CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-315

BIOEQUIVALENCE

JUL | 1996

Terazosin Hydrochloride Tablets
5 mg
ANDA # 74-315
Reviewer: Man M. Kochhar
74315W.596

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
May 3,1996

REVIEW OF AN AMENDMENT - BIOEQUIVALENCE STUDY

The firm has responded to our deficiency letter of February 7, 1996 regarding the change in raw material of terazosin hydrochloride

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. Results are presented in Table 1. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in minutes. The batch size was ets.

See Addendum dated 12/3c/96

COMMENTS:

1. The firm is changing the of terazosin hydrochloride tablet. The firm by conducting an acceptable bioequivalence study has shown that terazosin hydrochloride tablets(Geneva's) is bioequivalent to reference product Hytrin (terazosin hydrochloride tablets. Similarly Geneva's 5 mg capsules (F) were bioequivalent to Hytrin capsules reference). Therefore, the change of to Form should not change the bioavailability of the product.

2. The in vitro dissolution testing conducted for 5 mg tablets of the test and reference products shows greater than 75% of the labeled amount of the terazosin hydrochloride dissolved in 30 minutes.

3. The waiver of in vivo bioequivalence study requirement is granted.

DEFICIENCY: None

RECOMMENDATIONS:

1. The dissolution testing conducted by Geneva Pharmaceuticals on its Terazosin Hydrochloride Form IV 5 mg tablets is acceptable. The firm has previously conducted an acceptable fasting bioequivalence study on its 5 mg tablets . Therefore, the waiver of in vivo bioequivalence study requirement for Geneva Pharmaceuticals 5 mg tablets is granted. The 5 mg Terazosin Hydrochloride tablets from Geneva Pharmaceuticals are therefore bioequivalent to 5 mg, of Terazosin Hydrochloride

amend

manufactured by Geneva Pharmaceuticals based on 21 CFR 320.22 (d) (4).

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 XXIII apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

> Not less than of the labeled amount of the drug in the tablet dissolbed in minutes.

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramakant M. Mhatre 6/26/96

Concur: /S/ Date: 7/1/96
for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/6-13-96; 6-25-96; 74315 W

TABLE 1

DISSOLUTION

	Test Product	Ref. Product
Product	Terazosin HCl 5 mg tablets	Terazosin HCl 5 mg tablets
Manufacturer	Geneva	Geneva
Lot #	6495045	6493050
Exp.	6/97	8/95
Potency	94.5%	98.0%
Dissolution	97% @ 10 min 98% @ 20 min 98% @ 30 min 97% @ 40 min	100% @ 10 min 101% @ 20 min 101% @ 30 min 102% @ 40 min
Methodology	900 mL of Water @ 37°C Apparatus 2 (Paddle) @ 50 rpm Quantitation:	900 mL of Water @ 37°C Apparatus 2 (Paddle) @ 50 rpm Quantitation:
Specifications	NLT in	NLT in

Terazosin Hydrochloride Tablets
5 mg
ANDA #74-315
Reviewer: Moheb H. Makary
74315W.D98

Geneva Pharmaceuticals, Inc.
Broomfield, Co.
Submission Date:
May 3, 1996

Addendum to the May 3, 1996 Review

In the original review (review dated July 1, 1996), the reviewer stated that the firm is changing the Form II to Form IV raw material of Terazosin HCl Tablet. The reviewer's reference to the dihydrate was an error since both Forms ( ) were Terazosin HCl raw materials. This error has no impact on the bio waivers which have been granted for the change from

Moheb H Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

Concur: /S/ Date: 12/30/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

FEB 7 1996

Terazosin Hydrochloride Tablets
5 mg
ANDA # 74-315
Reviewer: Man M. Kochhar
74315W.993

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
January 18, 1996

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

The firm with an acceptable bioequivalence study has submitted the dissolution data for 5 mg tablets, in support for a waiver request for bioequivalence study for a change in the raw material Terazosin hydrochloride from

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. Results are presented in Table 1. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in minutes.

The batch size was tablets.

COMMENTS:

1. The firm is changing the different polymorph) of terazosin hydrochloride. The firm must show that this change in polymorph will not effect the bioavailability of the final product.

2. The in vitro dissolution testing conducted for 5 mg tablets of the test and reference products shows greater than of the labeled amount of the terazosin hydrochloride dissolved in minutes.

3. The waiver of in vivo bioequivalence study requirement can not be granted at this time.

DEFICIENCY: The firm must show that the change in polymorph of terazosin hydrochloride will not effect the bioavailability of the tablets.

RECOMMENDATIONS:

1. The dissolution testing conducted by Geneva Pharmaceuticals on its new material (raw material specifications) Terazosin Hydrochloride, 5 mg tablets is acceptable. The application is incomplete as descrived under deficiency. Therefore, the waivers of in vivo bioequivalence study requirement for Geneva Pharmaceuticals 5 mg tablets can not granted.

The firm should be informed of the deficiency.

Man M. Koehhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED MPARK
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TABLE 1

DISSOLUTION

	Test Product	Ref. Product
Product	Terazosin HCl 5 mg tablets	Terazosin HCl 5 mg tablets
Manufacturer	Geneva	Geneva
Lot #	6495045	6493050
Exp.	6/97	8/95
Potency	94.5%	98.0%
Dissolution	97% @ 10 min 98% @ 20 min 98% @ 30 min 97% @ 40 min	100% @ 10 min 101% @ 20 min 101% @ 30 min 102% @ 40 min
Methodology	900 mL of Water @ 37°C Apparatus 2 (Paddle) @ 50 rpm Quantitation:	900 mL of Water @ 37°C Apparatus 2 (Paddle) @ 50 rpm Quantitation:
Specifications	NLT Q) in n	NLT (Q) in min

OCT 16 1995

Terazosin Hydrochloride
5 mg Tablet
ANDA # 74-315
Reviewer: Man M. Kochhar
74315SWD.

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
April 21, 1995

REVIEW OF BIOEQUIVALENCE STUDY, WAIVER REQUEST, AND DISSOLUTION DATA

The purpose of this study is to compare the rate and extent of terazosin hydrochloride absorption in fasting healthy adult male volunteers following a single dose of 5 mg of test and reference product (Hytrin, Abbott). The protocol was designed for a two-way crossover, single dose bioequivalence study.

The firm is also requesting waiver of 1 mg, 2 mg, and 10 mg terazosin hydrochloride tablets.

BACKGROUND:

Terazosin hydrochlorideis a quinazoline derivative. It is freely soluble in water and isotonic saline. Terazosin hydrochloride tablets are available in 1 mg, 2 mg, 5 mg and 10 mg strengths.

Terazosin hydrochloride is an antihypertensive agent which appears to exert its pharmacological effect by selective blockade of alpha-1-adrenoreceptors. Systolic and diastolic blood pressures are lowered in both the supine and standing positions. Orally administered terazosin is essentially completely absorbed in man. Nearly all of the circulating dose is in the form of parent drug. Food has little or no effect on bioavailability. The plasma levels of the free base peak in about 1 hour, and then decline, with a half-life of approximately 12 hours. Hepatic metabolism is extensive, with approximately 60% of the drug excreted via bile-feces, and 40% excreted in urine.

Terazosin can cause marked hypotension, especially postural hypotension, and syncope, in association with the first dose, or first few doses of therapy. Occasionally, the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120 to 160 beats per minutes.

IN-VIVO STUDY:

The objective of this study is to compare the relative bioavailability of terazosin hydrochloride 5 mg tablet (Geneva) with that of Hytrin 5 mg tablet (Abbott) in healthy male volunteers under fasting conditions.

The firm is requesting a waiver of 1 mg, 2 mg and 10 mg terazosin hydrochloride tablets based on the fasting study of 5 mg tablets.

The study was conducted by PRACS Institute, Ltd, Fargo, ND, protocol # B-08143 under the supervision of

STUDY DESIGN:

The fasting study was designed as a randomized, single dose (5 mg tablet), two-way crossover bioequivalence study under fasting conditions.

Subjects:

The study employed twenty-six (26) healthy male volunteers (24 plus two alternates) between 18 and 41 years of age and within ±10% of the ideal body weight for their height and body frame (Metropolitan Insurance Company Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were not allowed to take any prescription medications and/or OTC preparations for at least two weeks prior to the start and until the end of the study. The volunteers should be non smokers and not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing and until study completion.
Blood pressure and heart rate were monitored prior to dosing and at 1, 2, 3, 4, 6, 8, 12, and 24 hours after the dose. Vital signs were measured at other times when it was deemed necessary.

The subjects were housed in the PRACS live-in facility from 12 hours before until 36 hours after the drug administration. The subjects returned for the blood draw at 48 and 60 hours.
The subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 2 hours of drug administration.

Method:

The product and dosage employed in this study were as follows:

A: Test: One 5 mg tablet terazosin hydrochloride (test drug), lot # 6493050 with 240 mL of water.
Batch Size: Expiry date: 8/95
Content Uniformity: 96.8% Potency: 99.1%

B. Reference: One 5 mg tablet of Hytrin (Abbott), lot # 47-581-AA-21 with 240 mL of water. Expiry date: 1/94.
Content Uniformity: 95.2% Potency: 98.7%

Ten (10) mL of venous blood were drawn in Vacutainers with EDTA at 0, 0.17, 0.33; 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 10, 12, 16, 24, 36, 48, and 60 hours. The plasma was separated and promptly

frozen for analysis.

WASHOUT PERIOD: 7 DAYS

ANALYTICAL METHODOLOGY:

Plasma terazosin was measured by a specific method using

ASSAY VALIDATION

1. Linearity: 1 to 150 ng/mL

2. Sensitivity: 1 ng/mL. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma sample from the subjects in the study indicated no interference with terazosin or the internal standard.

