CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75609

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-609 SPONSOR: KV Pharmaceutical Co.

DRUG AND DOSAGE FORM: **Doxazosin Mesylate Tablets**

STRENGTH (S): **1, 2, 4, and 8 mg**

TYPES OF STUDIES: Fasted and Fed Bioequivalence Studies and Dissolution Testing

CLINICAL STUDY SITE (S)

ANALYTICAL SITE (S):

STUDY SUMMARY: Fasted and Fed Bioequivalence Studies on 1-mg strength are acceptable.

DISSOLUTION/BIOWAIVER: Dissolution testing is acceptable. Biowaiver on 2-, 4- and 8-mg strength is granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : /S/ DATE : 7/13/00

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : /S/ DATE : 7/13/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 7/26/2000

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-609 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Doxazosin Mesylate 1, 2, 4 and 8 mg Tablets

The Division of Bioequivalence has completed its review of your amendment submission to ANDA 75-609 acknowledged on the cover sheet, and has no further questions at this time.

The following *in vitro* dissolution testing should be incorporated into your manufacturing controls and stability program:

Apparatus: USP Apparatus II (paddle) at 50 rpm
Medium: 900 mL of 0.01 N HCl at 37 °C
Tolerance: NLT (Q) in 30 minutes

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation in not approvable.
approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Doxazosin Mesylate Tablets
1, 2, 4 and 8 mg
ANDA #75-609
Reviewer: Chandra S. Chaurasia
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KV Pharmaceutical Co
St. Louis, Missouri
Submission date:
June 09, 2000
July 5, 2000

Review of Study Amendments

I. Objective

Review of KV Pharmaceutical's amendments responding to the Agency's fax communication dated April 24, 2000, and telephone communication dated June 27, 2000.

II. Background

KV Pharmaceutical Co. previously submitted single dose in vivo bioequivalence studies under fasted and fed conditions comparing its 1-mg doxazosin mesylate Tablets, Lot #R366-081, to Cardura® 1-mg tablet, manufactured by Pfizer (Submission Date: March 26, 1999; Review Date: April 30, 1999). The biostudies were found incomplete due to the deficiencies related to incomplete frozen stability data and unacceptable dissolution testing results.

In the subsequent amendment to ANDA 75-609 (Submission Date: February 09, 2000; Review Date: April 24, 2000), the firm responded to these deficiencies. The Division found the frozen stability data acceptable. However, the dissolution testing results were found incomplete, and the firm was advised of the following recommendations:

1) The firm's results showed that there was approximately % lower dissolution for the 2-mg and 4-mg strengths. Since the formulations of doxazosin 2-mg and 4-mg tablets are similar to those of the 1-mg and 8-mg tablets, respectively, the firm should explain the variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets especially those of the 2-mg and 4-mg strengths compared to the 1-mg strength that underwent bioequivalence testing.
2) The Agency may consider the firm's proposed specifications of NLT (Q) in 45 minutes after reviewing the firm's response to comment #1 above.

In the current amendments the firm has responded to the above recommendations.

III. Review of the Firm's Response

In the amendment submitted on June 9, 2000, the firm states that the variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets is due to the slight variations in the actual hydrochloric acid normality of the dissolution media used. The firm used either

As the viscosity of the HCl is dependent upon its concentration, it caused slight variances in the pipetted acid volumes.

The firm has improved its analytical method to clearly indicate that

The firm has also provided a new set of dissolution data for each strength following the corrective actions to the method of making the dissolution medium. These dissolution results are given in the table below (*Reviewer's Note: Single 45-minute time-point data only provided by the firm*):

Medium: 900 mL, 0.01 N HCl, 50 rpm, Sampling Time 45 minutes				
	% dissolved			
Strengths	1 mg	2 mg	4 mg	8 mg
Tablet #1				
Tablet #2				
Tablet #3				
Tablet #4				
Tablet #5				
Tablet #6				
Average	89	84	85	
SD	5.0	2.9	1.9	3.6
Range				

Citing the above dissolution results, the firm supports its proposed dissolution specification of Q at 45 min. for the doxazosin mesylate immediate release tablets over the Agency's proposed specification of NLT (Q) in 30 min.

However, in the absence of dissolution data at 30-minute, the firm's proposed specification of Q at 45 minutes remained questionable. And, therefore, the firm was advised (through a Telephone Call on June 27, 2000) to provide dissolution data at the 30-minute time point for each strength of its doxazosin mesylate tablets under similar dissolution conditions as used in the above case.

In the telephone amendment of July 5, 2000, the firm has provided the following dissolution data on each strength of its doxazosin mesylate tablets at 10-, 20-, 30- and 60-minute time points:

Medium: 900 mL, 0.01 N HCl, 50 rpm																
	Percent dissolved (%) per X minutes															
	1-mg Lot #R366081*				2-mg Lot #R376009*				4-mg Lot# R366082*				8-mg Lot #R366093*			
T1																
T2																
T3																
T4																
T5																
T6																
Ave	90	94	95	97	81	84	87	91	85	91	93	95	91	97	99	99
SD	6.8	2.1	1.7	1.3	3.8	3.6	3.9	2.9	6.4	3.5	3.2	1.8	6.3	2.1	0.8	0.5
Range																

*All of the above batches are the same as used in the original ANDA submission.

Reviewer's Comments:

1. The firm's response to the variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets is acceptable.

2. In the current submission, each of the six tablets from 1-, 2-, 4- and 8-mg strength doxazosin mesylate tablets exhibits a %dissolution value above %. This is in compliance with the Stage 1 specification of "Each of 6 units not less than %". Thus, the firm's dissolution data for each strength on its doxazosin mesylate tablets meets the Agency's recommended specification of NLT % (Q) in 30 minutes, and the firm's proposed specification of Q % at 45 minutes is not acceptable.

IV. Recommendations

1. The firm has previously conducted acceptable single-dose fasting and limited-food bioequivalence studies on its doxazosin mesylate, 1-mg tablet, Lot #R366-081, comparing it to the reference listed drug Cardura® 1-mg tablet, manufactured by Roering, Lot #7EPO43A. The study demonstrates that KV Pharmaceutical's doxazosin mesylate; 1-mg tablets are bioequivalent to the reference product Cardura® 1-mg tablets manufactured by Roering.

