CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75803

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 75-803 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Levonorgestrel/ Ethinyl Estradiol Tablets, USP 0.10 mg / 0.02 mg

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

We acknowledge that the dissolution testing will 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,

/S/

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

CC: ANDA 75-803
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney 5/23/00
HFD-652/ Y. Huang YH 5/24/2000
HFD-617/ J. Fan JFan 5/31/00
HFD-650/ D. Conner DW 5/25/00

BIOEQUIVALENCY - ACCEPTABLE Submission dates: February 15, 2000
April 10, 2000

1. FASTING STUDY (STF) OIC Strengths: 0.10 mg / 0.02 mg
Outcome: AC

Clinical:

Analytical:

5. STUDY AMENDMENT (STA) OIC Strengths: All
Outcome: AC

6. WAIVER (WAI) OIC Strengths: 0.10 mg/0.02 mg tablet - 28 day regimen
Outcome: AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:
The biostudy and dissolution data were found acceptable.

Levonorgestrel/ Ethinyl Estradiol, USP
0.10 mg / 0.02 mg Tablet - 21 Day Regimen
0.10 mg / 0.02 mg Tablet - 28 Day Regimen
ANDA 75-803
Reviewer: James Chaney

Barr Laboratories, Inc.
Pomona, NY
Submission Dates:
02/15/00 and 4/10/00

Review of a Bioequivalence Study (An Electronic Submission), Dissolution Data, Waiver Request and an Amendment

I. Introduction

Indication: Levonorgestrel is used as a steroidal contraceptive as a single agent, or in combination with an estrogen in various doses. Ethinyl estradiol is usually indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause, or used in combination with a progestin as an oral contraceptive.
Type of Submission: Original ANDA, electronic/paper submission
Contents of Submission: Bioequivalence study under fasting conditions and dissolution data and an amendment providing Master Page containing batch formulation and in-process controls for the Bioavailability/Bioequivalence section.
RLD: Levlite - 21 Day Regimen, Berlex Laboratories, Inc.
Recommended Dose: The usual daily dosages of ethinyl estradiol and levonorgestrel oral contraceptive combinations are: 0.02 mg-0.10 mg, and 0.03 mg-0.15 mg, respectively.
DBE Guidance: No.

NOTE: The amendment dated April 10, 2000 provides Master Formula pages which were omitted from the Bioavailability/Bioequivalence section of the original submission. These pages contain Batch Formulation and In-Process Controls.

II. Background

Based on the literature and study information on file, the following PK information was reported by the firm for a single dose of levonorgestrel (0.10 mg) and ethinyl estradiol (0.02 mg); for levonorgestrel Cmax is 2.8 ng/mL at approximately 1.6 hour; for ethinyl estradiol Cmax is 62 pg/mL at approximately 1.5 hour. The average elimination half life has been reported to range between 11 and 40 hours for levonorgestrel and between 6 and 20 hours for ethinyl estradiol.

III. Single-dose Fasting Bioequivalence Study

A. Study Information

Clinical Facility:
Medical Director:
Scientific Director:
Dosing Dates: 04/20/99 to 05/18/99
Analytical Facility
Principal Investigator:

Analytical Study Dates:	Levonorgestrel 05/25/99 to 06/10/99	Ethinyl Estradiol 05/30/99 to 07/25/99
Storage Periods:	Levonorgestrel The maximum time samples were stored frozen from the first day of collection (4/20/99) to the last day of analysis (6/10/99) was 51 days.	Ethinyl Estradiol The maximum time samples were stored frozen from the first day of collection (4/20/99) to the last day of analysis (7/25/99) was 96 days.

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levonorgestrel and Ethinyl Estradiol	Levlite
Manufacturer:	Barr Laboratories, Inc.	Berlex Laboratories
Manufacture Date:	3/23/99	N/A
Expiration Date:	N/A	N/A
ANDA Batch Size:		N/A
Full Batch Size:		N/A
Batch/Lot Number:	109659R01	W80234
Potency:	Levonorgestrel, 98.7% Ethinyl Estradiol, 98.0%	Levonorgestrel, 99.8% Ethinyl Estradiol, 99.8%
Content Uniformity:	Levonorgestrel 99.2%; RSD, 0.6%; 98.6–100.2% Ethinyl Estradiol 97.4%; RSD, 1.4%; 96.1–100.5%	Levonorgestrel 99.1%; RSD, 2.2%; 95.2–102.5% Ethinyl Estradiol 99.4%; RSD, 2.4%; 95.2–104.2%
Formulation	See Table 1	NA
Strength:	0.10 mg/0.02 mg	0.10 mg/0.02 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	3 Tablets	3 Tablets
Administration Route	Orally	Orally
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours pre-dose to 4 hours post-dose	10 hours pre-dose to 4 hours post-dose
Confinement	From 12 hours prior to dosing to 24 hr post-dose	From 12 hours prior to dosing to 24 hr post-dose

