CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-140

BIOEQUIVALENCE REVIEW(S)

3.1

Terazosin Hydrochloride
Capsules, 1mg, 2mg, 5mg & 10mg
ANDA #75-140
Reviewer: Sikta Pradhan
WP #75140AD.798

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
July 16, 1998

Review of an Amendment on Dissolution Data

Mylan Pharmaceuticals Inc. recently conducted an acceptable in vitro dissolution testing (dated January 30, 1998) and in vivo bioequivalence study on its test product, Terazosin hydrochloride capsules (submission dated June 6, 1997).

The firm has conducted the dissolution testing on the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in 900 mL of water at 37°C using USP Apparatus 2 (paddle) at 50 rpm. The dissolution data indicated that the test product meets the FDA (previously approved) dissolution specification of 80% (Q) of the labeled amount dissolved in 30 minutes. Recently, the FDA has widen the time range of the dissolution and the current specification is 80% (Q) of the labeled amount dissolved in 60 minutes. The test product met both specifications,and therefore, no further action is needed on this application.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

7/21/98

/S/

Concur:

Date: 8/5/98

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:#75-140 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. However, you should be informed of the following:

1. You have conducted the dissolution testing for the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in water. The dissolution data indicated that the test product meets the FDA dissolution specification of 80% (Q) of the labeled amount dissolved in 30 minutes.

2. As the test product meets the Tier I dissolution (in water), your request to use the Tier II dissolution method as published in the USP 23, Twentieth Interim Revision, page 4 for hard gelatin capsules is denied. Therefore, the dissolution testing conducted on the test and reference products using 0.1 N HCL plus pepsin as dissolution medium is not acceptable, and consequently, these dissolution data submitted to the Division of Bioequivalence will not be reviewed.

3. The Agency has recently revised the dissolution specification for Terazosin HCl Capsules. The modified dissolution specification for this product is the following:

   Medium: water, 900 mL
   Apparatus: USP 23, paddle
   Speed: 50 rpm
   Dissolution Specification: NLT 80% in 60 min.

4. The comparative dissolution testing data of the test and reference capsules of 1 mg, 2 mg and 10 mg strengths meet the currently revised dissolution specification, and therefore, the waiver of *in vivo* bioequivalence study on 1 mg, 2 mg and 10 mg strengths of the test product is granted.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-140 **SPONSOR :Mylan**
DRUG & DOSAGE FORM : Terazosin Hydrochloride Capsules
STRENGTH (s) : 1 mg, 2 mg & 10 mg
TYPE OF STUDY: **SD** **SDF** **MULT** **OTHER Dissolution & Waiver Request**

STUDY SITE: CLINICAL : N/A.

STUDY SUMMARY : The firm has previously conducted acceptable in vitro dissolution testing and in vivo bioequivalence study on its Terazosin Capsule, 5 mg.
The compositions of Mylan's Terazosin capsules, 1 mg, 2 mg, 5 mg & 10 mg are proportionally similar.

DISSOLUTION:
FDA Revised Dissolution Condition:
Medium: Water, 900 mL
Apparatus: USP 23, paddle
Speed: 50 RPM
Specification:

Test product, Terazosin capsules, 1 mg, 2 mg, & 10 mg met FDA revised dissolution specifications of
in vitro dissolution testing data are acceptable and the waiver is granted.

PRIMARY REVIEWER : /S/ **BRANCH : I**
INITIAL : _____ **DATE :** 3-10-98

BRANCH CHIEF : Yih Chain Huang **BRANCH : I**

INITIAL : _____ **DATE :** 3/11/98

/S/
DIRECTOR : Dale P. Conner
DIVISION OF BIOEQUIVALENCE

INITIAL _____ **DATE :** 3/18/98

/S/
DIRECTOR : Douglas L. Sporn
OFFICE OF GENERIC DRUGS

INITIAL : _____ **DATE :** _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:#75-140 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. However, you should be informed of the following:

1. You have conducted the dissolution testing for the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in water. The dissolution data indicated that the test product meets the FDA dissolution specification of 80% (Q) of the labeled amount dissolved in 30 minutes.

2. As the test product meets the Tier I dissolution (in water), your request to use the Tier II dissolution method as published in the USP 23, Twentieth Interim Revision, page 4 for hard gelatin capsules is denied. Therefore, the dissolution testing conducted on the test and reference products using 0.1 N HCL plus pepsin as dissolution medium is not acceptable, and consequently, these dissolution data submitted to the Division of Bioequivalence will not be reviewed.

3. The Agency has recently revised the dissolution specification for Terazosin HCl Capsules. The modified dissolution specification for this product is the following:

   Medium: water, 900 mL
   Apparatus: USP 23, paddle
   Speed: 50 rpm
   Dissolution Specification: NLT 80% in 60 min.

4. The comparative dissolution testing data of the test and reference capsules of 1 mg, 2 mg and 10 mg strengths meet the currently revised dissolution specification, and therefore, the waiver of *in vivo* bioequivalence study on 1 mg, 2 mg and 10 mg strengths of the test product is granted.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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

Terazosin Hydrochloride
Capsules, 1mg, 2mg, 5mg & 10mg
ANDA #75-140
Reviewer: Sikta Pradhan
WP #75140DW.198

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
January 30, 1998
February 6, 1998
February 24, 1998

Review of Dissolution Data and Waiver Request

Introduction:

Mylan Pharmaceuticals Inc. has recently conducted an acceptable in vitro dissolution testing and in vivo bioequivalence study on Terazosin hydrochloride 5 mg capsules (submission dated June 6, 1997). In this amendment, the firm has reported the dissolution testing data of its test product, Terazosin 1 mg, 2 mg and 10 mg capsules and requested the waiver of in vivo bioequivalence study on those strengths. The firm has also indicated that the dissolution of the 1 mg and the 2 mg products were observed to be unpredictable in water to meet the specification of NLT minutes. Therefore, the firm has proposed to adopt the Tier-2 dissolution method in 0.1 N HCL with pepsin as recently published in the USP 23, Twentieth Interim Revision, page 4, <711> guidance on dissolution of hard gelatin capsules.

Dissolution:

The firm has reported the following dissolution data:

1. The firm has conducted dissolution testing on the test and the reference (Hytrin^{R}) products, 1 mg, 2 mg, 5 mg and 10 mg Terazosin capsules using water (900 mL) as the dissolution medium.