4. Accuracy & Precision

Actual (ng/mL)	2.00	15.00	70.00
Observed (ng/mL)	2.01	14.20	74.00
Accuracy %	101	94.7	106
CV %	4.53	3.89	7.01

5. The assay was validated by analyzing three single standard curve sets with three sets of high (70.0 ng/mL), medium (15.0 ng/mL) and low (2.00 ng/mL) QC samples for a total of three days. The standard curve concentrations ranged from 1.00 to 150 ng/mL. The assay was documented to be reproducible. For standards, the intra-day precision was 5.7% or better for each of the three days, and the inter-day precision was 10.2% or better. The mean accuracy was within the range of 92.1% to 110%

6. The recovery was defined as the percent of terazosin recovered after extraction of matrix samples compared to an unextracted standard. (It is not possible to establish the true recovery in protein precipitation procedures due to the loss of some volume during the precipitation step). The mean recovery was 91.7%, 104% and 91.6%. The mean recovery of the internal standard, propranolol dihydrochloride, was determined from one set of three 1000 ng/mL samples to be 98.1%

7.The stability of terazosin at three different concentrations in plasma was evaluated over three freeze-thaw cycles. The three sets of controls included high (70.0), medium (15.0), and low (2.0). These samples were subjected to three freeze and thaw cycles before analyzing. The results show that the mean change for terazosin was +1.0%, -2.0% and -4.0%. The stability of terazosin in plasma during frozen storage was documented over the course of 46 days. The in process stability was performed at

three different concentrations (70.0 ng/mL, 15.0 ng/mL and 2.00 ng/mL). These samples were prepared and allowed to sit next to HPLC for 24 hours at room temperature prior to analysis. The results show that terazosin was stable during the maximum time required for sample processing at room temperature.

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) were carried out to compare formulations at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for terazosin pharmacokinetic parameters. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

All of the 26 subjects (24 plus 2 alternates) enrolled in the study completed the crossover. The plasma samples from first 24 subjects (the first 24 subject by number that completed the study) were assayed for terazosin as per the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of terazosin are given in Table 1 and 2. The mean plasma terazosin concentrations are given in Figure 1.

TABLE1

Mean Plasma Concentration of Terazosin (N=24)

Time (hours)	Geneva's Terazosin Lot # 6493050 ng/mL (CV%)	Abbott's Hytrin Lot # 47-581-AA21 ng/mL (CV%)	T/R
0	0.0 (-)	0.0 (-)	0.0
0.17	13.68 (121)	14.05 (187)	0.97
0.33	49.46 (63)	48.48 (96)	1.02
0.5	61.32 (50)	60.60 (68)	1.01
0.75	65.45 (39)	71.51 (49)	0.91
1	65.52 (37)	66.17 (47)	0.99
1.5	56.19 (35)	64.35 (44)	0.87
2	54.18 (32)	59.42 (44)	0.91
3	54.93 (25)	55.70 (46)	0.99
5	48.97 (19)	50.92 (46)	0.97
8	36.68 (23)	37.99 (44)	0.96
10	29.15 (27)	31.70 (53)	0.92
12	22.23 (29)	25.85 (52)	0.86
16	15.74 (29)	16.24 (49)	0.97
24	9.48 (25)	10.51 (58)	0.90
36	4.80 (29)	4.95 (56)	0.97
48	2.61 (24)	2.94 (48)	0.89
60	1.66 (51)	1.54 (70)	1.08

Table 2

A Summary of Pharmacokinetic Parameters for 24 subjects
TERAZOSIN

Parameters	Geneva's Terazosin	Abbott's Hytrin	T/R	90% Confidence Interval
AUC_{0-60} ng.hr/mL	840.3 (22.7)	893.0 (48.3)	.94	82; 106
AUC_{0-inf} ng.hr/mL	878.1 (21.9)	930.9 (47.4)	.94	82; 106
C_{max} ng/mL	76.7 (31.1)	79.4 (47.7)	.97	86; 107
T_{max} (hours)	1.0 (83.3)	1.2 (87.7)	.98	
$t_{1/2}$ (hours)	13.7 (17.6)	13.3 (13.1)	1.03	
K_{el} (1/hour)	0.052(16.7)	0.053(12.1)	.98	
Ln AUC_{0-60} ng.hr/mL	6.7 (3.4)	6.7 (5.2)		92; 106
Ln AUC_{inf} ng.hr/mL	6.7 (3.3)	6.7 (5.1)		92; 106
Ln C_{max}	4.3 (6.5)	4.3 (7.9)		92; 107

The terazosin AUC_{0-t} and AUC_{0-inf} produced by Geneva's formulation were 5.9% lower than the values for the reference drug. The C_{max} was 3.4 lower than the reference. T_{max} was 1.7% higher for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 3%. ANOVA performed on the plasma terazosin concentration data at each of the eighteen sampling times detected no statistically significant differences between the two formulations. The firm did calculate Ln AUC and Ln Cmax for terazosin and the 90% confidence intervals for log-transformed parameters were 92 to 106 for Ln AUC0-t, 92 to 106 for Ln AUCinf, and 92 to 107 for Ln Cmax.

The 90% confidence interval for terazosin forAUC_{0-60} and AUC_{0-inf} and C_{max} were well within ±20% limits set for defining product bioequivalence, in a fasting study.

There were minor adverse events reported; cough (1-dry), abdominal pain (1- stomachache), dry vomit (1- dry heaves),

dizziness (12- lightheaded), eye abnormality (29), headache (16), mouth dry (1- dry mouth); myalgia (1), nausea (4), pallor (8- skin pale), pharyngitis (3- sore throat), respiratory disorder (30- stuffy nose), right antecubital pain (1), sweating increased (1- sweating); Vomiting (1). There were no serious adverse effects which required dropping any subjects from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Geneva's terazosin hydrochloride 5 mg tablets and Abbott's Hytrin 5 mg tablets are bioequivalent under fasting conditions.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. Results are presented in Table 3. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in minutes.

The batch size was tablets.

COMMENTS:

1. The study was conducted in 26 healthy volunteers comparing the plasma concentrations from Geneva's terazosin hydrochloride 5 mg tablets to that of reference Hytrin 5 mg tablets manufactured by Abbott. The terazosin AUC_{0-60}, AUC_{0-inf}, C_{max} of the Geneva's formulation were 5.9% lower, 5.9% lower, and3.4% lower respectively than the corresponding Abbott's reference values. ANOVA performed on the plasma terazosin concentration data detected no statistically significant differences between two formulations. These results indicate that the test drug is bioequivalent to the reference product under fasting conditions.

2. Analysis of variance indicated no statistical significant treatment differences or group-by-sequence effect for AUC and Cmax for terazosin. The 90% confidence intervals were well within the limits of ±20%.

3. The validation studies conducted by the sponsor for terazosin are acceptable to the Division of Bioequivalence.

4. The elimination of terazosin from the plasma appeared to be biphasic for most of the subjects. The elimination rate constants were estimated from the plasma terazosin data for all subjects using the plasma concentrations of the final elimination phase as best as could be determined from the plasma drug concentration vs time plots (log scale) for the individual subjects. The half-life values and areas under the concentration-time curves to infinity using the elimination rate constants.

5. Sitting blood pressure and heart rate measurements were

monitored at approximately 1, 2, 3, 4, 6, 8, 12, 24 and 36 hours after drug administration. After dosing, all participants had a decrease in diastolic pressure of 12 mmHg or greater by 8 hours with resolution by 8 to 12 hours (post-dosing). All participants, had a 24 hour diastolic pressure within 10% of their 0 hour value. The heart rate varied above and below pre-dose values over the 24 hours post-dosing. These are illustrated in Figure 2, 3, and 4.

6. The firm is requesting a waiver of 1 mg, 2 mg and 10 mg terazosin hydrochloride tablets based on the fasting study of 5 mg tablet. The waiver for the higher strength (10 mg) can be granted because of hypotention, especially postural hypotension, and syncope, in association with the first dose. Therefore, the waiver for 1 mg, 2 mg and 10 mg is granted based on an acceptable fasting study of 5 mg tablet.

7. The in vitro dissolution testing conducted for 1 mg, 2 mg, 5 mg and 10 mg tablets of the test and reference products shows greater than of the labeled amount of the terazosin hydrochloride dissolved in minutes.

8. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

9. The in vivo fasting bioequivalence study is acceptable.

10. The firm has demonstrated that the formulations of its terazosin hydrochloride tablets, 1 mg, 2 mg, 5 mg and 10 mg, are proportional with respect to active and inactive ingredients (Table 4).

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Geneva Pharmaceuticals on its Terazosin Hydrochloride 5 mg tablets, lot # 6493050, comparing it to Hytrin 5 mg tablets, lot # 47-581-AA21 manufactured by Abbott Laboratories have been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Geneva's Terazosin Hydrochloride 5 mg tablets are bioequivalent to the reference product, Hytrin 5 mg tablets manufactured by Abbott.

2. The formulations for 1 mg, 2 mg, 10 mg Terazosin Hydrochloride tablets are proportionally similar to 5 mg Terazosin Hydrochloride tablet which underwent bioequivalent study. The waiver of in vivo bioequivalence study requirement for Geneva Pharmaceuticals 1 mg, 2 mg, and 10 mg tablets is granted. The 1 mg, 2 mg, and 10 mg Terazosin Hydrochloride tablets from Geneva Pharmaceuticals are, therefore, deemed bioequivalent to 1 mg, 2 mg, and 10 mg Hytrin tablets manufactured by Abbott based on 21

CFR 320.22 ~~(d)~~ (2).

3. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs.The dissolution testing should be conducted ~~in~~ 900 mL of water at 37°C using USP XXII apparatus 2 (Paddle) ~~at~~ 50 rpm. The test should meet the following specifications:

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

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramakant M. Mhatre 10/4/95

/S/

Concur: _____ Date: 10/16/95
Keith K. Chan, Ph.D. for
Director
Division of Bioequivalence

(Please select Typeover for Input.)