2. The firm has conducted an acceptable dissolution testing on doxazosin mesylate, 1-mg tablets, Lot #R366-081.

3. The firm has also conducted an acceptable dissolution testing on its doxazosin mesylate tablets 2-mg, lot # R376009, 4-mg, lot # R366082, and 8-mg, lot # R366093. The firm has conducted an acceptable in vivo bioequivalence study comparing its 1-mg tablet of test product with 1-mg tablet of the reference product Cardura® manufactured by Roering. The formulations for the 2-, 4- and 8-mg strengths are proportionally similar to the 1-mg strength that underwent bioequivalency testing. Waivers of in vitro bioequivalence study requirements for the 2-, 4-, and 8-mg strengths, doxazosin mesylate tablets are granted. The 2-, 4- and 8-mg tablets of doxazosin mesylate are therefore deemed bioequivalent, respectively to the 2-, 4- and 8-mg Cardura® tablets manufactured by Roering.

4. Based on the dissolution data submitted on July 10, 2000, the firm's proposed specification of Q % at 45 minutes is not acceptable. The following *in vitro* dissolution testing should be incorporated into the firm's manufacturing controls and stability program:

   Apparatus: USP Apparatus II (paddle) at 50 rpm
   Medium: 900 mL of 0.01 N HCl at 37 °C
   Tolerance: NLT % (Q) in 30 minutes

The above recommendations should be forwarded to the firm.

/S/
Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 7/13/00

RD INITIALED YHUANG /S/
FT INITIALED YHUANG

Date: 7/13/2000

Concur: /S/

Date: 7/20/2000

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA:75-609; KV Pharmaceutical Company
DRUG PRODUCT: Doxazosin Mesylate 1-, 2-, 4- and 8-mg Tablets

CC ANDA DUPLICATE/DIVISION FILE/HFD-652/Bio Secretary-Bio Drug File/HFD-650/C.Chaurasia

APR 24 2000

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-609 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Doxazosin Mesylate 1, 2, 4 and 8 mg Tablets

The Division of Bioequivalence has completed its review of your amendment submission to ANDA 75-609 acknowledged on the cover sheet. The Agency has the following recommendations:

Your results showed that there was approximately % lower dissolution for the 2-mg and 4-mg strengths. Since the formulations of doxazosin 2-mg and 4-mg tablets are similar to those of the 1-mg and 8-mg tablets, respectively, please explain the variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets especially those of the 2-mg and 4-mg strengths compared to the 1-mg strength that underwent bioequivalence testing.

The Agency may consider your proposed specifications of NLT %(Q) in 45 minutes upon reviewing your response to the above recommendations.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Doxazosin Mesylate Tablets
1, 2, 4 and 8 mg
ANDA #75-609
Reviewer: Chandra S. Chaurasia

KV Pharmaceutical Co
St. Louis, Missouri
Submission date:
February 09, 2000

Review of an Amendment

I. Objective

Review of KV Pharmaceutical's amendment responding to the deficiency letter by the Division of Bioequivalence dated October 19, 1999.

II. Introduction:

KV Pharmaceutical Co previously submitted single dose in vivo bioequivalence studies under fasted and fed conditions comparing its 1-mg Doxazosin Mesylate Tablets, Lot #R366-081, to Cardura® 1-mg tablet, manufactured by Pfizer (Submission Date: March 26, 1999; Review Date: April 30, 1999). The biostudies were found incomplete due to the following deficiencies:

1. The firm has submitted frozen stability data only for 35 days. It is to be noted that the maximum storage time for the plasma samples was 60 days.

2. The firm has used a rotation speed of rpm in its dissolution testing for 1, 2, 4 and 8 mg doxazosin mesylate tablets, as opposed to the Agency's recommended speed of 50 rpm. The dissolution testing is therefore, not acceptable.

   The firm is advised to conduct dissolution testing using the Agency's recommended method described below.

   Medium: 900 mL, 0.01 N HCl at 37 °C
   Apparatus: USP Apparatus 2(paddle), 50 rpm
   Sampling Time points: 10, 20, 30, 45 and 60 minutes

3. The firm has not submitted expiration dates for the innovator's Cardura® 2, 4 and 8 mg tablets used in the dissolution testing.

III. Background on Doxazosin Dissolution Criteria

Currently there is no USP dissolution method for doxazosin mesylate tablets. The DBE recommends the following

dissolution method for doxazosin tablets (Attachment I):
900 mL 0.01 N HCl, paddle, 50 rpm
Specification: NLT % in 30 minutes

IV. Review of the Firm's Response

Deficiency 1: You have submitted frozen stability data only for 35 days. It is to be noted that the maximum storage time for the plasma samples was 60 days.

Firm's Response:

The firm has provided additional long term frozen stability data for doxazosin in plasma stored at -20 °C for 71 days and one year. QC samples (theoretical concentrations: 0.1, 2.5 and 40.0 ng/mL) were prepared and analyzed after the specified storage period. The mean calculated concentrations were within ± 5-10% of the theoretical concentrations after the specified storage periods.

Reviewer's Comment:

The long-term frozen stability data are acceptable.

Deficiency 2: You have used a rotation speed of rpm in your dissolution testing for 1, 2, 4 and 8 mg doxazosin mesylate tablets, as opposed to the Agency's recommended speed of 50 rpm.
You are advised to conduct dissolution studies using the Agency's recommended method described below:

Medium: 900 mL, 0.01 N HCl at 37 °C
Apparatus: USP Apparatus 2(paddle), 50 rpm
Sampling Time points: 10, 20, 30, 45 and 60 minutes

Firm's Response:

The firm has evaluated the Agency-proposed dissolution specifications for the ANDA and reference batches as given in the table below:

Strength	Cardura batch no.	KV batch no.
1-mg	9EP012A & 7EP043A	R366081
2-mg	7EP053A	R376009

4-mg	7EP056A	R366082
8-mg	7EP057A	R366093

All of the above batches (for the innovator and test products) are the same as used in the original ANDA submission, except batch 9EP012A for the RLD. The firm used a second batch of Cardura 1-mg strength as the reference product for the biostudy had expired.

The firm conducted dissolution testing on its doxazosin 1-, 2-, 4-, and 8-mg batches in all packaging configurations (100's, 1000's and blisters) using the proposed DBE method. The firm's reported dissolution results are given in Attachment II. The firm notes that based on FDA's proposed specification of Q % at 30 minutes, the Stage 1 specification would be "Each of 6 units not less than %". In addition, 52 values out of 72 (72%) of its ANDA batch data did not meet the proposed criteria.

