CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-860

STATISTICAL REVIEW(S)

MAY 19 1998

Statistical Review and Evaluation
Clinical Studies

NDA No:	20-860
Applicant:	Berlex Laboratories Inc.
Name of Drug:	Micro-Levlen™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
Indication:	Oral Contraception
Medical Reviewer:	Ridgely Bennett, M.D.
Statistical Reviewer:	Moh-Jee Ng, M.S.
Documents Reviewed:	Vols 1.1, 1.28, 1.29, 1,30, and 1.39
45-Day filing Date:	July 14, 1997
User Fee Due Date:	June 13, 1998

1. Introduction

The applicant has presented the results of 5 clinical trials (bioavailability study A999, pharmacokinetics study AA00, ovulation inhibition study AG43, German multicenter study AL31 and US multicenter study 31101A) to establish the efficacy of Micro-Levlen™ for prevention of pregnancy. Micro-Levlen™ is a 21-day oral contraceptive; its regimen consists of 100 µg levonorgestrel (LNG) and 20 µg of ethinyl estradiol (EE). This regimen is a proportional dose reduction from a currently marketed OC containing LNG 150 µg and EE 30 µg (levlen). The primary objective of the study plan was to lower the components of oral contraception (OC) doses of estrogen and progestogen while preserving good cycle control and contraceptive efficacy. This review focuses on the pivotal German study (Report AL31) and supportive US study (Report 311-01A). Table 1, below, summarizes these two studies:

Table 1
Phase 3 studies listing

Report/Protocol or Study Number (dates conducted)	Number of Centers	Site	Design	Treatment and Dose	No. Subjects Enrolled	Max. Cycles	Total # of exposure cycles
AL31/94251 11/94 - 12/95	43	German	Uncontrolled Open label Multicenter	0.100 mg LNG plus 0.020 mg EE 21 out of 28-day cycles	950	6	4,400
311-01A 11/96 - 2/97	18	United States	Uncontrolled Open label Multicenter	0.100 mg LNG plus 0.020 mg EE 21 out of 28-day cycles plus 7 placebo tablets	770	6	3,616

German Uncontrolled Clinical Study (Report AL31) - Protocol 94251

The objectives of this study were to evaluate the contraceptive efficacy, cycle control, and tolerance of Micro-Levlen™. The study required that at least 600 women complete a minimum of 6 months in treatment.

This was an open label, non-controlled clinical study, conducted in forty-three centers in Germany. Subjects were recruited from healthy women who sought oral contraceptive counseling at outpatient gynecology clinics. Both starters, who had not used OCs, and switchers, who had been using another OC, were recruited. Switchers did not require a wash-out period before beginning treatment. The regimen consisted of a 21-day treatment of levonogestrel/ethinyl estradiol (100μg/20μg) tablets followed by a 7-day treatment-free interval from days 22-28. Subjects completed daily pill-intake and bleeding intensity diaries and had scheduled visits at baseline and after cycles 1, 3, and 6.

Patient Disposition

950 subjects enrolled
- 130 received no medication and were not included in the efficacy and safety evaluation
- 820 subjects were evaluated
  - 15 had no data after receiving drug
  - 805 subjects with total exposure of 4,400 cycles were evaluated for efficacy
    - 594 (74%) were switchers contributing 3,286 cycles of exposure to Micro-Levlen
    - 211 (26%) were starters contributing 1,114 cycles of exposure to Micro-Levlen

Of the 805 subjects, 680 (84.5%) subjects completed all 6 treatment cycles with total exposure of 4,080 cycle
- 640 subjects completed 6-cycles without other contraception
- 40 subjects completed 6-cycles with alternative method of contraception —

Of the 130 subjects who received no medication
- 16 did not return after the initial visit
- 46 withdraw their consent before medication was dispensed
- 37 had abnormal laboratory values at baseline
- 9 had abnormal findings on physical examination at baseline
- 9 became pregnant before medication was dispensed
- 7 smoked too many cigarettes/day
- 3 exceeded the weight limitation
- 2 too young for inclusion
- 1 wanted to become pregnant

US Uncontrolled Clinical Study (Report 311-01A)

The objective and design of the US study were similar to the German study.

This was also an open label, non-controlled clinical study, conducted in eighteen centers in United States. All subjects received the same treatment regimen of LNG 100 μg and EE 20 μg tablets for 21-day followed by a 7-day placebo regimen, as opposed to the 7-day treatment free interval in the German study. Subjects completed daily pill-intake and bleeding intensity diaries and had scheduled visits at baseline and after cycles 1, 3, and 6.

Patient Disposition

770 subjects with total exposure of 3,616 cycles were evaluated for efficacy
431 (56%) were switchers contributing 2,275 cycles of exposure to Micro-Levlen
339 (44%) were starters contributing 1,314 cycles of exposure to Micro-Levlen

Of the 770 subjects, 558 (72.3%) subjects completed all 6 treatment cycles
548 subjects completed 6-cycles without other contraception
10 subjects completed 6-cycles with alternative method of contraception

Patient Demographics and Baseline Characteristics

The sponsor analyzed the demographic characteristics of the German and US studies (Vol. 1.39, pg.12). The majority of the subjects in both studies were 21 to 30 years of age and were Caucasian nonsmokers. Subjects in the US study had a broader distribution for weight, height, and weight-for-height distribution than subjects in the German study.