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Balanced**	No. In Period 1, 18 received A & 17 received B. In Period 2, 16 subjects received A & 15 subjects received B.
No. of Groups (if appropriate)	NA	**Washout Period**	4 weeks
Randomization Scheme	AB: 2, 5, 8, 10, 11, 12, 16, 17, 20, 24, 26, 28, 30, 32 BA: 1, 3, 4, 6, 7, 13, 14, 15, 18, 23, 25, 27, 29, 31, 33, 35		
Blood Sampling Times	0, 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours post-dose		
Blood Volume Collected	1 x 5 mL to analyze plasma levonorgestrel and 1 x 7 mL to analyze plasma ethinyl estradiol.		

Blood Sample Processing/ Storage	Collected in EDTA blood tubes. Cooled promptly in an ice bath and were centrifuged @ 4°C. Plasma samples were stored @ -20°C until analysis.

IRB Approval	Y
Informed Consent	Y
No. Enrolled	35
No. Completing	30
No. With Samples Analyzed	30
No. of Dropouts	5
Sex(es) Included	Females
Healthy Subjects	Y
Restrictions	Standard inclusion/exclusion criteria were followed as per the protocol.
Safety Monitoring	Medical sub-investigator was present from dosing to 4 hours post-dose.

B. Study Results

1. Clinical

Dropout Information

Subject #.:	9	19	21
Reason:	Difficulty with vein	Adverse events unrelated to study medication	Positive urine drug screen
Period:	2	1	2
Replacement:	N	N	N
Subject No.:	22	34	
Reason:	Positive pregnancy test	Positive urine drug screen	
Period:	2	2	
Replacement:	N	N	

Adverse Events:	A total of 181 adverse events were experienced by 32 subjects during the study. Eighty-four events were judged possibly related to the study medications, 37 were judged remote. The intensity at onset of the adverse events was judged as follows: 138 were mild, 33 were moderate, 3 were severe, and the intensity of 6 were unknown. One hundred & twenty-one were possibly or remotely related to the study drug. Fifty-five followed the test product, 60 followed the reference product, and for 6 the relationship to test or reference was unknown.
Protocol Deviations:	There were no protocol deviations resulting in the integrity of study being compromised.

2. Analytical Method Validation

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Description of Analytical Method Validation

Analyte	**Ethinyl Estradiol**	**Levonorgestrel**
Assay Method		
Matrix	Plasma	Plasma
Internal Standard		

Pre-Study Assay Validation

a) Levonorgestrel

Conclusion: The analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

a) Levonorgestrel

Mean Plasma Concentrations	Table 2, Figure # 1
Mean PK Parameters	Tables 3 and 4
90% Confidence Intervals	LnAUCt, 94-108; LnAUCi, 95-107; LnCmax, 94-105
AUCt/AUCi ratio	Test, 0.83, (0.70-0.92), 7.2%CV
	Reference, 0.83 (0.56-0.96), 10%CV
Test/Reference Ratios	AUCt, 1.04 (0.66-2.16), 27%CV
Arithmetic Means	AUCi, 1.03 (0.76-1.91), 21%CV
	Cmax, 1.02 (0.60-1.33), 20%CV

Total standard deviation and root mean square error, ln-transformed PK data

Drug	Parameter	LnCmax	LnAUCt
Levonorgestrel	Total SD, test	0.28	0.37
Levonorgestrel	Total SD, reference	0.31	0.36
Levonorgestrel	Total SD, test & ref combined	0.01785179	0.02700457
Levonorgestrel	Root MSE, test & ref combined	0.13361060	0.16433068

Comments:

- Ke and AUCi were determined for 30/30 subjects for the test product and 30/30 subjects for the reference product. From inspection of the plots the reviewer agrees with the firm's decision to determine these parameters for all the subjects.
- There was only one measurable drug concentrations at 0 hr (subject 30 after the test treatment). There were no first measurable drug concentrations as Cmax.
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

b) Ethinyl Estradiol

Mean Plasma Concentrations	Table 5, Figure # 1
Mean PK Parameters	Tables 6 and 7
90% Confidence Intervals	LnAUCt, 93-105; LnAUCi, 96-108; LnCmax, 92-104
AUCt/AUCi ratio	Test, 0.84, (0.63-0.94), 7.7%CV, N=30
	Reference, 0.86 (0.68-0.94), 7%CV, N=30
Test/Reference Ratios	AUCt, 1.01 (0.71-1.91), 22%CV
	AUCi, 1.04 (0.78-2.33), 26%CV
	Cmax, 1.00 (0.64-1.46), 19%CV

Total standard deviation and root mean square error, ln-transformed PK data

Drug	Parameter	LnCmax	LnAUCt
Ethinyl Estradiol	Total SD, test	0.33	0.32
Ethinyl Estradiol	Total SD, reference	0.33	0.32
Ethinyl Estradiol	Total SD, test & ref combined	0.0183015	0.0169362
Ethinyl Estradiol	Root MSE, test & ref combined	0.13528316	0.13013908

Comments:

- Ke and AUCi were determined for 30/30 subjects for the test product and 30/30 subjects for the reference product. From inspection of the plots the reviewer agrees with the firm's decision to determine these parameters for all the subjects.
- There were no measurable drug concentrations at 0 hr. There were no first measurable drug concentrations as Cmax.
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

IV. Waiver Requests

i. Request for waiver on the 28 day regimen tablets

The drug products meet the following conditions:

a. The bioavailability of levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablet - 21 day regimen is demonstrated by an acceptable bioequivalence study.
b. The composition of the active levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablet - 28 day regimen is identical to the levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablet - 21 day regimen which underwent the acceptable bioavailability study.

V. Formulation

Formulation information is provided in Table 1.

Formulation Comments:

VI. Dissolution

A. Dissolution Method Used by Firm

The dissolution method is the USP method.

No. Units Tested: 12 tablets
USP XXIV apparatus 2 (paddle)
Medium: 5 ppm Tween 80 in water
Temperature: 37°C
Volume: 500 mL
Rpm: 75
Sampling Times: 15, 30, 45 and 60 & 90 minutes
Assay Method:
Firm's Dissolution Specification: NLT % in 60 minutes for levonorgestrel,
NLT % in 60 minutes for ethinyl estradiol.
(The firm used the USP specification.)

B. **Results:** Dissolution data are presented in Table 8.

C. Comments:

1. The dissolution testing is acceptable.

VII. COMMENTS

1. The general policy within the Division of Bioequivalence is that the time period of blood concentration measurement should cover at least 3 elimination half-lives in the terminal phase. In the current study the assay methodology used for ethinyl estradiol is not sensitive enough to measure ethinyl estradiol concentrations long enough to cover three elimination half-lives in the terminal phase as shown in the following table.

Table 9. Summary of Terminal Ethinyl Estradiol (EE) > LOQ's

PER	TIME			
	36 hrs	**48 hrs**	**72 hrs**	**96 hrs**
EE TRT A				
1	14/14 (100%)	5/14 (36%)	0/14 (0%)	0/14 (0%)
2	15/16 (94%)	9/16 (56%)	1/16 (6%)	0/16 (0%)
1+2	**29/30 (97%)**	**14/30 (47%)**	**1/30 (3%)**	**0/30 (0%)**
EE TRT B				
1	13/16 (81%)	7/16 (44%)	1/16 (6%)	0/16 (0%)
2	13/14 (93%)	6/14 (43%)	0/14 (0%)	0/14 (0%)
1+2	**26/30 (87%)**	**13/30 (43%)**	**1/30 (3%)**	**0/30 (0%)**
Total EE TRT A+B	**55/60 (92%)**	**27/60 (45%)**	**2/60 (3%)**	**0/60 (0%)**

LOQ = 5 pg/mL. Mean T1/2's (hours) found in this biostudy: test, 17.5, ref, 15.3.

