CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74446

BIOEQUIVALENCY REVIEW(S)

(4)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 74446 SPONSOR : Novopharm Ltd.

DRUG AND DOSAGE FORM : **Terazocin Hydrochloride Tablet**

STRENGTH(S) : **10 mg, 5 mg, 2 mg and 1 mg**

TYPES OF STUDIES : Amendment

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY :

DISSOLUTION : See Review

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Andre J. Jackson BRANCH : I

INITIAL : AJJ DATE : 8/2/99

TEAM LEADER : Y.C. Huang BRANCH : I

INITIAL : YCH DATE : 8/2/99

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

INITIAL : DPC DATE : 8/4/99

4.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-446 APPLICANT: Novopharm

DRUG PRODUCT: Terazocin HCL Tablets 10 mg, 5 mg, 2 mg and 1 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been 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 (II) at 50 rpm. The test product should meet the following specifications:
>
> Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these 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 P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Terazocin Hydrochloride
1 mg, 2 mg, 5 mg and 10 mg Tablets
ANDA # 74446
Reviewer: Andre J. Jackson

Novopharm Limited
Ontario Canada
Submission Date:
January 29, 1999

Review of Bioequivalence Study Amendment and Dissolution Data for 10 mg, 5 mg, 2 mg and 1 mg Tablets

Introduction:

The firm submitted a bioequivalence study on December 16, 1993 for their 5 mg tablet which was found to be acceptable by the Division of Bioequivalence. The 1 mg, 2 mg and 10 mg strenghts were granted waivers of the in vivo requirements based upon the 5 mg in vivo study. The firm is changing the source of their raw material from and are submitting dissolution data to support this change.

Comments:

1.The dissolution data in Table 1 are acceptable.

2.The submission is acceptable based upon CFR 320.24 (b) (6).

Recommendations:

1. The dissolution testing data conducted by Novopharm on its Terazocin Hydrochloride Tablets (raw material 10 mg, lot # 3187PD, 5 mg tablets lot # 3186PD, 2 mg tablets, lot # 3185PD and 1 mg tablets, lot # 3184PD, comparing it to Terazocin Hydrochloride Tablets (raw material 10 mg, lot # PD 2505, 5 mg tablets, lot # PD 2504, 2 mg Tablets, lot # PD 2503 and 1 mg tablets, lot # PD 2502 is acceptable. The firm has previously conducted an acceptable in vivo Bioequivalency study (December 16, 1993), comparing the test product with Hytrin 5 mg tablets manufactured by Abbott. Therefore, Novopharm's Terazocin Hydrochloride Tablets, 10 mg, 5 mg, 2 mg and 1 mg are bioequivalent to the reference products, Hytrin Tablets, 10 mg, 5 mg, 2 mg and 1 mg manufactured by Abbott.

2. The dissolution testing should be incorporated into the firm's manufacturing and controls 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:

Not less than % of the labeled amount of the drug is dissolved in 30 minutes.

Andre' J. Jackson /S/
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 8/2/99

Concur: /S/ Date 8/4/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Table 1 . In Vitro Dissolution Testing

Drug (Generic Name):Terazocin
Dose Strength:1 mg, 2 mg, 5 mg and 10 mg
ANDA No.:74-446
Firm:Novopharm
Submission Date:January 29, 1999
File Name:74446AW.199

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM:50
No. Units Tested: 12
Medium: Water Volume:900 ml
Specifications:NLT % in 30 min
Reference Drug: Hytrin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 3184PD Strength(mg) 1			Reference Product Lot # PD 2502 Strength(mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
10	44.9		21	94.7		6.6
20	74.4		14.3	99.1		2.5
30	83.7		10.9	99.2		2.3
40	87.9		8.5	99.3		2.2
50	89.9		7.3	99.2		2.2
60	91.7		6.5	99.2		2.2
Sampling Times (Minutes)	Test Product Lot # 3185PD Strength(mg) 2			Reference Product Lot # PD 2503 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
10	79.3		12.4	101.1		3.1
20	100.8		1.9	103.5		2.4
30	101.8		1.4	103.6		2.5
40	101.8		1.6	103.7		2.5

