

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

65-005

APPLICATION NUMBER:

BIOEQUIVALENCE

Minocycline Hydrochloride
100 mg and 50 mg Capsules
ANDA #65-005
Reviewer: Sikta Pradhan
XWP #65005SDW.198

Global Pharmaceutical Corp.
Philadelphia, PA
Submission Date:
January 16, 1998
May 13, 1998

Review of a Bioequivalence Study Dissolution Data and a Waiver Request

Background:

Minocycline HCL is a tetracycline antibiotic with broad-spectrum antibacterial activity. It is indicated for the treatment of infections of the gall bladder, urinary tract, skin and soft tissues and for those respiratory tract infections which are susceptible to minocycline. Following a single oral dose of 100 mg, peak plasma levels are reached in about 2 hours, with an elimination half-life of about 17 hours. The recommended dosing regimen for minocycline tablets is an initial 100 or 200 mg dose followed by 100 mg dose every 12 hours or 50 mg four times daily.

Objective:

The purpose of this single dose, two-way crossover study in healthy volunteers under fasting condition is to determine the bioequivalence of the test capsule, Minocycline HCL, 100 mg relative to the reference Minocin[®] 100 mg capsule marketed by Lederle Laboratories.

Study Sites:

Clinical: Phoenix Clinical Research Center, Montreal, Canada.

Analytical Laboratory Facility:

Canada.

Medical & Scientific Advisor:

Senior Scientific Director:

Protocol: #971701

Dosing Dates:

Period 1 September 18, 1997

Period 2 October 9, 1997

Study Design:

This was a randomized, single oral dose, two-way crossover design comparing the test capsules with the reference capsules in thirty (30) healthy male volunteers under fasting conditions. The two treatments were separated by a twenty-one (21) days washout period. Plasma samples were analyzed for drug concentrations.

Subject Selection:

Thirty (30) subjects were selected for this study after signing informed consent according to the following criteria:

1. Inclusion Criteria:

- Males, 18-50 years old
- Within \pm 15% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983)
- Good health as determined by interview, physical examination, hematology, serum chemistry, ECG, and urinalysis
- Laboratory values not to exceed 10% of normal limits (with the exception of parameters that are not clinically relevant)

2. Exclusion Criteria:

- History or presence of alcohol or drug of abuse, use of psychotropic agents, cardiac arrhythmias, adverse reactions or allergy to any methylxanthine
- Presence of significant systemic or organ disease, or acute illness or surgery in the four weeks prior to study start
- Exposure to an investigational drug in the four weeks prior to study start
- Use of tobacco products
- Use of any medication within two weeks of study start
- BP < 90/60 after a five minute rest
- Ingestion of alcohol or xanthine-containing beverages within 48 hours of study start

Treatments:

- A. 1x100 mg Capsule of Minocycline (test product) of Global Pharmaceutical corp., Lot #PF117; Lot size :apsules; Potency: 100.6%

B. 1x100 mg Capsule of Minocin^R (Reference product) manufactured by Lederle, Lot #445-892; Potency: 98.0%; Exp. Date: Feb., 2000.

Dose Administration:

A single oral dose of 100 mg minocycline (test or reference) was administered with 240 mL of water following a 10 hour fast. Subjects were not permitted to lie down for 4 hours following drug administration. They were not allowed to smoke from 1 hour before dosing and 4 hours after dosing and within 1 hour prior to scheduled blood pressure measurements.

Drug Washout Period: 21 days

Meal and Food Restrictions:

All volunteers fasted for 4 hours after drug administration. No fluid except that given with drug administration was allowed within 1 hour of dosing. Standard meal was served during the in-house confinement period. No caffeine-containing food or beverages were served during the study. All subjects were confined in the Clinical live-in facility from the evening before dosing until after the 36-hours blood draw. The subjects returned to the facility for 48 and 72 hour blood sample collection.

Safety Monitoring:

Subjects were monitored for medical events throughout the study. There were no significant or unexpected adverse events. All adverse events were mild in severity and resolved without medical treatment.