In the current study most subjects (97% for the test treatment and 87% for the reference treatment) had continuously measurable quantities of ethinyl estradiol up to 36 hours (approximately 2 half-lives.) For the test product 47% of the subjects had continuously measurable quantities of ethinyl estradiol up to 48 hours (approximately 3 half-lives), and for the reference product 43% of the subjects had continuously measurable quantities of ethinyl estradiol up to 48 hours. These findings are similar to other ANDA's with acceptable bioequivalence studies in which the LOQ was also 5 pg/mL.

2. The mean AUCT/AUCI ratios of greater than 80% for both levonorgestrel and ethinyl estradiol indicate that the duration of sampling was sufficient.

3. The LOQ of 5 pg/mL and the sampling times are adequate. The analytical study is acceptable

VIII. RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study conducted by Barr Laboratories, Inc. on its test product, levonorgestrel/ethinyl estradiol 0.10 mg / 0.02 mg tablets, lot #

109659R01, comparing it with the reference product, Levlite® - 21 Tablets manufactured by Berlex Laboratories has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Barr Laboratories' levonorgestrel/ethinyl estradiol 0.10 mg / 0.02 mg tablet is bioequivalent to the reference product Levlite® under fasting conditions.

2. The *in-vitro* dissolution testing conducted by Barr Laboratories, Inc. on its levonorgestrel/ethinyl estradiol 0.10 mg / 0.02 mg tablets has been found acceptable. The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of polysorbate 80 (5 ppm) in water at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

   Not less than % (Q), of the labeled amount of levonorgestrel and % (Q) of the labeled amount of ethinyl estradiol are dissolved in 60 minutes.

3. The composition of the levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablet - 28 day regimen is identical to the levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablet - 21 day regimen which underwent the acceptable bioavailability study. The request for waiver of *in vivo* bioequivalence study requirements for the levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablet - 28 day regimen may be granted. The firm's levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablets - 28 day regimen are therefore deemed bioequivalent to Berlex's levonorgestrel/ethinyl estradiol 0.10 mg/0.02 mg tablets - 28 day regimen.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 5/24/2000

Concur: /S/ Date 5/25/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/052300

Table 1. Formulation (mg/tablet)
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Ingredient	0.1 Mg/0.02 mg Mg/dose	0.1 mg/0.02 mg mg/dose	mg/dose
Core:	**21 Day Regimen (Active)**	**28 Day Regimen (Active)**	**28 Day Regimen (Placebo)**
Levonorgestrel, USP (Micronized)			
Ethinyl Estradiol, USP			
Anhydrous Lactose, NF			
Starch, NF			
Magnesium Stearate, NF			
Core weight (target)	80	80	80
Coating:	5mg	5mg	0mg
Coated tablet weight (target)	85	85	80

Table 2. Mean (%CV) Plasma Levonorgestrel Concentrations (ng/mL) Following an Oral Dose of 3X Levonorgestrel/Ethinyl Estradiol 0.10 mg/0.02 mg Tablets, Fasting Conditions (N=30)			
TIME (HR)	**TEST TREATMENT A**	**REFERENCE TREATMENT B**	**RATIO (A/B)**
Pre-dose	0.03 (547.72)	0.00 (----)	----
0.500	2.40 (55.97)	2.50 (76.86)	0.9617
1.00	5.28 (35.94)	5.38 (38.50)	0.9803
1.25	5.56 (33.48)	5.63 (32.97)	0.9873
1.50	5.51 (32.15)	5.59 (29.32)	0.9862
1.75	5.32 (30.08)	5.43 (28.40)	0.9798
2.00	5.04 (28.16)	5.16 (27.84)	0.9775
2.50	4.40 (25.01)	4.55 (26.48)	0.9671
3.00	3.81 (26.40)	3.89 (28.15)	0.9800
4.00	2.90 (26.55)	2.94 (28.57)	0.9869
6.00	1.81 (30.69)	1.84 (33.51)	0.9817
8.00	1.43 (32.02)	1.46 (36.39)	0.9811
10.0	1.25 (34.30)	1.27 (32.98)	0.9832
12.0	1.17 (35.28)	1.25 (35.93)	0.9402
16.0	1.02 (32.99)	1.04 (39.08)	0.9768
24.0	0.79 (40.29)	0.79 (38.40)	1.0023
36.0	0.66 (42.10)	0.65 (40.81)	1.0238
48.0	0.47 (47.58)	0.45 (43.08)	1.0307
72.0	0.20 (90.92)	0.19 (86.89)	1.0493
96.0	0.04 (229.86)	0.01 (381.02)	2.9048