50	101.7		1.5	103.8		2.5
60	101.8		1.5	103.9		2.4

Sampling Times (Minutes)	Test Product Lot # 3186PD Strength(mg) 5			Reference Product Lot # PD 2504 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	84.5		12.5	97.3		10.4
20	101.9		3.2	102.5		1.4
30	103.6		2.4	103		1.4
40	103.7		2.3	103.1		1.5
50	103.8		2.3	103.2		1.5
60	103.9		2.3	103.3		1.4

Sampling Times (Minutes)	Test Product Lot # 3187PD Strength(mg) 10			Reference Product Lot # PD 2505 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	55.1		12.5	89.9		11.2
20	88.3		8.1	99.2		2.1
30	97.7		3.8	99.7		1.1
40	99.8		2.2	100.0		1.3
50	100.1		2.0	9909		1.3
60	100.1		2.1	99.9		1.3

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74446 SPONSOR: Novopharm
DRUG: Terazocin HCL
DOSAGE FORM: Tablet
STRENGTH(s): 5 mg
TYPE OF STUDY: (Single)/Multiple (Fasting)/Fed
STUDY SITE:

STUDY SUMMARY: A single-dose two way cross-over study was done in 24 subjects comparing Terazocin to the reference product Hytrin manufactured by Abbot Labs. The 90% confidence intervals for Ln(max and Ln AUC were within the range of % of reference. The 10, 2 and 1 mg tablets were compositionally proportional to the 5 mg tablet. The waiver for the 10, 2 and 1 mg tablets was granted.

DISSOLUTION: Dissolution was done in water (900 ml) using USP II (paddle) at 50 rpm

PRIMARY REVIEWER: BRANCH: I

INITIAL: [signature] DATE: 4/22/94

BRANCH CHIEF: BRANCH:

INITIAL: /S/ DATE: 5/9/94

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 6/5/94

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: /S/ DATE: 6/7/94

JUN 5 1994

Terazocin Hydrochloride
5 mg Tablets
ANDA # 74446
Reviewer: Andre J. Jackson

Novopharm Limited
Ontario Canada
Submission Date:
December 16, 1993

Review of Bioequivalence Study, Dissolution Data and Waiver Request for 10 mg, 2 mg and 1 mg Tablets

Introduction:

Terazocin is a quinazoline derivative used as a selective alpha-1-selective adrenoceptor agent for the treatment of hypertension. Terazocin is completely absorbed and undergoes minimal first-pass metabolism. Peak concentrations of about 20 ng/ml are observed at 1 hour following a 1 mg oral dose. The reported elimination half-life is 12 hours and the drug is highly bound to plasma proteins and the oral absorption is not affected by food.

Objective:

To determine the rate and extent of Terazocin 5 mg tablets, as compared to Hytrin 5 mg tablets manufactured by Abbott Labs.

Study Design:
The study was done in 24 healthy male subjects as a single dose two-period two-treatment crossover study.

Study Facilities:

The clinical portion of the study was done at The study was conducted under the direction of The samples were analyzed by under the supervision of

Volunteer Selection Criteria:

A. Each volunteer subject was given a physical examination by the Principal Investigator or his staff, with a blood and urine sample taken for the determination of:

Blood Chemistry - Glucose, BUN, Creatinine, Uric Acid, Calcium, Phosphorus, Cholesterol, Triglycerine, Bilirubin (total), Alkaline Phosphatase, SGOT, SGPT, LDH, Total Protein, Sodium, Potassium, Chloride, CO_2.

Hematology - Hemoglobin, Hematocrit, Total and Differential Leukocyte Count and HIV III Screening Test.

Urinalysis - pH, Specific Gravity, Protein, Sugar and Microscopic Examination.

B. Subjects met the following criteria to be included in the study:

1. Male 18-45 years of age and within 10% of ideal body weight.

2. Normal vital organ/endocrine functions as reflected by medical history, physical examination, laboratory studies and ECG.

3. Chest X-ray within normal limits (optional if no indication of pulmonary abnormality).

C. Subjects with the following criteria were excluded:

1. Any cardiovascular disease including hypertension, ischemic heart disease, arrhythmias.

2. Known hypersensitivity to terazocin, prazocin or doxazocin.

3. Any condition requiring chronic medication, either prescription or OTC.

4. Alcoholism, narcotic, barbiturate, or poly-drug abuse.

5. Treatment with OTC/Rx drugs within 2 weeks prior to study.

6. Diabetes.

7. Thyroid disease.

8. History of Hepatitis.

9. Any evidence of significant current disease of major organ systems.

10. Use of enzyme-inducing and enzyme-inhibiting drugs such as phenobarbital, carbamazepine and cimetidine within 30 days prior to entry into the study.