Based on the data generated, the firm believes that the specification of NLT % at 30 minutes using 50 rpm is not appropriate for its proposed products.

The firm's positions on the Agency's proposed dissolution criteria are as follows:

Point 1: A higher than % rate of stage 2 dissolution release testing frequency is excessive and counter-productive.

The firm has enclosed excerpts from HUMAN DRUG cGMP NOTES, March 1966 in support of the above point (Attachment II).

Point 2: Out of specification results at the FDA proposed one-point dissolution criteria do not translate to in-vitro in-equivalence.

To demonstrate in-vitro equivalence between the reference and KV product, the firm has submitted dissolution profiles using the Agency's proposed dissolution conditions. The dissolution testing was done on 6 units each of the test and reference 1-, 2-, 4-, and 8-mg strength tablets. As noted above, the firm used a second batch of Cardura for the 1-mg strength. Dissolution results are presented on page 5 of Attachment II.

Based on the dissolution data, the firm believes that the single point release criteria may fall outside Stage 1

while the profile remains comparable to the reference product.

The firm has also provided evidence to show that the dissolution profile has not changed since the ANDA batches were manufactured (Attachment II: page 6).

Point 3: OGD can approve dissolution specifications that may be different from the reference drug product.

The firm states that the Guidance to Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, dated August 1997 specifies the following:

"In the case of a generic drug product, the dissolution specifications are generally the same as the reference listed drug. The specifications are confirmed by testing the dissolution performance of the generic drug product from an acceptable bioequivalence study. If the dissolution of the generic product is substantially different compared to that of the reference listed drug and the in vivo data remain acceptable, a different dissolution specification for the generic product may be set."

The firm has thus proposed the following dissolution criteria for its doxazosin tablets:
Q % at 45 minutes, 0.01 N HCl 900 mL, 50 rpm.

Reviewer's Comments:

The firm has provided the following dissolution data on 3 sets of doxazosin mesylate tablets on each strength (i.e., 1-, 2-, 4-, and 8-mg) using the DBE-recommended method. Each set consists of 6 tablets obtained from one of the three packaging configurations (100's, 1000's and blisters).

FDA recommended method: 900 mL 0.01 N HCl, Paddle, 50 rpm, Q: % at 30 min				
	Mean % dissolved (range)			
Packaging Type	1 mg	2 mg	4 mg	8 mg
100's	82	68	66	75
1000's	76	59	68	75
blister	75	61	69	77
Average	77.7	62.7	67.7	75.7

The firm notes that 52 out of 72 (or 72%) dissolution values are less than % (Q). In addition, the data showed that 2-mg and 4-mg tablets also failed stage 2 specifications with mean dissolution value less than % (Q). However, the 1-mg and 8-mg tablets do meet the stage 2 specifications. It is to be noted that the formulations of 2-mg and 4-mg strengths are similar to that of 1-mg and 8-mg strengths, respectively. Considering these formulation similarities, the firm should explain the variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets especially those of the 2-mg and 4-mg strengths compared to the 1-mg strength that underwent bioequivalence testing. The Agency may consider the firm's proposed specifications of NLT % (Q) in 45 minutes after reviewing the firm's comments.

Deficiency 3: You have not submitted expiration dates for the innovator's Cardura® 2, 4 and 8-mg tablets used in the dissolution testing.

Firm's Response:

The sponsor states that this information was submitted in the original application on page 274. The firm has provided the expiration dates again as shown in the table below:

Drug product	Lot #	Expiration Date
Cardura® Tablets, 1 mg	7EP043A	12/1999
Cardura® Tablets, 2 mg	7EP053A	1/2002
Cardura® Tablets, 4 mg	7EP056A	1/2002
Cardura® Tablets, 8 mg	7EP057A	2/2002

Reviewer's Comment:
The information provided by the firm is acceptable.

V. Summary comments:

1. The firm's long term frozen stability testing is acceptable.

2. The firm's results showed that there was approximately % lower dissolution for the 2-mg and 4-mg strengths. Since the formulations of doxazosin 2-mg and 4-mg tablets are similar to those of the 1-mg and 8-mg tablets, respectively, the firm should explain the variability

observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets especially those of the 2-mg and 4-mg strengths compared to the 1-mg strength that underwent bioequivalence testing.

3. The Agency may consider the firm's proposed specifications of NLT % (Q) in 45 minutes after reviewing the firm's response to comment #2 above.

VI. Recommendations

Comments 2 and 3 should be forwarded to the firm.

/S/
Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 4/11/00

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ Date: 4/11/2000

Concur: /S/ Date: 4/12/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

ANDA:75-609; KV Pharmaceutical Company

DRUG PRODUCT: Doxazosin Mesylate 1-, 2-, 4- and 8-mg Tablets

Table 1. Comparative Formulations of Doxazosin Mesylate Tablets as obtained from ANDA #75-609 Original Submission

Ingredient	Amount (mg) Per Tablet			
	1 mg	2 mg	4 mg	8 mg
	mg/tab (%w/w)	Mg/tab (%w/w)	mg/tab (%w/w)	mg/tab (%w/w)
Doxazosin Mesylate				
Lactose, NF Monohydrate				
Microcrystalline Cellulose, NF				
Sodium Lauryl Sulfate, NF				
Sodium Starch Glycolate, NF				
D&C Yellow No. 10 Aluminum Lake				
D&C Lake Blend, Red				
FD&C Blue No. 2 Aluminum Lake				
Magnesium Stearate, NF				
Total Tablet Weight	**125 (100)**	**125**	**250 (100)**	**250 (100)**

*equivalent to Doxazosin label claim

1.1

Doxazosin Mesylate Tablets
1, 2, 4 and 8 mg
ANDA [redacted]
Reviewer: Chandra S. Chaurasia

KV Pharmaceutical Co
St. Louis, Missouri
Submission date:
March 26, 1999

Review of Fasting and Post-prandial Single Dose Bioequivalence Studies, Dissolution Data and Waiver Request

I. Introduction

Indication: Treatment of Hypertension

Type of Submission: Original ANDA

Contents of Submission: Fasting and Fed Bioequivalence Studies
Dissolution data and Biowaiver Request

RLD: Cardura® 1, 2, 4 and 8 mg (manufactured by Roering, a Division of Pfizer). The Agency has designated Cardura®, 1-mg tablet, as the reference listed drug to minimize the potential postural hypotension and first dose syncope.