Table 3. Arithmetic Mean Plasma Levonorgestrel Pharmacokinetic Parameters in a Single-Dose Fasting Study Following 3X Levonorgestrel/Ethinyl Estradiol 0.10 mg/0.02 mg Tablets, N=30			
PK PARAMETER	**TEST TREATMENT A**	**REFERENCE TREATMENT B**	**RATIO (A/B)**
AUCT [ng.hr/mL]	64.28 (36.41)	63.44 (37.98)	1.0083
AUCI [ng.hr/mL]	76.38 (32.54)	75.14 (31.89)	1.0090
Cmax [ng/mL]	6.00 (27.12)	6.05 (29.22)	0.9932
Tmax [hr]	1.55 (36.41)	1.43 (32.37)	1.0839
K_{el} [1/hr]	0.0266 (31.32)	0.0270 (28.91)	0.9852
$T_{1/2}$ [hr]	28.48 (30.59)	28.01 (31.72)	1.0168

Table 4. Plasma Levonorgestrel Geometric LSMeans and 90% Confidence Intervals (C.I.) Following 3X Levonorgestrel/Ethinyl Estradiol 0.10 mg/0.02 mg Tablets, N=30				
PK PARAMETER	**TEST TREATMENT A**	**REFERENCE TREATMENT B**	**RATIO (A/B)**	**90% C.I.**
AUC(T) [ng.hr/mL]	59.63	59.14	1.0083	93.8 to 108.4
AUC(I) [ng.hr/mL]	71.93	71.29	1.0090	95.0 to 107.1
Cmax [ng/mL]	5.72	5.76	0.9932	93.6 to 105.3

Table 5. Mean (%CV) Plasma Ethinyl Estradiol Concentrations (pg/mL) Following an Oral Dose of 3X Levonorgestrel/Ethinyl Estradiol 0.10 mg/0.02 mg Tablets, Fasting Conditions (N=30)			
TIME (HR)	**TEST TREATMENT A**	**REFERENCE TREATMENT B**	**RATIO (A/B)**
Pre-dose	0.00 (----)	0.00 (----)	----
0.500	25.55 (67.08)	21.90 (87.75)	1.1667
1.00	90.67 (46.21)	87.91 (42.56)	1.0313
1.25	105.32 (39.63)	103.88 (36.62)	1.0139
1.50	111.86 (39.06)	109.61 (33.09)	1.0206
1.75	114.56 (35.42)	112.77 (30.85)	1.0159
2.00	111.98 (32.83)	112.49 (29.65)	0.9954
2.50	103.58 (32.17)	110.10 (33.82)	0.9408
3.00	92.48 (28.96)	99.32 (28.78)	0.9311
4.00	77.16 (30.63)	78.68 (26.54)	0.9807
6.00	52.44 (27.87)	53.71 (28.18)	0.9762
8.00	39.17 (24.71)	39.62 (27.54)	0.9887
10.0	33.49 (26.27)	33.44 (24.24)	1.0016
12.0	27.65 (26.84)	28.99 (26.10)	0.9538
16.0	23.26 (29.91)	22.90 (32.92)	1.0158
24.0	15.15 (27.80)	15.36 (35.23)	0.9863
36.0	9.47 (35.35)	8.38 (53.25)	1.1297
48.0	3.29 (118.36)	3.15 (125.44)	1.0426
72.0	0.31 (547.72)	0.00 (----)	----
96.0	0.00 (----)	0.00 (----)	----

Table 6. Arithmetic Mean Plasma Ethinyl Estradiol Pharmacokinetic Parameters in a Single-Dose Fasting Study Following 3X Levonorgestrel/Ethinyl Estradiol 0.10 mg/0.02 mg Tablets, N=30			
PK PARAMETER	**TEST TREATMENT A**	**REFERENCE TREATMENT B**	**RATIO (A/B)**
AUCT [pg.hr/mL]	1127.21 (30.32)	1136.36 (29.59)	0.9919
AUCI [pg.hr/mL]	1335.83 (27.35)	1308.12 (26.50)	1.0212
Cmax [pg/mL]	122.75 (32.14)	125.01 (30.36)	0.9819
Tmax [hr]	1.83 (36.43)	2.03 (34.59)	0.8987
K_{el} [1/hr]	0.0431 (23.61)	0.0491 (25.67)	0.8780
$T_{1/2}$ [hr]	17.49 (42.55)	15.29 (34.41)	1.1442

