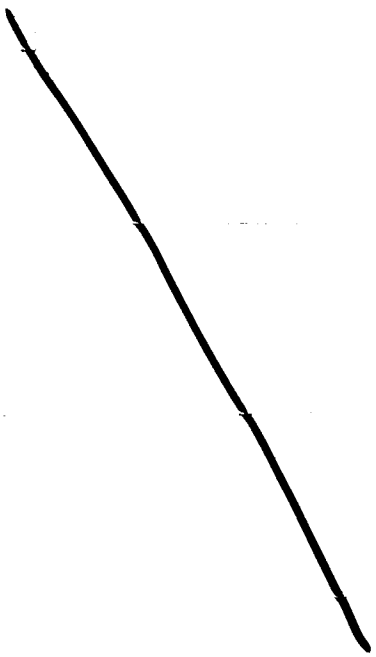
1. In order to better assess the individual clinical predictability from day to day for the control release 4 and 8 mg GITS tablets with respect to the immediate release product, the intrasubject pharmacokinetic variability is needed. In this submission the intrasubject variability values were not reported in any of the PK studies. Therefore, it is recommended that the sponsor reanalyze the pharmacokinetic data from studies DAZ-NY-96-007 (4 and 8 mg GITS) and DAZ-NY-96-009 (4 mg GITS) and provide the intraindividual variability information.

LABELING

1. [redacted] NDA 21-269 submitted to the Division of Reproductive and Urologic Drug Products [redacted] Therefore, reviewer labeling comments for the [redacted] BPH labeling provided in the original NDA, are not longer appropriate.

2. On February 11, 2002, the sponsor submitted an amendment to NDA 21-269 [redacted] for CARDURA XL providing a revised labeling for the benign prostatic hyperplasia (BPH) indication. A copy of the revised BPH-labeling is included in Appendix I. It should be noted that OCPB/DCRDP is reviewing the revised BPH-labeling, due to the fact that OCPB/DCRDP reviewed the original submission for CARDURA®XL.

3. It is recommended that the "Pharmacokinetics and Precautions" section of the proposed labeling for CARDURA®XL dated February 11, 2002, be modified as follows:



1 Page(s) Withheld

____ Trade Secret / Confidential

✓ Draft Labeling

____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-7

Lydia Velazquez Kieffer, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick J. Marroum, Ph.D. _____

OCPB Briefing held on February 8, 2002. Attendees were: M. Mehta, S. Huang, P. Lee, A. Dorantes, H. Malinowsky, A. Pareck, V. Jaragula, M. Hirsh, A. Karkowsky, K. Jongedyk, etc.

CC list: HFD-110: [redacted] 21-269; HFD-860: (VelazquezKiefferL, MarroumP, MehtaM); HFD-870 (MalinowskiH; ParekhA, Al-HabetS); CDER Central Document Room

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Executive Summary

Pfizer Pharmaceuticals is seeking approval of Cardura XL® for the treatment of [redacted] benign prostatic hyperplasia (BPH) in the Reproductive and Urologic Drug Prooducts Division. This review evaluates the NDA [redacted] from the Clinical Pharmacology and Biopharmaceutics perspective. A short file memo is attached in Appendix V of this review from the Clinical Pharmacology and Biopharmaceutics Reviewer in the Reproductive Division. Cardura XL® contains the active ingredient doxazosin mesylate, an alpha-antagonist agent previously approved under Pfizer's registration name Cardura®, the immediate release formulation [redacted]. The submitted NDA application is for the modified released tablet formulation of doxazosin mesylate which utilizes a controlled rate of delivery of doxazosin into the gastrointestinal lumen via the patented GITS (Gastrointestinal Therapeutic System) process. Cardura XL® is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin.

Section 6 of NDA [redacted] includes 7 studies. Four studies were conducted in healthy volunteers, one study was in patients with BPH, one in hepatically impaired subjects defined to be healthy, and one study was dedicated to dissolution development. The four studies conducted in healthy volunteers included 1 single dose and food effect study, 1 multiple dose study, 1 study of bioavailability, 1 study addressing the elderly and the young population, and subsequently an IVIVC study (submitted January 4th, 2002). The study performed in hepatically impaired patients was not reviewed since it was previously reviewed and deemed acceptable under original NDA 20-371 (Cardura® for hypertension) and NDA 19-668 (Cardura® for BPH).

Doxazosin mesylate is a quinazoline compound that is a selective inhibitor of the alpha-adrenergic receptor. Doxazosin undergoes extensive metabolism in the liver through O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety. There's evidence to indicate that doxazosin undergoes enterohepatic recycling. About 98% of the circulating drug is bound to plasma proteins. Elimination of doxazosin is biphasic. The initial dose of Cardura® (immediate release tablets) in patients with hypertension and/or BPH is 1 mg given once daily in the A.M. or P.M. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with Cardura®. The indicated dose for BPH is 1 to 8 mg once daily. For hypertension, the indicated dose is 1 to 16 mg once daily.

Cardura XL® (extended release tablet) is similar in appearance to a conventional tablet. However, it consists of an osmotically active core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. These layers are formed [redacted] to form a single tablet shaped core. The core is enclosed by a cellulose membrane that is permeable to water, but impermeable to ions. Some of the other marketed drugs with similar delivery systems

include Procardia XL® (nifedipine), Glucotrol XL® (glipizide), and Ditropan XL® (oxybutynin chloride) extended release tablets.

A single dose study examined the effects of food on the doxazosin 8 mg GITS tablet. Both C_{max} and $AUC_{0-\infty}$ were significantly greater in the fed state relative to the fasted state for the 8 mg GITS tablets, increasing by 32% and 18%, respectively. T_{max} occurred earlier in the fed (11 hours) compared to the fasted state (14 hours). The elimination kinetics of doxazosin were similar for both the fed and fasted states (16.1 and 15.0 hours).

Cardura XL® is to be given initially at the 4 mg dose with a maximum dose of 8 mg. Through extrapolation of these data, the sponsor has concluded that in the clinical situation, the initial 4 mg dose of Cardura XL® given will cause a maximum plasma concentration similar to 2 mg of the immediate release (IR) formulation. However, the starting dose for Cardura® is 1 mg; which is known to be well tolerated in the patient population and is to be used initially per current labeling prior to dose titration to obtain the maintenance dose of an individual.

After seven consecutive days of daily doses of either 4 mg GITS tablet, 8 mg GITS tablet, 4 mg IR, or 8 mg IR, the relative bioavailability of doxazosin from Cardura XL® compared with the IR product was 54% at the 4 mg dose and 59% at the 8 mg dose. Therefore, it was concluded that at steady state the two formulations were not bioequivalent to one another. This was expected due to the modified release properties of Cardura XL®. The data also indicated that the 4 mg and 8 mg doses for both formulations were approaching dose-proportionality indicating that any extrapolations between the two dose levels are valid. In addition, the fluctuating index of Cardura XL® was reduced by 40% compared to the IR formulation indicating that the plasma concentration of doxazosin may be more uniform from the Cardura XL® formulation over the dosing interval, with a lower peak. However, intrasubject variability was not assessed. Leaving the issue of the formulation's variability from day to day in an individual still unanswered.

C_{max} is reduced to about 40% after the Cardura XL® compared to the IR formulation while C_{min} is maintained regardless of formulation for a given dose.

A bioequivalence single dose study of the two strengths of Cardura XL® revealed that two 4mg GITS tablets were bioequivalent to an 8 mg GITS based on the 90% confidence intervals for AUC and C_{max}.

A single dose and multiple dose (7 days) pharmacokinetic analysis was performed between young and elderly females and males in order to observe any gender or age related effects with the administration of doxazosin. Upon a single 4 mg dose of the GITS formulation, a gender effect was observed to be more pronounced in the young group with females exhibiting C_{max} and AUC_{0-t} values greater than the males (45 and 46%, respectively). The elderly group had similar parameters between genders. Young females had a higher C_{max} and AUC_{0-t} when compared to the rest of the population as a whole

with an AUC 46% higher on day 1 and 20% higher on day 7 than young males. The highest number of adverse events were reported in young females

The adverse events declined as time progressed and steady state was achieved. No age related differences were observed to warrant dose adjustments between the elderly and young population.

An efficacy study in BPH patients revealed that there is no significant correlation between dose and plasma level for either doxazosin GITS or doxazosin IR. However, this may be due to the small sample sizes for some of the doses and the high intersubject variability oberved. In addition, PK/PD analysis was not part of the objectives of this clinical trial. A PK objective was not clearly defined; which may have influenced the outcome or may not have allowed for the optimization of prospective data collection and analysis.

The sponsor proposed the following dissolution method and specifications for doxazosin GITS tablets:

Apparatus:	USP Apparatus 2 (rotating paddle)	
Speed:	75 ± 3 rpm	
Medium:	SGF (900 mL) without enzymes	
Temperature:	37 ± 0.5° C	
Release Specifications:	4 hours:	Q [redacted] of Label Claim
	8 hours:	[redacted] of Label Claim
	16 hours:	Q [redacted] of Label Claim

The proposed dissolution method is acceptable. However, the proposed release specifications are not supported by appropriate IVIVC data and are not acceptable. The recommended specifications are as follows:

4 hours:	[redacted]	of Label Claim
8 hours:	[redacted]	of Label Claim
16 hours:	Q [redacted]	of Label Claim

The assay used to quantify doxazosin (HPLC/UV) was sensitive, specific, precise, and accurate. The limit of quantification of doxazosin in plasma is 0.200 ng/mL.

QUESTION BASED REVIEW

I. INTRODUCTION

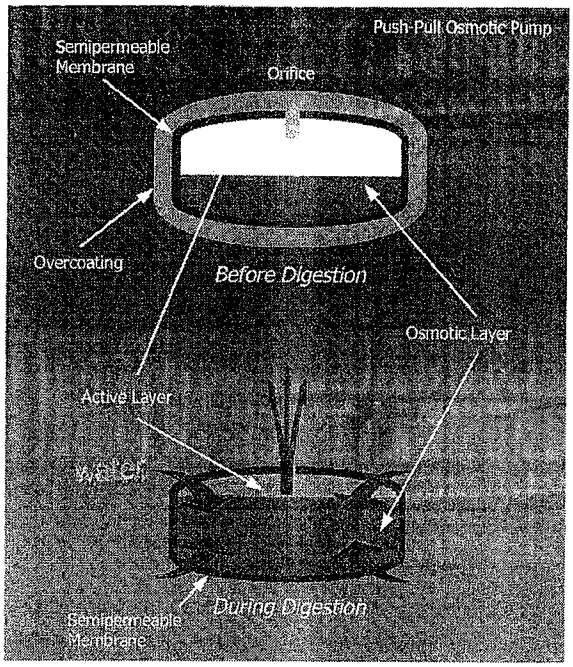
A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY, FORMULATION AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG AND DRUG PRODUCT?

FORMULATION AND MANUFACTURING

Cardura XL® contains the same active ingredient as Cardura®, doxazosin mesylate. It is to be marketed as 4 mg and 8 mg GITS tablets for oral administration. The 4 mg and 8 mg doxazosin GITS tablets have a common active layer, osmotic layer, and manufacturing process. Their compositions are as follows:

Component	Function	4 mg (mg/tablet)	8 mg (mg/tablet)
Doxazosin Mesylate[a]		5.093	10.185
Polyethylene Oxide			
Ferric Oxide Red			
Magnesium Stearate			
Polyethylene Oxide			
Sodium Chloride			
Ferric Oxide, Red			
Magnesium Stearate			
Cellulose Acetate			

An illustration of the release system is shown below:



B. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATIONS?