II. Background

Doxazosin mesylate is an alpha-adrenergic blocking agent used for management of benign prostatic hyperplasia and hypertension. Although several active metabolites have been identified, the pharmacokinetic of these metabolites have not been characterized.

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position. Marked orthostatic effects are most common with the first dose or when there is a dose increase. Doxazosin-induced postural effects are dose related and mostly likely to develop between 2 to 6 hours after administration.

Peak plasma levels of doxazosin mesylate occur at 1.5-3.6 hours after oral administration of therapeutic doses. Bioavailability is %, reflecting first pass metabolism by liver, although enterohepatic recycling is suggested by occasional second peaks of plasma doxazosin at 4 hours or at 16-24 hours. Plasma elimination of doxazosin is biphasic with terminal half-life of 19-22 hours. When Cardura® was administered with food, C_{max} was reduced by 18% and AUC was reduced by 12%.

III. Protocol No. AA1-US-31: A Two-Way Crossover Single-Dose, Randomized Study to Determine the Bioequivalence of Two Oral Doxazosin Mesylate Formulations (1x 1 mg tablet)

A. Study Information

Clinical Site:

Principal Investigators:

Clinical Dates: n=24, Period 1: 10/23/98
n=24, Period 2: 11/03/98

Subjects: Entered - 25 normal healthy, non-smoking, male volunteers, 20-42 years of age, weighing at least 132 lbs., and were within 15% of their ideal weights.

Completed - 24 (subject #13 dropped from the study due to failure to return for outpatient blood draw in Period 1)

Analytical Site:

Analytical Director:

Analysis Dates: 11/12/98 through 12/07/98

Storage Period: not more than 45 days at -20 °C

Study Design: Single-dose Fasting, two-way crossover

Washout Period: 7 days

Products Tested

Test Product: Doxazosin Mesylate tablets(1 mg)
KV Pharmaceuticals
Lot #R366-081
Manufacturing Date 06/15/98
Expiration Date N/A
Potency 96.7%, Content Uniformity 95.9%(RSD 0.8%)

Batch Size tablets

Reference Product: Cardura® tablets (1 mg)
Roering (Division of Pfizer Inc)
Lot #7EP043A, Expiration Date 12/99
Potency 97.9%,Content Uniformity 98.4% (RSD 1.6%)
Commercial Lot

Randomization: A = test, B = reference

A,B: 2,3,4,5,7,12,15,17,21,22,23,25

B,A: 1,6,8,9,10,11,13,14,16,18,19,20,24

Inclusion/Exclusion Criteria: Listed in Vol. 1.1, page 240. Subjects who participated in the study were in the age range of 18-45 years, and within 10% of their ideal body weight as specified in the protocol.

Restrictions/Confinement: Listed in Vol. 1.1, page 240. The protocol also specified that subjects were not to take any medication including OTC products, for 14 days prior to the initial dose of medication, during the study, or during the washout period. Subjects abstained from xanthine- or caffeine-containing foods or beverages within 48 hours prior to the initial dosing and during the study. Subjects were confined from at least 10 hours before dosing until after the 24-hr blood sample. Subjects made return visit for the 36, 48 and 72-hour blood draws.

Dosing: Subjects fasted overnight from 10 hours prior to and 4 hours after dosing. Each oral dose (1x1 mg) was administered with 240 mL of water.

Blood Sampling: Ten-mL each, prior to dosing (time 0) and at 0.5,1,1.5,2,2.5,3,4,6,8,12,16,24,36,60 and 72 hours post-dose, collected into Sodium Heparin Becton-Dickinson Vacutainers. Plasma samples were centrifuged to separate red-cells and stored at -20 °C until analysis.

Analytical Method:

B. Study Results

Clinical (24 subjects completed the study)

Dropouts: Subject #13 was dropped from the study due to failure to return for outpatient blood draws during period 1.

Adverse events: Adverse events as reported by the sponsor are summarized in the following table.

Complaint	Treatment* A	Treatment* B	Relationship to Drug /Intensity	Total # of Subjects
Emesis	0	1	Possible/moderate	1
Bradycardia, asymptomatic	0	1	Probable/mild	1
Headache	1	0	Remote/moderate	1
	Total of 1 complaint in 1 subject	Total of 2 complaints in 2 subjects		

*A Test Fasting, B Reference Fasting

Protocol Deviations: None other than minor sampling deviations.

Pharmacokinetic/Statistical Analysis

Summarized in Tables 1A and 1 B, and Figures 1A and 1B

Table 1A. Mean Plasma Doxazosin levels (ng/mL) versus time (CV%) following an oral dose of 1x1 mg, doxazosin mesylate tablet, fasted conditions, n=24

Time(Hr)	Test (A)	Reference (B)	Ratio(A/B)
pre-dose	0.0024 (490%)	0.0000 --	--
0.5	1.3509 (67%)	1.4498 (89%)	93.2
1	4.1621 (44%)	4.3454 (42%)	95.8
1.5	5.5242 (32%)	5.5242 (30%)	100.0
2	5.9483 (27%)	5.9638 (29%)	99.7
2.5	6.0458 (26%)	6.0496 (27%)	99.9
3	6.0363 (24%)	5.9667 (26%)	101.2
4	5.6488 (22%)	5.6317 (25%)	100.3
6	4.4317 (22%)	4.3988 (23%)	100.7
8	3.8500 (22%)	3.7625 (25%)	102.3
12	2.8092 (24%)	2.8021 (26%)	100.3
16	2.1521 (28%)	2.1379 (28%)	100.7
24	1.4524 (28%)	1.4736 (30%)	98.6
36	0.7904 (34%)	0.7997 (33%)	98.8
48	0.4753 (38%)	0.4577 (34%)	103.8
60	0.2922 (44%)	0.2815 (43%)	103.8
72	0.1941 (45%)	0.1817 (46%)	106.9

Table 1B. Pharmacokinetic Measures following an oral dose of 1x1 mg, doxazosin mesylate tablet, fasted conditions,n=24