2. The firm has also conducted dissolution testing on the test and the reference products using 0.1 N HCL with pepsin as dissolution medium, and proposed to use this method for its test product.

The data obtained from the dissolution testing conducted in water are presented in Table 1 below:

Table 1. In Vitro Dissolution Testing

Drug: Terazosin HCL
Dose Strengths: 5 mg, 10 mg, 2 mg and 1 mg Capsules
ANDA No.: 75-140
Firm: Mylan Pharmaceuticals Inc.

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 50
No. Units Tested: 12
Medium: Water, Volume: 900 mL
Specifications: NLT f the labeled amount is dissolved

Assay Methodology.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	**Test Product** Lot # 2C012N Strength 5 mg Capsules			**Reference Product** Lot # 17-010-AW-21 Strength 5 mg Capsules		
	Mean %	Range	%CV	Mean %	Range	%CV
15	98		6.8	88		21.1
30	101		3.8	109		1.6
45	102		3.0	109		1.4
Sampling Times (Minutes)	**Test Product** Lot # 2C013N Strength 10 mg Capsules			**Reference Product** Lot # 18-108-AW-21 Strength 10 mg Capsules		
15	92		5.0	75%		31.1
30	95		3.3	94%		3.8
45	96		2.6	92%		1.8
Sampling Times (Minutes)	**Test Product** Lot # 2C011N Strength 2 mg Capsules			**Reference Product** Lot # 13-657-AW-22 Strength 2 mg Capsules		
15	86%		10.5	67%		39.8
30	89%		7.6	91%		2.2
45	91%		6.1	91%		2.1
Sampling Times (Minutes)	**Test Product** Lot # 2C010N Strength 1 mg Capsules			**Reference Product** Lot # 15-852-AW-21 Strength 1 mg Capsules		
15	90%		6.1	82%		20.3
30	92%		3.9	92%		3.7
45	93%		3.3	92%		3.1

The in vitro dissolution testing conducted by the firm on its test product meets the FDA dissolution specification of 80% (Q)

of the labeled amount dissolved in 30 minutes.

Compositions

The comparative formulations of Terazosin Capsules, 1 mg, 2 mg, 5 mg and 10 mg are presented in Table 2 below. These formulations are proportionally similar.

Table 2

	10 mg Cap	5 mg Cap	2 mg Cap	1 mg Cap
Ingredient	mg/cap	mg/cap	mg/cap	mg/cap
Terazosin Hydrochloride, USP	10.94	5.47	2.188	1.094

see package insert

Total:	**150.0**	**150.0**	**150.0**	**150.0**

Comments:

1. The firm has conducted the dissolution testing for the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in water. The dissolution data indicated that the test product meets the FDA dissolution specification of of the labeled amount dissolved in

2. As the test product meets the Tier I dissolution (in water), the firm's request to use the Tier II dissolution method as published in the USP 23, Twentieth Interim Revision, page 4 for hard gelatin capsules is denied. Therefore, the dissolution testing conducted on the test and reference products using 0.1 N HCL plus pepsin as dissolution medium is not acceptable, and consequently, these dissolution data submitted to the Division of Bioequivalence will not be reviewed.

3. The Agency has recently revised the dissolution specification for Terazosin HCl Capsules. The modified dissolution specification for this product is the following:

   Medium: water, 900 mL
   Apparatus: USP 23, paddle
   Speed: 50 rpm
   Dissolution Specification:

4. The comparative dissolution testing data of the test and reference capsules of 1 mg, 2 mg and 10 mg strengths meet the currently revised dissolution specification, and therefore, the waiver of in vivo bioequivalence study on 1 mg, 2 mg and 10 mg strengths of the test product is granted.

Note: This comment is not for FOI

There is no USP dissolution method for Terazosin Hydrochloride Capsules. The reference product, Hytrin® capsule was tested against the FDA dissolution method (900 mL water, paddle 50 rpm, specification NLT 80% in 30 min.). Recently, the dissolution specification for the reference product has been changed, and the current dissolution specification for Hytrin® capsule is the following:

Medium: water, 900 mL
Apparatus: USP 23, paddle
Speed: 50 rpm
Dissolution Specification:

On the basis of the above information, the dissolution method for the generic product should also be changed, and the new specification should be

Recommendations:

1. The dissolution testings conducted by Mylan Pharmaceuticals Inc. on its test product, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg, lot #2C010N, lot #2C011N, and lot #2C013N, respectively, are acceptable. The firm has conducted an acceptable in vivo bioequivalence study (submission dated June 6, 1997) comparing its 5 mg Capsules of the test product with 5

mg capsules of the reference product, Hytrin® manufactured by Abbott. The formulation for the 1 mg, 2 mg and 10 mg strengths are proportionally similar to the 5 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 1 mg, 2 mg and 10 mg capsules of the test product is granted. The 1 mg, 2 mg and 10 mg capsules of the test product are therefore deemed bioequivalent to the 1 mg, 2 mg and 10 mg capsules of Hytrin® manufactured by Abbott.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHUANG 3/11/98
FT INITIALED YCHUANG

Concur. Date: 3/18/98

/S/

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

3.1

Terazosin Hydrochloride
Capsules, 1mg, 2mg, 5mg & 10mg
ANDA #75-140
Reviewer: Sikta Pradhan
WP #75140AD.798

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
July 16, 1998

Review of an Amendment on Dissolution Data

Mylan Pharmaceuticals Inc. recently conducted an acceptable in vitro dissolution testing (dated January 30, 1998) and in vivo bioequivalence study on its test product, Terazosin hydrochloride capsules (submission dated June 6, 1997).

The firm has conducted the dissolution testing on the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in 900 mL of water at 37°C using USP Apparatus 2 (paddle) at 50 rpm. The dissolution data indicated that the test product meets the FDA (previously approved) dissolution specification of
minutes. Recently, the FDA has widen the time range of the dissolution and the current specification is 80% (Q) of the labeled amount dissolved in 60 minutes. The test product met both specifications,and therefore, no further action is needed on this application.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG /S/ 7/21/98
FT INITIALED YCHUANG

Concur: /S/ Date: 8/5/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-140 **SPONSOR :Mylan**
DRUG & DOSAGE FORM : Terazosin Hydrochloride Capsules
STRENGTH (s) : 5 mg
TYPE OF STUDY: SD X SDF X MULT OTHER
STUDY SITE: CLINICAL : Clin.& Pharm.Res., Inc. : Phoenix Intl.