Blood Samples Collection

Blood samples were collected in tubes containing EDTA for analysis of minocycline at 0 (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after dosing. The plasma samples were separated and kept frozen at -22°C until analysis.

Blood samples collection for:

Period I: September 18, 1997 - September 21, 1997

Period II: October 09, 1997 - October 12, 1997

Assay Methodology:

Analysis Dates: October 16, 1997 - October 30, 1997.

Study samples were stored in the freezer at -22°C for a duration not exceeding 42 days.

Calibration standards and quality control samples (QC) were prepared on October 6, 1997 and stored in the freezer at -22°C .

Method: The plasma samples were analyzed for minocycline concentration by

Specificity: No interference was observed at the retention times of minocycline and internal standard

Linearity: The standard plots were linear in the concentration range of, 75 to 5000 ng/mL, for minocycline with at least a 0.998 correlation coefficient, r in each case.

Sensitivity: The lower limit of quantitation (LLOQ) was 75 ng/mL for minocycline. Any value below this limit was reported as zero.

Precision: Precision was defined as the coefficient of variation of individual replicates from the calculated values.

A. Pre-study validation:

Intraday Precision from QC Samples:

(N = 10)

2.3% (CV) at 75.0 ng/mL

2.2% (CV) at 225.2 ng/mL

2.7% (CV) at 1750.0 ng/mL

1.8% (CV) at 4250.0 ng/mL

Interday Precision from Standard Samples:

(N = 4)

1.4% (CV) at 75.0 ng/mL

1.6% (CV) at 150. ng/mL

1.1% (CV) at 500 ng/mL
1.7% (CV) at 1250.0 ng/mL
0.9% (CV) at 2500 ng/mL
2.3% (CV) at 3750.0 ng/mL
2.0% (CV) at 5000.0 ng/mL

B. Within-study validation:

Interday Precision from Standards:

(N = 10)

4.8% (CV) at 74.24 ng/mL
5.2% (CV) at 148.49 ng/mL
3.6% (CV) at 494.96 ng/mL
2.1% (CV) at 1237.40 ng/mL
5.2% (CV) at 2474.80 ng/mL
1.4% (CV) at 4454.63 ng/mL
1.9% (CV) at 5072.70 ng/mL

Interday Precision from Control Samples:

3.5% (CV) at 223.98 ng/mL; N=19
2.8% (CV) at 225.2 ng/mL; N=19
3.3% (CV) at 1750.0 ng/mL; N=20
3.4% (CV) at 4250.0 ng/mL; N=18

Stability:

1. Minocycline QC samples in human plasma at nominal temperature of -22°C were found to be stable for 104 days.
2. Minocycline QC samples in human plasma were found to be stable for at least 30.6 hours at 4°C in the autosampler.
3. Minocycline samples in human plasma were found to be stable through three freeze/thaw cycles.

Results:

Thirty (30) volunteers were selected for the study and 28 subjects completed both periods of the study. However, Subject No. 18's plasma samples were not analyzed as this subject vomited 9.4 hours after dosing in Period 2. Thus the statistical analyses were performed on data obtained from 27 subjects. All

subjects were monitored for adverse events during the study. There was no serious adverse event or any event which required terminating any subject from the study. Mean plasma minocycline levels and the pharmacokinetic parameters derived from them are presented in Table 1 (and in Fig.1 attached) and Table 2, respectively, below:

Table 1. Mean Plasma Minocycline Levels (ng/mL)

Time (hour)	TEST (A) Minocycline(Global) Lot #PF117	Reference (B) Minocin ^R (Lederle) Lot #445-892
Pre-dose	0	0
0.5	294.77 (54)	141.57 (76)
1.0	585.96 (25)	451.56 (42)
1.5	619.94 (19)	511.03 (28)
2.0	618.16 (15)	567.88 (24)
2.5	634.87 (25)	558.82 (22)
3.0	591.26 (18)	53.92 (19)
4.0	549.88 (13)	521.39 (20)
5.0	436.31 (10)	428.93 (20)
6.0	461.69 (18)	425.50 (18)
8.0	366.03 (18)	347.25 (21)
12.0	281.02 (15)	267.67 (23)
16.0	202.68 (19)	185.53 (21)
24.0	154.85 (18)	137.64 (30)
36.0	49.74 (100)	45.84 (111)
48.0	6.12 (361)	6.06 (361)
72.0	0	0