PK Measures	Test	Reference	Root MSE	T/R	90% CI
AUC_t (ng*hr/mL)[$]	103.52±25.27	103.02±27.66			
AUC_i (ng*hr/mL)[$]	108.86±27.66	105.55±28.75			
C_{max} (ng/mL)[$]	6.43±1.42	6.27±1.68			
t_{max} (hr)	2.67±1.33	2.42±0.67			
$t_{1/2}$ (hr)	16.13±2.03	15.44±1.97			
Ln AUC_t	4.61±0.25	4.60±0.29	0.142411		
Geometric mean	100.52	99.16		1.01	91.9-105.9%
Ln AUC_i	4.66±0.26	4.62±0.29	0.146684		
Geometric mean	105.42	101.53		1.04	90.6-105.5%
Ln C_{max}	1.84±0.23	1.80±0.29	0.167201		
Geometric mean	6.27	6.04		1.04	88.6-104.6%

[$]Data are arithmetic mean values(±S.D)

Comments on Bioequivalence Study (Fasting):

1. The pharmacokinetic measures (AUC_t, AUC_i and C_{max}) and 90% confidence intervals for doxazosin mesylate 1 mg tablet, re-calculated by the reviewer were in good agreement with the values determined by the firm.
2. There were no statistically significant period or sequence effects for any of these PK measures.
3. The 90% confidence intervals for ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

IV. Protocol No. AAI-US-32: A Three-Way Crossover Randomized Study to Determine the Bioequivalence of Two Oral Doxazosin Mesylate Formulations in a Fed State and Limited Food Effects Compared to One Formulation in the Fasting State (1x1 mg Tablets)

A. Study Information

Clinical Site:

Principal Investigators:

Clinical Dates: Period 1: 11/07/98
Period 2: 11/14/98
Period 3: 11/21/98

Subjects: *Entered* - 18 normal healthy, non-smoking, male volunteers, 21-43 years of age, weighing at least 144 lbs., and were within 15% of their ideal weights.

Completed - 18

Analytical Site:

Analytical Director:

Analytical Dates: 12/04/98 through 01/05/99

Storage Period: not more than 60 days at -20 °C

Study Design: Single-dose, three-way crossover

Washout Period: 7 days

Products tested: *Lot numbers of drug products administered in this study are the same as those for the fasting study.*

Randomization: A=test, fed
B=test, fed
C=reference, fasted

ABC: 11,12,16
ACB: 1,13,17
BAC: 4,7,9
BCA: 2,10,15
CAB: 3,8,18
CBA: 5,6,14

Inclusion/Exclusion Criteria: Listed in Vol. 1.1, page 240. Subjects who participated in the study were in the age range of 18-45 years, and within 10% of their ideal body weight as specified in the protocol.

Restrictions/Confinement: Listed in Vol. 1.1, page 240. The protocol also specified that subjects were not to take any medication including OTC products, for 14 days prior to the initial dose of medication, during the study, or during the washout period. Subjects abstained from xanthine- or caffeine-containing foods or beverages within 48 hours prior to the initial dosing and during the study. Subjects were confined from at least 10 hours before dosing until after the 24-hr blood sample. Subjects made return visit for the 36, 48 and 72-hour blood draws.

Dosing:

Fed Conditions: Subjects (Treatments A and B) were dosed within 30 minutes following consumption of a standardized breakfast with 240 mL of water.

Fasted Conditions: Subjects (Treatment C) received an oral dose after a supervised overnight fast (at least 10 hours) with 240 mL of water.

Blood Sampling: Ten-mL each, prior to dosing (time 0) and at 0.5,1,1.5,2,2.5,3,4,6,8,12,16,24,36,60 and 72

hours post-dose, collected into Sodium Heparin Becton-Dickinson Vacutainers. Plasma samples were centrifuged to separate red-cells and stored at -20 °C until analysis.

Analytical Method

Pharmacokinetic/Statistical Analysis

Summarized in Tables 2A and 2B, and Figure 2

Table 2A. Mean Plasma Doxazosin levels (ng/mL) versus time (CV%) following an oral dose of 1x1 mg, doxazosin mesylate tablet, fed conditions, n=18

Time (Hr)	$Test_{fed}$		Ref_{fed}		$Test_{fast}$		$(Test/Ref)_{fed}$
Pre-dose	0.0060	(291%)	0.0000	--	0.0040	(424%)	--
0.5	0.6259	(141%)	0.3944	(133%)	1.1218	(76%)	0.58
1	2.6503	(82%)	1.9903	(75%)	3.8294	(43%)	1.33
1.5	4.6561	(49%)	3.6911	(52%)	5.4100	(32%)	1.26
2	5.5872	(31%)	4.9944	(30%)	5.8922	(29%)	1.11
2.5	6.1089	(21%)	5.8556	(23%)	6.1394	(25%)	1.04
3	6.4311	(16%)	6.2878	(18%)	6.0283	(23%)	1.02
4	6.5544	(14%)	6.4378	(17%)	5.8794	(16%)	1.01
6	5.2922	(16%)	5.2372	(20%)	4.6072	(18%)	1.01
8	4.7333	(18%)	4.5256	(20%)	3.9872	(18%)	1.04
12	3.3956	(18%)	3.3339	(23%)	2.9433	(19%)	1.01
16	2.6478	(22%)	2.5300	(26%)	2.1989	(21%)	1.04
24	1.8006	(28%)	1.6722	(30%)	1.5089	(27%)	1.07
36	1.0154	(34%)	0.9238	(35%)	0.8700	(35%)	1.09
48	0.6029	(42%)	0.5529	(43%)	0.5234	(40%)	1.09
60	0.3651	(50%)	0.3523	(46%)	0.3077	(45%)	1.03
72	0.2439	(54%)	0.2244	(55%)	0.2061	(58%)	1.08

Table 2B. Pharmacokinetic Measures following an oral dose of 1x1 mg, doxazosin mesylate tablet, fed conditions, n=18

PK Measures	Test	Reference	Root MSE	T/R
AUC_t (ng*hr/mL)[$]	122.01±26.76	115.39±27.66		
AUC_i (ng*hr/mL)[$]	128.05±30.33	120.99±30.68		
C_{max} (ng/mL)[$]	6.83±1.12	6.64±1.18		
t_{max} (hr)	3.25±0.96	3.47±0.25		
$t_{1/2}$ (hr)	16.00±2.41	15.87±2.57		
Ln AUC_t	4.78±0.22	4.72±0.25	0.075144	
Geometric mean	119.25	112.15		1.06
Ln AUC_i	4.83±0.24	4.76±0.26	0.075768	
Geometric mean	124.69	117.22		1.06
Ln C_{max}	1.91±0.16	1.88±0.18	0.079693	
Geometric mean	6.75	6.54		1.03

[$]Data are arithmetic mean values(±S.D)

Comments on Bioequivalence Study (Non-Fasting):

1. The pharmacokinetic measures (AUC_t, AUC_i, and C_{max}) and ratio of their ln transformed means were recalculated by the reviewer. The reported values are in agreement with those obtained by the reviewer. There were no statistically significant period effects for any of these measures.
2. Ratios of means for AUC_t, AUC_i, and C_{max} between test non-fasting and reference non-fasting are within the acceptable limits of 80-125%.