Cardura XL® has the same mechanism of action as Cardura® [redacted] Cardura XL® and Cardura® are selective inhibitors of the alpha1 subtype of alpha adrenergic receptors. BPH is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retension and renal damage. A static and dynamic component contribute to the symptoms and reduce urinary flow rate associated with BPH. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the alpha1 adrenoceptor, which is present in high density in the prostate stoma, prostatic capsule and bladder neck. Blockade of the alpha1 receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In the human prostate, Cardura® antagonizes phenylephrine (alpha1 agonist)-induced contractions, *in vitro*, and binds with high affinity to the alpha1A adrenoceptor. The receptor subtype is thought to be the predominant functional type in the prostate. Since alpha1A adrenoceptors are of low density in the urinary bladder (apart from the bladder neck), Cardura® should maintain bladder contractility. Blockade of alpha1 (postjunctional) subtype adrenergic receptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance.

C. WHAT IS THE PROPOSED DOSAGE AND ADMINISTRATION?

The initial dose for Cardura XL® is 4 mg [redacted] BPH) given once daily. Depending on the patient's response, the dose may be increased to 8 mg; which is the maximum recommended dose [redacted]

II. CLINICAL PHARMACOLOGY

A. WERE THE CORRECT MOIETIES IDENTIFIED AND PROPERLY MEASURED TO ASSESS CLINICAL PHARMACOLOGY?

Doxazosin mesylate was quantified in plasma. No metabolites were quantified in this submission.

ASSAY VALIDATION

One assay was used to quantify doxazosin, HPLC/UV. The method was sensitive, specific, precise, and accurate. The limit of quantification of doxazosin in plasma using HPLC/UV is 0.200 ng/mL

B. WHAT ARE THE EXPOSURE-RESPONSE RELATIONSHIPS FOR EFFICACY AND SAFETY?

The clinical endpoint measured was the change in maximum urinary flow rate in patients with BPH. No hypertension studies were performed. PK/PD correlations were performed with no correlation found. However, the analysis was not part of the study objectives and may have been performed in retrospect preventing the benefit of prospectively planning the clinical trial and optimizing the collection of such data for PK/PD assessment.

C. WHAT DOSAGE REGIMEN ADJUSTMENTS IF ANY, ARE RECOMMENDED FOR EACH OF THESE GROUPS?

- *GENDER*

Data from study DAZ-NY-96-009 showed that the young female population would benefit from a dosage regimen adjustment due to the disproportionate higher number of adverse events and the differences in pharmacokinetic parameters observed. However, the 4 mg GITS is the lowest dose available in this formulation. So dose titration would not be possible in this population.

1. C_{max}, C_{min}, and $AUC_{0\text{-}tau}$ in the young females had the highest intersubject CV% on day one and day seven.

2. Young females had an AUC 46% higher on day 1 and 20% higher on day 7 than young males.

The differences in AUC was statistically significant on day 1 ($p < 0.05$); but not by day 7. Additionally, the difference in AUC of 46% observed on day 1 was not within the intersubject variation observed within this group; which was 40.1% for young females.

ARITHMETIC MEAN, COEFFICIENTS OF VARIATION AND ARITHMETIC MEAN RATIOS FOR Cmax, AUC(0-tau) AND Cmin

DOXAZOSIN PROTOCOL DAZ-MY-96-009 PAGE 1 OF 1

Parameter	Young Male	Young Female	Elderly Male	Elderly Female	Arithmetic mean ratio: Gender Male E : Y	Gender Female E : Y	Age Young F : M	Age Elderly F : M
Day 1 Cmax (ng/ml)	6.91(34.7%)	10.02(39.1%)	9.33(31.4%)	10.47(35.8%)	1.35	1.05	1.45	1.12
Day 7 Cmax (ng/ml)	15.86(32.7%)	19.26(59.8%)	20.42(21.5%)	20.72(18.8%)	1.29	1.08	1.21	1.01
Day 1 AUC(0-tau) (ng.h/ml)	106.7(25.0%)	155.8(40.1%)	151.2(32.0%)	163.3(31.7%)	1.42	1.05	1.46	1.08
Day 7 AUC(0-tau) (ng.h/ml)	307.5(33.1%)	368.1(62.4%)	408.7(26.6%)	428.5(21.3%)	1.33	1.16	1.20	1.05
Day 7 Cmin (ng/ml)	11.50(40.5%)	15.42(69.6%)	15.63(39.3%)	17.64(20.5%)	1.36	1.14	1.34	1.13

E = Elderly, Y = Young, F = Female, M = Male

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Thirty-four adverse events were reported in young females during the study with 31 being attributed to study drug. Fifteen of the 31 study drug related adverse events that were reported (48%) occurred by day 1. By day 2, a total of 22 adverse events had occurred, accounting for 71% of all study drug related adverse events occurring in the young females. By day four, 84% of all adverse events reported by this population had already occurred indicating that a possible dose titration for young females may be required. The standard doxazosin labeling recommends a starting dose of 1 mg for all patients and dose titration to the desired dose for that individual. However, the 4 mg GITS is the lowest dose available in this formulation. So dose titration would not be possible in this population. The adverse events declined as time progressed possibly indicating that young females adjusted to the initial dose given of 4 mg GITS (equivalent to a 2 mg standard formulation dose according to the bioavailability study reports submitted).

3. Additionally, young females appear to have experienced a higher spike in concentrations initially on day 1 than any other group possibly accounting for the adverse events seen on day 1 (48% of all adverse events were reported on day 1).

- *ELDERLY*

The sponsor did conduct a study evaluating the effects of age on the pharmacokinetics of doxazosin. However, the small differences observed in the pharmacokinetics and the safety profile of this population does not warrant a change in dose.

III. BIOPHARMACEUTICS

A. WAS AN ADEQUATE LINK ESTABLISHED BETWEEN THE CLINICAL AND TO-BE-MARKETED FORMULATIONS OF DOXAZOSIN?

All studies submitted were performed with the to be marketed formulation.

B. DOES THE 4 MG AND 8 MG GITS DOSAGE STRENGTHS MEET THE CONTROLLED RELEASE CLAIMS MADE FOR IT?

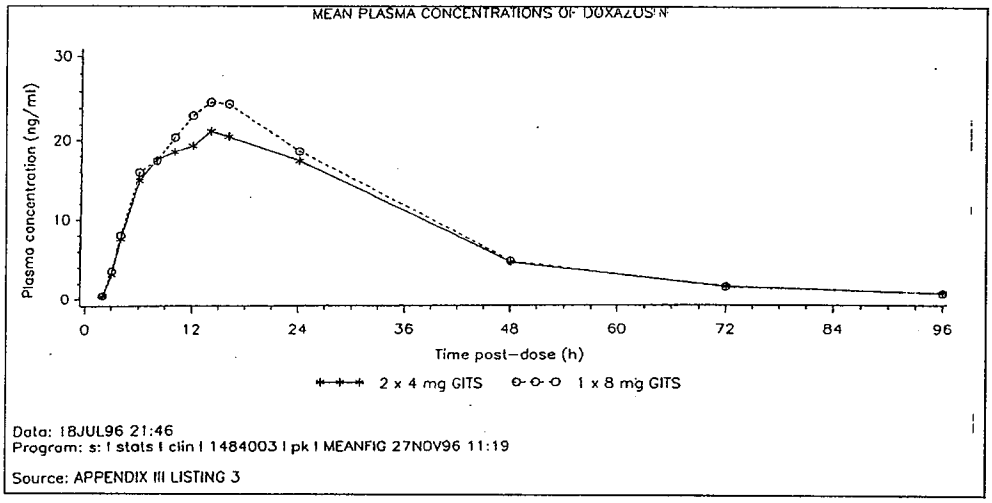
Yes, the formulation is a controlled release product; but it does not meet the true definition of a controlled release product as per "The Orange Book" and does not offer an extension of the current dosing interval for the immediate release formulation. A relative single-dose bioavailability study (DAZ-NY-96-008) was conducted between the 2 mg doxazosin standard formulation and the 8 mg GITS formulation under fasted conditions. The C_{max} that was achieved for the 8 mg GITS tablet was 17.3 ng/mL and 13.4 ng/mL for the standard formulation (C_{max} was smaller for the standard tablet compared to the GITS - approximately 29%). When the C_{max} was dose normalized to 2 mg, the GITS 8 mg formulation had a C_{max} that was 68% smaller than the 2 mg standard tablet.

The $AUC_{0-\infty}$ for the 8 mg GITS formulation was greater compared to the standard 2 mg tablet (64%). However when dose normalized to 2 mg, the 8 mg GITS tablet had an $AUC_{0-\infty}$ that was 30% smaller than the 2 mg standard tablet. In addition, T_{max} occurred significantly earlier with the standard tablet (2 hours) compared to GITS tablet (14 hours). Please refer to tables and graphs below in item C.

Bioequivalence was established between 2 GITS 4 mg tablets and one 8 mg GITS tablet as demonstrated below (no SD was given):

Parameter	Treatment		P value
	2 x 4 mg Doxazosin GITS	1 x 8 mg Doxazosin GITS	
C_{max} (ng/ml)	22.5	25.4	<0.05
T_{max} (h)	15	14	0.79
AUC_{0-t} (ng.h/ml)	719	765	0.25
$AUC_{0-\infty}$ (ng.h/ml)	735	780	0.27
Thalf (h)	16.6	15.8	0.11

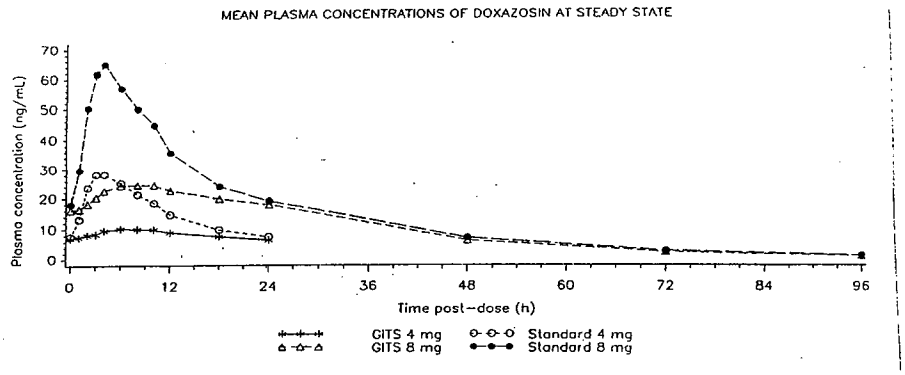
Parameter	Geometric Mean Ratio (%)	90% Confidence Interval of Geometric Mean Ratio (%)
C_{max} (ng/ml)	89	81, 97
AUC_{0-t} (ng.h/ml)	94	87, 103
$AUC_{0-\infty}$ (ng.h/ml)	95	87, 103



A multiple dose, two-way crossover pharmacokinetic (DAZ-NY-96-007) study demonstrated that the fluctuation index values were reduced for the GITS in comparison to the standard formulation (41% and 38%, respectively), consistent with controlled release properties of the system. C_{max} values for both the 4 and 8 mg GITS tablets when compared to the 4 and 8 mg standard tablet, were smaller as well (10.1 ng/ml versus 28.2 ng/ml for the GITS versus the standard, respectively and 25.8 ng/ml versus 64.4 ng/ml for the GITS versus the standard, respectively). However, the benefit of a controlled release formulation in this indication remains unclear since doxazosin standard and GITS formulations are both administered once daily. Below are the PK parameters for C_{max}, T_{max}, AUC, C_{min}, T_{half}, F_{rel}, and $FI_{(ratio)}$:

Parameter	Doxazosin GITS (4 mg)	Doxazosin Standard (4 mg)	P Value	Doxazosin GITS (8 mg)	Doxazosin Standard (8 mg)	P Value
C_{max} (ng/ml)	10.1	28.2	<0.05	25.8	64.4	<0.05
T_{max} (h)	8	4	<0.05	9	4	<0.05
$AUC_{(0-last)}$ (ng.h/ml)	183	356	<0.05	472	833	<0.05
C_{min} (ng/ml)	5.6	6.5	0.063	15.6	17.0	0.23
T_{half} (h)	NA	NA	NA	18.6	20.5	0.13
F_{rel} (%)	54.1	100	NA	58.6	100	NA
FI (ratio)	0.597	1.47	<0.05	0.517	1.37	<0.05

NA = Not applicable, terminal elimination phase unable to be defined
P Values are based on ANOVA



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C. DOES THE BIOAVAILABILTY PROFILE OF THE DRUG PRODUCT RULE OUT THE OCCURRENCE OF DOSE DUMPING?

