CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-796

Bioequivalence Review(s)

Ethinyl Estradiol and Levonorgestrel Tablets, USP 0.02 mg/0.1 mg
ANDA #75-796
Reviewer: Moheb H. Makary
W 75796SD.100

Duramed Pharmaceuticals, Inc.

Submission Date:

1/31/00 and 3/16/00

Review of Bioequivalence Study and Dissolution Data (Electronic Submission)

Introduction

Class: Combination of oral contraceptives
Type of Submission: Original ANDA
Contents of Submission: Single-dose fasting bioequivalence study.
RLD: Alesse-21 Tablets (Wyeth-Ayerst)
Recommended Dose: One tablet daily for 21 consecutive days, followed by 7 days when no tablets are taken.

Background

Ethinyl Estradiol has a mean bioavailability of 40 – 50% due to extensive first-pass metabolism. The elimination half-life is 13 to 27 hours. It is hepatically metabolized to inactive metabolites, with 29% to 64% of an oral dose undergoing metabolism. The inactive metabolites are excreted in the urine and bile. Peak concentrations occur in 0.5 to four hours. It is primarily metabolized by aromatic hydroxylation (via cytochrome- P450 enzyme CYP3A4) with 29% to 64% or an oral dose being converted to 2-hydroxy-ethinyl estradiol. This metabolite may be further converted to 2-methoxy-ethinyl estradiol and excreted as both sulfate and glucuronide metabolites. The drug can also form numerous other hydroxylated and methylated metabolites that are found free or as glucuronide and sulfate conjugates.

Levonorgestrel is rapidly and completely absorbed (bioavailability about 100%) and is not subject to first-pass metabolism. The most important metabolic pathway occurs in the reduction of the (delta)4-3-oxo group and hydroxylation at positions 2(alpha), 1(beta), and 16(beta), followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3(alpha),5(beta)-tetrahydro-levonorgestrel, while excretion occurs predominately in the form of glucuronides.

Levonorgestrel and ethinyl estradiol are indicated for oral contraception.

Protocol No.. , A pharmacokinetic study to assess the single dose bioequivalence of two formulations of Ethinyl Estradiol 0.02 mg/Levonorgestrel 0.1 mg Tablets.

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	MDS HARRIS
Medical Director:	
Scientific Director:	
Clinical Study Dates:	09/26/99 to 10/24/99
Analytical Facility	MDS HARRIS
Principal Investigator:	Alzah Kalim
Analytical Study Dates:	10/29/99 to 11/12/99

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levonorgestrel and Ethinyl Estradiol Tablets, USP	Alesse
Manufacturer:	Duramed Pharmaceuticals	Wyeth Ayerst
Manufacture Date:	8/24/99	N/A
Expiration Date:	N/A	10/2000
ANDA Batch Size:	[redacted] Tablets	N/A
Batch/Lot Number:	C-0082	9998018
Potency:	96.9%/96.6%	98.7%/96.8%
Content Uniformity:	97.9%/97.5%	100.7%/96.8%
Strength:	0.1/0.02 mg	0.1/0.020 mg
Dosage Form:	tablet	tablet
Dose Administered:	2X0.1 mg/0.02 mg Tablets	2x0.1 mg/0.02 mg Tablets
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:	Y
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:	26
Route of Administration:	oral	No. of Subjects Completing:	26
Dosing Interval:	hr	No. of Subjects Plasma Analyzed:	26
Number of Doses:	N/A	No. of Dropouts:	0
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:	18

Blood Samples: Blood samples were obtained at 0 (pre-dose) and 0.33, 0.67, 1, 1.5, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours after administration of the dose.

Study Results
1) Clinical

Adverse Events: No serious medical events were reported post-dose. The adverse events were similar for both treatments.

Protocol Deviations:
Dropouts:
No Dropouts Reported

2) Analytical (Not to be Released Under FOI)
Pre-Study Assay Validation:

ANALYTE:	ETHINYL ESTRADIOL	LEVONORGESTREL
ASSAY METHOD:		
MATRIX:	plasma	plasma
INTERNAL STANDARD:		
SENSITIVITY:	5 pg/mL	.05 ng/mL
STANDARD CURVE	5.0-500 pg/mL	0.05-10 ng/mL
R2 IS GREATER THAN:	0.995016	0.996407
SPECIFICITY:	Y	Y
ANALYTE RETENTION TIME:	2 minutes	1.5 minutes
INTERNAL STANDARD RETENTION TIME:	2 minutes	2.25 minutes

Recovery: The recovery was 63% for ethinyl estradiol and was 97.0% for levonorgestrel.

