

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75951

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-951

SPONSOR: Barr Laboratories

DRUG AND DOSAGE FORM: Norethindrone acetate tablets

STRENGTH(S): 5 mg

TYPES OF STUDIES: N/A

CLINICAL STUDY SITE(S): ()

STUDY SUMMARY: The fasting bioequivalence study is acceptable

DISSOLUTION: Meets USP specifications

WAIVER: N/A

DSI INSPECTION STATUS

Inspection needed: No	Inspection status: N/A	Inspection results: N/A
First Generic: Yes		
New facility <u> No </u>		
For cause <u> No </u>		
Other <u> None </u>		

PRIMARY REVIEWER: (Gur J.P. Singh, Ph.D.)

BRANCH: II

INITIAL: JSI

DATE: 11-3-00

TEAM LEADER: (Shrinivas Nerurkar, Ph.D.)

BRANCH: II

INITIAL: JSI

DATE: 11/8/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL: JSI

DATE: 11/30/00

21
Single J.S.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 75-951

APPLICANT: Barr Laboratories

DRUG PRODUCTS: Norethindrone acetate tablets USP 5 mg

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

We acknowledge that the dissolution testing will need to be incorporated into your stability and quality control programs. Dissolution testing should meet the USP 24 specifications.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

CC: ANDA: 75-951
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)

HFD-655/Reviewer

GOODS 11-3-00

HFD-655/Bio Team Leader

HFD-617/Project Manager

HFD-650/Dale Conner *BRD 11/30/00*

200 11/8/00

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 8/25/00

1. FASTING STUDY (STF)
Clinical:
Analytical

Strength: 5 mg
✓ Outcome: AC

DISSOLUTION DATA (DIS)

Strength: 5 mg
Outcome: AC

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 9/22/00

2. Study Amendment

Strengths: 5 mg
✓ Outcome: AC

WinBio Comments: The fasting bioequivalence study is acceptable.
Dissolution testing is acceptable.

Norethindrone Acetate

Tablets, 5mg

ANDA 75-951

Reviewer: Gur J.P. Singh

Barr Laboratories, Inc.

2 Quaker Road, Pomona, NY 10970

Submission Dates:

Aug 25 and Sept. 9, 2000

Review of a Fasting¹ Bioequivalence Study and Dissolution Data (Electronic Submission)

Introduction

Indication: Treatment of amenorrhoea, endometriosis and abnormal uterine bleeding

Type of Submission: Original (First Generic)

Contents of Submission: Fasting bioequivalence study and dissolution data.

RLD: Aygestin® 5 mg tablets (NDA #18405)

Recommended Dose: 2.5 mg - 10 mg daily

Background: The sponsor has previously been advised to conduct the bioequivalence study in healthy postmenopausal women (Letter date: 4/6/2000).

Financial Disclosure: Yes

Protocol No.: 00116. A randomized, two-way crossover, comparative bioavailability study of Barr Laboratories' 5mg norethindrone acetate and Wyeth-Ayerst laboratories' Aygestin® 5mg tablets administered as a 1 x 5 mg tablet under fasting conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: []

Medical Director: []

Scientific Director: []

Clinical Study Dates: 04/14/00 to 06/21/00

Analytical Facility Principal Investigator: []

Investigator: []

Analytical Study Dates: 05/30/00 to 07/14/00

TREATMENT INFORMATION

¹ In a previous correspondence with the firm, DBE did not request a food study. The reference product labeling does not contain any reference to food with regard to dosing or the drug product bioavailability.