5. Sponsor's Efficacy Results

Contraceptive effectiveness was measured by Pearl Index and Pregnancy Rate.

The Pearl Index was defined as the number of pregnancies times 1300 divided by the total number of exposure cycles and was evaluated in two ways:

Uncorrected Pearl Index = number of pregnancies * 1300 / total number of cycles
Corrected Pearl Index = number of pregnancies * 1300 / total number of cycles without alternative contraception

The Pregnancy Rate was defined as the number of pregnancies times 100 divided by the number of 6 cycle completers who used no alternative contraception.

Pregnancy Rate = (number of pregnancies / number of 6-cycle completers without other contraception) * 100

Table 2, below, presents the Pearl Index for the results of the German, US and Combined studies. This table also summarizes the Pregnancy Rate submitted by the sponsor in the original submission and the March 12, 1998 submission.

Table 2
Sponsor's Results
Pearl Index and Pregnancy Rate

	German Study	US Study	Combined Study
Number of patients	805	770	1575
Number of pregnancies	1	3	4
Total Cycles completed	4400	3616	8016
Total Cycles completed without other contraception	4352	3608	7960
Uncorrected Pearl Index	0.295	1.079	0.649
Corrected Pearl Index	0.299	1.081	0.653
Original submission			
Total number of subjects who completed 6-cycles	680	557	1237
Total number of subjects who completed 6-cycles who used alternative method of contraception during treatment	47	5	
Total number of subject who completed 6-cycles without other contraception	633	552	1185
Pregnancy Rate	0.158	0.543	0.338
March 12 submission			
Total number of subjects who completed 6-cycles	680	558	
Total number of subjects who completed 6-cycles who used alternative method of contraception during treatment	40 ***	10	
Total number of subject who completed 6-cycles without other contraception	640	548	*
Pregnancy Rate	0.156	0.547**	*

* Sponsor did not provide the pregnancy rate of Combined Study in 3/12/98 submission.

** In the original submission, the US Study data set was incomplete and contained only preliminary data. Therefore, with the March 12 submission, the sponsor claimed it was impossible to replicate the pregnancy rate of 0.543.

*** In order to bring the algorithm in line with the US Study, the sponsor adjusted to the formula used in the German Study, Instead of 47 subjects with alternative contraception use, 40 subjects with 1 or more such cycles are subtracted from the number of completers.

The sponsor provided the Uncorrected and Corrected Pearl Indexes. For the German study, they were 0.295 and 0.299 per 100 woman-years, respectively; for the US study 1.079 and 1.081; and for the combined study 0.649 and 0.653.

For the German study, the Pregnancy Rate in the sponsor's original submission was 0.158 based on 633 subjects and that for the March 12th submission was 0.156 based on 640 subjects. For the US study, the Pregnancy Rate for the sponsor's original submission was 0.543 based on 552 subjects and that for the March 12th submission was 0.547 based on 558 subjects. In the original submission, the Pregnancy Rate of the combined study was 0.338 per 100 woman-years.

Reviewer's Analyses

The Uncorrected and Corrected Pearl Indexes obtained by the sponsor were confirmed by this reviewer.

Table 3 presents this reviewer's summary of the German, US and Combined studies of Pregnancy Rate. SAS PROC LIFETEST was used to estimate the pregnancy rate at the end of Cycle 6 based on the data provided by the sponsor on March 12, 1998. All subjects were included, regardless of whether they had completed six cycles. Ninety-five percent confidence intervals were calculated.

Table 3
Reviewer's Result
Pregnancy Rate at Cycle 6

Study	Number of Subjects entering	Number of Pregnancies	Pregnancy Rate per 100 woman-years	95% CI
German	805	1	0.141	(0.00000, 0.4179)
US	673	3	0.479	(0.00000, 1.0216)
		5	0.828	(0.10389, 1.5569)
Combined	1478	4	0.294	(0.10389, 0.5824)
		6	0.454	(0.09077, 0.8165)

The Pregnancy Rate for the German Study is 0.141, [95% CI: (0., 0.4179)]. In the US Study, 5 pregnancies occurred during the treatment. However, the sponsor's result in Table 2 was based on only 3 pregnancies. The other two pregnancies were not consider due to treatment failures. Subject missed day 1 of cycle 6 but took 2 tablets on the day 2. However, she missed day 3, 4 and 5 of the same cycle and was discontinued by the investigator. Subject missed day 13 to day 20 of cycle 5. She resumed her tablets, however, with the placebo tablets for 7 days. She was discontinued because she was without active treatment for 14 consecutive days. This reviewer's result in Table 3 included both cases (3 and 5 pregnancies). The Pregnancy Rates for the US Study based on 3 and 5 pregnancies are 0.479, [95% CI: (0., 1.0216)] and 0.828, [95% CI: (0.10389, 1.5569)]. The Pregnancy Rates for the Combined Study based on 4 and 6 pregnancies are 0.294, [95% CI: (0.10389, 0.5824)] and 0.454, [95% CI: (0.09077, 0.8165)].