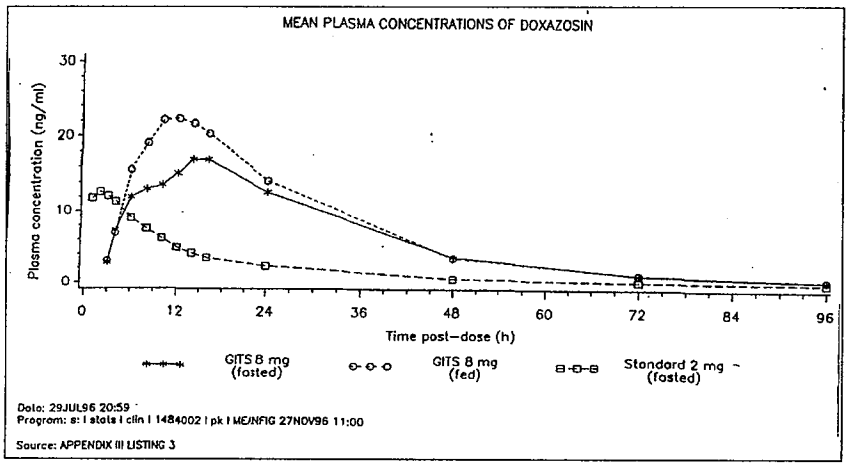
Yes. A food effect study (DAZ-NY-96-008) was conducted in which the comparative bioavailability of a doxazosin GITS 8 mg tablet in normal volunteers under fasted and fed conditions was determined and compared to the bioavailability of a standard doxazosin 2 mg tablet under fasted conditions.

Both C_{max} and AUC ($_{0-\infty}$ and $_{0-t}$) were significantly greater in the fed state relative to the fasted state for the 8 mg GITS tablets, increasing by 32% and 18%, respectively. T_{max} occurred significantly earlier in the fed (11 hours) compared to the fasted state (14 hours). The elimination kinetics of doxazosin were similar for both the fed and fasted states.

Parameter	Doxazosin GITS 8 mg (fasted)	Doxazosin GITS 8 mg (fed)	P-value	Doxazosin Standard 2 mg (fasted)	Doxazosin GITS 8 mg (fasted)#	P-value
C_{max} (ng/ml)	17.3	22.9	<0.05	13.4	4.3	<0.05
T_{max} (h)	14	11	<0.05	2	14	<0.05
AUC_{0-t} (ng.h/ml)	526	619	< 0.05	179	131	<0.05
$AUC_{0-\infty}$ (ng.h/ml)	536	630	<0.05	190	134	<0.05
Thalf (h)	15.0	16.1	0.097	13.9	15.0	0.053

#Data normalised to 2 mg

However, the differences observed did not result in the observance of dose dumping as demonstrated below:

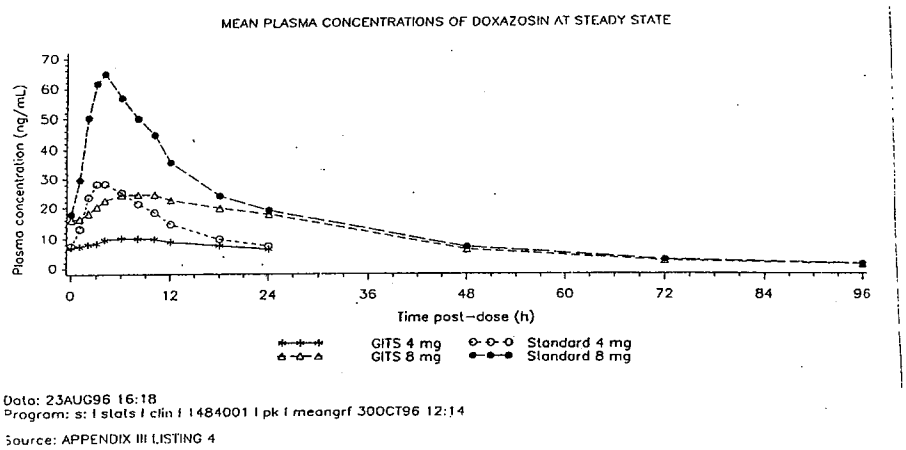


D. IS THE STEADY-STATE PERFORMANCE OF CARDURA XL® EQUIVALENT TO THE CURRENTLY MARKETED CARDURA® NONCONTROLLED RELEASE PRODUCT?

No. The GITS formulation's pharmacokinetic parameters are consistent with the properties of a controlled release formulation comparison to the standard currently marketed product.

Parameter	Doxazosin GITS (4 mg)	Doxazosin Standard (4 mg)	P Value	Doxazosin GITS (8 mg)	Doxazosin Standard (8 mg)	P Value
C_{max} (ng/ml)	10.1	28.2	<0.05	25.8	64.4	<0.05
T_{max} (h)	8	4	<0.05	9	4	<0.05
$AUC_{(0-last)}$ (ng.h/ml)	183	356	<0.05	472	833	<0.05
C_{min} (ng/ml)	5.6	6.5	0.063	15.6	17.0	0.23
T_{half} (h)	NA	NA	NA	18.6	20.5	0.13
F_{rel} (%)	54.1	100	NA	58.6	100	NA
FI (ratio)	0.597	1.47	<0.05	0.517	1.37	<0.05

NA = Not applicable, terminal elimination phase unable to be defined
P Values are based on ANOVA



E. DOES THE DRUG PRODUCT'S FORMULATION PROVIDE CONSISTENT PHARMACOKINETIC PERFORMANCE BETWEEN INDIVIDUAL DOSAGE UNITS?

Not able to assess if product provides consistent pharmacokinetic performance because intrasubject variability was not performed even though it is possible to assess in two studies (DAZ-NY-96-007and DAZ-NY-96-009). Much variability was observed throughout all the clinical trials. The intersubject CV% ranges were between 33.6 and 67.7 throughout the studies for the 8 mg GITS formulation. The 4 mg GITS formulation's intersubject CV% ranges between 47.2 and 74%. The intersubject CV% seems to be relatively wide and not consistent with the characteristics of a product that provides consistent pharmacokinetic performance between individual dosage units.

F. ARE THE SPONSOR PROPOSED DISSOLUTION MEDIUM AND SPECIFICATIONS ACCEPTABLE?

The following proposed dissolution method for Doxazosin 4 and 8 mg GITS Tablets is appropriate and acceptable.

Apparatus:	**USP Apparatus 2 (rotating paddle)**
Speed:	**75 ± 3 rpm**
Medium:	**SGF (900 mL) without enzymes**
Temperature:	**37 ± 0.5° C**

However, the following proposed release specifications for Doxazosin 4 and 8 mg GITS tablets are not acceptable.

4 hours:	Q [redacted] of Label Claim
8 hours:	[redacted] of Label Claim
16 hours:	Q [redacted] of Label Claim

OCPB considers that the proposed release specifications are not acceptable due to the following concerns:

a. The sponsor did not conduct a true IVIVC study and analyses for the development of adequate release specifications. Therefore, IVIVC cannot be used to support their proposed specifications.
b. The specifications are not tight enough to ensure product quality in the manufacturing of large amounts of the new formulation.

Therefore, in the absence of an acceptable IVIVC, the maximum width allowed, as per the guidance is the ± 10%. The following dissolution specifications are recommended for the 4 mg and 8 mg doxazosin GITS tablets.

Agency's recommended release specifications for Doxazosin 4 and 8 mg GITS tablets:

4 hours:	**[redacted] of Label Claim**
8 hours:	**[redacted] of Label Claim**
16 hours:	**Q [redacted] of Label Claim**

G. IS THE PROPOSED LABELING FOR CARDURA XL ACCEPTABLE?

The proposed labeling for Cardure XL is acceptable provided the Reviewer Labeling Comments described in the Recommendation (page 3) are addressed by the sponsor.

A copy of the proposed package insert for Cardura and Cardure XL is included in Attachment I.

13 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 8

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

/s/

Lydia Kieffer
2/22/02 02:24:32 PM
PHARMACOLOGIST

CPB Review Exec Summ and QBR

Angelica Dorantes
2/22/02 02:30:34 PM
BIOPHARMACEUTICS

APPENDIX II:
REVIEW OF INDIVIDUAL STUDIES

STUDY DAZ-N/S/DK-95-001 – A 15 WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY AND SAFETY OF DOXAZOSIN VERSUS DOXAZOSIN GITS IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

STUDY INVESTIGATOR AND SITE:	Multi-site study involving 97 sites in 3 countries (Denmark, Norway, and Sweden) and 98 Principal Investigators (see volume 32 for details)

REPORT # DAZ-N/S/DK-95-001
VOLUMES # 32 - 35

OBJECTIVES:
To compare the efficacy and safety of doxazosin controlled release (GITS) versus doxazosin IR-immediate release (standard) versus placebo in subjects with benign prostatic hyperplasia (BPH).

FORMULATIONS:

Doxazosin GITS	4 and 8 mg tablets (Lot nos. P-3190-01-001 and P-3191-01-001, respectively)
Placebo Doxazosin GITS	4 and 8 mg tablets (Lot nos. P-3189-01-001 and P-3192-01-001, respectively)
Doxazosin standard	1, 2, 4, or 8 mg tablets (Lot nos. P-2601-02-002, P-2602-02-003, P-2603-09-001, and P-2607-11-001, respectively)
Placebo Doxazosin standard	1 and 2 mg tablets (Lot no. P-2599-08-001) 4 and 8 mg tablets (Lot no. P-2605-07-001)

STUDY DESIGN:
This was a randomized, double-blind, double-dummy, parallel-group, multicenter trial of three oral treatments: doxazosin standard (1, 2, 4, or 8 mg), doxazosin GITS (4 or 8 mg), and placebo. Tablets were to be taken once daily (dose titration dependent on adverse events, blood pressure response, and BPH response). The trial consisted of a two week wash-out period (Phase I), a two-week single-blind placebo run-in (Phase II), and a 13-week double-blind treatment period (Phase III). A total of 1020 BPH patients were screened and 795 were randomized, of which 317 were randomized to the doxazosin GITS treatment group, 322 subjects to the doxazosin standard treatment group, and 156 to the placebo treatment group.

Drug Administration:
Phase I
No medication .
Washout period for 2 weeks.

Phase II
Placebo doxazosin standard (1, 2, 4 and 8 mg) and placebo doxazosin GITS (4 and 8 mg).
Once daily for 2 weeks.

