CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-059

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-059 APPLICANT: Ranbaxy Laboratories

DRUG PRODUCT: Amoxicillin Tablets, 500 mg and 875 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

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,

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

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Amoxicillin Trihydrate
500 mg and 875 mg Tablets
ANDA # 65-059
Reviewer: André Jackson

Ranbaxy Laboratories
Princeton, N.J.
Submission Date:
December 17, 1999

Review of A Fasting Bioequivalence Study on the 875 mg Tablet and a Waiver Request for the 500 mg Tablet and Dissolution Data

Class: Antibiotic

RLD: Amoxil® -Smith Kline Beecham

Background:

Amoxicillin is a semisynthetic aminopenicillin for oral use with a broad spectrum of bactericidal activity similar to that of ampicillin. It acts by inhibiting cell wall synthesis through binding to beta-lactam receptor protein and it is inactivated by those bacteria containing lactamase.

The peak plasma amoxicillin levels occur at 1 to 2 h (T_{max}) in adults and at earlier time in children. It is not highly protein bound (20%) as compared to penicillin G (60%). Most of the amoxicillin (60%) is excreted unchanged in urine within 6 to 8 hours. The half-life of amoxicillin in normal subjects is about 1 hour and is longer in patients with renal dysfunction.

Objective - The objective of this randomized, single-dose, two-way crossover study was to compare the oral bioavailability of the test formulation to an equivalent dose of the commercially available reference Amoxil®, in a test population of healthy adult male subjects under fasting conditions.

Study Facility Information:

Clinical Facility:	Phoenix International, Cincinnati, Ohio
Principal Investigator:	Thomas G. Borbos, M.D.
Clinical Study Date:	Period I-October 16, 1999 Period II-October 23, 1999
Analytical Facility:	
Analytical Study Date:	October 28, 1999-November 17, 1999
Special Conditions	Samples collected and processed under conditions to minimize exposure to U.V. light
Storage Period:	1 month

Study Design:

Protocol No.:	
Design Type:	Two-way crossover
Randomized:	Y
No. of Sequences:	2
Number of Groups	1
No. of Periods:	2
No. of Treatments:	2
Washout Period:	7 Days
Single, Multiple, Food:	Single

Subjects:

Normal Healthy Volunteers:	Y
IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	30
No. of Subjects Completing Study:	27*

Inclusion/Exclusion criteria	Vol. 1.2 pgs.200-201
Housing	Evening before dosing until after 8 hr blood draw

*Number 3 did not return for period 2 due to illness
Numbers 18 and 28 discontinued due to positive drug screen

Treatment Information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Amoxicillin Tablets	Amoxil®
Strength:	875 mg	875 mg
Manufacturer:	Ranbaxy	Smith-Kline Beecham
Batch/Lot No.:	AMTX **02LF	MD2340
Exhibit Batch Size:		N/A
Expiration Date:	August 2001	August 2000
Content Uniformity	99.4%	100.54%
Assay	99.4%	100.5%
Dose Administered:	875 mg with 240 ml water	875 mg with 240 ml water
Length of Fasting:	Overnight	Overnight
Meals	4 hrs post-dose	4 hrs post-dose

Table 1. RANDOMIZATION SCHEDULE

Sequence	Subjects
AB	1,3,5,7,9,11,13,14,15,20,21, 23,25,27,29,31
BA	2,4,6,8,10,12,16,17,18,19,22, 24,26,28,30,32

Blood Sampling: Plasma analyzed

Blood sample volume	5 mL
Time points	0.0.33,0.67,1,1.33,1.67,2,2.5,3,4,5,6 and 8 hrs

Formulation for the 875 mg amoxicillin trihydrate tablet

Component	mg/Tablet
Amoxicillin,	
Mycrocrystalline cellulose	
Crospovidone	
Sodium Starch	
Colloidal silicon dioxide	
Magnesium Stearate	
NF	

Analytical Method

The plasma samples were assayed for amoxicillin by with detection.

The details of the analytical method for amoxicillin are presented in Table 2:

Table 2: Validation data for amoxicillin.

Parameter	
Method	
Internal Standard	
Sensitivity/LOQ	0.1 ug/mL
Linearity (Standard curve samples)	0.1-19.77 ug/mL
Quality Control (QC) Samples	0.299 ug/mL 7.963 ug/mL 15.428 ug/mL

Precision of Standards (%CV)	8.7% @ 0.10 ug/mL 4.2% @ 19.77 ug/ml
Precision of QC Samples (%CV)	8.8% @ 0.299 ug/mL 3.5% @ 15.428 ug/mL
Accuracy of Standards (%)	99.3% @ 0.10 ug/mL 99.5% @ 19.77 ug/ml
Accuracy of QC Samples (%)	100.0% @ 0.299 ug/mL 101% @ 15.428 ug/mL
Stability	
Freeze-thaw	2 cycles
Processed Sample Stability at RT	4.56 hrs @ 20° C
Long term at -80° C	77 days
Recovery Low Med High	 100.3% @ 0.3 ug/mL 90.2% @ 8.01 ug/mL 90.4% @ 15.501 ug/mL

THE ANALYTICAL DATA IS ACCEPTABLE TO THE REVIEWER

STATISTICAL ANALYSIS:

AUC(0-T), AUCinf, Cpeak and log transformed AUC(0-T), AUCinf and Cpeak was analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, and study period in the statistical model.

The two one-sided hypotheses at the alpha=0.05 level of significance were tested for AUCT, AUCinf, Cpeak in original scale and after log transformation, by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and were reported relative to the reference means.