11. Asthma.

12. Glaucoma.

Dietary Restrictions:

All subjects abstained from ingesting xanthine containing foods and beverages (coffee, tea, cola beverages, chocolates) for 24

hours prior to, and throughout each study period. Subjects refrained from alcoholic beverages throughout the study.

The formulations investigated in the study were:

Drug A: Test Drug: Terazocin 5 mg tablets, lot # PD 2504, batch size tablets, potency 97.4%.

Drug B: Reference Drug:Hytrin 5 mg tablet, lot # 65-103-AA-21, expiry date Sept. 1, 1995

Subjects were fasted overnight and each received a total dose of 5 mg of terazocin with 240 ml of water at 7 AM(0 hour).

Blood Sampling Schedule:

Hour 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose.

A total of 430 ml of blood was taken over the two study phases.

There was a seven day washout between dosing periods.

Blood Pressure Measurements:

Blood pressure and pulse rate were monitored during each study phase at the following times:

0 (pre-drug), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36 and 48 hours post dose.

Analytical

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Analytical methods

Statistical Analysis

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Results

The pharmacokinetic data was analyzed on the Ln scale.

Table 1. Terazocin mean plasma levels (±sd) for the subjects that received the test and reference formulations after an overnight fast.

TREATMENT A TEST			TREATMENT B REFERENCE	
Time(hrs)	Mean	Sd	Mean	Sd
0	0.00	0.00	0.00	0.00
0.25	19.10	18.11	17.58	19.07
0.5	55.55	29.86	67.88	28.06
0.75	64.84	21.91	82.33	26.26
1	68.24	20.81	78.12	22.50
1.33	63.54	21.19	76.17	22.10
1.67	63.69	19.26	72.28	20.21
2.0	62.62	17.76	69.90	21.02
2.50	58.99	16.22	65.54	17.87
3.0	57.18	15.46	61.38	20.33
4.0	51.72	11.35	57.80	18.01
6.0	42.80	12.18	48.35	14.38
8.0	34.51	7.60	38.37	10.69
12.0	22.72	6.37	25.22	8.23
16.0	15.99	4.25	17.64	5.32
24.0	9.35	2.44	10.64	3.65
36.0	4.55	1.34	5.15	1.85
48.0	2.51	0.92	2.80	1.28

Table 2. Mean pharmacokinetic parameters ± SD and 90% geometric confidence intervals for subjects that received either the test or reference terazocin formulations following an overnight fast.

TREATMENT			
Variable	A=REF	B=Novopharm	Confidence Interval
AUCL2 (ng/mlxhr)	912.39±255.81	812.33±184.89	
LNAUCL4	6.78 ± 0.28	6.68 ± 0.22	84.7 to 96%
AUCI3 (µg/mlxhr)	959.91±275.40	855.92±194.16	
LNAUCI4	6.83 ± 0.28	6.73 ± 0.22	85.3 to 96%
CPEAK (µg/ml)	88.94± 24.22	78.86 ± 22.36	
LNCPEAK4	4.45 ± 0.28	4.33 ± 0.28	82 to 96%
KEL-1 (hr)	0.061±0.007	0.061±0.009	
HALF (hr)	11.40± 1.28	11.64± 1.75	
TPEAK (hr)	0.93 ± 0.36	1.06 ± 0.62	---

Observed Mean ± Standard Deviation
AUCL = AUC (0 to last measurable concentration)
UCI = AUC (0 - infinity)
og Transformed

There was a significant period effect $p<.05$ for LAUC(0-inf) for terazocin.

Subject Dropouts

There were no subject dropouts.

The ANOVA for diastolic pressure indicated a statistically significant difference only at 36 hours. There were no statistically significant differences for systolic pressure and heart rate between the formulations.

Adverse Effects

Adverse effects are listed in table 3.

In Vitro Dissolution Testing:

The submission also includes the results of in vitro dissolution testing conducted on the test and reference product.