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Terazosin HCl Tablets
Dose Strength: 5 mg, Lot # 6493050
ANDA No.: 74-315
Firm: Geneva Pharmaceuticals
Submission Date: 4/21/95
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications:
Reference Drug: Abbott's Hytrin Tablet. Lot #47-580-AA21
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes	Test Product Lot # 6493050 Strength(5 mg)			Reference Product Lot # 47-580-AA21 Strength(5 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	100		2.6	97		2.1%
20	101		3.0	100		2.5
30	101		2.8	100		1.3
40	102		2.7	101		1.5

Sampling Times Minutes	Test Product Lot # 6493051 Strength(10mg)			Reference Product Lot # 47-578-AA21 Strength(10mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	96		2.9	88		9.7
20	98		1.3	96		4.0
30	98		1.9	98		3.7
40	99		1.9	98		0.7

Sampling Times Minutes	Test Product Lot # 6493049 Strength(2 mg)			Reference Product Lot # 46-531-AA22 Strength(2 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	88		8.3	90		8.6
20	95		5.6	95		6.0
30	97		4.4	98		4.0
40	100		3.8	98		3.0

Sampling Times Minutes	Test Product Lot # 6493048 Strength(1 mg)			Reference Product Lot # 47-580-AA21 Strength(1 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	101		4.5	95		5.6
20	105		3.6	100		3.3
30	107		4.3	99		3.8
40	108		2.5	100		3.1

TABLE 4

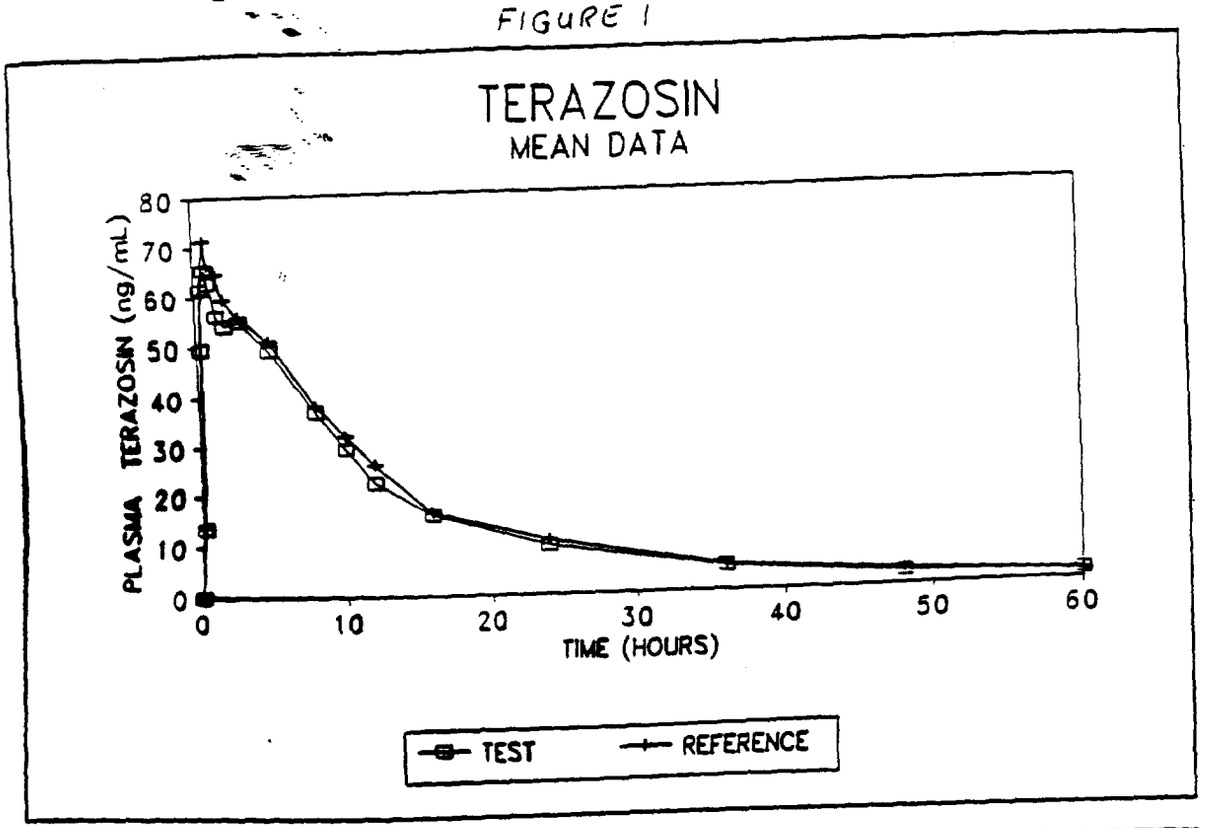
FORMULATION

Ingredients	1 mg	2 mg	5 mg	10 mg
	mg per tablet			
Terazosin *	1.	2.	5.	10.
Lactose				
Microcrystalline Cellulose				
Crosprovidone				
Magnesium Stearate				
F.D. & C. Yellow				
F.D. & C. Blue				
D. & C. Yellow	----	----		
Purified Water,	----	----		
TOTAL				