The detailed result are presented in Table I - V.

7. Review's Comments and Conclusions

For the German Study, the sponsor's analysis based on the 640 subjects who completed 6-cycles without other contraception yielded a Pregnancy Rate of 0.156. This reviewer's analysis based on all 805 subjects yielded a Pregnancy Rate of 0.141.

For the US Study, the sponsor's analysis based on 3 pregnancies from the 558 subjects who mpleted 6-cycles without other contraception yielded a Pregnancy Rate of 0.547. This reviewer's analysis based on the 673 subjects yielded Pregnancy Rates of 0.479 for 3 pregnancies and 0.828 for 5 pregnancies.

For the Combined Study, the sponsor's analysis based on 4 pregnancies from the 1185 subjects who completed 6-cycles without other contraception yielded a Pregnancy Rate of 0.338. This reviewer's analysis based on the 1478 subjects yielded Pregnancy Rates of 0.294 for 4 pregnancies and 0.454 for 6 pregnancies.

/S/

Moh-Jee Ng, M.S.
Mathematical Statistician

Concur: Lisa Kammerman, Ph.D. 5/19/98

Ed Nevius, Ph.D. 5/19/98

cc: Original NDA 20-713
HFD-580/ Division file
HFD-580/ Ridgely Bennett, M.D., M.P.H.
HFD-580/ Christina Kish
HFD-580/ Lisa Rarick, M.D.

HFD-715/ENevius,Lkammerman,MNg

Attachment

Table I
German Study
Pregnancy Rate

Cycle	Number of subjects entering	Number of pregnancies	Pregnancy rate	Lower 95% confidence limit	Upper 95% confidence limit
1	805	0	0.		
2	774	0	0.		
3	741	0	0.		
4	708	1	0.141		
5	682	0	0.141		
6	674	0	0.141		

Table II
US Study
Pregnancy Rate based on 3 pregnancies*

Cycle	Number of subjects entering	Number of pregnancies	Pregnancy rate	Lower 95% confidence limit	Upper 95% confidence limit
1	673	1	0.148		
2	632	1	0.306		
3	616	0	0.306		
4	577	1	0.479		
5	567	0	0.479		
6	552	0	0.479		

** Excluded two pregnancies, subjects 10014 and 14011.

Table III
US Study
Pregnancy Rate based on 5 pregnancies

Cycle	Number of subjects entering	Number of pregnancies	Pregnancy rate	Lower 95% confidence limit	Upper 95% confidence limit
1	673	1	0.00148		
2	632	1	0.00306		
3	616	0	0.00306		
4	577	1	0.00479		
5	567	2	0.00828		
6	552	0	0.00828		

Table IV
Combined Study
Pregnancy Rate based on 4 pregnancies*

Cycle	Number of subjects entering	Number of pregnancies	Pregnancy rate	Lower 95% confidence limit	Upper 95% confidence limit
1	1477	1	0.0677		
2	1408	1	0.139		
3	1358	0	0.139		
4	1285	2	0.294		
5	1251	0	0.294		
6	1230	0	0.294		

* Exclude two pregnancies in the US Study, subjects 10041 and 14011

Table V
Combined Study
Pregnancy Rate based on 6 pregnancies

Cycle	Number of subjects entering	Number of pregnancies	Pregnancy rate	Lower 95% confidence limit	Upper 95% confidence limit
1	1477	1	0.0677		
2	1408	1	0.1386		
3	1358	0	0.1386		
4	1285	2	0.2941		
5	1250	2	0.4536		
6	1228	0	0.4536		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-860

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 30 1998

BCLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA:	**20-860**
Compound:	LEVLITE™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets)
Sponsor:	Berlex
Type of Submission:	Original Amendment BB
Date of Submission:	June 2, 1998
Reviewer:	Sam H. Haidar, R.Ph., Ph.D.

I. Synopsis:

NDA 20-860 for LEVLITE™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg tablets) was submitted on June 13, 1997 by Berlex Labs., Inc. The proposed therapeutic indication for this product is oral contraception for women. Original amendment (BB) to NDA 20-860 was submitted on June 2, 1998. It contains the sponsor's response to the reviewer's comments in the Clinical Pharmacology/Biopharmaceutics review of NDA 20-860 (see Attachment).

Reviewer's Comment:

The sponsor's responses to the comments are acceptable with the exception of the response related to the *in-vitro* dissolution specifications. The sponsor proposed an *in vitro* dissolution specifications for estradiol and levonorgestrel of Q % at minutes. These specifications were not acceptable. However, they were revised to Q % at minutes, which was acceptable to the Agency, following a teleconference on June 10, 1998.