Table 7. Plasma Ethinyl Estradiol Geometric LSMeans and 90% Confidence Intervals (C.I.) Following 3X Levonorgestrel/Ethinyl Estradiol 0.10 mg/0.02 mg Tablets, N=30				
PK PARAMETER	**TEST TREATMENT A**	**REFERENCE TREATMENT B**	**RATIO (A/B)**	**90% C.I.**
AUC(T) [pg.hr/mL]	1068.75	1079.95	0.9896	93.4 to 104.8
AUC(I) [pg.hr/mL]	1279.65	1254.27	1.0202	96.0 to 108.5
Cmax [pg/mL]	115.57	118.09	0.9787	92.2 to 103.9

IN-VITRO COMPARATIVE DISSOLUTION STUDY

Table 8. Results of In Vitro Dissolution Testing

ETHINYL ESTRADIOL

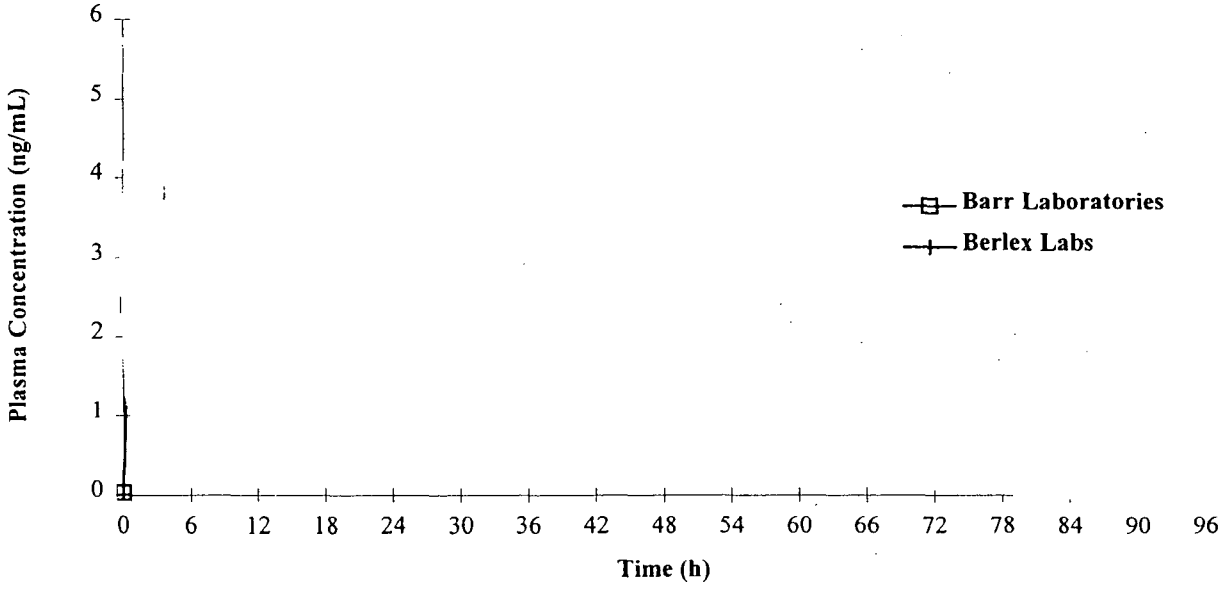
Sampling Times (Min)	Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg Batch No. 109659R01 Barr Laboratories, Inc.			Levlite™ 21 (Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg), Batch No.: W80234 Berlex Laboratories		
	Mean %	Range	%CV	Mean %	Range	%CV
15.00	61.63		17.47	46.20		32.57
30.00	94.78		7.86	87.63		9.42
45.00	97.57		4.28	93.82		5.75
60.00	98.57		2.34	96.65		2.86
90.00	99.90		1.37	97.47		2.22
Ethinyl Estradiol Similarity Factor = 54.9						