* equivalent to 1 mg, 2 mg, 5 mg, and 10 mg terazosin respectively

TERAZOSIN 5 MG TABLET STUDY

FIGURE 1



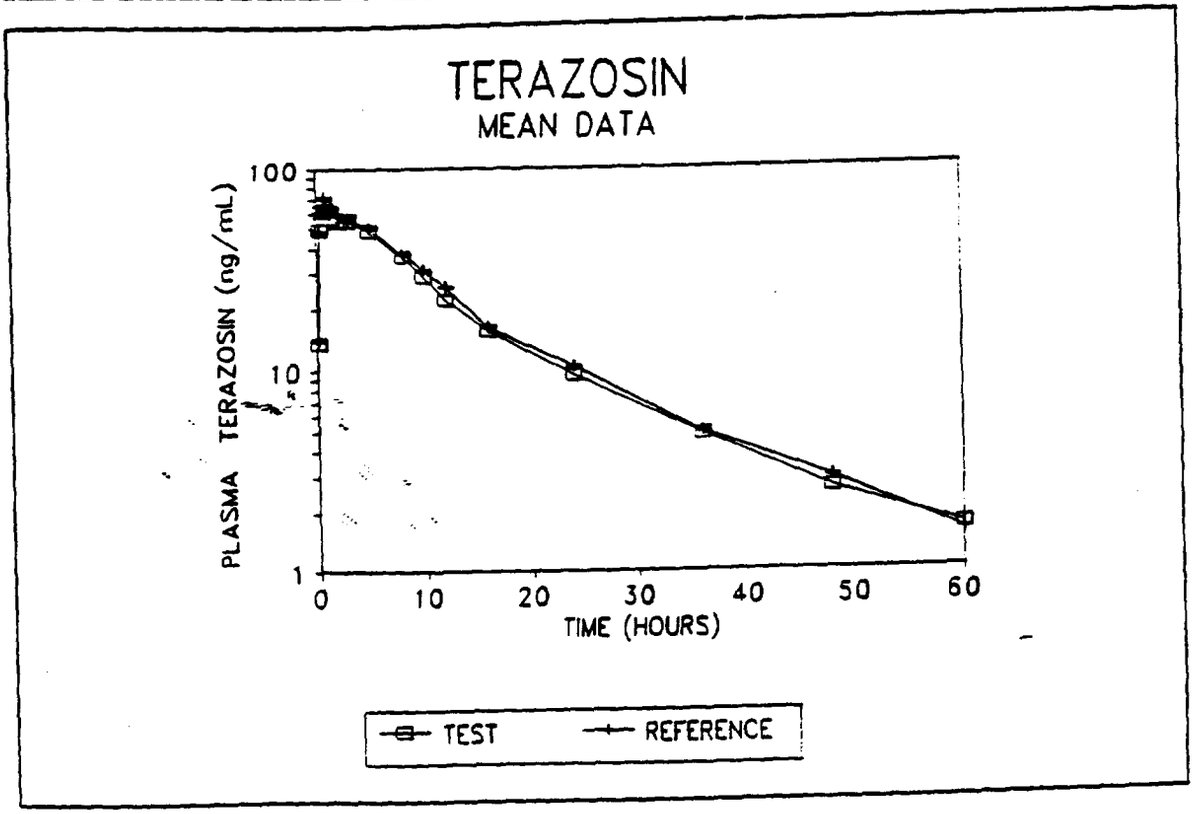


FIGURE 2

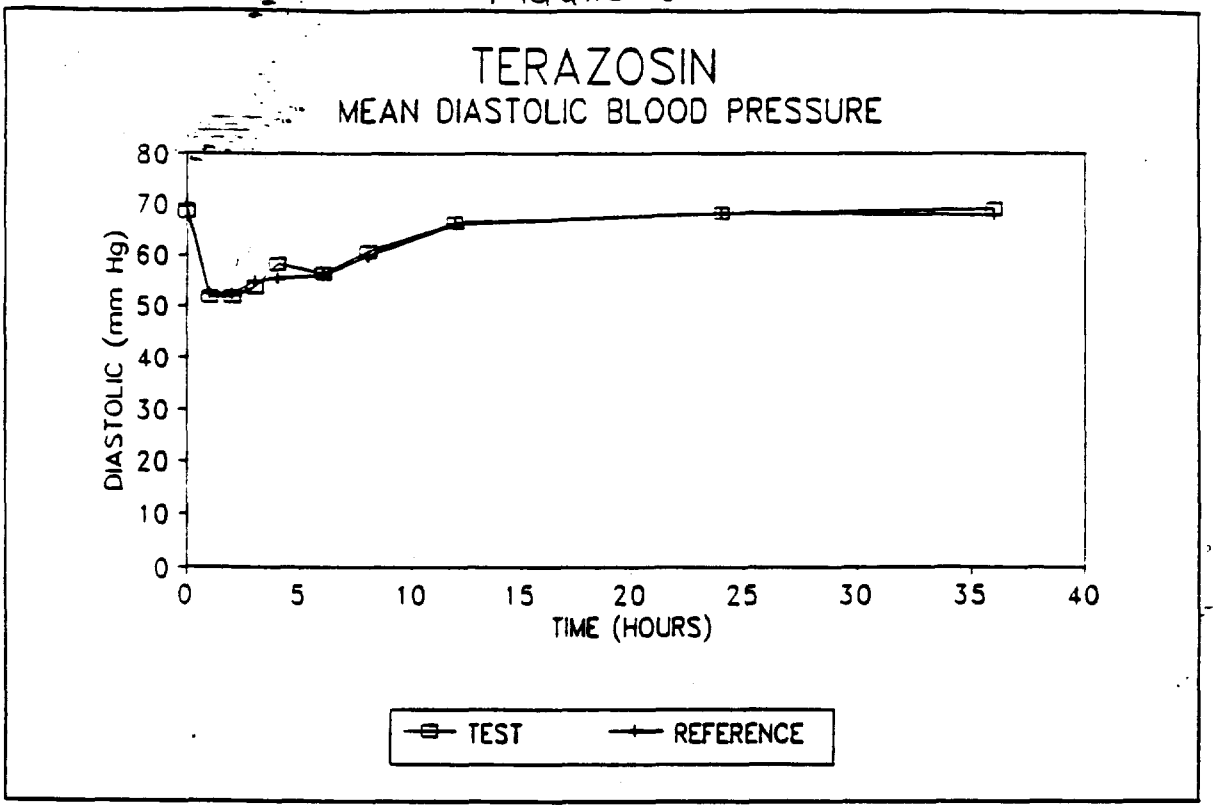


FIGURE-3

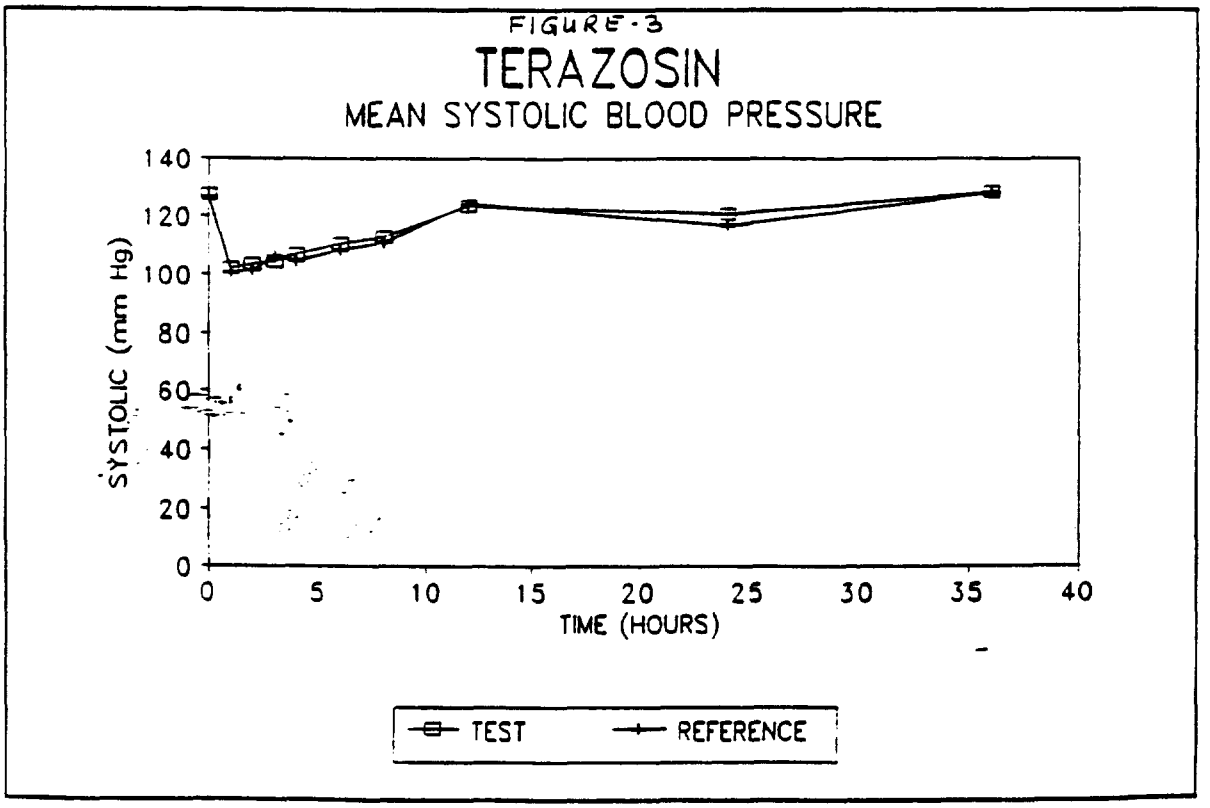
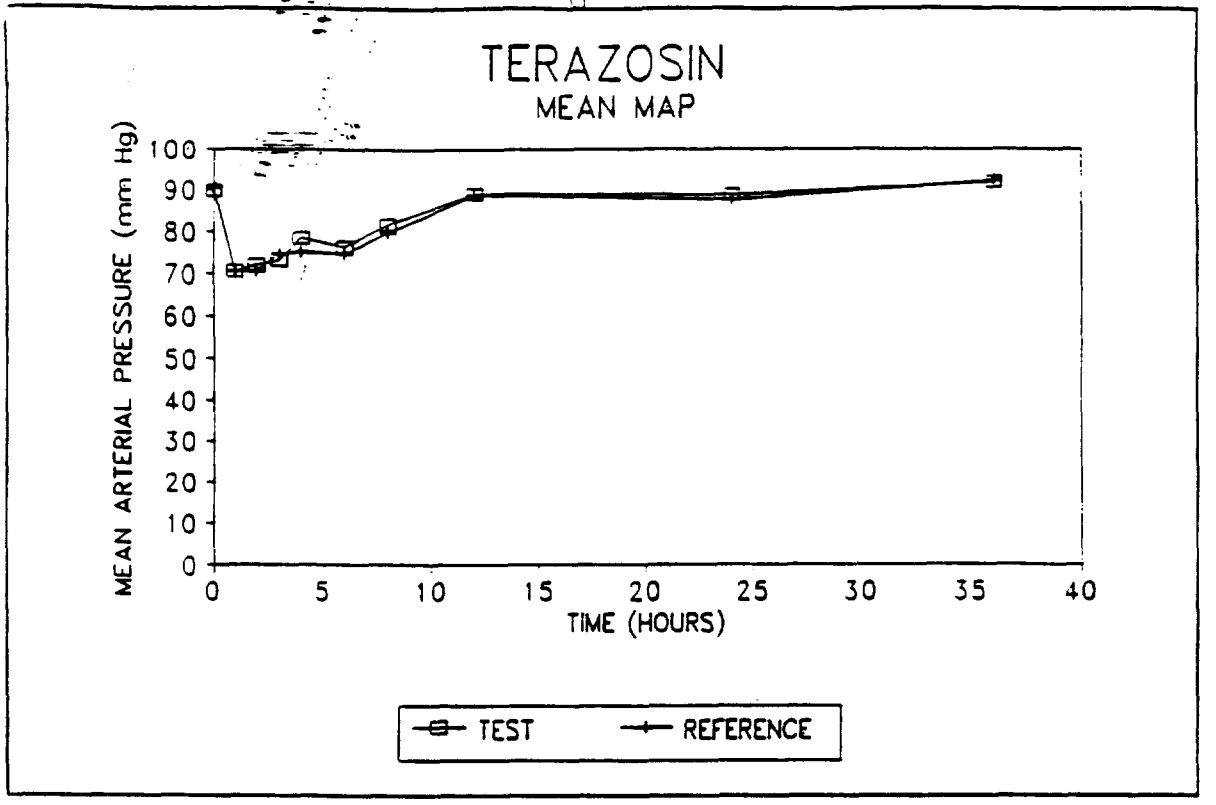


Figure 4


TERAZOSIN
MEAN MAP
MEAN ARTERIAL PRESSURE (mm Hg)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
TIME (HOURS)
TEST
REFERENCE