V. Formulations

The formulations and related information for test products are given in Tables 3A and 3B below. For comparison, reference products' formulations are summarized in table 4.

Table 3A. Comparative Formulations of Test Products

Ingredient	Amount (mg) Per Tablet			
	1 mg	2 mg	4 mg	8 mg
	mg/tab (%w/w)	Mg/tab (%w/w)	mg/tab (%w/w)	mg/tab (%w/w)
Doxazosin Mesylate				
Lactose, NF Monohydrate	)	)	)	)
Microcrystalline Cellulose, NF	)	)	)	)
Sodium Lauryl Sulfate, NF				
Sodium Starch Glycolate, NF				
D&C Yellow No. 10 Aluminum Lake				
D&C Lake Blend, Red				
FD&C Blue No. 2 Aluminum Lake				
Magnesium Stearate, NF				
Total Tablet Weight (mg):	**125(100)**	**125**	**250(100)**	**250(100)**

*equivalent to Doxazosin label claim

Table 3B. Content Uniformity and Assay Potency Of Test and Reference Products

Dosage Strength	Content Uniformity			Assay Potency
Test Products				
	Mean	Range	%RSD	
1 mg/tab	95.9%	%	0.8	96.7%
2 mg/tab	97.5%	%	1.4	97.9%
4 mg/tab	98.1%	%	1.4	95.8%
8 mg/tab	100.8%	%	1.5	97.6%
Reference Products				
1 mg/tab	98.4%	%	1.6	97.9%
2 mg/tab	99.6%	%	1.3	100.2%
4 mg/tab	98.3%	%	1.4	100.4%
8 mg/tab	99.9%	%	0.6	98.5%

THE FOLLOWING INFORMATION IS NOT TO BE RELEASED UNDER FOI

Table 4. Quantitative Comparisons of the RLD Cardura® 1,2,4 and 8 mg tablet Formulations

Ingredients	Amount Per Tablet			
	1 mg	2 mg	4 mg	8 mg
	mg/tab(%w/w)	Mg/tab(%w/w)	mg/tab(%w/w)	mg/tab(%w/w)
Doxazosin Mesylate				
Microcrystalline Cellulose, NF				
Sodium starch glycolate, NF				
Lactose NF				
Magnesium stearate, NF Sodium lauryl sulfate, NF				
Total	120.0(100%)	120.0(100%)	240.0(100%)	240.0(100%)

* equivalent to Doxazosin label claim

VI. Dissolution Testing and Waiver Requests for 2, 4 and 8mg Strengths

The dissolution method and the firm's proposed specifications are as follows:

Medium: 900 mL, 0.01 N HCl
Apparatus: USP Apparatus 2(paddle), rpm
Sampling Time: 15,30,45 and 60 minutes
Tolerance (Proposed Specifications): NLT (Q) % in 45 minutes.

Number of tablets: 12

Results: Summarized in Table 5 below.

Table 5. *In Vitro* Dissolution Testing

Drug name: Doxazosin Mesylate Tablets
Dose strength: 1, 2, 4 and 8 mg
ANDA No. 75-609
Firm: KV Pharmaceutical Company

Method: USP 23 Apparatus 2 (paddle) 75 rpm, 0.01N HCl 900 mL
Proposed Specifications: NLT % (Q) dissolved in 45 minutes
Agency Specifications: NLT % (Q) dissolved in 30 minutes
RLD: Cardura® tablets (Pfizer Inc.)
Assay methodology:

Results of dissolution testing for 1 mg doxazosin mesylate tablets

Sampling time (min)	Test product Lot No. #R366-081 Strength 1 mg			Reference product Lot No. 7EP043A Strength 1 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	100%	%	1.7	97%	%	4.2
30	99%	%	4.0	97%	%	3.5
45	101%	%	1.1	98%	%	5.2
60	101%	%	1.8	96%	%	4.7

Results of dissolution testing for 2 mg doxazosin mesylate tablets

Sampling time (min)	Test product Lot No. #R376-009 Strength 2 mg			Reference product Lot No. 7EP053A Strength 2 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	97%	%	2.6	94%	%	1.3
30	99%	%	1.5	95%	%	1.7
45	100%	%	1.1	95%	%	1.6
60	101%	%	1.1	96%	%	2.5

Results of dissolution testing for 4 mg doxazosin mesylate tablets

Sampling time (min)	Test product Lot No. #R366-082 Strength 4 mg			Reference product Lot No. 7EP056A Strength 4 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	86%	%	4.0	89%	%	2.7
30	90%	%	1.4	93%	%	1.9
45	89%	%	1.1	93%	%	2.0
60	90%	%	1.3	93%	%	1.4

Results of dissolution testing for 8 mg doxazosin mesylate tablets						
Sampling time (min)	Test product Lot No. #R366-093 Strength 8 mg			Reference product Lot No. 7EP057A Strength 8 mg		
	Mean	Range	%CV	Mean	Range	%CV
15	96%	%	1.3	96%	%	1.7
30	95%	%	1.1	97%	%	1.6
45	95%	%	1.0	98%	%	1.6
60	95%	%	1.2	98%	%	2.0

f_2 values

The f_2 comparisons for test and reference products are summarized in Table 6A-C below.

Table6A: Comparison of f_2 similarity factor for Doxazosin Tablets

No.	Products (test/reference) compared, strength		f_2 values
1	Test, 1 mg	Reference, 1 mg	76.45
2	Test, 1 mg	Test, 2 mg	86.40
3	Test, 1 mg	Test, 4 mg	46.62
4	Test, 1 mg	Test, 8 mg	64.72

Table6B: Comparison of f_2 similarity factor for Doxazosin tablets

No.	Products (test/reference) compared, strength		f_2 values
1	Reference, 1 mg	Test, 1 mg	76.45
2	Reference, 1 mg	Reference, 2 mg	78.12
3	Reference, 1 mg	Reference, 4 mg	54.59
4	Reference, 1 mg	Reference, 8 mg	97.58

Table6C: Comparison of f_2 similarity factor for Doxazosin tablets

No.	Products (test/reference) compared, strength		f_2 values
1	Test, 1 mg	Reference, 1 mg	76.45
2	Test, 2 mg	Reference, 2 mg	67.61
3	Test, 4 mg	Reference, 4 mg	73.25
4	Test, 8 mg	Reference, 8 mg	79.68

Comments On Dissolution Testing:

1. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence studies where applicable.
2. Currently there is no USP dissolution method for doxazosin mesylate tablets.