/S/

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 6/30/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 6/30/98

cc:
NDA 20-860
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (C. Kish, R. Bennett)
CDR (Barbara Murphy For Drug)

Attachment
NDA 20-860
Sponsor's Responses

II. Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-860, submitted on June 13, 1997 and its amendment (BM), dated October 31, 1997. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewer has the following comments:

1. **The sponsor's proposed dissolution release specifications for LNG and EE2 are Q % at minutes. This specification value is given in the USP for the dissolution of both LNG and EE2. However, these specifications are not justified by the dissolution data presented; therefore, they are not acceptable. The recommended release specifications for LNG and EE2 are Q % at minutes.**

On May 26, 1998, we submitted an amendment to the NDA which addressed the Chemistry, Manufacturing and Controls comments as well as two preliminary Clinical Pharmacology comments communicated to us in the Division's letter of May 11, 1998. Comment #1 above was included in the May 11th letter and was addressed in our May 26th amendment. Our reply is provided below, verbatim.

Originally we based our specifications on USP 23 for sugar-coated tablets containing levonorgestrel and ethinyl estradiol setting a Q % at minutes. However, based on all dissolution data available to date, we will revise our release specification to Q % at minutes (see dissolution profiles provided in Attachment 2).

2. **The analytical methods used for the estimation of EE2 and LNG concentrations in serum are less than desirable. Information available to the Agency indicate that more sensitive assays can be utilized for the determination of EE2 and LNG in serum.**

We acknowledge your comment that more sensitive assays can now be utilized for the determination of EE2 and LNG in serum.

5. Metabolism

The metabolism of LNG and EE2 is well defined and no new studies were needed.

We acknowledge your comment that the metabolism of LNG and EE2 is well defined and no new studies were needed.

6. Drug Interactions

No studies were done to evaluate drug interactions.

We acknowledge that no studies were done to evaluate drug interactions.

7. PK/PD Relationships and Population Pharmacokinetics

No studies were done to examine PK/PD relationships or population pharmacokinetics.

We acknowledge that no studies were done to examine PK/PD relationships or population pharmacokinetics.

VIII. Labeling Comments

The sponsor's proposed labeling is included in Attachment A. Recommended changes to the proposed labeling are listed below:

Berlex agrees to incorporate the changes as noted above into the final printed labeling for LEVLITE.

In addition, please note that the original proposed Berlex trade name for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, which appears throughout the above labeling comments, was MICRO-LEVLEN. The Labeling and Nomenclature Committee found this name unacceptable. The new trade name, LEVLITE, which was approved by the Labeling and Nomenclature Committee, will be substituted for MICRO-LEVLEN throughout the final printed labeling for this product.

2. **Figure for EE2 concentrations (in Figure 1) should be removed or altered so that concentration points below the lower limit of quantitation for the assay are not included.**

As communicated in our telefax of May 29th and as agreed during telephone conversations on May 29 and June 1, 1998, between Dr. Sam Haidar of OCPB and Dr. Armen Melikian and the undersigned of Berlex, the following wording will be placed immediately below the Figure for EE2 concentrations (in Figure 1) in the final printed labeling for LEVLITE:

The figure itself will not be removed or altered.

3. **Arabic numeral 1 for Table 1 should be replaced by Roman numeral I (i.e., Table I); a legend under Table I should define the pharmacokinetic parameters listed in the Table.**

4. **Under Clinical Pharmacology, Pharmacokinetics, the section under *Distribution* should be replaced by the following:**

Berlex agrees to incorporate the changes as noted above into the final printed labeling for LEVLITE.

5. **Other sections of the labeling appear to be appropriate, and no changes are recommended.**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: **20-860**

MAY 20 1998

Compound: MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets)

Sponsor: Berlex

Type of Submission: Original NDA and Amendments

Date of Submission: June 13, 1997
October 31, 1997 (Amendment BM)

Reviewer: Sam H. Haidar, R.Ph., Ph.D.

I. Synopsis:

NDA 20-860 for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg tablets) was submitted on June 13, 1997 by Berlex Labs., Inc. The proposed therapeutic indication for this product is oral contraception for women. "MICRO-LEVLEN™ contains Levonorgestrel (LNG) and Ethinyl Estradiol (EE) in the same 5:1 ratio as the Berlex marketed product, LEVLEN® but is only two thirds of the dose"; LEVLEN® has been on the market since the early 1980's. Additionally, MICRO-LEVLEN™ has been approved and marketed in Germany under the trade name Miranova since April 1996.

In support of NDA 20-860, the sponsor has submitted the following pharmacokinetic and bioavailability studies:

1. Report No. A999, evaluated the bioavailability of LNG/EE tablets relative to a methylcellulose suspension containing equivalent doses of LNG and EE.

2. Report No. AA00, evaluated the pharmacokinetics and accumulation of LNG and EE using the recommended dosing over 3 menstrual cycles. Protein binding and sex hormone binding globulin (SHBG) levels were also determined in this study.