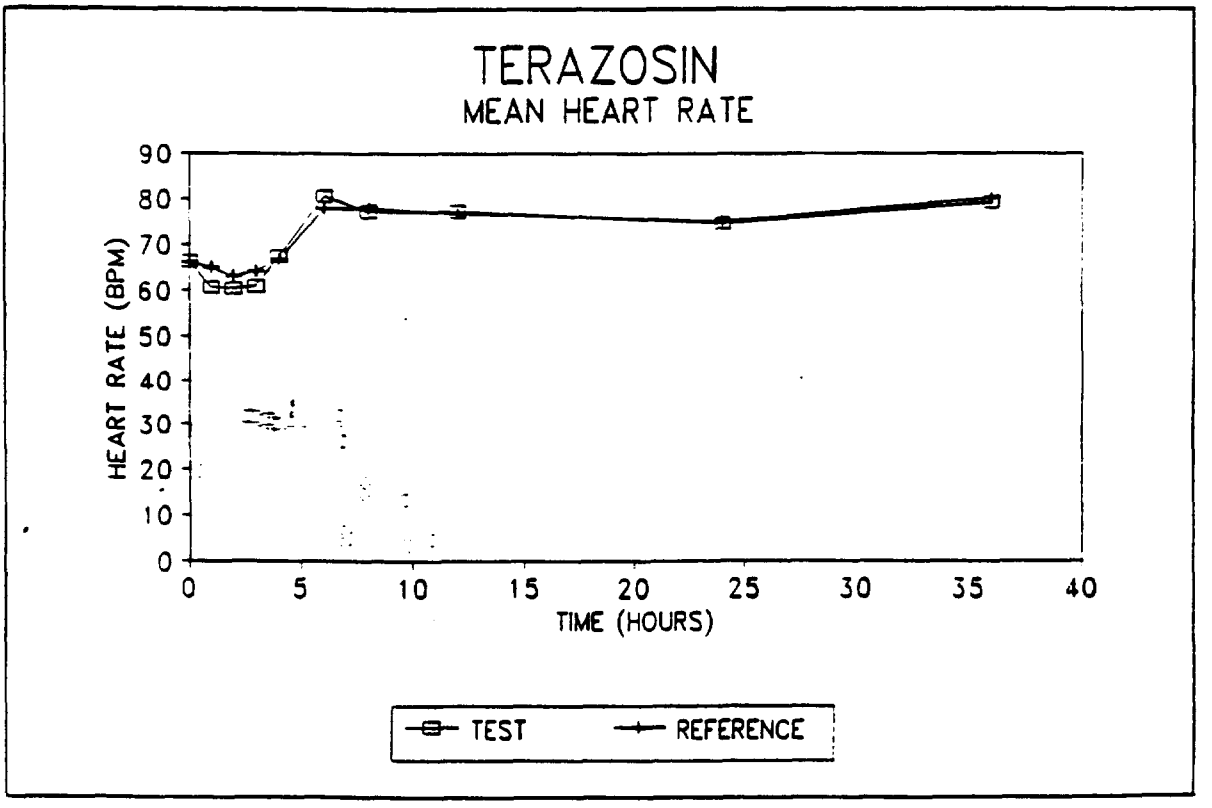
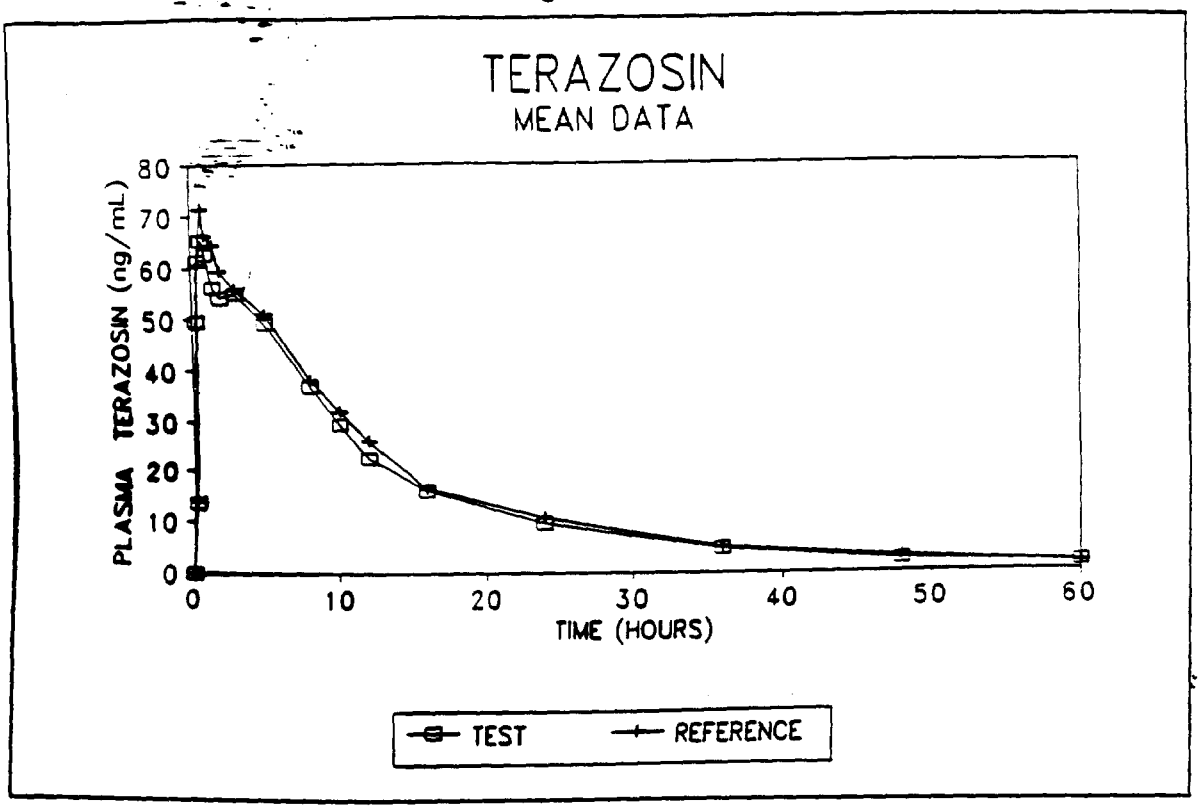
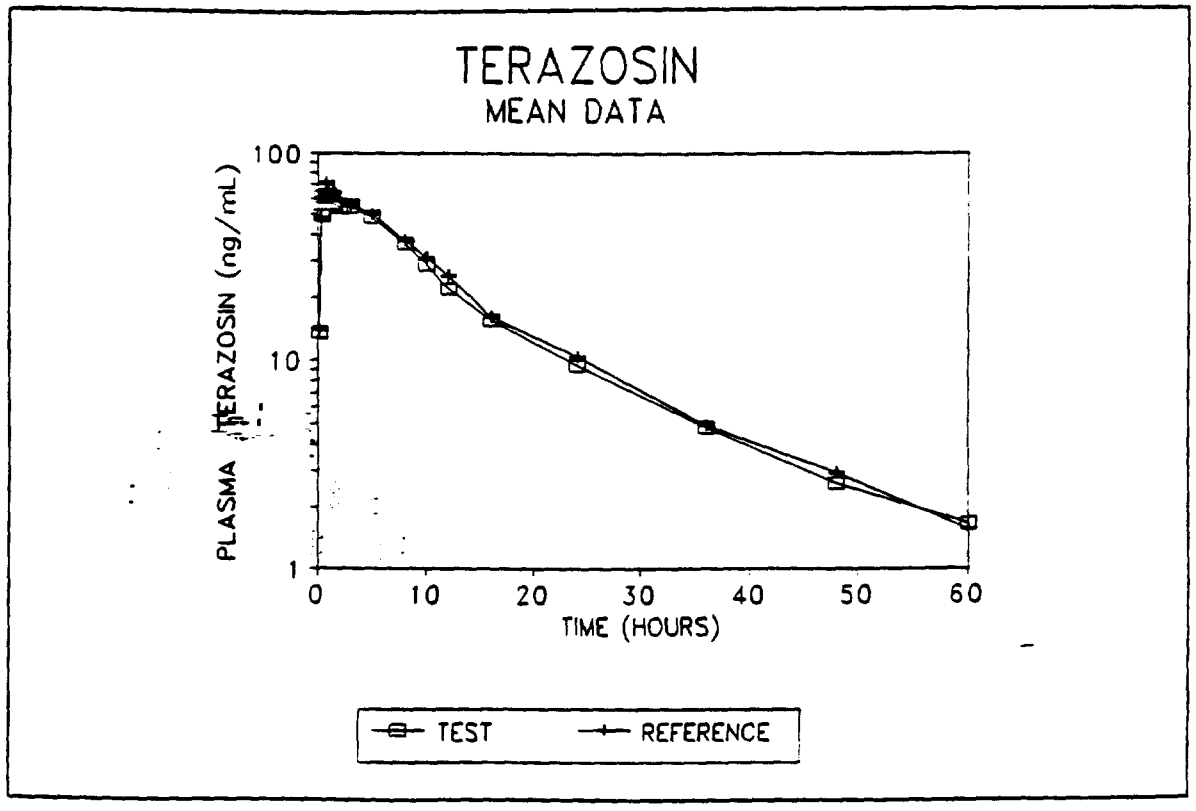

TERAZOSIN
MEAN HEART RATE
HEART RATE (BPM)
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
TIME (HOURS)
TEST
REFERENCE

FIGURE 1


TERAZOSIN
MEAN DATA
PLASMA TERAZOSIN (ng/mL)
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
TIME (HOURS)
TEST
REFERENCE


TERAZOSIN
MEAN DATA
PLASMA TERAZOSIN (ng/mL)
100
10
1
0
10
20
30
40
50
60
TIME (HOURS)
TEST
REFERENCE

JUN 7 1994

Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg and 10 mg
ANDA # 74-315
Reviewer: Man M. Kochhar
74315W.993

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
September 10, 1993

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

The firm with an acceptable bioequivalence study has submitted the dissolution data for 1 mg, 2 mg, 5 mg, and 10 mg tablets, in support for a waiver request for bioequivalence study for a change in the formulation of the tablet. The firm is changing

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXII apparatus 2 (paddle) at 50 rpm. Results are presented in Table 1. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in minutes.

The batch size was tablets for all strengths.

COMMENTS:

1. The firm is changing granulation process. Microcrystalline cellulose is and can be That is why it is mainly used in of the tablets. As the firm is changing from to of the tablets, it may be necessary to change to

2. The firm has demonstrated that the formulations of its Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg, are proportional with respect to active and inactive ingredients (Table 2).

3. The in vitro dissolution testing conducted for 1 mg, 2 mg, 5 mg and 10 mg tablets of the test and reference products shows greater than 75% of the labeled amount of the terazosin hydrochloride dissolved in 30 minutes.

4. The waiver of in vivo bioequivalence study requirement should be granted based on 21 CFR 320.22 (d)(5).

DEFICIENCY: None

RECOMMENDATIONS:

1. The dissolution testing conducted by Geneva Pharmaceuticals on its new formulation (changing
Cellulose) Terazosin Hydrochloride, 1 mg, 2 mg, 5 mg and 10 mg tablets is acceptable. The firm has previously conducted an acceptable bioequivalent study on its 5 mg Terazosin Hydrochloride Tablet. Therefore, the waivers of in vivo bioequivalence study requirement for Geneva Pharmaceuticals 1 mg, 2 mg, 5 mg and 10 mg tablets is granted. The 1 mg, 2 mg, 5 mg and 10 mg Terazosin Hydrochloride Tablets from Geneva Pharmaceuticals are, therefore, deemed bioequivalent to 1 mg, 2 mg, 5 mg and 10 mg Hytrin Tablets manufactured by Abbott based on 21 CFR 320.22 (d) (2).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs.The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED MPARK
FT INITIALLED MPARK 6/7/94

Drug (Generic Name): Terazosin HCl Firm: Geneva

Dose Strength: ~~1mg, 2mg, 5mg~~ & 10mg

NDA # 74-315 Submission Date: Sept 10, 1993

Table 1 - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ___ Paddle ✓ RPM 50 No. Units Tested: 12

Medium: Water Volume: 900 ml

Reference Drug: (Manuf.) Old Batch of Geneva

Assay Methodology: UV @ 245 nm

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product Lot # 6493050 Strength (mg) 5mg Mean % Dissolved	Range	(CV) RSD %	Reference Product Lot # 92-039 Strength (mg) 5 Mean % Dissolved	Range	(CV) RSD %
10	100		(2.6)	101		(4.6)
20	101		(3.0)	105		(2.3)
30	101		(2.8)	105		(2.5)
40	102		(2.7)	105		(2.1)
___	___	___	( )	___		( )

	~~Lot~~ # 6493051 Strength (mg) 10			Lot # 92-040 Strength (mg) 10	
10	96		(2.9)	100	(2.1)
20	98		(1.3)	101	(2.6)
30	98		(1.9)	101	(2.2)
40	99		(1.9)	101	(2.2)
___	___	___	( )	___	( )

Specification:

Table [illegible] [Con't.]

Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) (Hr.)	Test Product Lot # 6493048 Strength (mg) [illegible] mg Mean % Dissolved	Range	(CV) RSD %	Reference Product Lot # [illegible] 92-037 Strength (mg) [illegible] mg Mean % Dissolved	Range	(CV) RSD %
10	101		(4.5)	98		(2.7)
20	105		(3.6)	98		(3.0)
30	107		(4.3)	98		(2.8)
40	108		(2.5)	98		(2.8)
			( )			( )
			( )			( )
			( )			( )
			( )			( )

	Test Product Lot # 6493049 Strength (mg) 2mg Mean % Dissolved	Range	(CV) RSD %	Reference Product Lot # 92-038 Strength (mg) 2 Mean % Dissolved	Range	(CV) RSD %
10	88		(8.3)	98		(5.9)
20	95		(5.6)	101		(3.5)
30	97		(4.4)	103		(3.5)
40	100		(3.8)	102		(3.3)
			( )			( )
			( )			( )
			( )			( )
			( )			( )

TABLE 2

FORMULATION

1 mg	2 mg	5 mg	10 mg

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #74-315
SPONSOR: Geneva Pharmaceuticals, Inc.
DRUG: Terazosin Hydrochloride
DOSAGE FORM: Tablets
STRENGTH: 5 mg
REFERENCE PRODUCT: Hytrin® Tablets by Abbott
TYPE OF STUDY: Single dose under fasting condition
STUDY SITE: PRACS Institute, Inc. & Fargo, ND

STUDY SUMMARY:

The study under fasting condition is acceptable. The 90% confidence intervals for Terazosin for AUC and Cmax were well within ±20% limits set for defining product bioequivalence, in a fasting study. The 90% confidence interval for the log-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} under fasting conditions were all within the acceptable range of 80-125%.