* Coefficient of Variation; Number of Subjects 27

Table 2. Mean Pharmacokinetic Parameters for Plasma Minocycline

Parameters (Arithmetic mean)	Test (A)	Ref. (B)	A/B	90% C.I.
AUC _{0-T} (ng.hr/mL)	8473.4 (21)*	7719.2 (26)	1.13	
LnAUC _{0-T} Geometric Mean	9.03349* 8379.05	8.92709** 7533.31	1.11	104; 119
AUC _{0-inf} (ng.hr/mL)	10647.8 (17)	9470.8 (23)	1.16	
LnAUC _{0-inf} Geometric Mean	9.2668** 10580.71	9.13656** 9288.75	1.14	107; 121
C _{MAX} (ng/mL)	708.25 (22)	635.26 (20)	1.14	
LnC _{MAX} Geometric Mean	6.5343** 688.35	6.4546** 635.62	1.08	103; 118
T _{max} (hour)	2.002 (44)	2.26 (47)		
t _{1/2} (hour)	13.44 (21)	12.16 (26)		
KE (1/hour)	0.054 (21)	0.061 (26)		

Number of Subjects 27

* Coefficient of Variation

** Based on Least Squares Means (LSM)

Intra-subject variability(%) for: LnAUC(0-t)=13.8

LnAUC(0-inf)=12.4

LnCmax=14.3

Both test and reference drugs produced minocycline peak concentration between 1.5 hour to 2.5 hours after their administration. The differences between the test and reference products in LnAUC_{0-T}, LnAUC_{0-inf} and LnC_{MAX} were less than 10%. The 90% confidence intervals for , LnAUC_{0-T} , LnAUC_{0-inf} and LnC_{MAX} for minocycline of the test product remained within the acceptable range of 80 - 125%.

In-Vitro Dissolution:

The firm has conducted dissolution testing on the test and reference

products. The data are presented in Table 5.

Table 5. In Vitro Dissolution Testing						
Drug: Minocycline Hydrochloride Capsules Dose Strengths: 50 mg & 100 mg AND No.: 65-005 Firm: Global Pharmaceutical Corp. Submission Date: January 16, 1998						
I. Conditions for Dissolution Testing: (USP method)						
USP XXIII Paddle RPM: 50 No. Units Tested: 12 Medium: Water at 37°C Volume: 900 Specifications: Assay Methodology:						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	<u>Test Product</u>			<u>Reference Product</u>		
	Minocycline Hydrochloride Capsules Lot # PF129 Strength 50 mg			Minocin [®] Lot # 445-074 Strength 50 mg		
	Mean %	Range%	%CV	Mean %	Range%	%CV
15	94.42		3.80	29.50		16.61
30	97.29		2.32	47.82		2.07
45	97.42		1.75	64.61		14.19
60	97.67		2.19	76.93		10.88
Sampling Times (Minutes)	<u>Test Product</u>			<u>Reference Product</u>		
	Minocycline Hydrochloride Capsules Lot # PF117 Strength 100 mg			Minocin [®] Lot # 445-892 Strength 100 mg		
15	95.78		3.23	37.57		11.53
30	101.57		2.43	59.22		9.41
45	102.10		2.52	73.97		7.35
60	102.45		2.12	85.05		6.53

The test product (both strengths, 50 mg & 100 mg) meets the dissolution specification of dissolved in minutes, but the reference product does not meet that specification. The dissolution testing conducted on the test product is acceptable.

Compositions:

The compositions of the test capsules are presented in Table 6 attached herewith.

Comments:

1. The firm's in vivo bioequivalence study conducted under fasting conditions on the test product, Minocycline Hydrochloride Capsules, 100mg, and the reference product, Lederle's Minocin^R Capsules is acceptable.
2. The in vitro dissolution testing conducted on the 50 mg and 100 mg capsules of the test product is acceptable.
3. The formulations of the test product, 50 mg and 100 mg capsules are identical. The waiver of in vivo bioequivalence study requirements for 50 mg capsules of the test products is granted.