The tablets used in the above studies came from a lot produced by a pilot manufacturing plant. The formulation to be marketed was linked to those used in the clinical studies by a comparative dissolution study, "according to a Level 3 change situation as specified in the SUPAC guidance for immediate release tablets".

II. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-860, submitted on June 13, 1997 and its amendment (BM), dated October 31, 1997. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewer has the following comments:

1. The sponsor's proposed dissolution release specifications for LNG and EE2 are Q . . % at minutes. This specification value is given in the USP for the dissolution of both LNG and EE2. However, these specifications are not justified by the dissolution data presented; therefore, they are not acceptable. The recommended release specifications for LNG and EE2 are Q % at minutes.

2. The analytical methods used for the estimation of EE2 and LNG concentrations in serum are less than desirable. Information available to the Agency indicate that more sensitive assays can be utilized for the determination of EE2 and LNG in serum.

Comments 1 and 2 and recommendation should be communicated to the sponsor as appropriate.

/S/

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 05/07/98
FT signed by Angelica Dorantes, Ph.D., Team Leader Dorantes 5/20/98

cc:
NDA 20-860
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (C. Kish, R. Bennett)
CDR (Barbara Murphy For Drug)

TABLE OF CONTENTS: **Page**

Attachments

III. Background:

Female sex steroids, synthetic estrogen and synthetic progesterone (progestin) have been widely used for contraception (suppression of ovulation) in females. Oral estrogen or oral progestin alone can inhibit ovulation, but the doses required are large. When the two are combined, however, synergism takes place, and much lower doses are needed to suppress ovulation. Combination oral contraceptives (OC) decrease the pituitary gland's ability to synthesize gonadotropins following stimulation by hypothalamic gonadotropin-releasing hormone (GnRH). As a result, basal levels of FSH and LH are suppressed, ovarian follicles do not mature, little estradiol is produced, and no surge in LH levels takes place, thus blocking ovulation. Other contraceptive effects of OC's may include changes in cervical mucus thickness, causing interference with sperm transport. This suppression of ovulation by combination OC is dose dependent: the higher the dose, the greater the blockade. Associated with the higher doses, however, have been reports of venous thrombosis, heart disease and stroke in some patient populations. The current trend has been to decrease the dose of the estrogen and progestin to the minimum needed to provide effective contraception, thus decreasing the side effects of OC.

This NDA, No. 20-860, is for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg tablets), which is a combination OC that uses a lower dose of estrogen and progestin compared to Levlen®, an older product on the market. The proposed therapeutic indication for this product is oral contraception for women. "MICRO-LEVLEN™ contains Levonorgestrel (LNG) and Ethinyl Estradiol (EE) in the same 5:1 ratio as the Berlex marketed product, LEVLEN® but is only two thirds of the dose"; LEVLEN® has been on the market since the early 1980's. Additionally, MICRO-LEVLEN™ has been approved and marketed in Germany under the trade name Miranova since April 1996.

IV. Formulation

Three batches of LNG 0.100/EE 0.020 tablets were used in the clinical studies (See Table I). Lots 3323 and 3322 were produced at a pilot plant and were used in the pharmacokinetic studies and one pivotal clinical trial in Europe (Report AL31). Lot 54003, which was manufactured at the production plant, was used in a supporting clinical trial in the U.S. The pilot and production batches used in the pharmacokinetic and clinical studies have the same formulation as the "to be marketed formulation", but they differ in batch size. Micro-Levlen's scale-up manufacturing process from pilot to production batches was supported by a comparative dissolution study, according to a Level 3 change situation as specified in the SUPAC guidance for immediate release tablets.

Table I. List of formulations used in the clinical and pharmacokinetic studies.

Report No. (Study No.)	Type of Study	Drug Content (mg) (% of label)	Lot No.	Batch size (Tablets)	Manufacture Site
A999 (94010)	Relative bioavailability	LNG 0.0988 (98.8) EE 0.0198 (99.0)	3323		Wedding, PHT* Germany
AA00 (ME90411)	Multiple dose Pharmacokinetics	LNG 0.0988 (98.8) EE 0.0198 (99.0)	3323		Wedding, PHT Germany
AG43 (ME93102)	Ovulation Inhibition Study	LNG 0.0977 (97.7) EE 0.0198 (98.5)	3322		Wedding, PHT Germany
Protocol No. (311-01A)	Oral Contraception	LNG 0.0985 (98.5) EE2 0.0194 (97.0)	54003		Wedding, W1** Germany
AL31 (ME94251)	Oral Contraception	LNG 0.0988 (98.8) EE2 0.0198 (99.0)	3323		Wedding, PHT Germany

* PHT = Pharma Technicum, Pilot Plant
** W1 = Wedding, Production Plant

Reviewer Comments

1. The clinically tested formulation and the "to be marketed" formulation are the same, except for batch size. The two were linked by a comparative dissolution study, "according to a Level 3 change situation as specified in the SUPAC guidance for immediate release tablets".

2. It should be noted that the manufacturing site for the clinical batches and production batches is the same, however, different manufacturing plants were used.