Phase III

Test	Doxazosin GITS 4 or 8 mg and placebo doxazosin standard 1, 2, 4, or 8 mg. Once daily for a total of 13 weeks. Doxazosin GITS 4 mg and placebo doxazosin standard for 7 weeks followed by 4 or 8 mg doxazosin GITS and placebo doxazosin standard for six weeks.
Reference A	Doxazosin standard 1, 2, 4, or 8 mg and placebo doxazosin GITS 4 or 8 mg. Once daily for a total of 13 weeks. Doxazosin standard 1 mg and placebo doxazosin GITS for one week followed by automatic up-titration to 2mg for two weeks. After this time, 2 mg or 4 mg for four weeks followed by 2 mg or 4 mg or 8 mg for six weeks plus placebo doxazosin GITS.
Reference B	Placebo doxazosin GITS and placebo doxazosin standard. Once daily for a total of 13 weeks (see dosing schedules above).

ANALYTICAL METHODS:

Plasma samples were to be shipped to the analytical laboratory for assay of doxazosin levels using a pre-validated analytical method. Further details were not provided

PK SAMPLE COLLECTION:

Plasma samples were collected at centers in Norway only. On weeks 0, 9, and 15 (visits 1, 5, and 6), blood samples (10 mL) were collected at trough (20 to 28 hours after the previous dose).

PK/PD ANALYSIS:

The plasma levels of doxazosin from the two active treatment groups were categorized and used to summarize the change in maximum urinary flow rate at weeks 9 and 15. Plasma levels were also summarized by dose level of doxazosin at weeks 9 and 15.

RESULTS:

There was no significant correlation between dose and plasma level for either doxazosin GITS or doxazosin standard. The results of the t-test of within treatment differences in plasma levels were not statistically significant. This may be due to the small sample sizes for some of the doses and to the high between-subject variability observed. A summary of doxazosin plasma levels by dose is presented below:

	Dose (mg/day)	Doxazosin GITS (n=317)		Doxazosin Standard (n=322)	
		n	median (ng/ml)	n	median (ng/ml)
Week 9	1	0	NA	0	NA
	2	0	NA	4	7.34
	4	24	7.52	24	7.53
	8	0	NA	0	NA
p-value		NA		0.791	
Spearman's Correlation Coefficient (p-value)		NA		0.1137 (0.564)	
Week 15	1	0	NA	0	NA
	2	0	NA	0	NA
	4	12	10.75	5	13.30
	8	20	12.85	25	16.60
p-value		0.078		0.072	
Spearman's Correlation Coefficient (p-value)		0.2167 (0.233)		0.2893 (0.121)	

NA=Not Applicable

There was no statistically significant correlations between plasma level of doxazosin and change from baseline in maximum urinary flow rate for either treatment group at weeks 9 and 15. Some of the sample sizes were small and between subject variability was high. Given the lack of a statistically significant correlation between dose and plasma level, a correlation between plasma level and maximum urinary flow rate is not necessarily expected. The change from baseline in maximum urinary flow rate categorized by doxazosin plasma levels is summarized in the table below:

	Doxazosin Plasma Level (ng/ml)	Doxazosin GITS (n=317)		Doxazosin Standard (n=322)	
		n	median (ml/sec)	n	median (ml/sec)
Week 9	≤6.92	9	2.40	14	1.75
	>6.92-10.45	8	1.60	7	-0.40
	>10.45-16.10	4	2.30	5	2.10
	>16.10	3	0.50	2	0.45
Pearson's Correlation Coefficient (p-value)		-0.173 (0.418)		0.056 (0.776)	
Week 15	≤6.92	5	-0.50	2	-0.65
	>6.92-10.45	8	2.00	4	4.25
	>10.45-16.10	11	2.30	9	2.10
	>16.10	8	1.80	15	2.30
Pearson's Correlation Coefficient (p-value)		-0.215 (0.254)		0.042 (0.828)	

SAFETY:

No pharmacodynamic correlation was performed between adverse events and doxazosin pharmacokinetics. The most commonly reported treatment-emergent adverse events were dizziness, headache, vertigo, asthenia, flu-syndrome, back pain, postural hypotension, and nausea with the majority being mild or moderate. The most common treatment-emergent adverse events leading to discontinuation and considered to be related to study drug were

dizziness, headache, vertigo, postural hypotension, and tiredness. One event in the doxazosin standard treatment group was considered to be a treatment related serious adverse event.

CONCLUSIONS:

The correlation between dose and plasma level was not statistically significant for either doxazosin GITS or doxazosin standard. Similarly, there was no correlation of statistical significance between plasma level of doxazosin GITS or doxazosin standard and change from baseline in maximum urinary flow rate. No PK/PD correlations were performed between the safety data collected and doxazosin PK.

REVIEWER'S COMMENTS:

1. PK/PD analysis was not part of the objectives of this clinical trial. A PK objective was not clearly defined; which may have influenced the outcome or may not have allowed for the optimization of prospective data collection and analysis.

STUDY DAZ-NY-96-008 – COMPARATIVE BIOAVAILABILITY OF THE DOXAZOSINGITS 8 MG TABLET IN HEALTHY VOLUNTEERS WHEN ADMINISTERED UNDER FASTED AND FED CONDITIONS VERSUS A STANDARD DOXAZOSIN2 MG TABLET.

STUDY INVESTIGATOR AND SITE:

REPORT # DAZ-NY-96-008
VOLUME # 9 and 10

OBJECTIVES:
To determine the comparative bioavailability of a doxazosin gastrointestinal therapeutic system (GITS) 8 mg tablet in normal volunteers when administered under fasted and fed conditions versus a standard doxazosin 2 mg tablet.

FORMULATIONS:
TEST – GITS 8 mg tablet (Lot no. P-3191-01-001)
REFERENCE – Doxazosin standard 2 mg tablet (Lot no. P-2602-04-001)

STUDY DESIGN:
An open-label, single-dose, three-way crossover study, with a seven day washout between treatments, in 24 healthy male subjects aged 18 – 40 years. The study comprised three phases with subjects receiving a doxazosin GITS 8 mg tablet under fed and fasted conditions and a doxazosin standard 2 mg tablet under fasted conditions. The comparatively low dose of the standard formulation was used, as initial doses above 2 mg are known to be poorly tolerated (i.e., syncope, dizziness, or orthostatic hypotension). However, the initial starting dose of Cardura® is indicated as a 1 mg dose once daily. Subjects receiving the dose regimen under fed conditions had a high fat breakfast immediately prior to dosing. Contents of the breakfast was not provided. Subjects receiving the dose regimen under fasted conditions were fasted for at least 10 hours before dosing and received no food until lunch at approximately 4 hours post-dose. Subjects were randomly assigned to treatment groups according to a computer-generated randomization code. The treatment for each study phase was:

Group	No. of Subjects	Phase I (Day 1)	Phase II (Day 8)	Phase III (Day 15)
A	8	2 mg Standard – fasted	8 mg GITS – fasted	8 mg GITS – fed
B	8	8 mg GITS – fasted	8 mg GITS – fed	2 mg Standard - fasted
C	8	8 mg GITS – fed	2 mg Standard - fasted	8 mg GITS – fasted

ANALYTICAL METHODS:

Plasma samples were assayed for doxazosin by [redacted] using a validated HPLC assay with fluorescence detection.

Linearity

The standard curve was linear over a range of 0.200 to 20.0 ng/mL ($r^2 \geq 0.9975$).

Precision

The variability of the back-calculated concentrations of the calibration standards ranged from 1.9% to 5.7%. The between-day variability did not exceed 6.8%. The within-day reproducibility did not exceed 2.3%.

Accuracy

The accuracy of the method was determined by comparing the means of the measured concentrations with the theoretical concentration of doxazosin in fortified plasma. The deviations of the mean values for the QC samples did not exceed 2.4%.

Lower Limit of Quantitation (LLOQ)

This was set at 0.200 ng/mL with a relative standard deviation for the back-calculated concentration of 5.7% and a deviation of 8.1% from the theoretical concentration.

SAMPLE COLLECTION:

On days 1, 8, and 15, blood samples (10 mL) were collected at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 48, 72, and 96 hours post-dose.

RESULTS:

The pharmacokinetic parameters of doxazosin obtained from the three phases are listed below.

Mean variables (geometric for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, arithmetic for T_{max} and T_{half}; n=24):

Parameter	Doxazosin GITS 8 mg (fasted)	Doxazosin GITS 8 mg (fed)	P-value	Doxazosin Standard 2 mg (fasted)	Doxazosin GITS 8 mg (fasted)#	P-value
C_{max} (ng/ml)	17.3	22.9	<0.05	13.4	4.3	<0.05
T_{max} (h)	14	11	<0.05	2	14	<0.05
AUC_{0-t} (ng.h/ml)	526	619	< 0.05	179	131	<0.05
$AUC_{0-\infty}$ (ng.h/ml)	536	630	<0.05	190	134	<0.05
Thalf (h)	15.0	16.1	0.097	13.9	15.0	0.053
#Data normalised to 2 mg						

Both C_{max} and AUC ($_{0-\infty}$ and $_{0-t}$) were significantly greater in the fed state relative to the fasted state for the 8 mg GITS tablets, increasing by 32% and 18%, respectively. T_{max} occurred

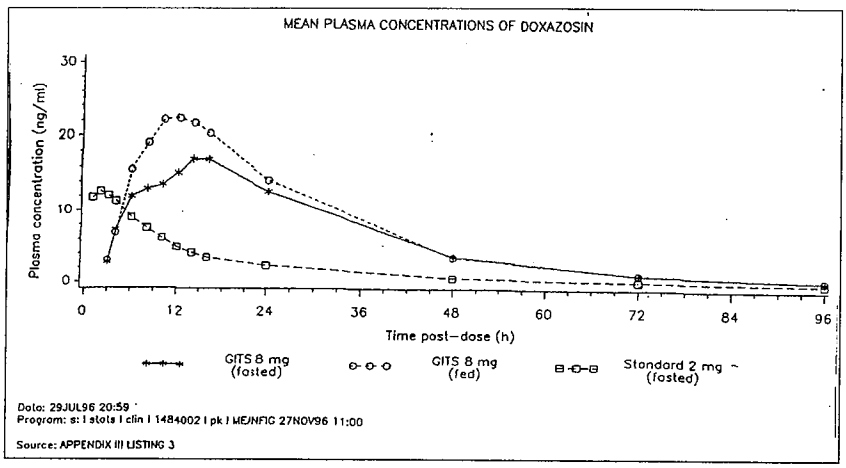
significantly earlier in the fed (11 hours) compared to the fasted state (14 hours). The elimination kinetics of doxazosin were similar for both the fed and fasted states. Intersubject variability was performed with all of the modes of administration of doxazosin. C_{min} at 24 hours in the fed state; which would theoretically be the next time for a new dose of doxazosin GITS resulted in a mean of 14.1 ng/ml with a standard deviation of 6.252 ng/ml and a CV% of 44.1 (raged from 5.63 to 33.10 ng/ml). Since this was a single dose study, a 96 hour final plasma level was obtained resulting in a concentration of 0.4 ng/ml ± 0.314, and a CV% of 67.7 (range: 0.00 to 1.48 ng/ml).