STUDY SUMMARY :

Fasting Study: Two-way crossover fasting study in 25 subjects using 5 mg Terazosin Capsule (Mylan) vs 5 mg Hytrin^{R} Capsule of Abbott Lab. is acceptable. All parameters, $LnAUC_{0-t}$, $LnAUC_{0-inf}$ and LnC_{MAX}, are within 80-125% range of 90% CI.

Fed Study: Three-way crossover study in 17 subjects under fasting and fed conditions is acceptable. Mean differences (LSM) in AUC_{0-t} and AUC_{0-inf} of the test and reference products dosed under fed conditions were within 3% only and that in C_{MAX} was 15%. Geometric mean differences in $LnAUC_{0-t}$ and $LnAUC_{0-inf}$ were within 4% and that in LnC_{MAX} was within 13%.

DISSOLUTION :
Conditions: FDA Dissolution condition
Test product met FDA dissolution specifications of Q = 80% in 30 minutes. The in vitro dissolution testing data are acceptable.

PRIMARY REVIEWER : Sikta Pradhan **BRANCH : I**

INITIAL : /S/ **DATE :** 10-24-97

BRANCH CHIEF : Yih Chain Huang **BRANCH : I**

INITIAL : /S/ **DATE :** 10/24/97

ACTING DIRECTOR : Rabindra N. Patnaik,
DIVISION of BIOEQUIVALENCE

INITIAL /S/ **DATE :** 1/16/98

DIRECTOR : Douglas L. Sporn
OFFICE OF GENERIC DRUGS

INITIAL : _____ **DATE :** _____

OCT 2 1 1997

Terazosin Hydrochloride
Capsules, 5 mg
ANDA #75-140
Reviewer: Sikta Pradhan
WP #75140SD.697

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
June 6, 1997
September 3, 1997

Review of Bioequivalence Studies and Dissolution Data

Introduction:

Terazosin hydrochloride is an anti-hypertensive agent, It appears to exert its pharmacological effect by selective blockade of alpha-1-adrenoreceptors. It is indicated for the treatments of symptomatic benign prostatic hyperplasia and hypertension. It may be used alone or in combination with other anti-hypertensives. Terazosin is rapidly and almost completely absorbed following oral administration, with an oral bioavailability of about 90%. Food has little or no effect on the extent of absorption but it may delay the absorption. Terazosin has been shown to undergo minimal hepatic first-pass metabolism and nearly all of the circulating dose is in the form of the parent drug. The drug is highly bound to plasma proteins. Following oral administration of a single dose of 5 mg Terazosin hydrochloride, peak plasma levels have been observed at about 60 minutes with a half-life of 12 hours.

Terazosin is currently marketed as Hytrin®, 1, 2, 5 and 10 mg capsules, and as 2, 5 and 10 mg tablets by Abbott Lab. The recommended initial dose of terazosin hydrochloride is 1 mg taken at bedtime. Effective doses usually range from 1 to 5 mg daily.

In-Vivo Study:

The study was conducted by
Samples were analyzed at the
Canada, under the supervision of Principal Investigator and Richard
, Senior Scientific Director.

Study Design:

A randomized, open-label, single dose, two-way crossover bioequivalence study on the test product, Terazosin HCl, 5 mg capsules (Mylan) and reference product, Hytrin® (Abbott) 5 mg capsule was conducted according to the protocol # TERA9688 #961846).

Subjects: Twenty-six (26) healthy, non-smoking, male volunteers between 18-45 years of age, weighing within 10% of ideal weight for the height and body frame (according to the 1983

Metropolitan Life Insurance Table) were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.). The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink caffeine or alcoholic beverages for 48 hours prior to the initiation of the study until after completion of the study. No over - the - counter (OTC) medication, including vitamins were allowed for 48 hours prior to or during each study period. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

A. 1 x 5 mg Terazosin HCl capsule (Mylan), Lot # 2C012N
Lot size: apsules, Potency of the capsule is 99.0%

B. 1 x 5mg Hytrin^{R} capsules (Abbott), Lot # 17-010-AW-21
Potency of the capsule is 98.5%.

Dose Administration: A single dose of 5 mg Terazosin was administered with 240 mL of water.

Study Dates:
Clinical Period 1: January 31, 1997 - February 3, 1997
Clinical Period 2: February 14 1997 - February 17, 1997

Drug Washout Period: Fourteen days

Meal and Food Restrictions: All volunteers fasted for 10 hours prior to and 5 hours after drug administration. Water was given ad lib one hour before and one hour after dosing. A standard meal was served after the 5 hour post-dose blood collection. No alcohol, caffeine and xanthine-containing beverages was served during the study. Subjects remained at the clinic through the 36 hour blood draw. Subjects were required to return to the clinic for the 48 and 60 hour blood draw.

Dates of Dosing:
Period 1 was dosed on February 1, 1997
Period 2 was dosed on February 15, 1997.

Blood Sample Collection:

Blood samples (1x7 mL each) were collected in vacutainers tubes containing heparin before dosing at 0, and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 9.0, 12, 16, 24, 36, 48 and 60 hours after dosing. The plasma samples were separated and kept frozen at -12^{0}C or lower until analysis.

Date of First Sample Analysis: February 19, 1997

Date of Last Sample Analysis: March 13, 1997
Duration of Sample Storage: Less than a month

Assay Methodology:

Method: A
Detection was uased for the determination of Terazosin in human plasma.
Specificity: No interference was observed.

Linearity: The standard plots were linear in the concentration range of 0.5 ng/mL to 299.4 ng/ mL for terazosin. The average correlation coefficient of the calibration line was greater than 0.9975 or better.

Sensitivity: The lower limit of quantitation (LLOQ) was 0.5 ng/mL for terazosin; any value less than this was reported as zero.