The FDA recommends the following method(see Attachment I).

Medium: 900 mL, 0.01 N HCl at 37 °C
Apparatus: USP Apparatus 2(paddle), 50 rpm
Tolerance: NLT (Q) % in 30 minutes

3. The firm has used a speed of rpm in its dissolution testing compared to that of the Agency's recommended 50 rpm.

   The dissolution data are not acceptable. The firm is advised to conduct its dissolution testing following the Agency's recommended method.
4. The test doxazosin mesylate tablets, 2, 4, and 8 mg are compositionally proportional to the 1 mg tablet. Furthermore, the pattern of proportionality was the same as for the innovator product in NDA 19-668. In addition, compositions of the innovator's drug Cardura® tablets 1, 2 ,4 and 8 mg strengths (NDA #19-668) are comparatively similar to that of the Sponsor's respective dose-strength doxazosin tablets.
5. The f_2 comparison values for the test and reference products are more than 50 except that between the test 1 mg vs. test 4 mg doxazosin mesylate tablets.
6. The firm has not provided the expiration dates for the innovator's 2, 4, and 8 mg Cardura® tablets used in the dissolution testing.

VII. Deficiencies

1. The firm has submitted frozen stability data only for 35 days. It is be noted that the maximum storage time for the plasma samples was 60 days.
2. The firm has used a rotation speed of rpm in its dissolution testing for 1, 2, 4 and 8 mg doxazosin mesylate tablets, as opposed to the Agency's recommended speed of 50 rpm. The dissolution testing is therefore, not acceptable.
3. The firm has not submitted expiration dates for the innovator's Cardura® 2, 4 and 8 mg tablets used in the dissolution testing.

The firm should be informed of these deficiencies.

VIII. Recommendations

1. The single-dose fasting and limited-food bioequivalence studies conducted by KV Pharmaceutical Co., on its Doxazosin Mesylate, 1mg, tablets, Lot #R366-081, comparing it to Cardura® 1 mg tablet have been found incomplete by the Division of Bioequivalence due to the deficiencies #1-2 mentioned above.
2. Waiver request on KV Pharmaceutical's doxazosin mesylate 2, 4 and 8 mg tablets can not be granted due to incomplete bioequivalence study on its doxazosin 1-mg strength.
3. The dissolution testing conducted by KV Pharmaceutical on its doxazosin 1 mg tablets, lot # R366-081, 2 mg tablets, lot #R376-009, doxazosin 4 mg tablets, lot #R366-082, and doxazosin 8 mg tablets, lot #R366-093 is not acceptable. The firm should be advised to conduct dissolution testing on 12 individual dosage units of the corresponding test and reference products employing 900 of 0.01N HCl at 37 °C using USP Apparatus 2 (paddle) at 50 rpm at sampling time points of 10, 20, 30, 45 and 60 minutes.

The firm should be informed of the above recommendations.

/S/

Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 4/30/99

RD INITIALED YHUANG /S/
FT INITIALED YHUANG

Date: 4/30/99

Concur: /S/
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Date: 4/30/99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:75-609 APPLICANT: KV Pharmaceutical Company

DRUG PRODUCT: Doxazosin Mesylate 1, 2, 4 and 8 mg Tablets

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have submitted frozen stability data only for 35 days. It is be noted that the maximum storage time for the plasma samples was 60 days.

2. You have used a rotation speed of rpm in your dissolution testing for 1, 2, 4 and 8 mg doxazosin mesylate tablets, as opposed to the Agency's recommended speed of 50 rpm.

   You are advised to conduct dissolution studies using the Agency's recommended method described below.

   Medium: 900 mL, 0.01 N HCl at 37 °C
   Apparatus: USP Apparatus 2(paddle), 50 rpm
   Sampling Time points: 10, 20, 30, 45 and 60 minutes

3. You have not submitted expiration dates for the innovator's Cardura® 2, 4 and 8 mg tablets used in the dissolution testing.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FIGURE 1A.

DOXAZOSIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME, N=24
1 MG SINGLE-DOSE FASTING STUDY (AAI-US-31)