The maximum plasma concentration under fasted conditions that was achieved for the 8 mg GITS tablet was 17.3 ng/mL and 13.4 ng/mL for the standard formulation. C_{max} was smaller for the standard tablet compared to the GITS (approximately 29%). The $AUC_{0-\infty}$ for the 8 mg GITS formulation was greater compared to the standard 2 mg tablet (64%). In addition, T_{max} occurred significantly earlier with the standard tablet (2 hours) compared to GITS tablet (14 hours). C_{min} at 24 hours for doxazosin GITS under fasted conditions resulted in a mean of 12.6 ng/ml with a standard deviation of 4.893 ng/ml and a CV% of 38.8 (raged from 4.06 to 21.3 ng/ml). Once again since this was a single dose study, the final plasma level collected was at 96 hours; which had a corresponding concentration of 0.4 ng/ml ± 0.257, and a CV% of 63.8 (range: 0.00 to 1.01 ng/ml).

The CV% for the fasted 2 mg standard formulation was 32.7 ng/ml at 24 hours with a mean of 2.2 ng/ml ± 0.745 (ranged from 0.86 to 3.97 ng/ml). At 96 hours, there was insufficient data to make the analysis. However, at the 72 hour time point the C_{min} had a mean of 0.1 ng/ml ± 0.168 and a CV% of 100.2. All CV% information for all studies can be found in Appendix III.

For the GITS treatment, plasma concentrations of doxazosin remained at a plateau until approximately 16 to 24 hours post-dose before a gradual decline in a mono-exponential manner. There was no plateau in the plasma concentrations of doxazosin and the disposition phase was biphasic for the standard tablet treatment. The mean elimination half-life was similar for both treatments (mean values of 15.0 and 13.9 h for GITS and standard treatment, respectively).

Below is the mean plasma concentration time profiles of all three phases.



The geometric mean ratios and 90% confidence interval of the ratios for comparisons of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ between the fed and fasted states for the 8 mg GITS were:

Parameter	Geometric Mean Ratio	90% Confidence Interval of Geometric Mean Ratio
C_{max} (ng/ml)	1.32	1.19, 1.48
AUC_{0-t} (ng.h/ml)	1.18	1.08, 1.29
$AUC_{0-\infty}$ (ng.h/ml)	1.18	1.07, 1.29

SAFETY:
No subjects discontinued the study due to adverse events and no deaths were reported. All subjects completed the study with no serious adverse events reported.

CONCLUSIONS:
The 90% confidence interval between the fed and fasted state was not passed. However, the differences observed in C_{max} and AUC for GITS under the fed and fasted conditions will likely not result in clinically significant differences. Therefore, Doxazosin GITS tablet can be administered with or without food.

STUDY DAZ-NY-96-010 – COMPARATIVE BIOAVAILABILITY OF TWO4 MG DOXAZOSIN GITS TABLETS VERSUS ONE8 MG DOXAZOSIN GITS TABLET IN HEALTHY VOLUNTEERS

STUDY INVESTIGATOR AND SITE: Dr. D. Kleinermans
Pfizer Clinical Research Unit
808 Rue De Lennick
Brussels
Belgium, B-1070

REPORT # DAZ-NY-96-010
VOLUME # 13

OBJECTIVES:
To determine the relative bioavailability and pharmacokinetics of 2 X 4 mg doxazosin GITS versus 1 X 8 mg GITS tablet.

FORMULATIONS:
TEST: GITS 4 mg tablet (Lot no. P-3190-01-001)
REFERENCE: GITS 8 mg tablet (Lot no. P-3191-01-001)

STUDY DESIGN:
An open-label, randomized, single-dose, two-way crossover study, with a seven day washout between treatments, in 24 healthy male subjects aged 18 – 40 years. The study comprised two phases. In the first study phase, GITS tablets (2 X 4 mg tablets or 1 X 8 mg tablets) were administered orally with 180 mL of water, according to the randomization schedule. In the second study phase, the alternative treatment was administered following the same treatment regimen. Subjects received their dose under fasted conditions and were fasted for at least 10 hours before dosing and received no food until lunch at approximately 4 hours post-dose.

ANALYTICAL METHODS:
Plasma samples were assayed for doxazosin by [redacted] using a validated HPLC assay with fluorescence detection.

Linearity
The relationship between the peak and height ratio and concentration was linear over a range of 0.200 to 20.0 ng/mL ($r^2 \geq 0.9965$).

Precision
The variability of the back-calculated concentrations of the calibration standards ranged from 2.5% to 8%. The between-day variability did not exceed 10.7%.

Accuracy
The accuracy of the method was determined by comparing the means of the measured concentrations with the theoretical concentration of doxazosin in fortified plasma. The deviations of the mean values for the QC samples did not exceed 5.3%.

Lower Limit of Quantitation (LLOQ)
This was set at 0.200 ng/mL with a relative standard deviation for the back-calculated concentration of 7.6% and a deviation of 4.5% from the theoretical concentration.

SAMPLE COLLECTION:
On days 1 and 8, blood samples (10 mL) were collected at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 48, 72, and 96 hours post-dose.

RESULTS:
The pharmacokinetic parameters of doxazosin obtained from the two phases are listed below.

Mean parameters (geometric for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, arithmetic for T_{max} and T_{half}; n=23):

Parameter	Treatment		P value
	2 x 4 mg Doxazosin GITS	1 x 8 mg Doxazosin GITS	
C_{max} (ng/ml)	22.0	25.1	0.071
T_{max} (h)	15	15	0.94
AUC_{0-t} (ng.h/ml)	687	751	0.36
$AUC_{0-\infty}$ (ng.h/ml)	702	785	0.38
Thalf (h)	16.0	15.6	0.20

There were no statistically significant phase or group effects nor any statistically significant differences between treatments for any of the pharmacokinetic parameters analyzed. However, the bioavailability of doxazosin was greater for the 1 X 8 mg dose strength with mean C_{max} and AUC values being higher in comparison with the 2 X 4 mg dose strength.

The geometric mean ratios and 90% confidence interval of the ratios for comparisons between the 2 X 4 mg (test) and 1 X 8 mg (reference) dose strengths were as follows:

Parameter	Geometric Mean Ratio (%)	90% Confidence Interval of Geometric Mean Ratio (%)
C_{max} (ng/ml)	88	78, 99
AUC_{0-t} (ng.h/ml)	92	79, 107
$AUC_{0-\infty}$ (ng.h/ml)	92	80, 107

Intersubject variability for C_{min} at 24 hours post the single 2 X 4 mg dose was 36.6% with a mean of 17.3 ng/ml ± 6.339 and a range of 4.19 to 33.1 ng/ml. At the final 96 hours collection time point, the mean resulted in a C_{min} of 0.634 ng/ml ± 0.4219 ng/ml and a CV% of 66.6 (range: 0.00 to 1.49 ng/ml). The 1 X 8 mg GITS dose had statistical parameters of 18.5 ng/ml ± 6.208 for C_{min}, a CV% of 33.6 ng/ml, and a range of 7.05 to 32.2 ng/ml at the 24 hour time point. At 96 hours C_{min} was observed to be 0.581 ± 0.321 ng/ml (range of 0.00 to 1.28 ng/ml) and a CV% of 55.2. please refer to Appendix III for further details by study number.

There were 2 subjects who were considered to be pharmacokinetic outliers: Subject 3 at the

2 X 4 mg dose and Subject 22 at the 1 X 8 mg dose who had $AUC_{0-\infty}$ ratios of 2.375 and 0.206, respectively. As a result, a second analysis of the data was performed which excluded these two subjects. The mean parameters (geometric for C_{max}, AUC_{o-t} and $AUC_{0-\infty}$, arithmetic for T_{max} and T_{half}; n=21) excluding the pharmacokinetic data for the mentioned subjects were:

Parameter	Treatment		P value
	2 x 4 mg Doxazosin GITS	1 x 8 mg Doxazosin GITS	
C_{max} (ng/ml)	22.5	25.4	<0.05
T_{max} (h)	15	14	0.79
AUC_{0-t} (ng.h/ml)	719	765	0.25
$AUC_{0-\infty}$ (ng.h/ml)	735	780	0.27
Thalf (h)	16.6	15.8	0.11

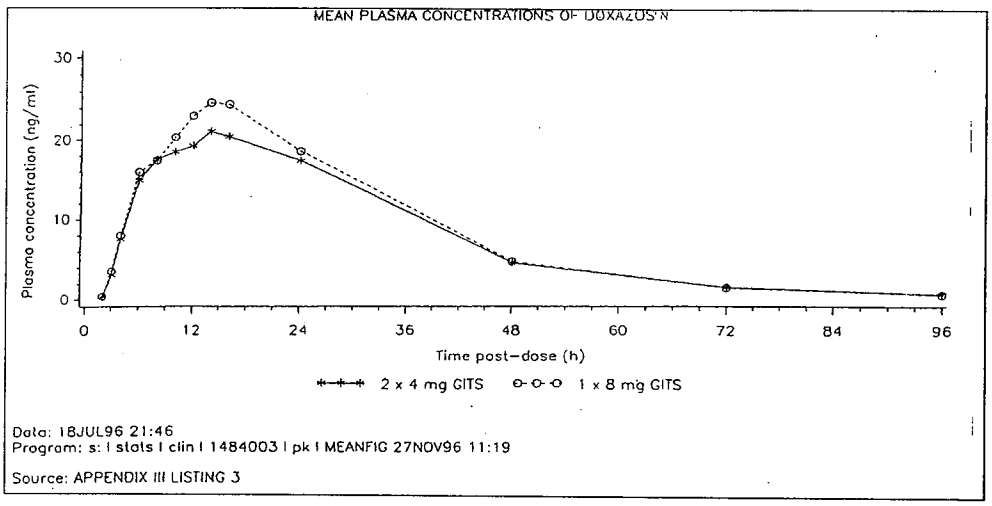
There were no statistically significant phase or group effects and there were no statistically significant differences between treatments for any of the pharmacokinetic parameters analyzed, with the exception of C_{max}, which was 13% higher for the 1 X 8 mg dose.

The geometric mean ratios and 90% confidence interval of the ratios for comparisons between the 2 X 4 mg (test) and 1 X 8 mg (reference) dose strengths (excluding data from subjects 3 and 22) were as follows:

Parameter	Geometric Mean Ratio (%)	90% Confidence Interval of Geometric Mean Ratio (%)
C_{max} (ng/ml)	89	81, 97
AUC_{0-t} (ng.h/ml)	94	87, 103
$AUC_{0-\infty}$ (ng.h/ml)	95	87, 103

Indicating that the two treatments were bioequivalent.

Below is the mean plasma concentration versus time profiles of doxazosin for both treatment groups.



SAFETY:
No subjects discontinued treatment or had the planned dose regimen modified because of adverse events. All subjects completed the study with no serious adverse events reported.

CONCLUSIONS:
Twenty four male subjects were recruited into the study with 23 completing the study. Subject 23 withdrew from the study for personal reasons. He received the 1 X 8 mg doxazosin GITS treatment in the first study phase. He withdrew from the study 3 days after dosing and did not receive treatment in the second study phase. Subject 22 was deleted from the second analysis since he was considered to be an outlyer. Upon exclusion of his data, no clinically significant differences between the two treatment groups were observed. The 2 X 4 mg and 1 X 8 mg dose strengths of doxazosin GITS resulted in pharmacokinetic profiles which could be considered to be bioequivalent.

STUDY DAZ-NY-96-007 – PHARMACOKINETIC EVALUATION OF DOXAZOSIN GITS FORMULATION TABLETS 4 MG AND 8 MG VS DOXAZOSIN STANDARD FORMULATION TABLETS 4 MG AND 8 MG IN HEALTHY MALE VOLUNTEERS

STUDY INVESTIGATOR AND SITE:

REPORT # DAZ-NY-96-007
VOLUME # 11 AND 12

OBJECTIVES:

To assess the pharmacokinetic characteristics of multiple doses of doxazosin GITS formulation, 4mg and 8 mg tablets, versus the standard formulation tablets containing 4 mg and 8 mg doxazosin, in healthy male volunteers.