The comparative dissolution testing data for four strengths met the FDA/USP dissolution specifications.

PRIMARY REVIEWER: Man M. Kochhar, Ph.D. BRANCH: III

INITIAL: Manu Kochhar DATE: 6/30/93

ACTING BRANCH CHIEF: Moo Park, Ph.D. BRANCH: III

INITIAL: Moo Park DATE: 6/30/93

ACTING DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: Ramesh M. Nikte DATE: 8/19/93

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE: 10/20/93

OCT 20 1993

Terazosin Hydrochloride Tablets
5 mg
ANDA # 74-315
Reviewer: Man M. Kochhar
A.74315SDW.193

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
January 12 and June 9, 1993

REVIEW OF BIOEQUIVALENCE STUDY, WAIVER REQUEST, AND DISSOLUTION DATA

The purpose of this study is to compare the rate and extent of terazosin hydrochloride absorption in fasting healthy adult male volunteers following a single dose of 5 mg of test and reference products (Hytrin, Abbott). The protocol was designed for a two-way crossover, single dose bioequivalence study.

BACKGROUND:

Terazosin hydrochloride is an antihypertensive agent which appears to exert its pharmacological effect by selective blockade of alpha-1-adrenoreceptors. Systolic and diastolic blood pressure is lowered in both the supine and standing positions. Orally administered terazosin is essentially completely absorbed in man. Nearly all of the circulating dose is in the form of parent drug. Food has little or no effect on bioavailability. The plasma levels of the free base peak in about 1 hour, and then decline, with a half-life of approximately 12 hours. Hepatic metabolism is extensive, with approximately 60% of the drug excreted via bile-feces, and 40% excreted in urine.

Terazosin can cause marked hypotension, especially postural hypotension, and syncope, in association with the first dose, or first few doses of therapy. Occasionally, the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120 to 160 beats per minute.

STUDY DESIGN:

The study was conducted by PRACS Institute, Ltd, Fargo, ND, protocol # B-03202 under the supervision of
and
The study employed twenty-six (26) healthy male volunteers (24 plus two alternates) between 18 and 41 years of age and within ±10% of the ideal body weight for their height and body frame (Metropolitan Insurance Company Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were not allowed to take any prescription medications and/or OTC preparations for at least two weeks prior to the start and until the end of the study. The volunteers should be non smokers. The volunteers were

not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing and until study completion.

Blood pressure and heart rate were monitored prior to dosing and at 1, 2, 3, 4, 6, 8, 12, and 24 hours after the dose. Vital signs were measured at other times when it was deemed necessary.

The subjects were housed in the PRACS live-in facility from 12 hours before until 36 hours after the drug administration. The subjects will return for the blood draw at 48 and 60 hours. The subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 2 hours of drug administration.

The products and dosage employed in this study were as follows:

A: Test: One 5 mg tablet terazosin hydrochloride (test drug), lot # 92-039 with 240 mL of water.
Batch Size: Expiry date: 6/94
Potency: 100.6% (2.1% RSD)
Content Uniformity: 101.4% (2.2% RSD)

B. Reference: One 5 mg tablet of Hytrin (Abbott), lot # 47-581-AA-21 with 240 mL of water. Expiry date: 1/94.
Potency: 98.7%
Content Uniformity: 95.2% (1.5% RSD)

Ten (10) mL of venous blood were drawn in Vacutainers with EDTA at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 60 hours. The plasma was separated and promptly frozen for analysis.

WASHOUT PERIOD: 7 DAYS

ANALYTICAL METHODOLOGY:

Plasma terazosin was measured by a specific ethod using

ASSAY VALIDATION

1. Linearity: 1 to 100 ng/mL

2. Sensitivity: 1 ng/mL. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma sample from the subjects in the study indicated no interference with terazosin or the internal standard.

4. Accuracy & Precision

Actual (ng/mL)	2.00	15.00	70.00
Observed (ng/mL)	2.01	14.20	74.00

Accuracy %	101	94.7	106
CV %	4.73	3.89	7.01

5. The assay was validated by analyzing three single standard curve sets with three sets of high (70.0 ng/mL), medium (15.0 ng/mL) and low (2.00 ng/mL) QC samples for a total of three days. The standard curve concentrations ranged from 1.00 to 150 ng/mL. The assay was documented to be reproducible. For standards, the intra-day precision was 5.7% or better for each of the three days, and the inter-day precision was 10.2% or better. The mean accuracy was within the range of 92.1% to 110%

6. The recovery was defined as the percent of terazosin recovered after extraction of matrix samples compared to an unextracted standard. (It is not possible to establish the true recovery in protein precipitation procedures due to the loss of some volume during the precipitation step). The mean recovery was 91.7%, 104% and 91.6%. The mean recovery of the internal standard, propranolol hydrochloride, was determined from one set of three 1000 ng/mL samples to be 98.1%

7.The stability of terazosin at three different concentrations in plasma was evaluated over three freeze-thaw cycles. The three sets of controls included high (70.0), medium (15.0), and low (2.0). These samples were subjected to three freeze and thaw cycles before analyzing. The results show that the mean change for terazosin was +1.0%, -2.0% and -4.0%. The stability of terazosin in plasma during frozen storage was documented over the course of 46 days. The in process stability was performed at three different concentrations (70.0 ng/mL, 15.0 ng/mL and 2.00 ng/mL). These samples were prepared and allowed to sit next to HPLC for 24 hours at room temperature prior to analysis. The results show that terazosin was stable during the maximum time required for sample processing at room temperature.

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) were carried out to compare plasma levels at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for terazosin pharmacokinetic parameters. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the 26 subjects (24 plus 2 alternates) enrolled in the study, one did not complete the crossover. Subject #1 did not return to the clinic for second dosing period, and all attempts to contact him have failed to date. The plasma samples from 24 subjects (

the first 24 subject by number that completed the study) were assayed for terazosin as per the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of terazosin are given in Table 1 and 2. The mean plasma terazosin concentrations are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Terazosin (N=24)

Time (hours)	Geneva's Terazosin Lot # 92-039 ng/mL (CV%)	Abbott's Hytrin Lot # 47-581-AA-21 ng/mL (CV%)
0	0.0 (-)	0.0 (-)
0.25	31.33 (95.4)	31.42 (67.9)
0.5	68.08 (51.0)	70.55 (40.7)
0.75	74.76 (35.2)	73.53 (35.9)
1	75.57 (30.2)	72.81 (31.6)
1.5	75.94 (27.4)	72.48 (29.9)
2	75.35 (27.4)	72.02 (28.7)
3	71.53 (24.5)	68.93 (26.5)
4	65.97 (21.9)	65.70 (25.5)
6	53.71 (23.5)	53.86 (26.6)
8	43.80 (22.3)	43.85 (24.0)
10	34.98 (23.8)	34.84 (25.7)
12	27.97 (24.2)	28.46 (24.2)
16	19.75 (27.4)	20.74 (30.2)
24	11.40 (28.5)	11.59 (27.5)
36	4.95 (32.1)	5.20 (31.9)
48	2.54 (44.0)	2.57 (33.2)
60	1.49 (61.8)	1.43 (67.8)

Table 2

A Summary of Pharmacokinetic Parameters for 24 subjects
TERAZOSIN

Parameters	Geneva's Terazosin	Abbott's Hytrin	% Diff	90% Confidence Interval
AUC_{0-t} ng.hr/mL	1014.3 (25.0)	1019.1 (25.2)	.47	97; 103
AUC_{0-inf} ng.hr/mL	1042.7 (25.1)	1047.5 (25.1)	.46	97; 103
C_{max}	84.5 (29.5)	84.5 (25.4)	0	95; 105

ng/mL				
T_{max} (hours)	1.3 (69.5)	1.0 (80.0)	30.0	
$t_{1/2}$ (hours)	10.6 (14.0)	10.6 (12.3)	0	
K_{el} (1/hour)	0.067(15.2)	0.066(13.9)	1.52	
Ln AUC_{0-t} ng.hr/mL	6.9 (3.6)	6.9 (3.7)		97; 103
Ln AUC_{inf} ng.hr/mL	6.9 (3.6)	6.9 (3.7)		97; 103
Ln C_{max}	4.4 (6.0)	4.4 (5.5)		94; 104

The terazosin AUC_{0-t} and AUC_{0-inf} produced by Geneva's formulation were 0.47% lower and 0.46% lower respectively than the values for the reference drug. The C_{max} is same for test and reference. T_{max} was 30% higher for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 1.5%. ANOVA performed on the plasma terazosin concentration data at each of the eighteen sampling times detected no statistically significant differences between the two formulations. The firm did calculate Ln AUC and Ln Cmax for terazosin and the 90% confidence intervals for these parameters were 97 to 103 for AUC0-t, 97 to 103 for AUCinf, and 94 to 104 for Cmax.

The 90% confidence interval for terazosin forAUC_{0-t} and AUC_{0-inf} and C_{max} were well within ±20% limits set for defining product bioequivalence, in a fasting study.

Subject # 1 did not show up for Phase 2. There were minor adverse events reported; cough (2-dry), cramps leg (2), diarrhea (1), dizziness (10-lightheaded), eye abnormality (4), fatigue (4), gastritis (1), headache (19), hot flushes (1), malaise (2), dry mouth (2), nausea (2), pharyngitis (2), respiratory disorder (43-stuffy nose/nasal congestion), rhinitis (1), drowsy (1), and vomiting (1). There were no serious adverse effects which required dropping any subjects from the study or required therapeutic medical intervention.

On the basis of fasting <u>in vivo</u> bioavailability data it is determined that Geneva's terazosin hydrochloride 5 mg tablets and Abbott's Hytrin 5 mg tablets are bioequivalent under fasting conditions.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXII apparatus 2 (paddle) at 50 rpm. Results are presented in Table 3. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in minutes.