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Norethindrone Acetate Tablets, USP 5 mg	Aygestin 5 mg tablet
Manufacturer:	Barr Laboratories, Inc. USA	Wyeth-Ayerst Laboratories, USA
Manufacture Date:	3/23/00	N/A
Expiration Date:	N/A	N/A
ANDA Batch Size:	-	-
Full Batch Size:	-	-
Batch/Lot Number:	102110001R	3990372
Potency:	99.5%	97.1%
Content Uniformity:	100.2%	98.1%
Strength:	5 mg	5 mg
Dosage Form:	tablet	tablet
Dose Administered:	5 mg	5 mg
Study Condition:	fasting	fasting
Length of Fasting:	10 hours	10 Hours

RANDOMIZATION

DESIGN

Randomized:	Y	Design Type:	crossover
No. of Sequences:	2	Replicated Treatment Design:	N
No. of Periods:	2	Balanced:	N
No. of Treatments:	2	Washout Period:	28 days

DOSING

SUBJECTS

Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	30
Route of Administration:	oral	No. of Subjects Completing:	29
Dosing Interval:	N/A	No. of Subjects Plasma Analyzed:	29
Number of Doses:	N/A	No. of Dropouts:	1
Loading Dose:	N/A	Sex(es) Included:	female
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	46

- Dietary Restrictions:** Abstain from food or drink containing xanthine (coffee, tea, caffeine-containing sodas, colas, chocolate etc) grapefruit products (fresh, canned, or frozen), Acetaminophen, and alcohol from 48 hours prior to drug administration.
- Activity Restrictions:** Subjects were required to use non-hormonal method of contraception from prior to study commencement until the end of each blood collection. Normal activity after dosing avoiding complete rest. Vigorous physical activity was prohibited.
- Drug Restrictions:** No concomitant medications, other than those used to counter adverse events, were utilized during this study.
- Blood Sampling:** 7-mL samples collected in tube EDTA containing tubes at zero (pre-dose), 0.167, 0.33, 0.5, 0.75, 1.00, 1.25, 1.50, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 24 and 36 hours after dosing.

Study Results

1) Clinical Adverse Events: A total of 46 adverse events were experienced by 20 subjects during the study. Fourteen (14) events were judged to be unrelated to the study medications, 11 were judged unlikely (equivalent to remote), and 21 were judged possibly (equivalent to possible) related to the study medications. The intensity at onset of the adverse events was judged as follows: 24 were mild, 1 was moderate, and 21 were recorded as "not applicable" (14 were associated with menstrual irregularities and 7 were associated with post-study laboratory test results). Note that 4 pre-dose adverse events were judged possibly (equivalent to possible) related to the study medications.

Protocol Deviations (As electronically submitted by the firm):

At screening, the determination of a regular menstrual cycle (28 ± 4 days; Inclusion Criterion) was made based on only 1 menstrual cycle, not 2, as specified in the protocol.

Subjects abstained from food or drink containing caffeine from 48 hours prior to dosing until after the 36.0-hour post-dose blood draw in each period, with the exception of Subject No. 12 who consumed approximately 50 mL of Diet Pepsi® (cola beverage) 1 day 5 hours 38 minutes post-dose in Period 1.

The study medication was stored in an environmentally-controlled room. However, humidity levels (as recorded using a Rees® system) in the medication room dropped beneath the normal range on 3 occasions (to as low as 30.58%RH; duration of these

occasions: approximately 6 hours 40 minutes, 10 hours 36 minutes, and 9 hours 24 minutes) and rose to as high as 61.34%RH on 1 occasion (duration of approximately 2 minutes) during drug storage.

The study medication was administered with 240 mL of room-temperature water, with the exception of Subject Nos. 09 and 18: a few drops of water were spilled at the time of drug administration in Period 1.

All subjects were served a meal approximately 9 hours post-dose, in each period. However, Subject No. 27 was not served the 9-hour post-dose meal in Period 2 (reason unknown).

Subjects did not lie down for the first 4 hours after dosing, with the exception of Subject No. 08 who lay down from 1 hour 17 minutes to 1 hour 19 minutes post-dose in Period 1.

Contrary to the protocol, pregnancy tests were performed at the time of admission in both periods for Subject No. 24 (subject was surgically sterile).