FORMULATIONS:

TEST:	GITS	4 mg tablet (Lot no. P-3190-01-001)
		8 mg tablet (Lot no. P-3191-01-001)
	Placebo	4 mg tablet (Lot no. P-3189-01-001)
REFERENCE:	DOXAZOSIN STANDARD	1 mg tablet (Lot no. P-2601-05-001)
		2 mg tablet (Lot no. P-2602-04-001)
		4 mg tablet (Lot no. P-2603-05-001)
		8 mg tablet (Lot no. P-2607-01-002)

STUDY DESIGN:

This was an open, randomized, two-way crossover study to comparatively evaluate the multiple dose pharmacokinetics of doxazosin GITS and doxazosin standard formulation in 35 healthy male subjects aged 18 – 60 years. The study comprised two Phases. Subjects were randomized to receive single oral daily doses of either GITS or standard formulations in Phase I (Day 1 to 21). After a wash-out period of 7 days, subjects were crossed-over to receive the other formulation in Phase II (Days 29 to 49). The GITS formulation was administered as placebo for 7 days, 4 mg for 7 days and 8 mg for 7 days. The standard formulation was administered as 1 mg for 2 days, 2 mg for 5 days, 4 mg for 7 days and 8 mg for 7 days.

Phase1					
Days	**1-2**	**3-7**	**8-14**	**15-21**	**22-28**
Group 1	**Placebo**	**Placebo**	**GITS 4 mg**	**GITS 8 mg**	**Washout**
Group 2	**Standard 1 mg**	**Standard 2 mg**	**Standard 4 mg**	**Standard 8 mg**	**Washout**
		Cross-Over			
Phase 2					
Days	**29-30**	**31-35**	**36-42**	**43-49**	**50-53**
Group 1	**Standard 1 mg**	**Standard 2 mg**	**Standard 4 mg**	**Standard 8 mg**	**Washout**
Group 2	**Placebo**	**Placebo**	**GITS 4mg**	**GITS 8 mg**	**Washout**

ANALYTICAL METHODS:

Plasma samples were assayed for doxazosin by [redacted] using a validated HPLC assay with fluorescence detection.

Linearity

The relationship between the peak and height ratio and concentration was linear over a range of 0.200 to 20.0 ng/mL ($r^2 \geq 0.9957$).

Precision

The variability of the back-calculated concentrations of the calibration standards ranged from 3.4% to 9%. The between-day variability did not exceed 15.4%.

Accuracy

The accuracy of the method was determined by comparing the means of the measured concentrations with the theoretical concentration of doxazosin in fortified plasma. The deviations of the mean values for the QC samples did not exceed 4.6%.

Lower Limit of Quantitation (LLOQ)

This was set at 0.200 ng/mL with a relative standard deviation for the back-calculated concentration of 9% and a deviation of 4.5% from the theoretical concentration.

PK SAMPLE COLLECTION:

Days 1, 13, 20, 29, 41 and 48: Pre-dose
Days 14 and 42: Pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours post-dose.
Days 21 and 49: Pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 48, 72 and 96 hours post-dose.

RESULTS:

Below is a summary of the analysis for C_{min} (ng/ml) at steady state and a comparison between days 5, 6, and 7. Steady state was obtained by day 7 for both strengths and formulations. The 13% difference between doses 6 and 7 was not considered pharmacokinetically or clinically important.

4 mg formulations	Number of doses (once daily)			Day Comparison P Value	
	5	6	7	5 vs 6	6 vs 7
Doxazosin GITS	6.36	6.10	5.57	0.42	0.074
Doxazosin standard	6.53	6.49	6.46	NA	NA

8 mg formulations	Number of doses (once daily)			Day Comparison P Value	
	5	6	7	5 vs 6	6 vs 7
Doxazosin GITS	13.3	14.3	15.6	0.22	0.11
Doxazosin standard	13.9	15.8	17.8	<0.05	<0.05

Intrasubject variability assessment for the 4 and 8 mg GITS formulation for 3 different time points would have been possible; but was not performed by the sponsor. Intersubject variability was performed for each of the three individual time points for the 4 mg GITS resulting in a CV% for C_{min} of 54.7 for day 13/41, 47.2 for day 14/42, and 49.8 for day 15/43 prior to switching dose. C_{min} for these time points was at 24 hours since it was a multiple dose study with once daily dosing.

The intersubject variability for the 8 mg GITS C_{min} observed was 49.0 for day 20/48, 44.1 for day 21/49, and 52.5 for day 22/50 (prior to the washout period). The two dates given above correspond to what randomization schedule the subject received. More detailed information can be found in Appendix III under the individual study report.

Mean parameters (geometric for C_{max}, C_{min}, AUC_{o-t}, arithmetic for T_{max}, T_{half}, F_{rel}, and FI) after 7 days of daily dosing were:

Parameter	Doxazosin GITS (4 mg)	Doxazosin Standard (4 mg)	P Value	Doxazosin GITS (8 mg)	Doxazosin Standard (8 mg)	P Value
C_{max} (ng/ml)	10.1	28.2	<0.05	25.8	64.4	<0.05
T_{max} (h)	8	4	<0.05	9	4	<0.05
$AUC_{(0-tau)}$ (ng.h/ml)	183	356	<0.05	472	833	<0.05
C_{min} (ng/ml)	5.6	6.5	0.083	15.6	17.0	0.23
T_{half} (h)	NA	NA	NA	18.6	20.5	0.13
F_{rel} (%)	54.1	100	NA	58.6	100	NA
FI (ratio)	0.597	1.47	<0.05	0.517	1.37	<0.05

NA = Not applicable, terminal elimination phase unable to be defined
P Values are based on ANOVA

T_{half} for the 4 mg GITS and Standard formulation were not reported. The relative bioavailability of doxazosin from the GITS compared to the standard formulation was 54% at the 4 mg dose and 59% at the 8 mg dose. Comparison of the GITS (test) to the standard (reference) formulation showed lower Cmax values (ratios of 36% at the 4 mg dose level and 40% at the 8 mg dose level) and longer Tmax values (8 hours compared to 4 hours at the 8 mg dose level). The FI values were reduced for the GITS than the standard formulation (41% and 38% at the 4 and 8 mg dose, respectively), consistent with the controlled release properties of the system. Within each formulation, this parameter was independent of dose level.

Below is a comparison of the 8 mg dose normalized data to the 4 mg dose for the GITS and standard tablet in geometric mean ratios and 90% CI.

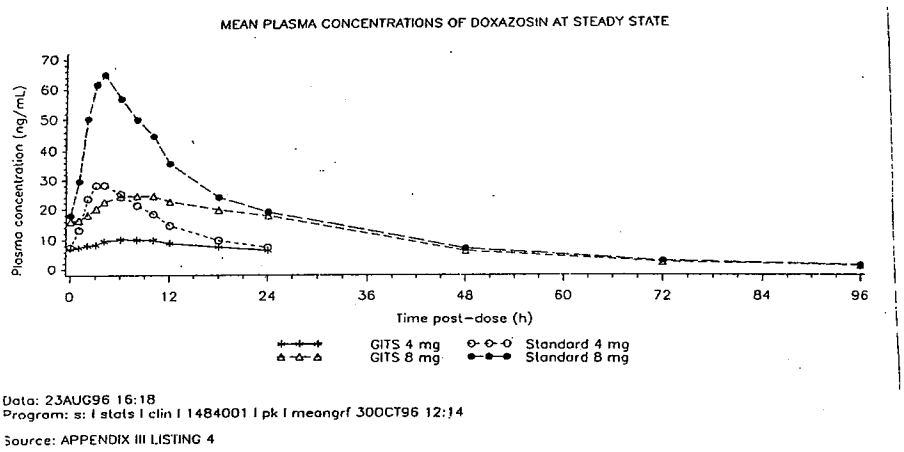
Formulation	Parameter	Geometric mean	P Value	90% CI
GITS 8 mg/GITS 4 mg	C_{max}(norm) (ng/ml)	1.27 ratio	<0.05	1.16, 1.39
	AUC (norm) (ng.h/ml)			
Standard 8 mg/Standard 4 mg	C_{max}(norm) (ng/ml)	1.14 1.27	<0.05 <0.05	1.04, 1.25 16, 1.39
	AUC (norm) (ng.h/ml)	1.18 1.29	<0.05 <0.05	1.08, 1.28 19, 1.41
Standard 8 mg/Standard 4 mg	C_{max}(norm) (ng/ml)	1.14	<0.05	1.04, 1.25
norm = normalised to 4 mg dose level	AUC_{0-tau}(norm) (ng.h/ml)	1.18	<0.05	1.08, 1.28

P Values are based on ANOVA

norm = normalised to 4 mg dose level

Sponsor states that the data indicates that the 4 mg and 8 mg doses for both the GITS and standard formulations are approaching dose proportionality. Increases of approximately 30% were measured for the GITS 8 mg dose compared to the 4 mg dose and increases of < 20% were measured for the standard 8 mg dose compared to the 4 mg dose. However, the differences in Cmax and AUC between the doses were within the intersubject variability of GITS (34 to 50%) and the standard tablets (26 to 35%).

The mean concentration-time profiles showed a more gradual absorption of doxazosin for the GITS formulation at both doses, consistent with the controlled-release properties of the system. Below is the mean plasma concentration versus time profiles of doxazosin for both formulations and dosage strengths.



SAFETY:

No subjects discontinued treatment or had the planned dose regimen modified because of adverse events. There were no serious adverse events during study. There were fewer adverse events considered related to the study drug during treatment with the GITS formulation compared to the standard. There were no clinically important changes in laboratory safety parameters, vital signs or ECGs.

CONCLUSIONS:

Thirty-five subjects entered the study with four subjects discontinuing treatment for reasons considered unrelated to the study drug. The sponsor indicated that the 4 mg and 8 mg dose levels for both the GITS and standard formulations were approaching dose proportionality with the increases of approximately 30% for the GITS 8 mg dose compared to the 4 mg dose in C_{max} and AUC observed being within the intersubject variability of GITS (34 to 50%).

REVIEWER'S COMMENTS:

1. Intrasubject variability assessment for the 4 and 8 mg GITS formulation for three different time points would have been possible; but was not performed by the sponsor. The sponsor should reanalyze the data and submit a summary of the results found from intraindividual variability analysis in order to better assess the formulations predictability in an individual from one day to another.

STUDY **DAZ-NY-96-009** – PHARMACOKINETIC EVALUATION OF DOXAZOSIN 4 MG GITS TABLETS IN YOUNG AND ELDERLY VOLUNTEERS

STUDY INVESTIGATOR AND SITE:

[redacted]

REPORT # DAZ-NY-96-009
VOLUME # 14 AND 15

OBJECTIVES:
To determine the steady-state relative bioavailability and pharmacokinetics of 4mg doxazosin GITS tablets in young and elderly male and female volunteers.

FORMULATIONS:
GITS 4 mg tablet (Lot no. P-3190-01-001)

STUDY DESIGN:
This was an open, multiple dose study, with four parallel groups of subjects dosed once daily for seven days. Each group consisted of at least 10 subjects (young males and females, elderly males and females). Young subjects were defined between the ages of 18 to 40. Elderly individuals were defined as ≥ 65 years. Subjects arrived at the study site the evening before dosing on day 1 and were then confined to the study site for seven days and discharged after the 24 hour blood sample on day 8. Subjects then returned to the study site for further blood sampling and evaluations on days 9, 10, and 11.