Interday precision: Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from 4.8% to 16.4% for ethinyl estradiol and ranged from 5.2% to 12.6%for levonorgestrel.

Stability: Freeze-Thaw Stability: Ethinyl estradiol and levonorgestrel were spiked into plasma at three concentrations and found to be stable for ethinyl estradiol and levonorgestrel through six and three freeze/thaw cycles, respectively.

Long term stability: Stability was assessed by quantitation of QC samples which were frozen (-20°C) prior to initiation of the fasted study. The results showed no significant degradation of ethinyl estradiol and levonorgestrel for 182 days and 167 days, respectively.

3) Pharmacokinetics:

PARAMETER	PROGRAM USED	CALCULATION METHOD
LnCmax	SAS	ANOVA
Tmax	N/A	Observed maximum
lnAUCt	SAS	ANOVA
lnAUCinf	SAS	ANOVA
Kel	WinNonLin	N/A
T1/2	WInNonLin	N/A

The mean plasma concentrations and pharmacokinetic parameters for ethinyl estradiol and levonorgestrel are shown in Tables I and II.

Table I

Mean Plasma Concentrations (pg/mL) of Ethinyl Estradiol Following 2x Ethinyl Estradiol 0.02 mg/Levonorgestrel 0.1 mg Tablets

Collection Time (Hr)	Means (pg/mL)		Statistical Significance *
	Test	Reference	
0	-0.00	-0.00	NS
0.33	14.64	22.29	NS
0.67	72.98	65.56	NS
1	93.89	85.89	0.0470
1.5	102.96	93.82	0.0234
2	94.43	92.10	NS
2.25	88.85	88.87	NS
2.5	88.97	83.76	NS
3	77.56	76.42	NS
4	60.96	60.14	NS
6	41.93	40.82	NS
8	29.59	28.87	NS
10	25.56	24.71	NS
12	21.02	20.80	NS
16	16.30	16.37	NS
24	11.41	10.11	NS
36	5.09	3.89	NS
48	1.53	0.75	NS
72	0.24	-0.00	NS
96	0.32	-0.07	NS
120	-0.00	0.21	NS

NS= Not significant at the p = 0.05 level

Parameter	Test Mean	Reference Mean	Test/Reference Ratio	90% Confidence Interval
$AUC_{(0-t)}$ hr•pg/mL	877.2	814.9	-	-
$AUC_{(0-\infty)}$ hr•pg/mL	1010	953.2	-	-
C_{max} (pg/mL)	110.1	102.4	-	-
T_{max} (hr)	1.56	1.83	-	-
K_{el} (hr^{-1})	0.0549	0.0585	-	-
$T_{1/2}$ (hr)	13.7	12.9	-	-
ln $AUC_{(0-t)}$	6.724	6.655	107.2	100.8 – 113.9
ln $AUC_{(0-\infty)}$	6.876	6.820	105.8	99.1 – 113.0
ln C_{max}	4.656	4.589	106.9	100.6 – 113.6

1. The mean ethinyl estradiol plasma levels peaked at 1.5 hours for both the test and the reference products following their administration under fasting conditions.

2. For Duramed's ethinyl estradiol, the mean AUC(0-t), AUCinf and Cmax values were 8.8%, 6.0% and 7.5% higher, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCI and Cmax.

Table II

Mean Plasma Concentrations (ng/mL) of Levonorgestrel Following 2x Ethinyl Estradiol 0.02 mg/Levonorgestrel 0.1 mg Tablets

Collection Time (Hr)	Means (ng/mL)		Statistical Significance *
	Test	Reference	
0	0.00	0.00	NS
0.33	0.73	1.01	NS
0.67	2.29	2.31	NS
1	3.01	2.61	0.0116
1.5	3.07	2.73	0.0280
2	2.69	2.69	NS
2.25	2.50	2.59	NS
2.5	2.46	2.52	NS
3	2.01	2.24	NS
4	1.60	1.69	NS
6	1.12	1.12	NS
8	0.83	0.89	NS
10	0.75	0.76	NS
12	0.66	0.68	NS
16	0.55	0.56	NS