3. A production batch of the "to be marketed" formulation was used in one supportive clinical study in the U.S.

V. *In Vitro* Drug Dissolution

The *in vitro* release methodology and the proposed specifications for MICRO-LEVLEN™ are presented in Table II. Table III (LNG) and Table IV (EE2) provide *in vitro* release data for the clinically tested batches.

Table II. Proposed dissolution method and specifications.

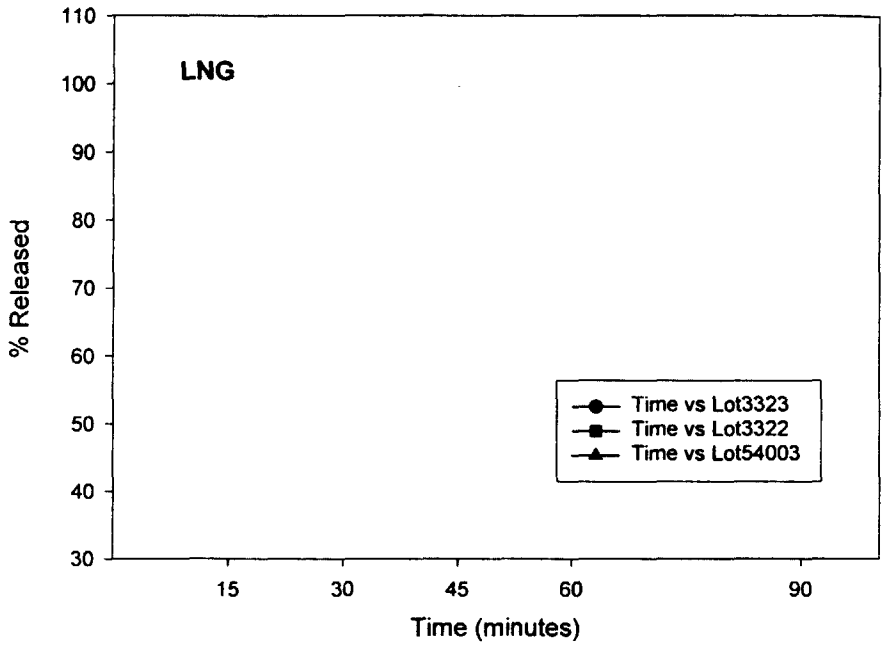
Apparatus Type	USP Apparatus 2 (paddle)
Medium	5 ppm polysorbate 80 in water
Volume	500 mL (37.0 °C ±0.5°C)
Paddle Speed	75 ± 3 rpm
Sampling Time	minutes
Proposed Specifications	Q % at ninutes for LNG and EE2

Table III. Dissolution profiles of clinically tested batches (LNG).

Lot Number	Clinical Report Number	Batch Size	Percent label claim released [mean (±SD)] n = 12					
			Time (minutes)					
3323	A999			40.8 (10.6)	87.1 (6.2)	96.3 (4.8)	100.8 (2.0)	102.8 (1.8)
3322	AA00			48.3 (9.3)	88.1 (3.4)	97.0 (2.8)	100.2 (2.4)	102.2 (2.0)
54003	Protocol No. 311-01A			48.8 (13.6)	90.3 (3.7)	98.5 (2.3)	100.9 (2.4)	102.2 (2.1)

Table IV. Dissolution profiles of clinically tested batches (EE2).

Lot Number	Clinical Report Number	Batch Size	Percent label claim released [mean (±SD)] n = 12					
			Time (minutes)					
3323	A999			50.2 (12.3)	90.0 (4.4)	92.6 (2.7)	94.5 (2.2)	95.0 (1.7)
3322	AA00			61.7 (12.3)	92.2 (2.5)	93.7 (2.1)	94.7 (2.3)	95.4 (2.0)
54003	Protocol No. 311-01A			59.2 (14.7)	90.3 (2.7)	92.1 (2.6)	92.8 (2.8)	93.4 (1.6)