ANALYTICAL METHODS:
Plasma samples were assayed for doxazosin by [redacted] using a validated HPLC assay with fluorescence detection.

Linearity
The relationship between the peak and height ratio and concentration was linear in the curve range of 0.200 to 20.0 ng/mL ($r^2 \geq 0.9959$).

Precision
The variability of the back-calculated concentrations of the calibration standards ranged from 2.7% to 5.9%. The between-day variability did not exceed 10%.

Accuracy
The accuracy of the method was determined by comparing the means of the measured concentrations with the theoretical concentration of doxazosin in fortified plasma. The deviations of the mean values for the QC samples did not exceed 5.2%.

Lower Limit of Quantitation (LLOQ)
The useful LLOQ was set at 0.200 ng/mL with a relative standard deviation for the back-calculated concentration of 5.9% and a deviation of 5% from the theoretical concentration.

PK SAMPLE COLLECTION:
Days 1 and 7: Pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post-dose.
Days 5 and 6: Pre-dose.
Days 9, 10 and 11: 48, 72 and 96 hours post-dose from day 7.

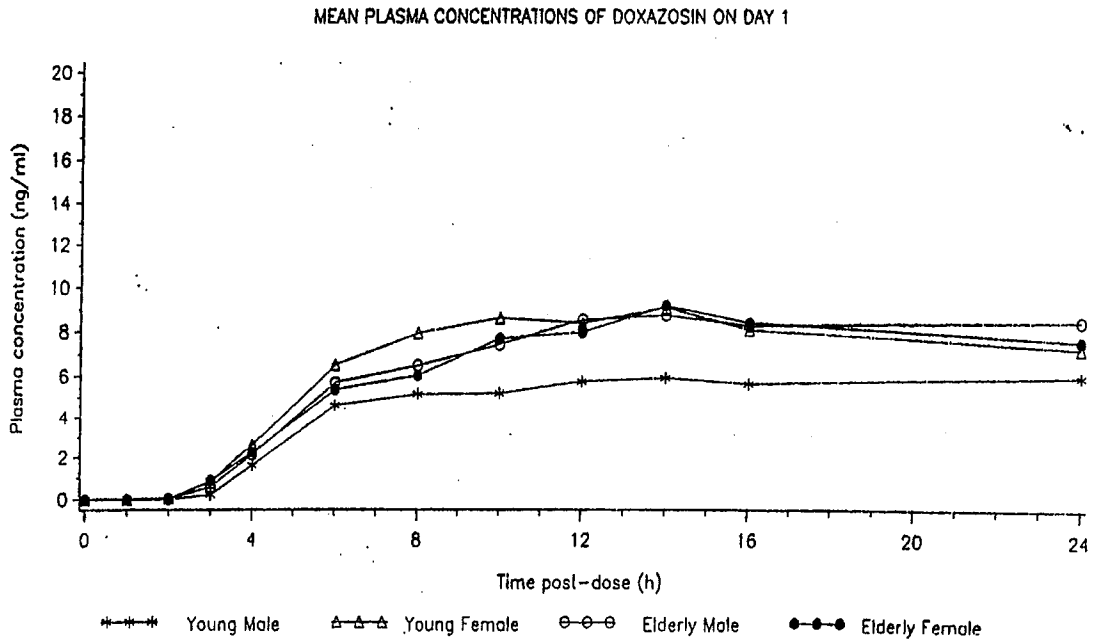
RESULTS:
Steady State Analysis - Below is a summary of the analysis for C_{min} (ng/ml) at steady state and a statistical comparison between days 4, 5, 6, and 7. Steady state was obtained by day 7 for the young and elderly males upon visual examination of the mean data. For the young females, there was a 27% increase in C_{min} between day 6 and 7. There was also an increase of 18% in C_{min} observed between days 6 and 7 in the elderly females. The sponsor believes that although these increases were statistically significant, they were within the variation (20.5 to 69.6%, for elderly and young females, respectively) and does not invalidate the conclusion that steady-state was also achieved in the young and elderly females.

Doxazosin 4 mg GITS C_{min} (ng/ml) at steady state

Group	Study day				Day Comparison - P-Value		
	4	5	6	7	4 vs 5	5 vs 6	6 vs 7
Young Male	9.54	9.86	11.61	10.68	NA	NA	NA
Young Female	10.18	9.92	9.94	12.59	0.7390	0.9832	<0.05
Elderly Male	14.71	15.12	15.38	15.64	NA	NA	NA
Elderly Female	15.64	13.82	14.74	17.32	0.1364	0.4149	<0.05

NA = not applicable (overall F-statistic not significant)

Single dose PK – After a single dose of doxazosin GITS 4 mg, plasma concentrations were bellow the lower limit of quantitation until 3 hours post-dose in most subjects regardless of age and gender. Maximum plasma levels were observed around 8 hours post-dose and remained stable up to 24 hours post-dose (time of the next dose).



Mean parameters (geometric for C_{max}, AUC_{o-t}, arithmetic for T_{max}) are summarized below.

Parameter	Young Males	Young Females	Elderly Males	Elderly Females
C_{max} (ng/ml)	6.59	9.41	8.92	9.81
T_{max} (h)	16.6	13.4	15.6	15.1
AUC_{0-tau} (ng.h/ml)	103.5	146.0	145.0	155.2

The coefficients of variation for each age and gender group ranged from 31.4 to 39.1% for C_{max} and 25 to 40.1% for AUC_{o-t}. Mean T_{max} ranged from 13.4 hours for young females to 16.6 hours for young males.

The data below illustrates that both C_{max} and AUC_{o-t} were greater in elderly males than young males (35 and 42%, respectively) in contrast to the young and elderly females; which were similar. A gender effect was observed to be more pronounced in the young group with females exhibiting C_{max} and AUC_{o-t} values greater than the males (45 and 46%, respectively). The elderly group had similar parameters between genders with females exhibiting a less pronounced disparity between C_{max} and AUC_{o-t} (12 and 8% higher, respectively). Upon analysis of the logarithmically transformed data, young females had a significantly higher C_{max} and AUC_{o-t} when compared to the young males. AUC_{o-t} was significantly greater in the elderly males compared to the young males. Arithmetic mean ratios were calculated for C_{max} and AUC_{o-t} shown together with ANOVA P-values:

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Comparison : AGE	Parameter	Arithmetic mean ratio	P-Value
Male Elderly vs Young	C_{max} (ng/ml)	1.35	0.0622
	AUC_{0-tau} (ng.h/ml)	1.42	<0.05
Female Elderly vs Young	C_{max} (ng/ml)	1.05	0.8015
	AUC_{0-tau} (ng.h/ml)	1.05	0.6855

Comparison : GENDER	Parameter	Arithmetic mean ratio	P-Value
Young Female v Male	C_{max} (ng/ml)	1.45	<0.05
	AUC_{0-tau} (ng.h/ml)	1.46	<0.05
Elderly Female vs Male	C_{max} (ng/ml)	1.12	0.5615
	AUC_{0-tau} (ng.h/ml)	1.08	0.6498

P-values from ANOVA of logarithmically transformed data

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Multiple dose PK – Following the final dose of doxazosin GITS 4 mg on day 7, plasma concentrations of the parent drug fell slightly in the first 2 hours after dosing, then increased

to reach a maximum levels by about 8 hours post-dose. Plasma concentrations remained relatively constant until 24 hours post-dose then declined exponentially with plasma concentrations still quantifiable in all subjects 96 hours post-dose. Mean plasma concentrations of doxazosin were similar in the elderly population and slightly lower in the young females with young males having the lowest plasma concentrations.

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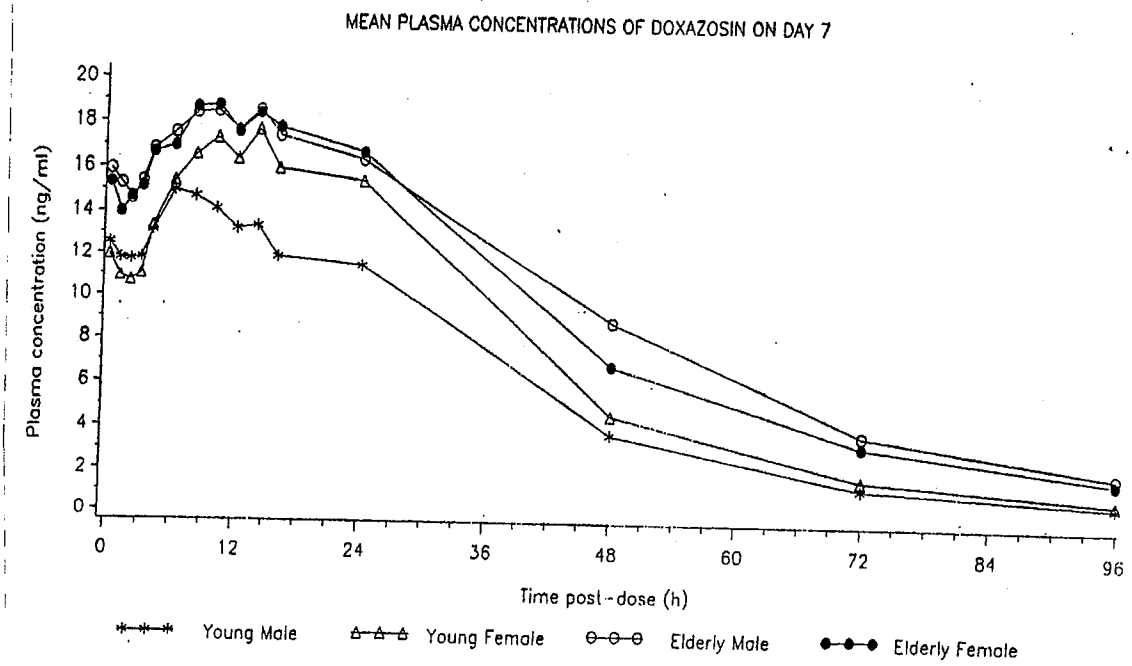

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The mean elimination half-life ranged from 20.07 hours (young females) to 24.74 hours (elderly females). The accumulation of doxazosin from GITS 4 mg tablets was similar for all age and gender groups. The fluctuation index was fairly narrow ranging from 0.18 for elderly females to 0.35 for young males. In the elderly groups, two males and one female had fluctuation index values of zero resulting from C_{max} occurring at 24 hours post-dose.