24	0.43	0.42	NS
36	0.31	0.31	NS
48	0.21	0.22	NS
72	0.11	0.11	NS
96	0.05	0.04	NS
120	0.01	0.02	NS

NS= Not significant at the p = 0.05 level

Parameter	Test Mean	Reference Mean	Test/Reference Ratio	90% Confidence Interval
$AUC_{(0-t)}$ hr•ng/mL	36.07	36.68	-	-
$AUC_{(0-\infty)}$ hr•ng/mL	38.94	39.35	-	-
C_{max} (ng/mL)	3.3476	3.4161	-	-
T_{max} (hr)	1.55	1.72	-	-
K_{el} (hr^{-1})	0.0281	0.0281	-	-
$T_{1/2}$ (hr)	26.5	26.7	-	-
ln $AUC_{(0-t)}$	3.501	3.492	100.9	96.1 – 106.0
ln $AUC_{(0-\infty)}$	3.589	3.588	100.2	95.8 – 104.8
ln C_{max}	1.151	1.164	98.7	88.7 – 109.8

1. The mean levonorgestrel plasma levels peaked at 1.5 hours for both the test and the reference products following their administration under fasting conditions.

2. For Duramed's levonorgestrel, the mean AUC(0-t), AUCinf and Cmax values were 1.7%, 1.0% and 2.0% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCI and Cmax.

Formulation:(Not to be released under FOI)

Duramed's formulation for its Ethinyl Estradiol, 0.02 mg/ Levonorgestrel , 0.1 mg Tablet, is shown below:

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Ingredient                                          Strength
                                                    0.1/0.02 mg

ETHINYL ESTRADIOL                        \
LEVONORGESTREL
LACTOSE MONOHYDRATE      -                          ED
MAGNESIUM STEARATE
MICROCRYSTALLINE CELLULOSE,

                STARCH
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SODIUM STARCH GLYCOLATE, NF

Total

Dissolution

Dissolution Method: USP 24
Dissolution Medium: Polysorbate 80 (5 ppm) in water
Volume: 500 mL water
Dissolution Apparatus: USP Method II (Paddle) at 75 rpm
Specifications: Not less than of the labeled amount of levonorgestrel and of the labeled amount of ethinyl estradiol are dissolved in 60 minutes.

Mean Dissolution Data

Ethinyl Estradiol

	TEST			REFERENCE		
	Lot No.: C-0082			Lot No.: 9998018		
	Strength: 0.020 mg			Strength: 0.020 mg		
	No. of Units: 12			No. of Units: 12		
Time (Min)	Mean	Range	%CV	Mean	Range	%CV
10	102.69		2.99	99.78	3	3.69
20	104.63	3	1.22	101.81	1	2.73
30	104.28	3	1.63	100.98		3.05
60	103.93	101.2 - 9	2.48	100.95		2.6

Levonorgestrel

	Strength: 0.10 mg			Strength: 0.10 mg		
Time (Minutes)	Mean	Range	%CV	Mean	Range	%CV
10	67.49		12.32	71.88		7.42
20	80.97		3.74	84.78		2.91
30	86.59		2.17	89.52		3.0
60	96.08		1.02	98.13		2.57

Comments:

1. The firm's single-dose bioequivalence study #441-01 under fasting conditions, conducted on its 0.02 mg/0.1 mg Ethinyl Estradiol and Levonorgestrel Tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for Ethinyl Estradiol and Levonorgestrel.

2. The dissolution testing conducted by the firm on its Ethinyl Estradiol and Levonorgestrel Tablets, 0.02 mg/0.1 mg, lot #C0082, is acceptable.

3. The firm's financial disclosure statements submitted with the bioequivalence section in support of this application did not indicate any conflict of interests between the CRO's investigators and the firm. The reviewer agrees with that conclusion.

Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Duramed Pharmaceuticals, Inc., on its Ethinyl Estradiol and Levonorgestrel and Tablet, 0.02 mg/0.1 mg, lot #C0082, comparing it to Wyeth-Ayerst's Alesse^{R}-21 Tablet, 0.02 mg/0.1 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Duramed's Ethinyl Estradiol and Levonorgestrel Tablet, 0.02 mg/0.1 mg, is bioequivalent to the reference product Alesse^{R}–21 Tablet, 0.02 mg/0.1 mg, manufactured by Wyeth-Ayerst.

2. The dissolution testing conducted by Duramed Pharmaceuticals, Inc., on its Ethinyl Estradiol and Levonorgestrel Tablets, 0.02 mg/0.1 mg, lot #C0082, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of the medium 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 of the labeled amount of levonorgestrel and of the labeled amount of ethinyl estradiol are dissolved in 60 minutes.

The firm should be informed of the above recommendations

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 4/17/00
FT INITIALLED BDAVIT Date: 4/17/00

Concur: Date: 4/19/00
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-796 APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Ethinyl Estradiol and Levonorgestrel Tablets, USP 0.02 mg/0.1 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,

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