Apparatus:	Apparatus II-Paddle
Medium:	Distilled Water at 37^{0}C-900 ml
Sampling Times:	10, 20, 30, 40, 50 and 60 min.
Speed:	50 rpm
No.of units tested:	12

The results of the dissolution testing are attached in table 4.

Comments

1. The calibration curve run on 10/25/93 for subjects 16, 17 and 18 did not have an acceptable calibrator at ng/ml which is the lower limit of detection. However, the controls assayed on 10/25/93 were acceptable. Therefore, the firm should have set the level of assay sensitivity at 2.0 ng/ml for the following samples for subjects 16, 17 and 18.

Sample Number	Reported Value
Sub 16, 48 hr-T	ng/ml
Sub 18, 48 hr-T	ng/ml
sub 18, 48 hr-R	ng/ml

Due to the small number of samples affected by the extrapolation below the level of the curve the overall impact on the analysis would not be detectable. Nonetheless, in the future the firm should not extrapolate below the level of the lowest calibrator.

2. The 90% confidence intervals for the difference between the test and reference means for AUC(0-t),AUC(0-inf) and Cmax for Terazocin were within the acceptable limits of % of the reference mean on the log scale.

3. The observed significant period effect for Terazocin did not affect the study outcome since least square means, which gives equal weight to each period, were used to estimate confidence intervals.

4. The dissolution data presented by the firm was acceptable.

5. The 10 mg, 2 mg, and 1 mg tablets were compositionally proportional(table 5).

Recommendations:

1. The fasting bioequivalence study conducted by Novopharm on its Terazocin Hydrochloride Tablets 5 mg, lot # PD 2504, comparing it to Hytrin Tablets 5 mg, lot # 65-103-AA-21,

manufactured by Abbott Laboratories has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions that Novopharm's Terazocin Hydrochloride Tablets, 5 mg, are bioequivalent to the reference product, Hytrin Tablets, 5 mg, manufactured by Abbott.

2. The formulations for the 1 mg, 2 mg and 10 mg Terazocin Hydrochloride Tablets are proportionally similar to the 5 mg tablet which underwent a bioequivalency study. The waiver of the in vivo bioequivalence study requirements for Novopharm',s 1 mg, 2 mg and 10 mg tablets is granted. The 1 mg, 2 mg and 10 mg Terazocin Hydrochloride Tablets from Novopharm are therefore deemed bioequivalent to the 1 mg, 2 mg and 10 mg Terazocin Hydrochloride Tablets manufactured by Abbott.

3. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing and controls 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:

   Not less than % of the labeled amount of the drug is dissolved in 30 minutes.

4. The firm should receive comment 1.

Andre' J. Jackson /S/
Division of Bioequivalence
Review Branch I

RD INITIALLED ATWU /S/
FT INITIALLED ATWU

Concur: /S/ Date: 6/3/94
Ramakant M. Mhatre, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA #74-446 (original), HFD-600(Hare), HFD-630, HFC-130 (JAllen), HFD-652 (Jackson, Wu), HFD-344(CViswanathan), Drug File.

[redacted]

Table . In Vitro Dissolution Testing

Drug (Generic Name):Terazocin
Dose Strength:1 mg, 2 mg, 5 mg and 10 mg
ANDA No.:74-446
Firm:Novopharm
Submission Date:December 16, 1993
File Name:74446SDW.D93

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM:50
No. Units Tested: 12
Medium: Water Volume:900 ml
Specifications:NLT % in 30 min
Reference Drug: Hytrin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PD 2502 Strength(mg) 1			Reference Product Lot # 65-104-AA-21 Strength(mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
10	84.2		13	92.5		12
20	97.8		3.4	98.1		6
30	99.1		2.9	99.5		5
40	99.6		2.6	100.4		4.8
50	100		2.7	100.8		4.2
60	100.4		2.4	101.3		4.0
Sampling Times (Minutes)	Test Product Lot # PD 2503 Strength(mg) 2			Reference Product Lot # 65-116-AA-21 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
10	94.6		8.2	78.2		11
20	100.1		4.8	91.5		8.9
30	100.5		4.2	96.1		7.4
40	100.8		3.8	97.9		6.5
50	101.3		3.7	98.8		6.3
60	101.4		3.4	99.3		6.0