MEAN PHARMACOKINETIC PARAMETERS OF DOXAZOSIN

DOXAZOSIN PROTOCOL DAZ-NY-96-009 PAGE 1 OF 1

Day		Young Male	Young Female	Elderly Male	Elderly Female	Comparison - P Value+ Gender Male E v Y	Gender Female E v Y	Age Young F v M	Age Elderly F v M
1 Cmax (ng/ml)	Geometric Mean	6.59	9.41	8.92	9.81	0.0622	0.8015	0.0296	0.5615
7 Cmax (ng/ml)	Geometric Mean	15.11	16.71	19.98	20.39	0.0861	0.2284	0.5298	0.9016
1 Tmax (h)	Arithmetic Mean	16.6	13.4	15.6	15.1	0.6919	0.5101	0.2094	0.8503
7 Tmax (h)	Arithmetic Mean	7.8	10.4	13.0	13.8	0.0169	0.1216	0.2179	0.7171
1 AUC(0-tau) (ng.h/ml)	Geometric Mean	103.5	146.0	145.0	155.2	0.0262	0.6855	0.0233	0.6498
7 AUC(0-tau) (ng.h/ml)	Geometric Mean	293.1	315.9	396.2	420.1	0.0777	0.1034	0.6536	0.7332
7 Cmin (ng/ml)	Geometric Mean	10.68	12.59	14.63	17.32	0.1277	0.1327	0.4201	0.4205
7 Thalf (h)	Arithmetic Mean	20.33	20.07	23.36	24.74	0.1161	0.0209	0.8904	0.4793
7 FI (ratio)	Arithmetic Mean	0.35	0.30	0.30	0.18	0.6124	0.2179	0.6204	0.2219
7 AI (ratio) (Cmax)	Arithmetic Mean	2.43	1.84	2.34	2.22	0.7950	0.2741	0.0854	0.7231
7 AI (ratio) (AUC)	Arithmetic Mean	2.99	2.25	2.82	2.81	0.6472	0.1481	0.0546	0.9943

+ P Values are based on ANOVA with effects for AGE, SEX and SEX*AGE interaction
E = Elderly, Y = Young, F = Female, M = Male

On day 7, the CV for C_{max} and AUC_{o-t} appeared to be smaller for the elderly subjects (range 18.8 to 26.6%) than for the young subjects (range 32.7 to 62.4%). Young females exhibited the highest intersubject variation on day 7 where the CV% for C_{max} and AUC_{o-t} was 59.8 and 62.4% , respectively. T_{max} occurred earlier by day 7 in all groups. Intrasubject variability was not performed in this study. Details are listed below:

ARITHMETIC MEAN, COEFFICIENTS OF VARIATION AND ARITHMETIC MEAN RATIOS FOR Cmax, AUC(0-tau) AND Cmin

DOXAZOSIN PROTOCOL DAZ-NY-96-009 PAGE 1 OF 1

Parameter	Young Male	Young Female	Elderly Male	Elderly Female	Arithmetic mean ratio Gender Male E : Y	Gender Female E : Y	Age Young F : M	Age Elderly F : M
Day 1 Cmax (ng/ml)	6.91(34.7%)	10.02(39.1%)	9.33(31.4%)	10.47(35.8%)	1.35	1.05	1.45	1.12
Day 7 Cmax (ng/ml)	15.86(32.7%)	19.26(59.8%)	20.42(21.5%)	20.72(18.8%)	1.29	1.08	1.21	1.01
Day 1 AUC(0-tau) (ng.h/ml)	106.7(25.0%)	155.8(40.1%)	151.2(32.0%)	163.3(31.7%)	1.42	1.05	1.46	1.08
Day 7 AUC(0-tau) (ng.h/ml)	307.5(33.1%)	368.1(62.4%)	408.7(26.6%)	428.5(21.3%)	1.33	1.16	1.20	1.05
Day 7 Cmin (ng/ml)	11.50(40.5%)	15.42(69.6%)	15.63(39.3%)	17.64(20.5%)	1.36	1.14	1.34	1.13

E = Elderly, Y = Young, F = Female, M = Male

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Program: P:\1484004\STATS\PK\CITAB5 20JAN97 14:53

Source: APPENDIX III LISTINGS 4.1-4.4

Upon further investing the effect of age and gender on the pharmacokinetics of doxazosin at steady state, the data indicates that there is an age related difference in males than females. Based on AUC values, the relative bioavailability of doxazosin is 33 and 16% higher in the elderly males and females, respectively compared to the corresponding younger subjects. Plasma concentrations were slightly higher in female subjects compared to males in both groups. The relative bioavailability of doxazosin was 20% higher in young females and 5% higher in elderly females when compared to their corresponding male subjects. Even though

differences were observed between the age and gender groups, statistical analysis of the logarithmically transformed data revealed that the differences were not statistically significant.

SAFETY:

Subject 10 (young male) was discontinued from treatment due to study drug. The adverse event was an episode of dizziness and fainting about 17 minutes prior to dose administration on day 2 of the study. Blood pressure (128/76 mmHg) and pulse (93 bpm) were normal. After recovering in the supine position for about 30 minutes, he felt faint again on attempting to leave the study site. It was decided to withdraw the subject from further dosing and was kept under observation at the study site until the morning of day 5, even though he was asymptomatic. At that time, he was discharged. Subject 10 was replaced by subject 110.

Subject 110 (young male) returned in the afternoon after being discharged from the study site on day 8 due to a headache. He was kept under observation in the unit overnight and left the following afternoon.

Treatment emergent adverse events was greatest for the young females (34) and lowest for the young males (8). The frequency of adverse events was similar for the elderly males and females (18 and 15, respectively). The sponsor believes that the abnormally high incidence of adverse events in the young females, despite the similar pharmacokinetics in all groups, was possibly related to confinement of 7 days in the clinical research unit.

The most common treatment-emergent adverse events for all groups were headache and dizziness. Severe adverse events occurred in the young population only and were dizziness (3 events), syncope (1), headache (1), and palpitations (1). There were no serious adverse events during study.

CONCLUSIONS:

Forty-one subjects entered the study with one subject discontinuing treatment due to study drug. Visual inspection and statistical analysis of the trough (C_{min}) plasma concentration data on days 4 to 7 showed that steady state had been achieved by day 7 for the young and elderly male groups. C_{min} values on day 7 for young and elderly females increased by 27% and 18%, respectively compared to those on day 6; which were statistically significant. However, these differences were within subject variation (20.5% to 69.6% for elderly and young females, respectively).

The plasma elimination half-life of doxazosin was longer in the elderly subjects (23.4 and 24.7 hours for male and females, respectively) compared to 20.3 and 20.1 hours in the corresponding young subjects. After both a single dose, on day 1 and at steady state on day 7, plasma concentrations of doxazosin were higher in the females than males for both age groups.

Young females had an AUC 46% higher on day 1 and 20% higher on day 7 than young males possibly due to females having a lower body weight than the males. The differences observed were not statistically significant and were within the variation observed within each group.

Plasma doxazosin concentrations were higher in elderly subjects than young subjects both after a single dose and at steady state. The AUC for elderly males was 33% higher than the young males on day 7. In the females, the age related difference in AUC was lower at 16%. These differences were not statistically significant and were within the variation observed within each group.

According to the sponsor, the differences observed between males and females and young and elderly subjects in the relative bioavailability are not pharmacokinetically or clinically significant and would not warrant any dosage adjustment based on age and gender.

REVIEWER'S COMMENTS:

1. Young females had an AUC 46% higher on day 1 and 20% higher on day 7 than young males possibly due to females having a lower body weight than the males, as stated by the sponsor.

   The differences in AUC was statistically significant on day 1 ($p < 0.05$); but not by day 7. Additionally, the difference in AUC of 46% observed on day 1 was not within the variation observed within this group; which was 40.1% for young females. The sponsor had stated that the disparity in AUC was within the variation observed in this population.

   Thirty-four adverse events were reported in young females during the study with 31 being attributed to study drug. The sponsor believes that the abnormally high incidence of adverse events in the young females, despite the similar pharmacokinetics in all groups, was possibly related to confinement of 7 days in the clinical research unit. Upon further examination of the safety data, 15 of the 31 study drug related adverse events that were reported (48%) occurred by day 1. By day 2, a total of 22 adverse events had occurred, accounting for 71% of all study drug related adverse events occurring in the young females. By day four, 84% of all adverse events reported had already occurred indicating that a possible dose titration for young females may be required and adverse events occurring may not be due to confinement in a clinic for 7 days. It would seem that if confinement to the clinic throughout the study were the cause of adverse events in this group, they would progressively get worse as time progresses. The contrary occurred. The adverse events declined as time progressed.

2. The sponsor states that plasma doxazosin concentrations were higher in elderly subjects than young subjects both after a single dose and at steady state. However, upon examination of the plasma concentration versus time curve for day 1, the young females appear to have experienced a higher spike in concentrations initially on day 1 than any other group possibly accounting for the adverse events seen on day 1 (48% of all adverse events were reported on day 1).

3. The current food effect study for the GITS formulation performed in normal volunteers revealed an increase in Cmax (32%) and $AUC_{0-\infty}$ (18%) for subjects in the fed state as compared to the fasted state that may not be significant in that setting. It is unclear if subjects in this current study were in the fasted or fed state. If the young females were in a fasted state for Cardura XL administration throughout this study, the pharmacokinetic values observed in this study may be more pronounced and may lead to additional adverse event reporting in this population.

STUDY R-0357 – COMPARATIVE SINGLE-DOSE PHARMACOKINETICS OF DOXAZOSIN IN HEALTHY AND HEPATICALLY IMPAIRED VOLUNTEERS

STUDY INVESTIGATOR AND SITE: [redacted]

REPORT # R-0357
VOLUME # 16

OBJECTIVES:
To determine the pharmacokinetics of doxazosin in patients with hepatic impairment, and to compare its pharmacokinetics with that of normal subjects.

FORMULATIONS:
DOXAZOSIN STANDARD — 2 mg tablet (Lot no. C2348-QC1238)

STUDY DESIGN:
This was an open-label, single dose, nonrandomized, parallel-group study. The study consisted of 12 chronic, stable, cirrhotic patients and 12 healthy subjects.

STUDY RESULTS:
Plasma doxazosin concentrations were slightly higher at all time points for the hepatically impaired subjects compared to normal volunteers, and were detectable till the last sampling time point (120 hours post dose). Oral absorption at a slightly slower rate in hepatically impaired patients (Tmax: 4 ± 1 versus 3 ± 1 in normals). Mean Cmax values were comparable between groups; but $AUC_{0-\infty}$ was 43% larger in impared subjects (246 ± 84 ng•hr/mL) compared to normals (172 ± 61 ng•hr/mL; p=0.02). The between group difference in CL was 149.2 ± 45.0 mL/min for the impaired patients and 214.3 ± 67.6 mL/min for the normal volunteers (p=0.02) even when normalized for body weight (50% decrease in CL). Half-life between the groups was comparable with no statistically significant differences (impaired, 24 ± 9 hrs versus 22 ± 7 hrs for normals). A disparity was observed between the groups when mean residence time was compared (impaired 21 ± 5 hr; normals 14 ± 4 hr); which was statistically significant (p<0.001). In other words, it took 50% longer for the impaired group to eliminate the same proportion of doxazosin as compared to the normal subjects.

REVIEWER'S COMMENT:
1. The present study was previously reviewed when NDA 19-668 (SLR-009) was submitted on 10/4/96. Subsequent labeling changes were made due to the data presented in the study results. As a result, study 0357 was not reviewed with the current submission of [redacted] Please refer to the Clinical Pharmacology and Biopharmaceutics review dated March 12, 1997 by reviewer Ameeta Parekh, Ph.D for further details.
2. The current food effect study for the GITS formulation performed in normal volunteers revealed an increase in Cmax (32%) and $AUC_{0-\infty}$ (18%) for subjects in the fed state as compared to the fasted state that may not be significant in that setting. However, if subjects with hepatic impairment were to administer Cardura XL with food the pharmacokinetic values observed in the hepatic study may be more pronounced.

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/s/

Lydia Kieffer
2/22/02 02:42:14 PM
PHARMACOLOGIST

CPB Review App 2 Studies Reviewed

Angelica Dorantes
2/22/02 04:05:12 PM
BIOPHARMACEUTICS

APPENDIX III:
DISSOLUTION

21 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 9

Appendix IV
Intersubject Variability Data for each Individual Study

30 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 10

APPENDIX V:
OCPB – DIVISION OF REPRODUCTIVE & UROLOGIC PRODUCTS REVIEW
BY DR. SAYED AL HABET