Results

Table 3. Mean amoxicillin plasma levels (ug/mL) for the test and reference products. Values are mean +_SD.

	TEST		REFERENCE	
HOUR0	0.00	0.00	0.00	0.00
HOUR0.25	0.25	0.36	0.33	0.41

HOUR0.5	2.41	1.76	3.34	2.51
HOUR0.75	5.49	2.71	6.59	3.57
HOUR1	7.93	3.50	8.93	4.06
HOUR1.25	9.17	3.44	10.16	3.90
HOUR1.5	10.08	2.95	10.68	3.56
HOUR1.75	10.10	3.02	10.64	2.54
HOUR2	10.11	2.83	10.42	2.38
HOUR2.5	8.63	1.71	8.71	2.09
HOUR3	7.20	1.92	6.44	1.84
HOUR3.5	5.62	2.07	4.79	1.56
HOUR4	4.27	1.60	3.66	1.41
HOUR6	1.29	0.64	1.06	0.47
HOUR8	0.42	0.23	0.37	0.15

Table 4. Mean test and reference parameters for amoxicillin. Values are mean ± SD.

	TEST		REFERENCE		RATIO(T/R)
CPEAK ug/mL	11.64	2.46	12.05	3.11	0.96
LCPEAK ug/mL	2.43	0.21	2.46	0.26	0.97[1]
AUCL[2] ug/mL x hr	33.80	5.70	33.15	5.79	1.02
LAUCL ug/mL x hr	3.51	0.18	3.49	0.17	1.02
AUCI[3] ug/mL x hr	34.58	6.03	33.86	5.89	1.02
LAUCI ug/mL x hr	3.53	0.18	3.51	0.17	1.02
TMAX, hr	1.82	0.58	1.62	0.50	---
KEL, hr-1	0.58	0.09	0.55	0.09	---
THALF, hr	1.23	0.20	1.31	0.26	---

1. Ratio of geometric means
2. AUC to last measured concentration
3. AUC to time infinity

Table 5. 90% confidence intervals

Parameter	
LCPEAK	88-106
LAUCL	95-108
LAUCI	95-108

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER

Adverse Events:

There were 3 adverse events 2 for test and 1 for reference. They were lightheadedness and headache.

Sample Repeats:

There were 864 samples analyzed. Seven samples(0.83%) were reanalyzed.

IN-VITRO DISSOLUTION TESTING

The dissolution testing for the test and reference products was conducted using 900 mL of water at 37° C using USP apparatus II (paddle) at 75 rpm.

Comparative Formulations:

Component	875 mg/Tablet	500 mg/Tablet
Amoxicillin		
Mycrocrystalline cellulose		
Crospovidone		
Sodium Starch		
Colloidal silicon dioxide	2	
Magnesium Stearate		
le		
Coating Material		

RECOMMENDATIONS:

1.The fasting bioequivalence study conducted by Ranbaxy Laboratories on its 875 mg, amoxicillin trihydrate tablet(lot AMTX**02LF), comparing it to Smith-Kline Beecham's Amoxil® 875 mg tablet lot number MD2340 has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Ranbaxy's 875 mg amoxicillin trihydrate tablet is bioequivalent to the reference Amoxil® 875 mg tablet manufactured by Smith-Kline Beecham.

2. The in vitro dissolution testing conducted on the 875 mg tablet is acceptable

3.The in vitro dissolution testing conducted on the 500 mg amoxicillin trihydrate tablet (lot # AMT***02LF) has been found to be acceptable. The firm has conducted an acceptable in vivo bioequivalence study comparing its 875 mg amoxicillin trihydrate tablet of the test product with Amoxil® 875 mg tablet. The formulation for the 500 mg tablet strength is proportionally similar to the 875 mg amoxicillin trihydrate tablet strength of the test product which underwent bioequivalency testing. The waiver of in-vivo bioequivalence study requirements for the 500 mg amoxicillin trihydrate tablet of the test products is granted. Therefore, Ranbaxy's 500 mg amoxicillin trihydrate tablet is deemed bioequivalent to Smith-Kline Beecham's Amoxil® 875 mg tablet.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should be conducted in 900 mL of water at 37° C using USP apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 90 minutes

André J. Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date 4/3/2000

Concur: _____ Date 4/5/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Amoxicillin
Dose Strengths:875 mg and 500 mg
ANDA No.:65-059
Firm: Ranbaxy
Submission Date: December 17, 1999
File Name:

I. Conditions for Dissolution Testing:

USP XXIV Basket: Paddle: x RPM: 75
No. Units Tested: 12
Medium: Water
Wavelength 230 nm
Volume: 900 mL
Specifications:
NLT in 90 minutes

Reference Drug: Amoxil®
Assay Methodology:

THIS IS A USP METHOD

II. Results of In Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot #AMT***02LF Strength(mg)500			Reference Product Lot #KW 2093 Strength(mg) 500		
	Mean	Range	SD	Mean	Range	SD
15	94.6		1.1	88		3
30	98.2		1.2	96		2
45	100.2		1.4	98		2
60	100.2		1.8	99		3
90	100.7		1.0	103		2

Sampling Times (min)	Test Product Lot #AMTX**02LF Strength(mg) 875			Reference Product Lot # MD 2340 Strength(mg) 875		
	Mean	Range	SD	Mean		SD
15	95.5		1.9	92		2
30	97.2		2.3	101		2

45	98.1	
60	100.0	
90	102.2	

	2.9	102	
	1.6	102	
	1.9	103	

2
2
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