Precision:
(I) Pre-study validation

Interday Precision from Standards (N=3):
5.9% (CV) at 0.50 ng/mL
1.3% (CV) at 4.97 ng/mL
1.1% (CV) at 44.74 ng/mL
1.1%(CV) at 223.7 ng/mL
0.9%(CV) at 298.27 ng/mL

Intraday Precision from Control Samples:
10.9% (CV) at 0.5 ng/L; (N=8)
6.4% (CV) at 1.5 ng/mL; (N=9)
1.4% (CV) at 179.77 ng/mL; (N=10)
1.9% (CV) at 239.69 ng/mL ; (N=10)

Interday Precision from Control Samples:
8.5% (CV) at 0.5 ng/mL; (N=20)
6.6% (CV) at 1.5 ng/mL; (N=21)
2.9% (CV) at 179.77 ng/mL; (N=22)
2.3% (CV) at 239.69 ng/mL; (N=22)

(ii) Within-study validation

Interday Precision from Standards (N=15 or 16):
11.9% (CV) at 0.50 ng/mL
4.5% (CV) at 4.99 ng/mL
6.5% (CV) at 44.91 ng/mL
5.5%(CV) at 224.57 ng/mL
7.5%(CV) at 299.43 ng/mL

Interday Precision from Control Samples:
5.4% (CV) at 1.5 ng/mL; (N=32)
5.9% (CV) at 179.66 ng/mL; (N=31)
6.0% (CV) at 239.54 ng/mL; (N=32)

Recovery:

The absolute recovery (after extraction and injection) of Terazosin in human plasma:
36.3% (CV) at 1.50 ng/mL; (N=10)
36.7% (CV) at 20.09 ng/mL; (N=9)
37.6% (CV) at 40.19 ng/mL; (N=10)

Stability:

Long Term (Frozen): Stable for 104 days at a nominal temperature of -22°C.

Short Term (Bench top): Stable at 22°C for 4 hours.

Freeze-Thaw: Stable after three freeze-thaw cycles.

Autosampler: Samples (after extraction) stable in the autosampler at a nominal temperature of 20°C for 21.9 hours

Stock Stability for Terazosin in Methanol: Stable at -22°C for 27 days.

Stock Stability for Prazosin (IS) in Methanol: Stable at -22°C for 45 days

SOP Deviation:

There were no significant SOP or protocol deviations in this study.

Results:

Twenty-six (26) volunteers were selected for the study. Subject #5 elected to withdraw from the study after Period 1 due to personal reasons and twenty-five volunteers completed the study. Fifty-seven (57) adverse events, including lightheadedness, pallor, headaches, dizziness, nausea, vomiting, nasal congestion, fainting, shortness of breath and hot flushes, were observed during the study. However, none of these effects were severe, and no medication was required for any clinical complaint. There were a total of 19 blood collection time deviation from the target times. The deviations ranged from 2 to 49 minutes late. The actual blood collection times were used for the calculations of the values for the pharmacokinetic parameters. All twenty-five (25) volunteers' plasma samples were analyzed. Mean plasma terazosin levels are presented in Table 1 (and Fig.1, attached) below:

Table 1
Mean Plasma Terazosin Levels (ng/mL)

Time (hour)	Test (A) 1x5 mg Capsule (Mylan) Lot # 2C012N	N	Reference (B) 1x5 mg Capsule (Abbott) Lot # 17-010-AW-21	N
0	0.00	25	0.00	25
0.25	3.66 (305)*	25	17.54 (192)	25
0.50	54.44 (74)	25	71.38 (57)	25
0.75	79.34 (39)	25	81.77 (33)	25
1.0	78.58 (36)	25	79.34 (29)	24
1.25	79.24 (29)	25	75.99 (24)	25
1.5	77.07 (27)	25	75.30 (17)	25
1.75	79.85 (24)	25	76.90 (14)	25
2.0	79.79 (23)	25	75.03 (14)	25
2.5	74.65 (23)	25	72.57 (15)	25
3.0	72.72 (22)	25	68.98 (15)	25
4.0	67.32 (21)	25	66.60 (16)	25
6.0	52.82 (21)	25	51.32 (14)	25
9.0	39.95 (24)	25	37.78 (17)	25
12.0	26.94 (22)	25	26.32 (18)	25
26.0	18.54 (25)	25	17.92 (20)	25
24.0	10.75 (27)	25	10.29 (21)	25
36.0	4.91 (29)	25	4.65 (26)	25
48.0	2.81 (31)	24	2.42 (29)	24
60.0		24	1.51 (34)	25

* Coefficient of Variation
N Number of Subjects

The pharmacokinetic parameters derived from plasma terazosin levels are presented in Table 2. Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM).

Table 2
Mean Pharmacokinetic Parameters for Plasma Terazosin (ng/mL)

Parameters	Test(A)	Ref.(B)	%Difference between A & B	
(Subjects=25)				
(Using Arithmetic Means)				
AUC_{0-T} (ng.hrs/mL)	1001.40 (20)*	975.21 (16)		2.7
AUC_{0-inf} (ng.hrs/mL)	1037.19 (21)	1007.57 (16)		2.9
C_{MAX} (ng/mL)	96.61 (23)	95.77 (18)		0.9
T_{max} (hour)	1.290 (64)	0.910 (62)		
t1/2 (hour)	14.65 (16)	14.57 (17)		
KE (1/hour)	0.0484 (16)	0.0490 (18)		
Parameters	Test(A)	Ref.(B)	A/Bx100	90% C.I.
Using least squares means (LSM)				
$LnAUC_{0-T}$	6.8898	6.8708		**97; 107**
Geometric mean:	982.20	963.72	101.9	
$LnAUC_{0-inf}$	6.9245	6.9030		**97; 108**
Geometric mean	1016.89	995.26	102.2	
LnC_{MAX}	4.5446	4.5471		**93; 108**
Geometric mean	94.12	94.36	100.0	
Intrasubject CV%:	10.56 ($LnAUC_{0-T}$)			
	10.72 ($LnAUC_{0-inf}$)			
	16.12 (LnC_{MAX})			

* Coefficient of Variation

Both test and reference drugs produced peak concentration in terazosin between 30 minutes to 2 hours after their administration. The differences between the test and reference products in AUC_{0-T}, AUC_{0-inf} and C_{MAX} were less than 3%. All these differences were statistically nonsignificant. The 90% confidence intervals for , $LAUC_{0-T}$, , $LAUC_{0-inf}$ and LC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

Limited food study (Protocol #TERA-9689):

The firm has submitted the results of a single oral 5 mg dose three-way crossover post-prandial bioequivalence study conducted on the test (1x5 mg terazosin capsule of Mylan) and reference product (1x5 mg Hytrin[R] capsule) in order to determine the effect of food on the bioavailability of those products.
Eighteen healthy male volunteers entered into the study after completing a physical examination and laboratory screening tests.