The batch size was tablets.

COMMENTS:

1. The study was conducted in 24 healthy volunteers comparing the plasma concentrations from Geneva's Terazosin Hydrochloride Tablets 5 mg to those of reference Hytrin Tablets 5 mg manufactured by Abbott. The terazosin AUC_{0-t}, AUC_{0-inf}, and C_{max} of the Geneva's formulation were 0.47% lower, 0.46% lower, and 0% difference respectively than the corresponding Abbott's reference values. ANOVA performed on the plasma terazosin concentration data detected no statistically significant differences between two formulations.

2. Analysis of variance indicated no statistical significant treatment differences for AUC and Cmax for terazosin. The 90% confidence intervals were well within the limits of ±20%. The firm calculated Ln AUC and Ln Cmax for terazosin and the 90% confidence intervals for these parameters were 97 to 103 for AUC0-t and AUCinf and 94 to 104 for Cmax. These parameters were well within the range acceptable to the Division of Bioequivalence.

These results indicate that the test drug is bioequivalent to the reference product under fasting conditions.

3. The validation studies conducted by the sponsor for terazosin are acceptable to the Division of Bioequivalence.

4. Subject # 1 did not show up for Period 2.

5. The elimination of terazosin from the plasma appeared to be monophasic for most of the subjects, but some subjects appeared to have a biphasic elimination. The elimination rate constants, and thus the half-life values and areas under the concentration-time curves to infinity, were estimated from the plasma terazosin data for all subjects using the plasma concentrations of the final elimination phase as best as could be determined from the plasma drug concentration vs time plots (log scale) for the individual subjects.

6. Sitting blood pressure and heart rate measurements were monitored at approximately 1, 2, 3, 4, 6, 8, 12, 24 hours after drug administration. After dosing, all participants had a decrease in diastolic pressure of 10 mmHg or greater by 8 hours

with resolution by 8 to 12 hours (post-dosing). All participants, except subject # 2, had a 24 hour diastolic pressure within 10% of their 0 hour value. The heart rate varied above and below pre-dose values over the 24 hours post-dosing. These are illustrated in Figure 2, 3, and 4.

7. The in vitro dissolution testing conducted for 1 mg, 2 mg, 5 mg and 10 mg tablets of the test and reference products shows greater than 75% of the labeled amount of the terazosin hydrochloride dissolved in 30 minutes.

8. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

9. The in vivo fasting bioequivalence study is acceptable.

10. The firm has demonstrated that the formulations of its Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg, are proportional with respect to active and inactive ingredients (Table 4).

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Geneva Pharmaceuticals on its Terazosin Hydrochloride Tablets 5 mg, lot # 92-039, comparing it to Hytrin Tablets 5 mg, lot # 47-581-AA-21 manufactured by Abbott Laboratories have been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Geneva's Terazosin Hydrochloride Tablets 5 mg are bioequivalent to the reference product, Hytrin Tablets 5 mg manufactured by Abbott.

2. The formulations for 1 mg, 2 mg, 10 mg Terazosin Hydrochloride Tablets are proportionally similar to 5 mg Terazosin Hydrochloride Tablet which underwent bioequivalent study. The waivers of in vivo bioequivalence study requirement for Geneva Pharmaceuticals 1 mg, 2 mg, and 10 mg tablets is granted. The 1 mg, 2 mg, and 10 mg Terazosin Hydrochloride Tablets from Geneva Pharmaceuticals are, therefore, deemed bioequivalent to 1 mg, 2 mg, and 10 mg Hytrin Tablets manufactured by Abbott based on 21 CFR 320.22 (d) (2).

3. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs.The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

ıtes.

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

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED MPARK
FT INITIALLED MPARK 6/30/93

Concur: Ramakant M. Mhatre Date: 8/19/93
Ramakant M. Mhatre, Ph.D.
Acting, Director
Division of Bioequivalence

TABLE 4

FORMULATION

1 mg	2 mg	5 mg	10 mg

TABLE 3

Drug (Generic Name): Trazosin Hydrochloride Firm: Geneva

Dose Strength: 5 mg

ANDA # 74-315 Submission Date: 1/12 & 6/9/93

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ___ Paddle ✓ RPM 50 No. Units Tested: 12

Medium: Water Volume: 900 ml

Reference Drug: (Manuf.) Abbott Hytrin

Assay Methodology: UV

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) ~~(Hr.)~~	Test Product Lot # 92-039 Strength (mg) 5 Mean % Dissolved	Range	(CV) RSD %	Reference Product Lot # 47-581-AA-21 Strength (mg) 5 Mean % Dissolved	Range	(CV) RSD %
10	101		(4.6)	97		(2.1)
20	105		(2.3)	100		(2.5)
30	105		(2.5)	100		(1.3)
40	105		(2.1)	101		(1.5)
___	___	___	( )	___	-	( )

Sampling Times (Min.) ~~(Hr.)~~	~~Lot~~ # 92-040 Strength (mg) 10 Mean % Dissolved	Range	(CV) RSD %	Lot # 47-578-AA-21 Strength (mg) 10 Mean % Dissolved	Range	(CV) RSD %
10	100		(9.4)	88		(9.4)
20	~~96~~ 101		(4.0)	96		(4.0)
30	~~98~~ 101		(3.7)	98		(3.7)
40	~~98~~ 101		(1.7)	98		(1.7)
___	___		( )	___	___	( )

Specification:

Table 3 Continued

Drug (Generic Name): _____ Firm: _____

Dose Strength: _____

NDA # _____ Submission Date: _____

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle ____ RPM ____ No. Units Tested: ____

Medium: _____ Volume: _____ ml

Reference Drug: (Manuf.) _____

Assay Methodology: _____

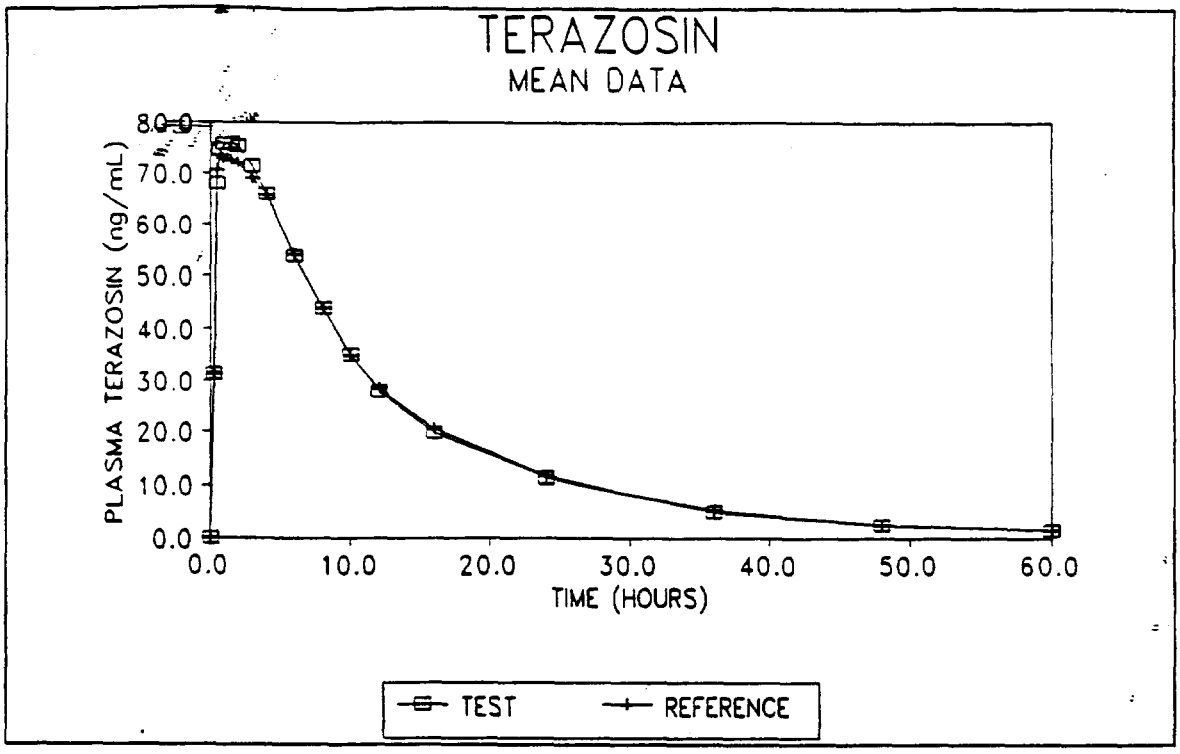
II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) ~~(Hr.)~~	Test Product Lot # ~~2mg~~ 92-038 Strength (mg) 2 Mean % Dissolved	Range	~~CV~~ RSD	Reference Product Lot # ~~2mg~~ 46-531-AA-22 Strength (mg) 2 Mean % Dissolved	Range	~~CV~~ RSD
10	98		(5.9)	90		(8.6)
20	101		(3.5)	95		(6.0)
30	103		(3.8)	98		(4.0)
40	102		(3.3)	98		(3.0)
____	_____		( )	_____	_____	( )

	Lot # 92-037 Strength (mg) 1mg			Lot # 47-580-AA-21 Strength (mg) 1mg		
10	98		(2.7)	95		(5.6)
20	98		(3.1)	100		(3.3)
30	98		(2.8)	99		(3.8)
40	98		(2.9)	100		(3.1)
____	_____		( )	_____	____	( )

Specification:

FIGURE 1


TERAZOSIN
MEAN DATA
PLASMA TERAZOSIN (ng/mL)
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
TIME (HOURS)
TEST
REFERENCE