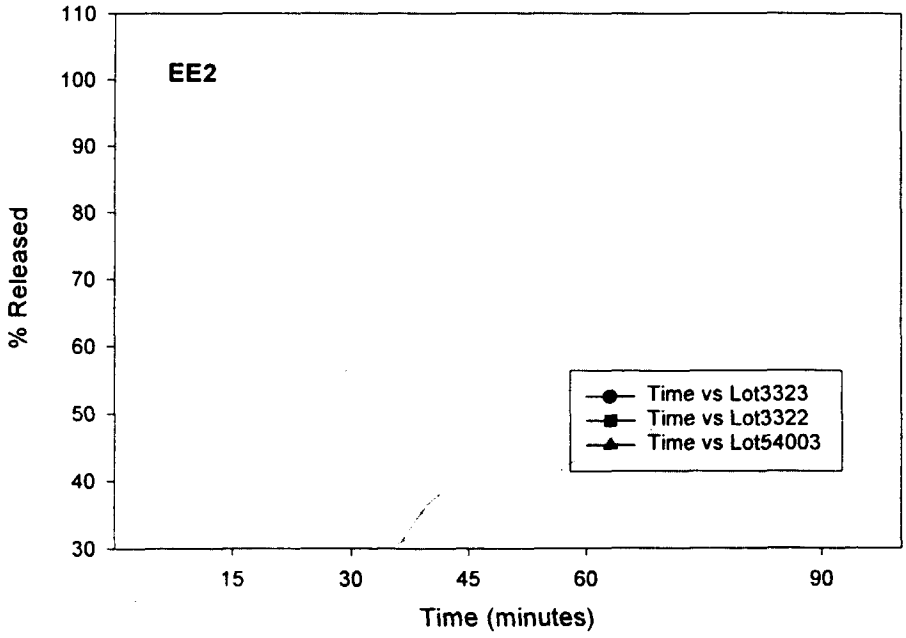


Figure 1. Dissolution profiles (LNG and EE2) over time of clinically tested batches.

Reviewer Comments

1. The proposed *in vitro* dissolution method is acceptable.

2. The proposed release specifications are not acceptable. The dissolution data presented do not justify Q % at minutes; the recommended release specifications for levonorgestrel and ethinyl estradiol are Q % at minutes.

VI. Analytical Methodology

Table V. Ethinyl estradiol assay validation.

	Nominal Ethinyl Estradiol Concentrations (pg/mL)			
	20	**50**	**125**	**250**
Mean	28.4	58	114.4	252.1
Accuracy (%)	142.1	116.1	91.5	100.8
Intra-assay Precision (%CV)	10.4	8.1	7.5	7.4
Inter-assay Precision (%CV)	25.7	12.3	9.9	7.1

The lower limit of quantitation was set to pg/mL.

Table VI. Levonorgestrel assay validation.

	Nominal Levonorgestrel Concentrations (pg/mL)		
	200	**1000**	**5000**
Mean	226	1096	5090
Accuracy (%)	113	110	102
Intra-assay Precision (%CV)	10	5	8
Inter-assay Precision (%CV)	16	6	7

The lower limit of quantitation was set to pg/mL depending on the dilution of the samples.

Reviewer Comments

1. The analytical method for the estimation of EE2 and LNG concentrations in serum is less than desirable. Information available to the Agency indicate that more sensitive assays can be utilized for the determination of EE2 and LNG in serum.

2. Assay for LNG was validated using a nominal concentration of pg/mL, which is higher than the lower limit of quantitation (LOQ). Assay performance at LOQ pg/mL) is unknown.

VII. Clinical Pharmacology and Biopharmaceutics Studies

Table VII. Summary of clinical studies.

Study No.	Study Design	Dosage Form	Subjects
Pivotal Pharmacokinetic Studies			
94010	Open-label, randomized two-period cross-over with a washout phase of one cycle; a relative bioavailability study	3 Sugar coated tablets, (0.3 mg LNG and 0.06 mg EE2); and 100 mL of microcrystalline cellulose suspension (0.3 mg LNG and 0.06 mg EE2)	17
94011	Open-label, single and multiple dose pharmacokinetics over 3 x 21 days	Sugar coated tablet, 0.1 mg LNG and 0.02 mg EE2	18
Supportive Studies			
93102	Ovulation inhibition study	Sugar coated tablet, 0.1 mg LNG and 0.02 mg EE2	24
311-01A	Oral Contraception (Protocol)		

1. Pharmacokinetics:

a) *Single and Multiple Dose*

The single dose and multiple dose pharmacokinetics of EE2 and LNG following administration of MICRO-LEVLEN® were evaluated in study 94011. This study was carried out in healthy, young female subjects between the ages of 18 and 35 who were not taking hormonal contraceptives (N = 18). The results are listed in Table VIII and Table IX below.

Additionally, protein binding data is given in Table X. Figure 2 presents concentration over time profiles for LNG. EE2 concentrations for most time points were below the detectable limit of 20 pg/mL, therefore, no profiles were generated.

Table VIII. Summary of pharmacokinetic parameters (mean ± SD) for EE2 levels obtained from 18 subjects after single dose (0.1 LNG + 0.02 EE2), and following administration (once daily) over 3x21 days.

Parameter	Single Dose	Day 1 Cycle 2	Day 21 Cycle 2	Day 1 Cycle 4	Day 21 Cycle 4
C_{max} (pg/mL)	49.5(13.4)	50.1(14.9)	66.2(29.5)	48.9(12.5)	58.1(19.3)
$^{*}T_{max}$ (hr)	1.5(0.4)	1.4(0.7)	1.4(0.4)	1.5(0.5)	1.4(0.3)
AUC_{0-t} (pg.hr/mL)	143(47)	132(50)	203(103)	129(40)	178(59)
AUC_{0-24} (pg.hr/mL)	298(215)	203(145)	596(494)	231(166)	417(289)
AUC_{0-last} (pg.hr/mL)	224(153)	163(117)	629(802)	167(107)	362(288)

Table IX. Summary of pharmacokinetic parameters (mean ± SD) for LNG levels obtained from 18 subjects after single dose (0.1 LNG + 0.02 EE2), and following administration (once daily) over 3x21 days.