LEVONORGESTREL

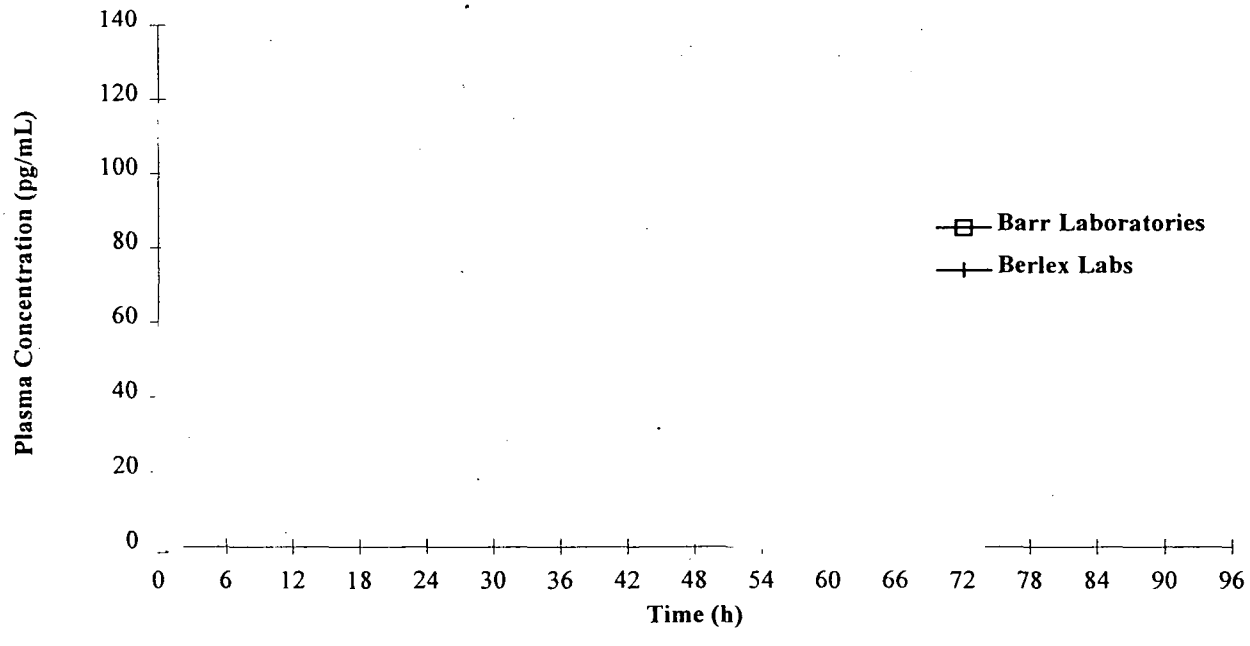
Sampling Times (Min)	Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg Batch No. 109659R01 Barr Laboratories, Inc.			Levlite™ 21 (Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg), Batch No.: W80234 Berlex Laboratories		
	Mean %	Range	%CV	Mean %	Range	%CV
15.00	40.04		21.12	33.48		31.82
30.00	78.23		13.43	73.04		9.90
45.00	89.73		7.62	87.18		6.41
60.00	93.98		4.76	94.08		4.35
90.00	96.50		3.45	98.03		2.11
Levonorgestrel Similarity Factor = 69.5						

FIGURE 1. PLASMA CONCENTRATIONS (ng/mL and pg/mL respectively) VERSUS TIME SINGLE-DOSE FASTING STUDY #99027

a) **Levonorgestrel**



b) **Ethinyl Estradiol**



OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-803 SPONSOR : Barr Laboratories, Inc.
DRUG AND DOSAGE FORM : Levonorgestrel/ Ethinyl Estradiol Tablet
STRENGTH(S): 0.10 mg / 0.02 mg
TYPES OF STUDIES: Fasting
CINICAL STUDY SITE:

ANALYTICAL SITE:

STUDY SUMMARY: Acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: JEC DATE: 5/24/00

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: YCH DATE: 5/24/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : DPC DATE : 5/25/00

BIOEQUIVALENCY COMMENTS

ANDA: 75-803 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Levonorgestrel/ Ethinyl Estradiol Tablets, USP 0.10 mg / 0.02 mg

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

We acknowledge that the dissolution testing will 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,

/S/

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