Sampling Times (Minutes)	Test Product Lot # PD 2504 Strength(mg) 5			Reference Product Lot # 65-103-AA-21 Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	95.6		2.4	91.6		5.4
20	98		2.1	94.8		1.5
30	98.3		2.2	94.7		1.3
40	98.3		2.1	94.9		1.3
50	98.3		2.1	94.5		1.4
60	98.2		2.0	94.8		1.3

Sampling Times (Minutes)	Test Product Lot # PD 2505 Strength(mg) 10			Reference Product Lot # 62-908-AA-21 Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	79.5		11.3	98.1		2.5
20	98.1		2.8	100.9		1.9
30	99.8		1.2	101.2		1.7
40	100.5		0.86	101.4		1.7
50	100.8		0.73	101.5		1.7
60	100.7		0.921	101.6		1.7

TABLE 3

TERAZOSIN 5 mg
STUDY NO. 1364
ADVERSE EVENTS

SUBJECT'S NUMBER	SUBJECT'S INITIALS	PHASE	REGIMEN**	SYMPTOMS	SEVERITY*	TREATMENT	DURATION
02		I	A	Tiredness Lightheaded Headache	Mild Mild Mild	None Placed on right side Placed on right side	1 hr., 45 min. 47 min. 47 min.
05		I	B	Headache	Mild	None	1.5 hrs.
07		I	A	Headache	Moderate	Ice pack applied	10.5 hrs.
09		I	A	Lightheaded	Mild	Placed in bed	30 min.
11		I	A	Lightheaded	Mild	Placed on right side	1 hr., 28 min.
02		II	B	Nausea	Mild	None	50 min.
05		II	A	Headache	Mild	None	7 hrs.
10		II	A	Drowsiness	Mild	None	3.5 hrs.
11		II	B	Dizziness Headache Dizziness	Moderate Mild Moderate	Placed on right side None Placed on right side	0.5 hr. 2hrs.,35 min. 2hrs.,54min.

CODES:

*SEVERITY

MILD: Symptom an annoyance to the patient but did not hinder baseline functioning level; intermittent or continuous; prescription drug not ordinarily indicated but may have been prescribed because of the personality of the patient.

MODERATE: Symptom uncomfortable and/or embarassing to the patient; some interference with normal functioning; not hazardous to health; prescription drug may have been given.

SEVERE: Symptom caused severe discomfort; severely limited or prevented usual functioning; a definite hazard to health; prescription drug may have been given and/or patient may have been hospitalized.

**REGIMEN

A: Terazosin 5 mg Tablets (Novopharm)

B: Hytrin 5 mg Tablets (Abbott Laboratories, U.S.A.)

TABLE 5 A. PROPORTIONALITY DATA BY WEIGHT

Terazosin Hydrochloride Tablets

1 mg, 2 mg, 5 mg, and 10 mg

INGREDIENT	COMPOSITION PER TABLET (mg)			
	1 mg	2 mg	5 mg	10 mg
1. Terazosin Hydrochloride				
2. Lactose				
3. Starch (Corn)				
4. Povidone (K:25 or K:26-28), USP				
5. Talc,				
6. Magnesium Stearate,				
7. FD&C Yellow #6				
8. D&C Red #30				
9. FD&C Blue #1				
10. FD&C Blue #2				
11. D&C Yellow #10				
Total Tablet Weight:	**mg**	**mg**	**mg**	**mg**

N/A= not applicable (ingredient does not appear in product)

TABLE 5 B. PROPORTIONALITY DATA BY PERCENTAGE

Terazosin Hydrochloride Tablets

1 mg, 2 mg, 5 mg, and 10 mg

INGREDIENT	COMPOSITION PER TABLET (%)			
	1 mg	2 mg	5 mg	10 mg
1. Terazosin Hydrochloride				
2. Lactose				
3. Starch (Corn)				
4. Povidone				
5. Talc,				
6. Magnesium Stearate,				
7. FD&C Yellow #6				
8. D&C Red #30				
9. FD&C Blue #1				
10. FD&C Blue #2				
11. D&C Yellow #10				
Total Percentage:	%	%	%	%

I/A= not applicable (ingredient does not appear in product).