Date of Study: Clinical Period I: January 24, 1997- January 27, 1997
Clinical Period II: February 7, 1997 - February 10, 1997
Clinical Period III: February 21, 1997 - February 24, 1997

Analytical Period: February 27, 1997 - March 18, 1997

Dosing Dates: Period I: January 25, 1997
Period II: February 8, 1997
Period III: February 22, 1997

Dosing Schedule:

Treatment A: 1x5 mg Terazosin HCL capsule (Mylan), Lot #2C012N, after an overnight fast of at least 9.5 hours; Production Lot)sules

Treatment B: 1x5 mg Terazosin HCL capsule (Mylan), Lot #2C012N, immediately after a standard breakfast

Treatment C: 1x5 mg Hytrin[R] capsule (Abbott), Lot # 17-010-AW-21 (Exp. 8/98), after a standard breakfast

The randomization for this study is as follows:

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

Following dosing, subjects remained seated for 4 hours after dosing. For safety, sitting blood pressure and heart rate were measured predose and at 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48 and 60 hours after dosing.

Drug Washout Period: Two weeks

Meal and Food Restrictions: Water was given ad lib one hour before and one hour after dosing. A standard meal was served after the 5 hour post dose followed by an evening meal 10 hours after dosing and snacks at appropriate times thereafter. No alcohol, caffeine and xanthine-containing beverages was served during the study. Subjects remained at the clinic through the 36 hour blood draw. Subjects were required to return to the clinic for the 48 and 60 hour blood draw.

Blood Sample Collection:

Blood samples (1x7 mL each) were collected in vacutainers tubes containing heparin before dosing at 0, and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 9.0, 12, 16, 24, 36, 48 and 60 hours after dosing. The plasma samples were separated and kept frozen at -12°C or lower until analysis.

Samples were Assayed at
Date of First Sample Analysis: February 27, 1997
Date of Last Sample Analysis: March 18, 1997
Duration of Sample Storage: Less than a month

Assay Methodology:

Method: A d with was used for the determination of Terazosin in human plasma. The method validation has previously been discussed in the fasting study. As mentioned earlier in this review report (page 2, 3 & 8), the fasting study samples were analyzed in the period of February 19, 1997 - March 13, 1997, and the fed study samples were analyzed in the period of February 27, 1997 - March 18, 1997, under same conditions of experiments. Therefore, it is not necessary to discuss the analytical method validation again in this fed study. The within-study validation data in both studies were similar as expected.

Results:

One (Subject # 7) volunteer could not complete the study, and therefore, the study was completed by seventeen (17) subjects. There were 58 post-dose medical events reported for this study. Of these, 47 were listed as probably or possibly drug related. Subject #7 was withdrawn from the study after Period 2 dosing due to a medical event (tachycardia) which was determined to be mild and possibly drug related. There were no serious or life-threatening medical events reported for this study. Mean plasma terazosin levels are presented in Tables 3 (and in Figure 2 attached) below. The pharmacokinetic parameters derived from plasma terazosin levels are presented in Table 4.

Table 3
Mean Plasma Terazosin Levels (ng/mL)

Time (hour)	Test 5 mg Cap. (Mylan) Lot # 2C012N **Fasted (A)**	Test 5 mg Cap. (Mylan) Lot # 2C012N **fed (B)**	Reference 5 mg Cap. (Abbott) Lot# 17-010-AW-21 **fed (C)**
0.0	0.0	0.0	0.0
0.33	11.55 (112)*	2.74 (351)	10.15 (252)
0.67	70.86 (54)	15.17 (203)	33.50 (105)
1.0	74.89 (40)	23.22 (129)	45.35 (80)
1.33	73.68 (35)	32.41 (90)	55.93 (60)
1.67	71.80 (31)	42.76 (63)	62.66 (43)
2.0	71.78 (26)	53.21 (41)	67.34 (33)
2.5	69.44 (27)	61.37 (29)	71.60 (28)
3.0	68.00 (22)	68.11 (26)	70.18 (25)
4.0	62.78 (24)	66.95 (27)	66.80 (26)
6.0	52.95 (21)	55.65 (26)	54.10 (24)
9.0	39.37 (23)	41.56 (28)	40.10 (25)
12.0	26.72 (26)	28.45 (28)	28.37 (27)
16.0	18.75 (28)	19.78 (30)	19.75 (30)
24.0	11.01 (32)	11.80 (34)	12.12 (33)
36.0	5.06 (38)	5.27 (44)	5.27 (39)
48.0	2.93 (38)	2.91 (51)	3.05 (46)
60.0	1.68 (51)	1.82 (63)	1.72 (49)

* Coefficient of Variation
Number of Subjects = 17

Table 4
Mean Pharmacokinetic Parameters of Terazosin
(Number of Subjects = 17)

Parameters (using arithmetic means)	Test(A) Fasted	Test(B) Fed	REF.(C) Fed
AUC_{0-T} (ng.hrs/mL)	982.69 (25)*	952.35 (26)	990.69 (24)
AUC_{0-inf} (ng.hrs/mL)	1023.16 (25)	995.64 (28)	1028.76 (25)
C_{MAX} (ng/mL)	89.22 (28)	74.29 (23)	85.41 (23)
T_{max} (hour)	1.363 (59)	2.922 (40)	2.127 (68)
t1/2 (hour)	15.323 (15)	15.19 (16)	14.691 (14)
KE (1/hour)	0.046 (16)	0.046 (13)	0.048 (13)

Parameters (using LS means)	Test(A) Fasted	Test(B) Fed	REF.(C) Fed	T/R (B/C)	T/T (B/A)
AUC_{0-T}	980.35	958.34	987.03	0.97	0.98
AUC_{0-inf}	1020.43	1000.14	1026.99	0.97	0.98
C_{MAX}	88.72	73.68	86.51	0.85	0.83

Parameters	Test(A) Fasted	Test(B) Fed	REF.(C) Fed	T/R (B/C)	T/T (B/A)
$LnAUC_{0-T}$	6.8616	6.8277	6.8694		
Geometric mean	954.89	923.06	962.37	0.96	0.97
$LnAUC_{0-inf}$	6.9011	6.8683	6.9057		
Geometric mean	993.37	961.31	997.95	0.96	0.97
LnC_{MAX}	4.4531	4.2847	4.4220		
Geometric mean	85.89	72.58	83.26	0.87	0.84

* Coefficient of Variation

Results of this fed study indicate that food has little or no effect on the extent of absorption but it delayed the time to peak concentration by about 1 hour.