Post-study procedures were performed following the final blood collection in Period 2, with the exception of Subject Nos. 02 and 06, whose urine collection was performed prior to the blood collection.

The Principal Investigator judged the deviations reported above unlikely to have affected the bioavailability comparison.

With the exceptions listed in the table below, all post-dose blood samples were obtained within 3 minutes of their scheduled times. These blood sampling time deviations have no impact on the conclusion of the study, as only exact times were used for pharmacokinetic calculations.

Period	Sampling Time (post-dose)	Subject No.	Deviation	Reason
1	1.00	23	4 minutes late	G
	8.00	24	5 minutes late	G
	10.0	25	5 minutes late	G
		26	12 minutes late	G
	12.0	25	4 minutes late	G
	14.0	03	Sample not obtained	C
	16.0	11	4 minutes late	C
		29	Sample not obtained	C
	24.0	18	4 minutes late	C
		29	5 minutes late	C
36.0	02	1 hour 53 minutes late	B	

Period	Sampling Time (post-dose)	Subject No.	Deviation	Reason
		20	7 minutes late	H
		24	1 hour 56 minutes early	F
		28	1 hour 18 minutes early	F
2	6.00	25	5 minutes late	G
	8.00	01	9 minutes late	G
		21	4 minutes late	G
	10.0	25	4 minutes late	C
	16.0	11	6 minutes late	C
	24.0	03	4 minutes late	C
		25	5 minutes late	C
		29	5 minutes late	C
	36.0	05	5 minutes late	C
		11	14 minutes late	C
		17	20 minutes late	B
25		9 minutes late	B	

Dropouts: Subject #08 was withdrawn by a Medical Sub-Investigator prior to the Period 2 drug administration, as subject was pregnant. Thus, 29 subjects completed the study

Comments: In the reviewer's opinion, protocol deviations reported by the firm should not influence bioavailability comparisons.

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

Stability: The firm submitted acceptable data for stability during sample processing at room temperature, for 501 days under storage at -20° C, and following five freeze-thaw cycles (pp. 06-271 - 06-278, Vol. 1.2)

Recovery: Norethindrone (72-75%), Internal Standard (%)

Reproducibility and Accuracy:

Precision Accuracy

<i>Pre-study Validation</i>	QCs	4.19-8.09%	90.01-101.3%
<i>Within the Sample Analysis Period</i>	QCs	3.99-8.08%	92.41-99.87%
	Calib. Stand.	1.99-4.76%	97.45-102.5%

Repeat Assays: In this study a total of 98 samples were re-assayed due to a variety of reasons (pp. 06-199, vol. 1.2). Repeat-assay values were reported for these samples.

Conclusion: The Analytical Method is acceptable

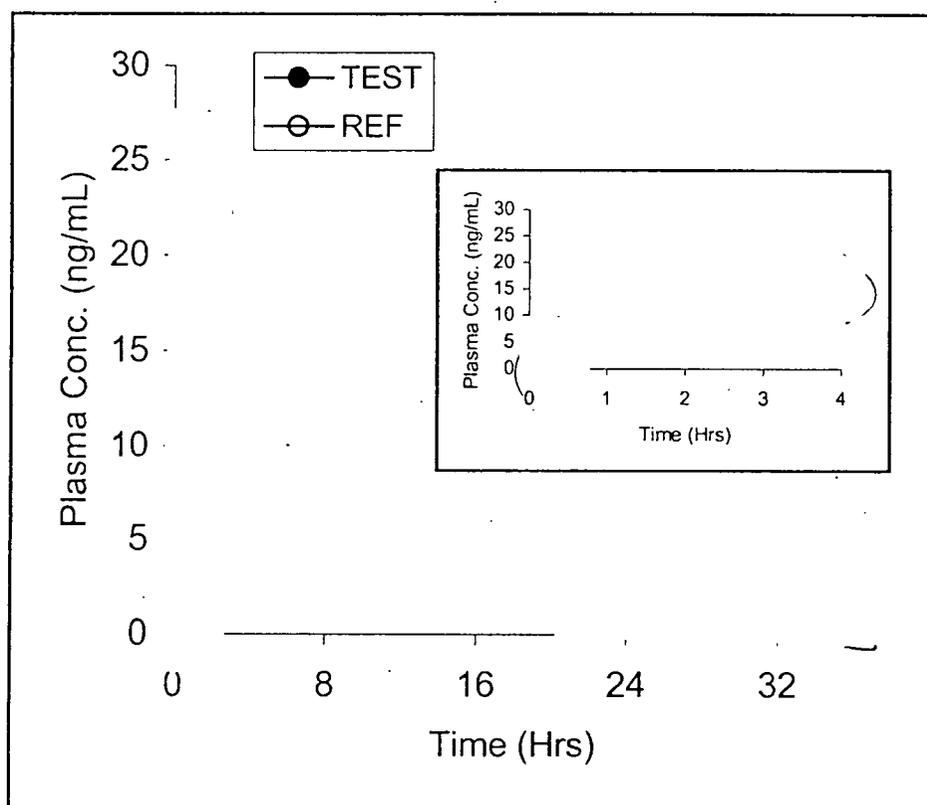
3) Pharmacokinetic:

PARAMETER	PROGRAM USED	CALCULATION METHOD
AUCO-T	SAS	TRAPEZOIDAL
AUCO-INF	SAS	AUCO-T+ OBSERVED CT/KEL
Cmax	SAS	Observed Data
Tmax	SAS	Observed Data
Kel	SAS	Ln-linear regression of the terminal elimination phase
Thalf	SAS	(Ln2) /Kel

Mean Plasma Concentrations:

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
Pre-dose	0.00 (----)	0.00 (----)	----
0.167	0.07 (204.43)	0.06 (299.54)	1.1444
0.333	2.18 (76.09)	2.48 (83.15)	0.8802
0.500	7.30 (51.84)	9.32 (56.31)	0.7835
0.750	14.70 (36.56)	17.14 (41.99)	0.8576
1.00	18.70 (34.64)	21.94 (37.59)	0.8521
1.25	20.73 (32.34)	25.20 (33.85)	0.8227
1.50	22.05 (25.15)	24.59 (31.01)	0.8965

1.75	22.62 (25.61)	24.69 (28.30)	0.9161
2.00	23.03 (29.14)	25.01 (28.41)	0.9207
2.50	20.76 (31.04)	22.11 (26.97)	0.9389
3.00	17.99 (31.93)	18.63 (30.37)	0.9656
4.00	13.44 (37.81)	13.38 (36.66)	1.0044
6.00	7.80 (41.31)	7.78 (40.33)	1.0014
8.00	5.57 (40.59)	5.64 (40.23)	0.9876
10.0	4.32 (41.50)	4.42 (48.38)	0.9778
12.0	4.03 (49.17)	3.83 (41.61)	1.0526
14.0	3.19 (46.30)	3.07 (45.84)	1.0397
16.0	2.97 (46.39)	2.73 (43.18)	1.0885
24.0	1.22 (56.88)	1.20 (60.10)	1.0173
36.0	0.54 (77.88)	0.54 (72.14)	1.0019



Pharmacokinetic Parameters and AUC/AUCI:

SUB	SEQ	TEST				REF				TEST/REF		
		AUC	AUCI	AUC/AUCI	Cmax	AUC	AUCI	AUC/AUCI	Cmax	AUC	AUCI	Cmax
1	2											
2	1											
3	2											
4	2											
5	1											
6	1											
7	1											
9	2											
10	1											
11	2											
12	2											
13	2											
14	2											
15	1											
16	1											
17	2											
18	1											
19	1											
20	1											
21	1											
22	1											
23	2											
24	2											
25	2											
26	1											
27	2											
28	2											
29	1											
30	1											
Mean		158.34	166.90	0.95	26.19	163.00	171.22	0.95	29.08	0.98	0.98	0.94
%CV		33.30	33.72	2.74	23.65	33.40	33.83	2.83	25.57	15.81	15.59	28.05