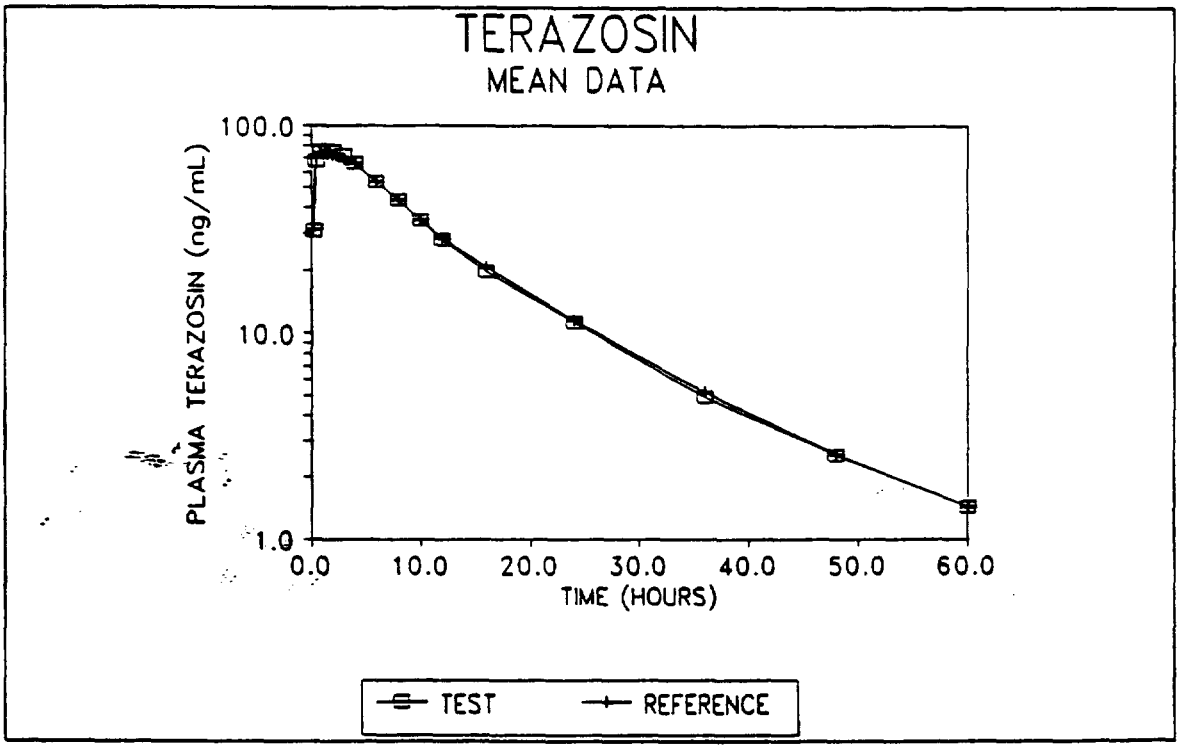

TERAZOSIN
MEAN DATA
PLASMA TERAZOSIN (ng/mL)
100.0
10.0
1.0
0.0
10.0
20.0
30.0
40.0
50.0
60.0
TIME (HOURS)
TEST
REFERENCE

FIGURE 2

TERAZOSIN BLOOD PRESSURE DATA

MEAN VALUES

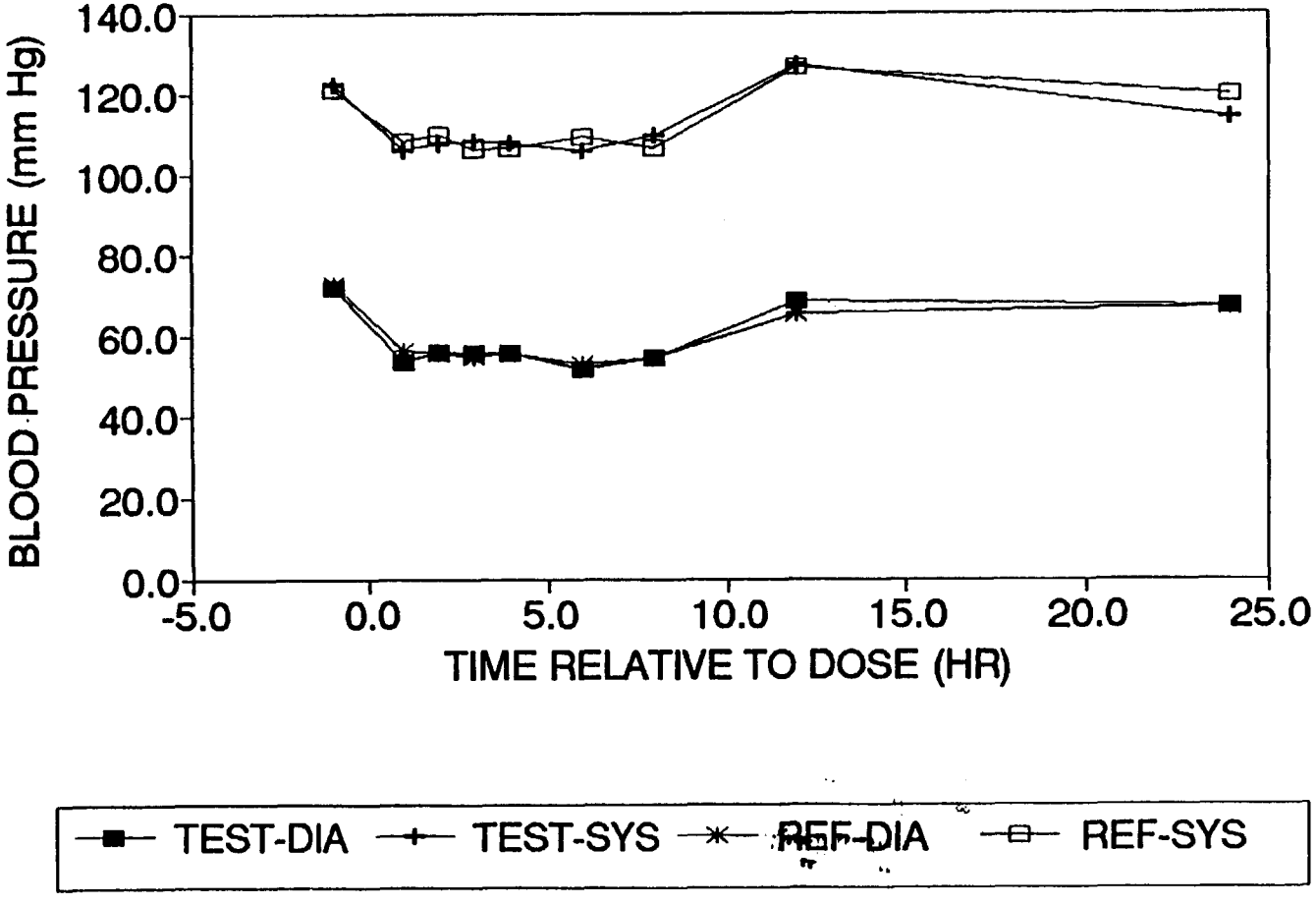


FIGURE 3

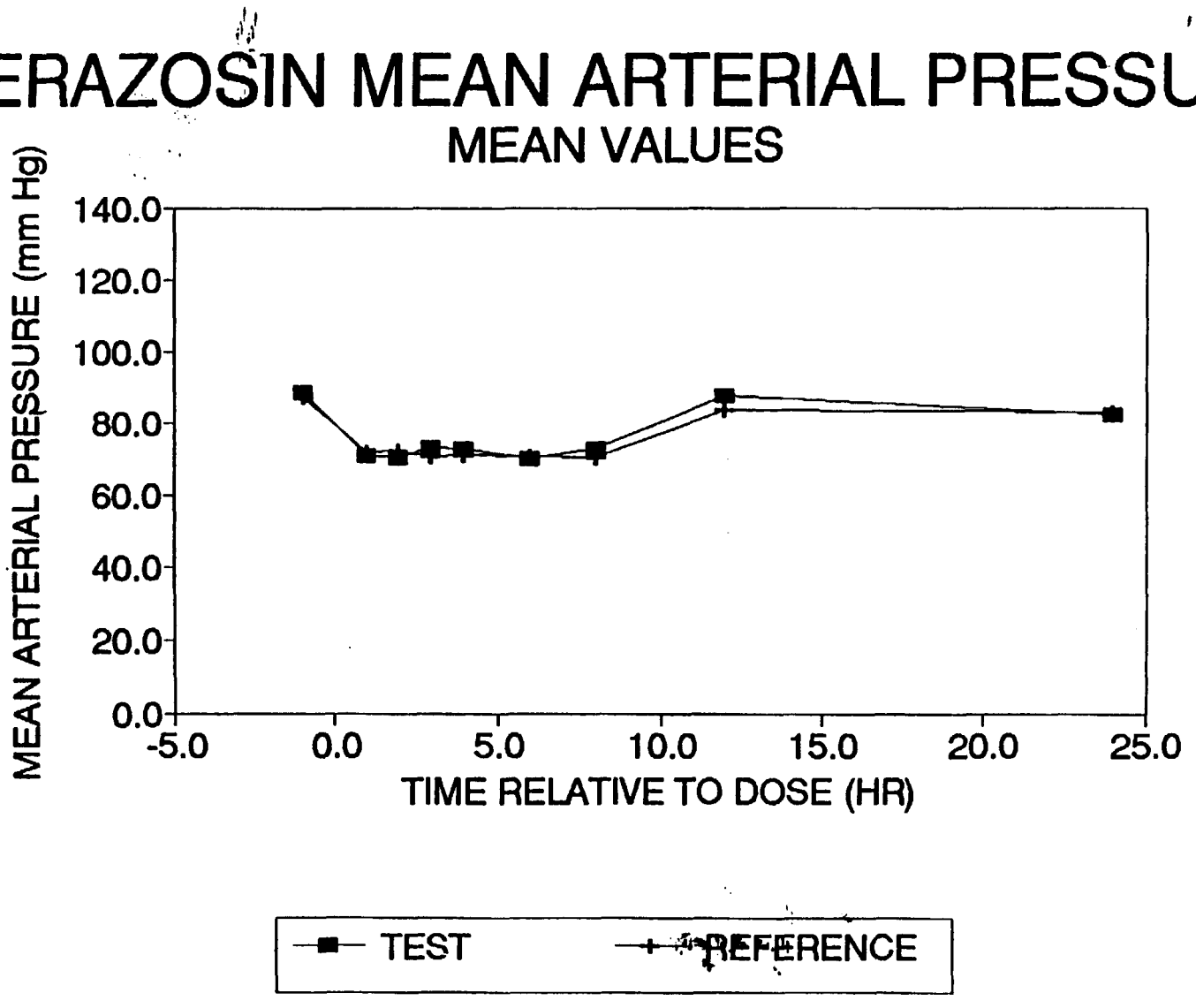

TERAZOSIN MEAN ARTERIAL PRESSURE
MEAN VALUES
MEAN ARTERIAL PRESSURE (mm Hg)
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
-5.0
0.0
5.0
10.0
15.0
20.0
25.0
TIME RELATIVE TO DOSE (HR)
TEST
REFERENCE

FIGURE 3

TERAZOSIN HEART RATE DATA

MEAN VALUES