In-Vitro Dissolution:

The firm has conducted an acceptable dissolution testing on Terazosin HCl capsules using FDA dissolution conditions. The dissolution testing data are presented in Table 5 below:

Table 5. In Vitro Dissolution Testing

Drug: Terazosin HCL
Dose Strengths: 5 mg Capsules
ANDA No.: 75-140
Firm: Mylan Pharmacal, Inc.
Submission Date: June 6, 1997
File Name: 75140SD.697

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 50
No. Units Tested: 12
Medium: Water, Volume: 900 mL
Specifications: NLT : the labeled amount is dissolved
:es (Mylan proposed).
Reference Drug: Abbott's HytrinR Capsules, 5 mg
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 2C012N Strength 5 mg Capsules			Reference Product Lot # 17-010-AW-21 Strength 5 mg Capsules		
	Mean %	Range	%CV	Mean %	Range	%CV
15	98		6.8	88		21.1
30	101		3.8	109		1.6
45	102		3.0	109		1.4

Compositions

The compositions of Terazosin Capsules, 5 mg are presented below:

Ingredient	Amounts/Capsule
Terazosin Hydrochloride, USP	5.47
Total:	**150.0**

Comments:

1. The firm's in vivo bioequivalence study under fasting conditions is acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for $LnAUC_{0-t}$, $LnAUC_{inf}$ and Ln C_{max} are within the acceptable range of 80-125% under fasting conditions.

2. The in vivo bioequivalence study conducted on the test and reference products under non-fasting conditions is also acceptable.

3. The in vitro dissolution testing conducted on 5 mg Terazosin Hydrochloride Capsules using FDA dissolution conditions is acceptable. On the basis of the dissolution data, the Division of Bioequivalence recommends the following tolerance for the test product:

Note: This comment is not for FOI

According to the current bioequivalence requirements of the Division, the non-fasting study for Terazosin tablets, has been waived. However, it is not known at the present time, if the same policy is applicable to Terazosin Capsules also.

Recommendations:

1. The in vivo bioequivalence study conducted under fasted conditions by Mylan Pharmaceuticals Inc. on its 5 mg Terazosin Capsules of Lot # 2C012N, versus the listed reference product, Hytrin^R 5 mg Capsules manufactured by Abbott has been found acceptable to the Division of Bioequivalence.

2. The in vivo bioequivalence study conducted under fed conditions by Mylan Pharmaceutical, Inc. on its 5 mg Terazosin Capsules of Lot # 2C012N, versus the listed reference product, Hytrin^R 5 mg Capsules manufactured by Abbott has been found acceptable to the Division of Bioequivalence.

   These studies demonstrate that Mylan's Terazosin capsules, 5 mg are bioequivalent to the reference product, Hytrin^R capsules, 5 mg, manufactured by Abbott.

3. The in vitro dissolution testing conducted by Mylan Pharmaceutical, Inc. on its Terazosin Hydrochloride 5 mg capsules (lot # 2C012N) is acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at

37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

g

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

(S)

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- 10/17/97

Concur: ---------- (S) Date: 10/21/97
Rabindra Patnaik, Ph. D.
Acting Director, Division of Bioequivalence

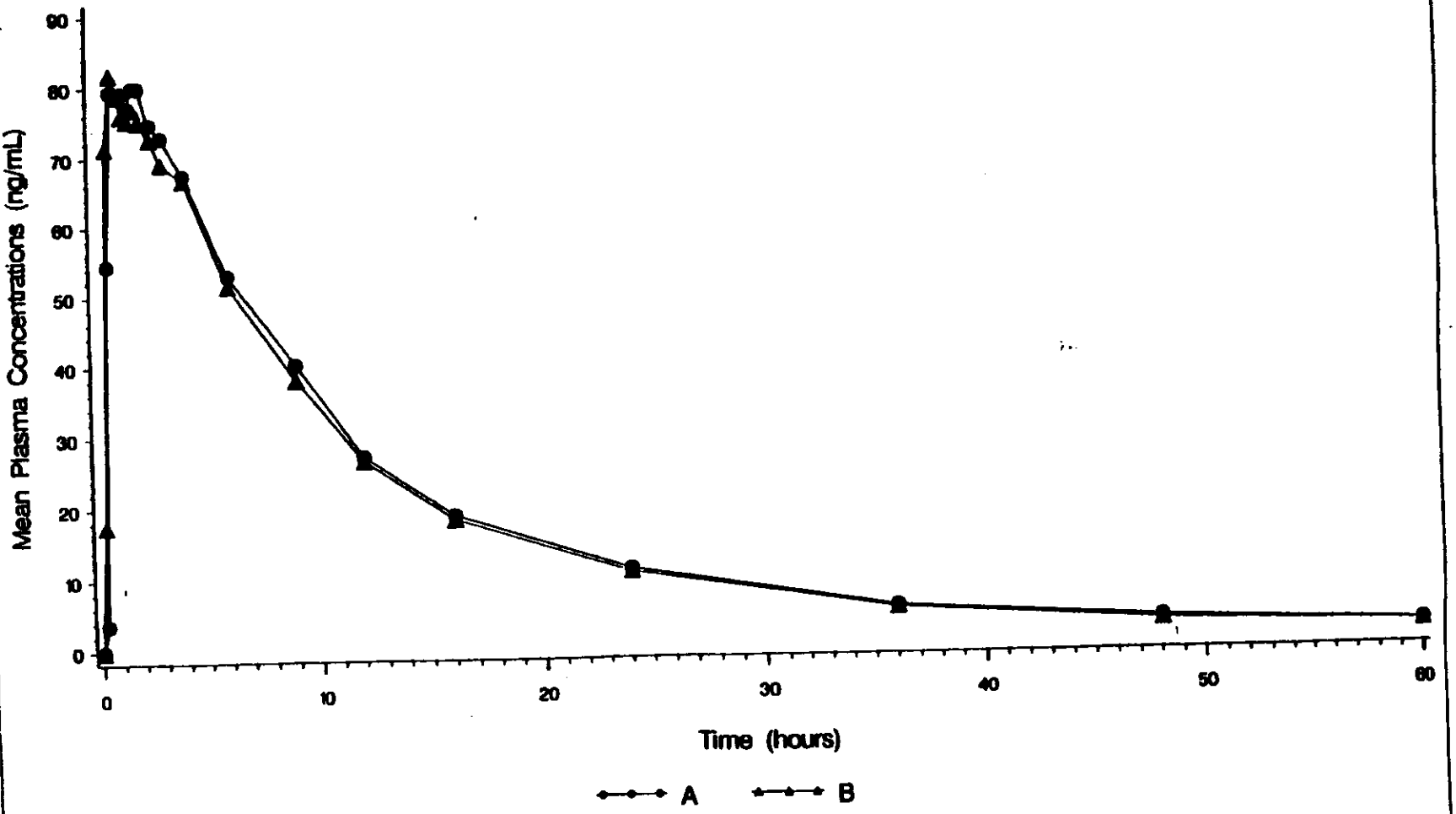
Fig 1

TERAZOSIN (TERA—9688)