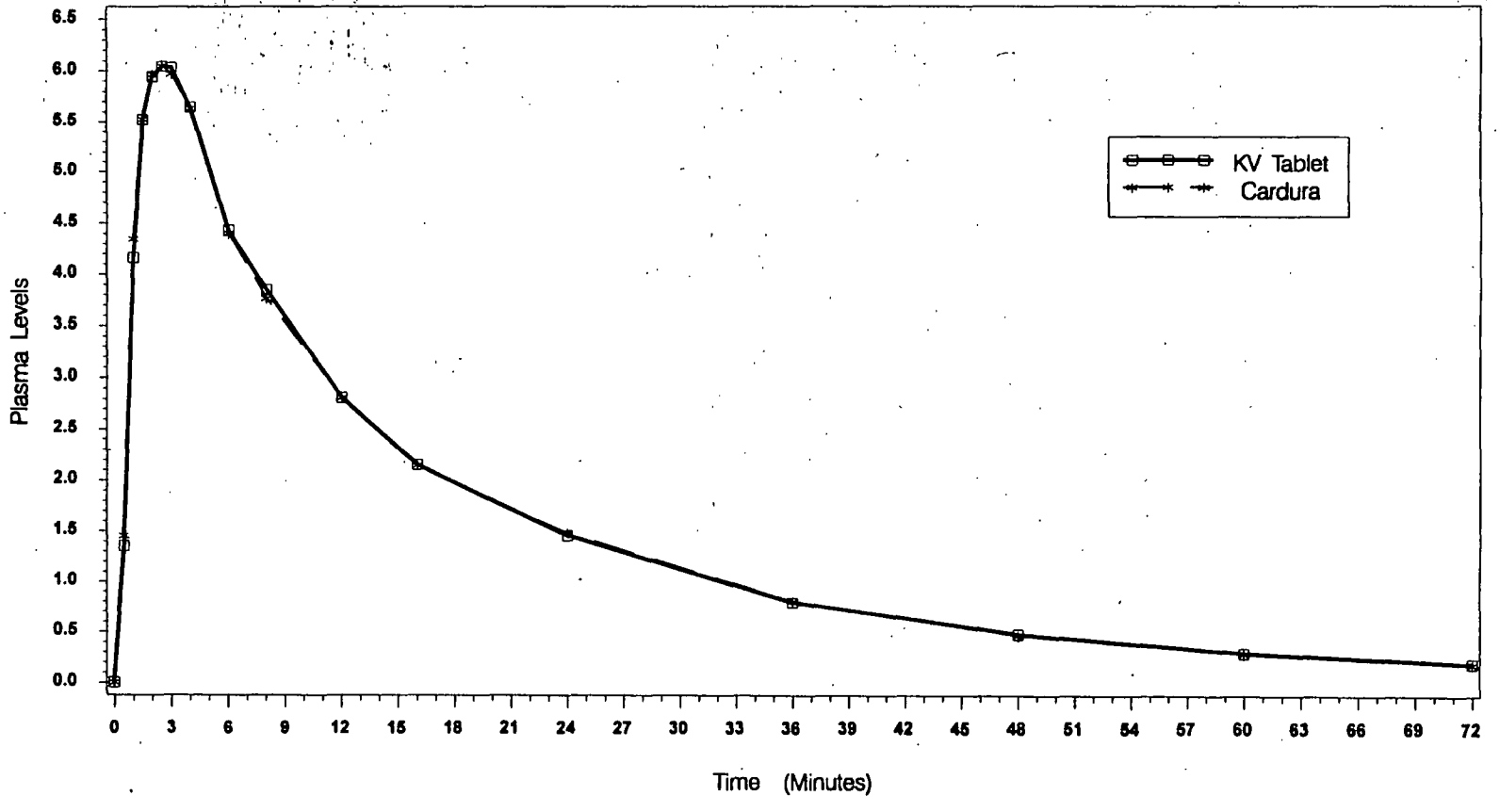

FIGURE 1B.

DOXAZOSIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME, N=23
1 MG SINGLE-DOSE FASTING STUDY (AAI-US-31)

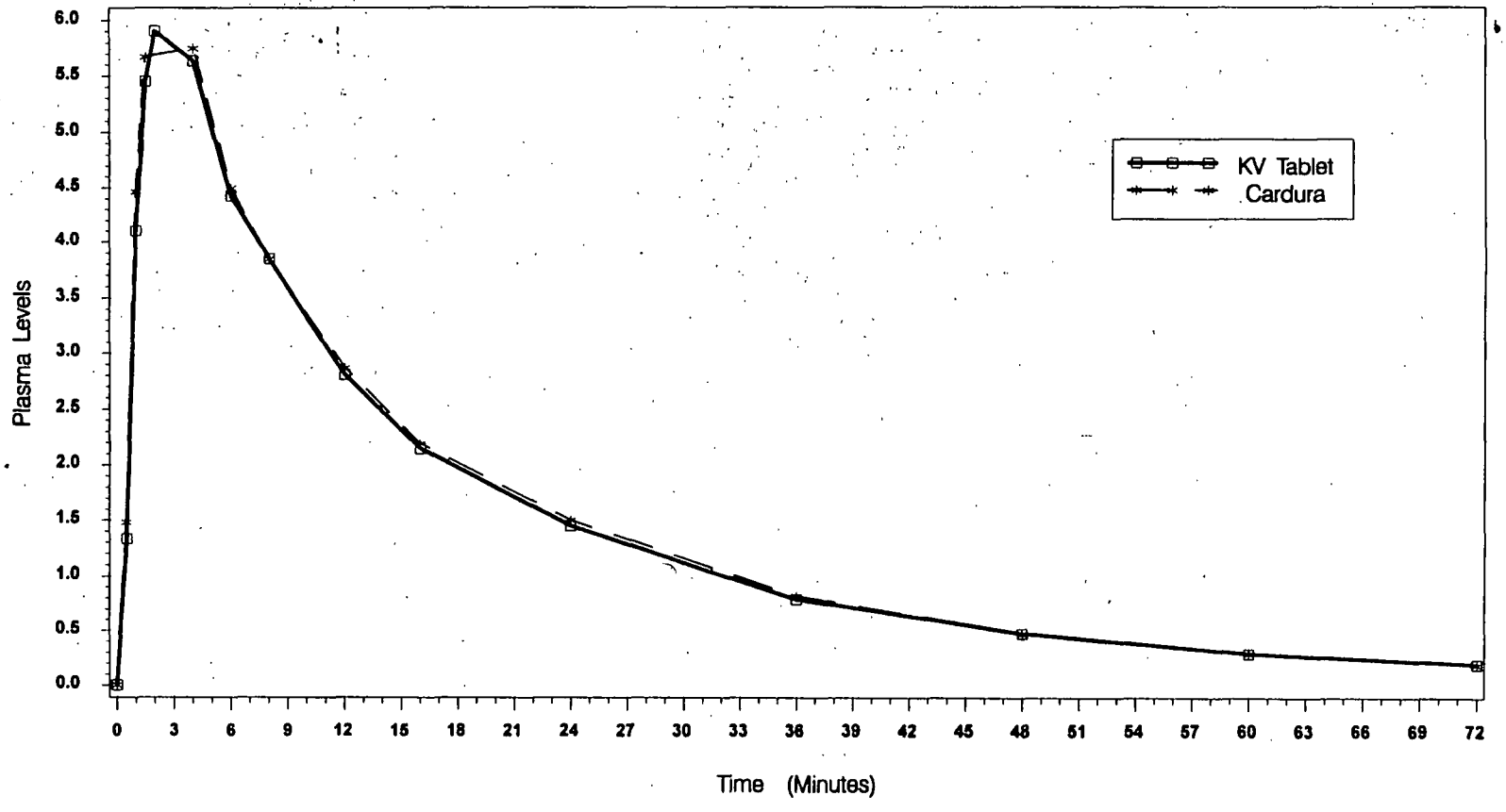

FIGURE 2.

DOXAZOSIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME, N=18
1 MG SINGLE-DOSE FED STUDY (AAI-US-32)