90% Confidence Intervals:

Parameter	TEST (A)		REF (B)		A/B	90%- CI	ISV
	Mean	%CV	Mean	%CV			
AUC (ng/mL*hr)	158.34 <i>157.85</i>	33.30	163.00 <i>162.59</i>	33.40	0.97 <i>0.97</i>	91.76-101.44	10.88%
AUCI ng/mL*hr)	166.90 <i>166.40</i>	33.72	171.22 <i>170.79</i>	33.83	0.97 <i>0.97</i>	92.19-101.80	10.66%
C _{MAX} (ng/mL)	26.19 <i>26.18</i>	23.65	29.08 <i>29.04</i>	25.57	0.90 <i>0.90</i>	97.64-111.80	18.44%
T _{MAX} (hr)	1.83	31.47	1.71	30.08	1.07		
K _{EL} (hr ⁻¹)	0.087	26.55	0.085	26.64	1.02		
T _{HALF} (hr)	8.51	25.69	8.56	22.94	0.99		

*Data given in italics are based on LS means
90%CI are based on log-transformed data
ISV = Intrasubject Variability*

Comments:

The 90% confidence intervals are within the acceptable limit of 80-125%.

Conclusion: The bioequivalence study is acceptable

Waiver Request: Not applicable

Formulation(Not to be released under FOI)

Ingredient	Strength
Norethindrone Acetate, USP	5 mg
Anhydrous Lactose, NF	✓
Magnesium Stearate, NF	
Microcrystalline Cellulose, NF	✓

Formulation Comments: The inactive ingredients used in the test product are within the range given in the *Inactive Ingredient Guide* for approved oral tablets. The formulation is acceptable. Both the test and reference products are tablets are scored and white in color.

Dissolution Testing(Not to be released under FOI)

Dissolution Methods/ Results

Dissolution Method: 1

Dissolution Medium: Dilute hydrochloric acid (1 in 100) containing 0.02% SLS

Volume: 900 mL

Dissolution Apparatus: USP Dissolution Apparatus 1, 100 rpm

USP Specifications: NLT $\frac{1}{2}$ % (Q) in 60 minutes

Mean Dissolution Data

	Test			Reference		
	Lot No.: 102110001R			Lot No.: 3990372		
	Strength: 5 mg Tablet			Strength: 5 mg Tablet		
	No. of Units: 12			No. of Units: 12		
Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
15	86.42		4.85	85.75		5.52
30	93.75		1.45	90.75		4.46
45	98.83		2.62	97.0		2.92
60	100.42		2.7	101.58		3.79
90	102.17		2.24	101.67		2.15

Dissolution Comments: The test product meets USP 24 specifications. The test and reference dissolution profiles are similar ($F_2 = 81.96$)

Recommendations

1. The *in-vivo* bioequivalence study conducted under fasting condition by Barr Laboratories on its norethindrone acetate 5 mg tablet, lot #102110001R, comparing it to the reference product Aygestin® 5 mg tablets, lot #3990372, manufactured Wyeth-Ayerst, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Barr norethindrone acetate 5 mg tablets are bioequivalent to Aygestin® 5 mg tablets manufactured Wyeth-Ayerst
2. The *in vitro* dissolution testing conducted by Barr Laboratories on its Aygestin® 5 mg tablets meets USP specifications. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of HCl (1 in 100) containing 0.02% SLS using USP XXIV

apparatus I (basket) at 100 rpm. The dissolution testing should meet the following specifications.

Not less than $\hat{\quad}$ % of the labeled amount of norethindrone acetate is dissolved from the dosage form in 60 minutes.

From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence on its norethindrone acetate 5 mg tablet.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR:

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

(ISI)
ISI
ISI
ISI

11-3-00

11/8/2000

TE: 11/30/00