Recommendation:

1. The in vivo bioequivalence study conducted by Global Pharmaceutical Corporation under fasting conditions on the test product, Minocycline Hydrochloride Capsules, 100mg, lot #PF117, comparing it to Lederle's Minocin^R 100 mg Capsules has been found acceptable by the Division of Bioequivalence. The study demonstrates that Minocycline Hydrochloride 100 mg Capsules of Global Pharmaceutical Corporation is bioequivalent to the reference product, Minocin^R 100 mg Capsules manufactured by Lederle.
2. The in vitro dissolution testings conducted by Global Pharmaceutical Corporation on its Minocycline Hydrochloride Capsules, 100mg, lot #PF117 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 specifications:

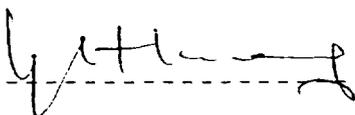
Not less than _____ of the labeled amount of the drug in the tablet is dissolved in _____ minutes.

3. The in vitro dissolution testing conducted by Global Pharmaceutical Corporation on its Minocycline Hydrochloride Capsules, 50 mg, lot #PF129 is acceptable. The formulation of the 50 mg strength is proportionally similar to that of the 100 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for 50 mg capsules of the test product is granted. The 50 mg capsule of the test product is therefore deemed bioequivalent to the 50 mg Capsule of Minocln^R manufactured by Lederle.



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

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FT INITIALED YCHUANG

 5/19/98

Concur: 

Date: 5/20/98

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

MEDICAL EVENTS

Subj	Per Dosing Time/Date	Sign/Symptom		Serious-ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up		
		Time after dosing	Dur-ation							Time after dosing	Evolu-tion	Inten-sity

Product Code A

2	07:34am 09/OCT/97	Headache		NS	D	PO	SP	M	MP	8.1h	I	MO	Applied cold compress on forehead 8 hours post-dose
		10.2h	U							MO	Took Tylenol 2 x 500 mg oral		
		10.8h	D							M	None		
		15.4h	R							N/A	None		
2	07:34am 09/OCT/97	Feels feverish		NS	D	U	SP	M	MP	9.9h	U	M	BP: 124/80, Pulse: 60, Temperature: 36.8°C, 10.1 hours post-dose
		10.2h	U							M	Took Tylenol 2 x 500 mg		
		10.8h	U							M	None		
		15.4h	R							N/A	None		
2	07:34am 09/OCT/97	Vomited		NS	D	PO	SP	M	None	9.4h	R	N/A	None
2	07:34am 09/OCT/97	Feels dizzy		NS	D	PO	E	M	None	10.1h	U	M	BP: 124/80, Pulse: 60, Temperature: 36.8°C at 10.1h post-dose
		10.8h	D							M	None		
		15.4h	R							N/A	None		

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d-Days	PO-Physician Obs	S-Serious	D-Drug	D-Definite	E-Elicited	M-Mild	I-Increased	N/A = Not Applicable
h-Hours	AC-Addit. Comment	NS-Non-Serious	P-Procedure	PR-Probable	SP-Spontaneous	MO-Moderate	U-Unchanged	N/R = Not Recorded
m-Minutes	MP-Med. Prescrip.		O-Other-MD's Comment	PO-Possible	O-Observed	S-Severe	D-Decreased	
				U-Unlikely			R-Resolved	

A = Global Pharmaceutical 1 x 100mg minocycline HCl powder-filled capsule.
B = Lederle (Minocin) 1 x 100mg minocycline HCl pellet-filled capsule.



MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur- ation	Serious- ness	Caus- ality	Proba- bility	Report Method	Intensity at Onset	Forms Used	Follow-Up		
											Time after dosing	Evolu- -tion	Inten- -sity

Product Code A

1	07:44am 18/SEP/97	Loose stool	3.8h	10.0m	NS	D	PO	SP	M	None	4.0h	R	N/A	None
1	07:44am 18/SEP/97	Loose stools (intermittent)	10.0h	1.0h	NS	D	PO	SP	M	None	11.0h	R	N/A	None
1	07:44am 18/SEP/97	Loose stool	1.1d	15.0m	NS	D	PO	SP	M	None	1.1d	R	N/A	None
1	07:44am 18/SEP/97	Loose stools	2.2d	12.4d	NS	D	U	SP	M	None	3.0d 14.6d	U R	M N/A	Had loose stool, 2.4 days and 2.9 days post-dose None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO-Physician Obs	S-Serious	D-Drug	D-Definite	E-Elicited	M-Mild	I-Increased	N/A - Not Applicable
h=Hours	AC-Addit. Comment	NS-Non-Serious	P-Procedure	PR-Probable	SP-Spontaneous	MO-Moderate	U-Unchanged	N/R - Not Recorded
m=Minutes	MP-Med. Prescrip.		O-Other-MD's Comment	PO-Possible U-Unlikely	O-Observed	S-Severe	D-Decreased R-Resolved	

A - Global Pharmaceutical 1 x 100mg minocycline HCl powder-filled capsule.
B - Lederle (Minocin) 1 x 100mg minocycline HCl pellet-filled capsule.

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MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom		Serious -ness	Caus- ality	Proba- bility	Report Method	Intensity at Onset	Forms Used	Follow-Up			
			Time after dosing	Dur- ation							Time after dosing	Evolu- -tion	Inten- -sity	Action/Comment

Product Code B

1	07:36am 18/SEP/97	Headache	11.9h	1.8d	NS	D	U	SP	M	MP	14.9h	U	M	None
			16.6h	I	MO	Given Tylenol 2 x 500mg								
			1.0d	D	M	None								
			1.3d	U	M	None								
			1.4d	I	M	Applied cold compress								
			1.5d	D	M	None								
			1.5d	U	M	Given acetaminophen 2 x 500 mg								
			2.0d	U	M	None								
			2.3d	R	N/A	None								
			1	07:36am 18/SEP/97	Nausea	11.9h	17.5h	NS	D	U	SP	M	None	14.9h
16.6h	U	M				None								
1.0d	D	M				None								
1.2d	R	N/A				None								

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med. Prescrip.		O=Other-MD's Comment	PO=Possible U=Unlikely	O=Observed	S=Severe	D=Decreased	
							R=Resolved	

A = Global Pharmaceutical 1 x 100mg minocycline HCl powder-filled capsule.
B = Lederle (Minocin) 1 x 100mg minocycline HCl pellet-filled capsule.

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MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur- ation	Serious -ness	Caus- ality	Proba- bility	Report Method	Intensity at Onset	Forms Used	Follow-Up				
											Time after dosing	Evolu- -tion	Inten- -sity	Action/Comment	
Product Code B															
1		07:36am 18/SEP/97	Vomited	11.9h	5.0m	NS	D	U	SP	M	None	12.0h	R	N/A	None
1		07:36am 18/SEP/97	Vomited	16.6h	5.0m	NS	D	U	SP	M	None	16.7h	R	N/A	None
1		07:36am 18/SEP/97	Nausea	1.3d	3.0h	NS	D	U	SP	M	None	1.4d	R	N/A	None
1		07:38am 18/SEP/97	Mild stomach pain	4.4h	5.0h	NS	D	PR	SP	M	None	9.4h	R	N/A	None
2		07:42am 09/OCT/97	Feels dizzy	1.0h	3.5h	NS	D	PO	SP	M	None	2.1h 4.5h	N/A R	N/A N/A	BP: 97/70, Pulse: 48 None
1		07:46am 18/SEP/97	Loose stools	13.4d	6.0h	NS	D	PO	SP	M	None	13.7d	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med. Prescrip.		O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Global Pharmaceutical 1 x 100mg minocycline HCl powder-filled capsule.
B = Lederle (Minocin) 1 x 100mg minocycline HCl pellet-filled capsule.

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