Total Dose: 5 mg (1x5mg Capsule), Study Type: Fasting

Mean Terazosin Plasma Concentrations

N= 25



Treatment A is A (Terazosin)
xtment B is B (Hytrin)

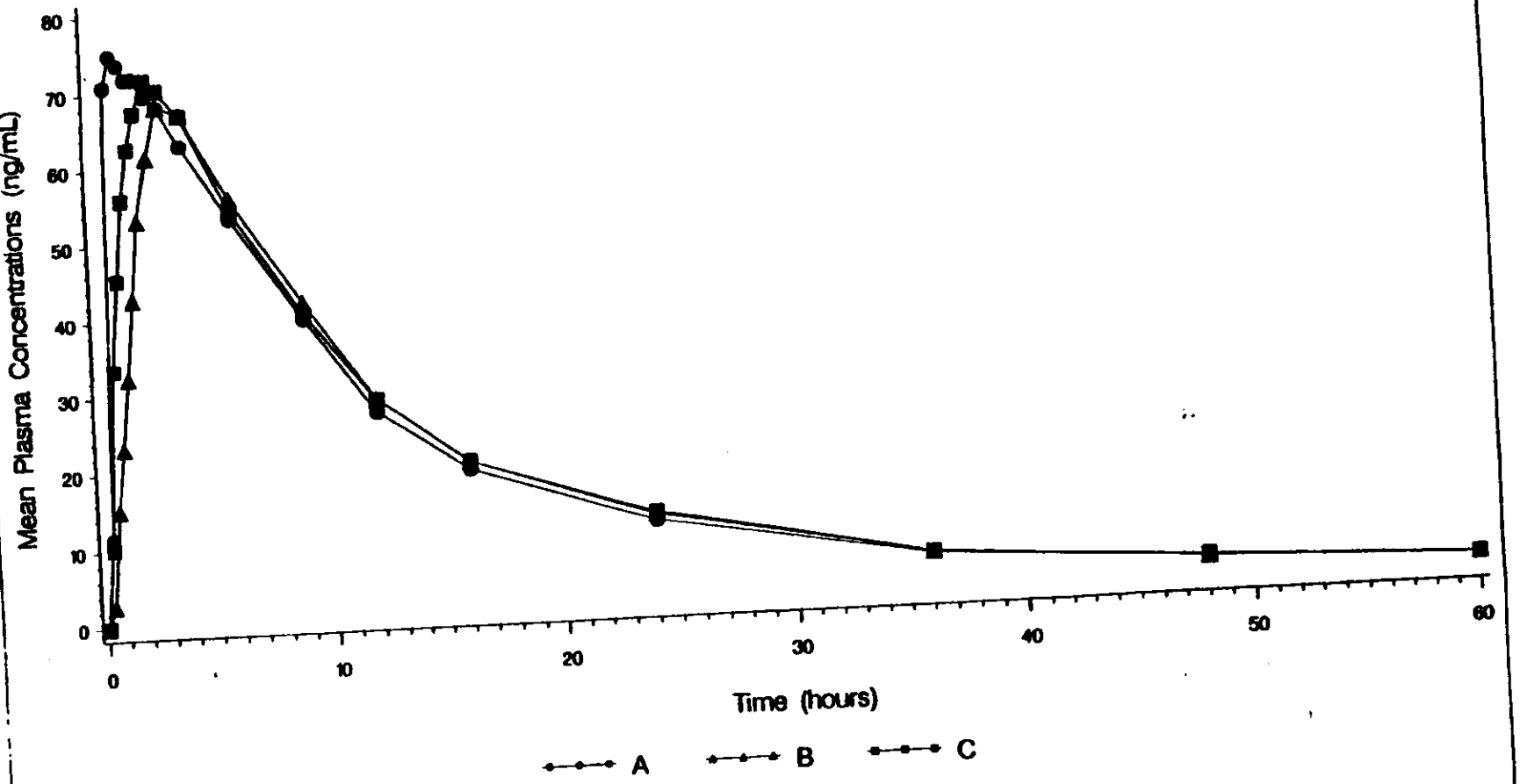
Fig. 2

TERAZOSIN (TERA–9689)

Total Dose: 5 mg (1x5mg Capsule), Study Type: Fed

Mean Terazosin Plasma Concentrations

N= 17



Treatment A is A (Terazosin–Fast)
Treatment B is B (Terazosin–Fed)
Treatment C is C (Hytrin–Fed)

ATTACHMENT 1

ATTACHMENT 2

MAR 18 1998

FILE COPY

Terazosin Hydrochloride
Capsules, 1mg, 2mg, 5mg & 10mg
ANDA #75-140
Reviewer: Sikta Pradhan
WP #75140DW.198

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
January 30, 1998
February 6, 1998
February 24, 1998

Review of Dissolution Data and Waiver Request

Introduction:

Mylan Pharmaceuticals Inc. has recently conducted an acceptable in vitro dissolution testing and in vivo bioequivalence study on Terazosin hydrochloride 5 mg capsules (submission dated June 6, 1997). In this amendment, the firm has reported the dissolution testing data of its test product, Terazosin 1 mg, 2 mg and 10 mg capsules and requested the waiver of in vivo bioequivalence study on those strengths. The firm has also indicated that the dissolution of the 1 mg and the 2 mg products were observed to be unpredictable in water to meet the specification of NLT minutes. Therefore, the firm has proposed to adopt the Tier-2 dissolution method in 0.1 N HCL with pepsin as recently published in the USP 23, Twentieth Interim Revision, page 4, <711> guidance on dissolution of hard gelatin capsules.

Dissolution:

The firm has reported the following dissolution data:

1. The firm has conducted dissolution testing on the test and the reference (Hytrin®) products, 1 mg, 2 mg, 5 mg and 10 mg Terazosin capsules using water (900 mL) as the dissolution medium.

2. The firm has also conducted dissolution testing on the test and the reference products using 0.1 N HCL with pepsin as dissolution medium, and proposed to use this method for its test product.

The data obtained from the dissolution testing conducted in water are presented in Table 1 below:

Table 1. In Vitro Dissolution Testing

Drug: Terazosin HCL
Dose Strengths: 5 mg, 10 mg, 2 mg and 1 mg Capsules
ANDA No.: 75-140
Firm: Mylan Pharmaceuticals Inc.

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 50
No. Units Tested: 12
Medium: Water, Volume: 900 mL
Specifications: [illegible] labeled amount is dissolved
[illegible] tes.
Assay Methodology.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	**Test Product** Lot # 2C012N Strength 5 mg Capsules			**Reference Product** Lot # 17-010-AW-21 Strength 5 mg Capsules		
	Mean %	Range	%CV	Mean %	Range	%CV
15	98		6.8	88		21.1
30	101		3.8	109		1.6
45	102	9[illegible]	3.0	109		1.4
Sampling Times (Minutes)	**Test Product** Lot # 2C013N Strength 10 mg Capsules			**Reference Product** Lot # 18-108-AW-21 Strength 10 mg Capsules		
15	92	84% - 98%	5.0	75%	35-97%	31.1
30	95	91% - 99%	3.3	94%	97-98%	3.8
45	96	93% - 100%	2.6	92%	89-94%	1.8
Sampling Times (Minutes)	**Test Product** Lot # 2C011N Strength 2 mg Capsules			**Reference Product** Lot # 13-657-AW-21 Strength 2 mg Capsules		
15	86%		10.5	67%		39.8
30	89%		7.6	91%		2.2
45	91%		6.1	91%		2.1
Sampling Times (Minutes)	**Test Product** Lot # 2C010N Strength 1 mg Capsules			**Reference Product** Lot # 15-852-AW-21 Strength 1 mg Capsules		
15	90%		6.1	82%		20.3
30	92%		3.9	92%		3.7
45	93%		3.3	92%	[illegible]	3.1

The in vitro dissolution testing conducted by the firm on its test product meets the FDA dissolution specification of [illegible].

of the labeled amount dissolved in

Compositions

The comparative formulations of Terazosin Capsules, 1 mg, 2 mg, 5 mg and 10 mg are presented in Table 2 below. These formulations are proportionally similar.

Table 2

	10 mg Cap	5 mg Cap	2 mg Cap	1 mg Cap
Ingredient	mg/cap	mg/cap	mg/cap	mg/cap
Terazosin Hydrochloride, USP	10.94	5.47	2.188	1.094
Total:	**150.0**	**150.0**	**150.0**	**150.0**

Comments:

1. The firm has conducted the dissolution testing for the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in water. The dissolution data indicated that the test product meets the FDA dissolution specification of 80% (Q) of the labeled amount dissolved in 30 minutes.

2. As the test product meets the Tier I dissolution (in water), the firm's request to use the Tier II dissolution method as published in the USP 23, Twentieth Interim Revision, page 4 for hard gelatin capsules is denied. Therefore, the dissolution testing conducted on the test and reference products using 0.1 N HCL plus pepsin as dissolution medium is not acceptable, and consequently, these dissolution data submitted to the Division of Bioequivalence will not be reviewed.

3. The Agency has recently revised the dissolution specification for Terazosin HCl Capsules. The modified dissolution specification for this product is the following:

Medium: water, 900 mL
Apparatus: USP 23, paddle
Speed: 50 rpm
Dissolution Specification: NLT

4. The comparative dissolution testing data of the test and reference capsules of 1 mg, 2 mg and 10 mg strengths meet the currently revised dissolution specification, and therefore, the waiver of in vivo bioequivalence study on 1 mg, 2 mg and 10 mg strengths of the test product is granted.

Note: This comment is not for FOI

There is no USP dissolution method for Terazosin Hydrochloride Capsules. The reference product, Hytrin® capsule was tested against the FDA dissolution method (900 mL water, paddle 50 rpm, specification NLT 80% in 30 min.). Recently, the dissolution specification for the reference product has been changed, and the current dissolution specification for Hytrin® capsule is the following:

Medium: water, 900 mL
Apparatus: USP 23, paddle
Speed: 50 rpm
Dissolution Specification:

On the basis of the above information, the dissolution method for the generic product should also be changed, and the new specification should be NLT

Recommendations:

1. The dissolution testings conducted by Mylan Pharmaceuticals Inc. on its test product, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg, lot #2C010N, lot #2C011N, and lot #2C013N, respectively, are acceptable. The firm has conducted an acceptable in vivo bioequivalence study (submission dated June 6, 1997) comparing its 5 mg Capsules of the test product with 5

mg capsules of the reference product, Hytrin® manufactured by Abbott. The formulation for the 1 mg, 2 mg and 10 mg strengths are proportionally similar to the 5 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 1 mg, 2 mg and 10 mg capsules of the test product is granted. The 1 mg, 2 mg and 10 mg capsules of the test product are therefore deemed bioequivalent to the 1 mg, 2 mg and 10 mg capsules of Hytrin® manufactured by Abbott.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG /S/ 3/11/98
FT INITIALED YCHUANG

Concur: /S/ Date: 3/18/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:#75-140 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. However, you should be informed of the following:

1. You have conducted the dissolution testing for the test and reference products, Terazosin Hydrochloride Capsules, 1 mg, 2 mg and 10 mg in water. The dissolution data indicated that the test product meets the FDA dissolution specification of of the labeled amount dissolved in es.

2. As the test product meets the Tier I dissolution (in water), your request to use the Tier II dissolution method as published in the USP 23, Twentieth Interim Revision, page 4 for hard gelatin capsules is denied. Therefore, the dissolution testing conducted on the test and reference products using 0.1 N HCL plus pepsin as dissolution medium is not acceptable, and consequently, these dissolution data submitted to the Division of Bioequivalence will not be reviewed.

3. The Agency has recently revised the dissolution specification for Terazosin HCl Capsules. The modified dissolution specification for this product is the following:

   Medium: water, 900 mL
   Apparatus: USP 23, paddle
   Speed: 50 rpm
   Dissolution Specification:

4. The comparative dissolution testing data of the test and reference capsules of 1 mg, 2 mg and 10 mg strengths meet the currently revised dissolution specification, and therefore, the waiver of <u>in vivo</u> bioequivalence study on 1 mg, 2 mg and 10 mg strengths of the test product is granted.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

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 reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

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