Parameter	Single Dose	Day 1 Cycle 2	Day 21 Cycle 2	Day 1 Cycle 4	Day 21 Cycle 4
C_{max} (ng/mL)	2.36(0.79)	2.43(0.78)	4.04(2.08)	2.47(0.88)	4.53(1.94)
$^{*}T_{max}$ (hr)	1.3(0.4)	1.1(0.3)	1.0(0.3)	1.1(0.3)	1.0(0.3)
AUC_{0-z} (ng.hr/mL)	29.2(10)	-	100.2(64.3)	-	116.2(78.6)
AUC_{0-24} (ng.hr/mL)	15(5.8)	15.3(6.4)	43.8(22.4)	16.5(7.3)	49.5(24.5)
$t_{1/2}$ (hr)	25.4(9.7)	-	27.7(6.7)	-	28.6(7.4)
MRT (hr)	30.6(13.2)	-	37.3(9.8)	-	38.4(10.6)
CL (mL/min/kg)	1.0(0.3)	-	0.73(0.34)	-	0.65(0.33)
CL_u (mL/min/kg)	100(27.5)	-	89.2(24.6)	-	78.7(22.9)
Vd (L)	129(46)	-	106(0.42)	-	96(35)

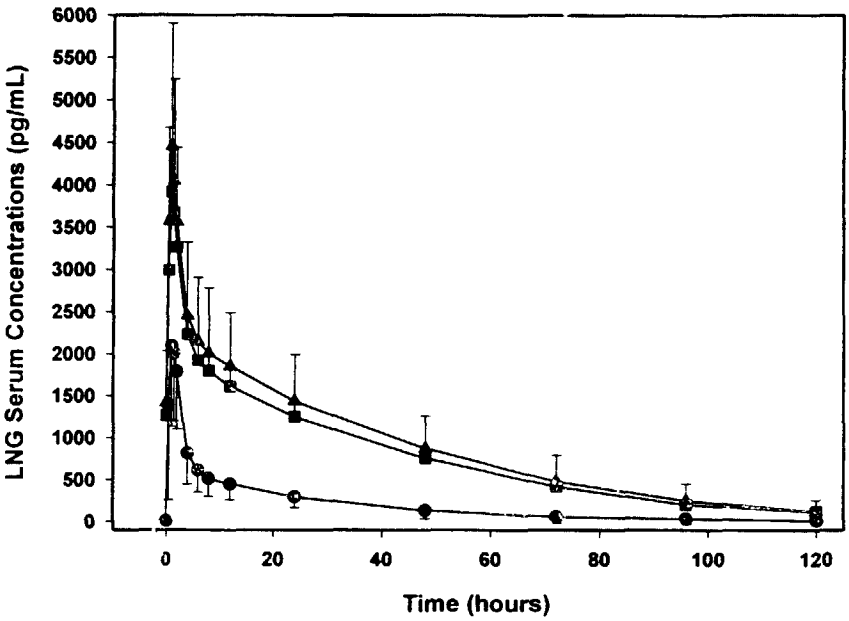


Figure 2. Mean (SD) LNG serum concentrations following single dose administration (●), and following administration at day 21 during cycle 2 (■) and cycle 4 (▲).

Reviewer Comments:

1. The study design appears to be adequate to determine the pharmacokinetics of MICRO-LEVLEN® after single dose, and following administration (once daily) over 3x21 days.

2. Multiple dosing of MICRO-LEVLEN® caused an increase in SHBG levels. As a consequence, the fraction of LNG bound to SHBG also increased. This caused decreased clearance of LNG, as reflected by higher AUC's during cycles 2 and 4 relative to the AUC's obtained after a single dose. Protein binding is addressed further in the section labeled **Protein Binding**.

2. Protein Binding

Levonorgestrel in serum is primarily bound to sex hormone binding globulin (SHBG); it binds plasma albumin to a lesser extent. Ethinyl estradiol binds mainly to plasma albumin, but it induces the production of SHBG. As the levels of SHBG increase, more LNG is bound resulting in decreased clearance and higher plasma levels (of LNG). This was observed in Study 94011, where multiple dosing of MICRO-LEVELEN® caused an increase in SHBG and decreased clearance of LNG. Observed maximum levonorgestrel concentrations increased from day 1 to day 21 of the 1st and 3rd cycles by 66% and 83%, respectively. Unbound levonorgestrel was 1.1% after a single dose and 0.8% after 21 days of multiple dosing. The binding of levonorgestrel to SHBG increased from 64.5% after a single dose of MICRO-

LEVLEN to about 75% on day 21 after multiple dosing. The protein binding data for LNG are presented in Table X.

Table X. Protein binding (mean ± SD) of LNG in pools of serum samples collected from 18 subjects after single dose (0.1 LNG + 0.02 EE2), and following administration (once daily) over 3x21 days.

Parameter	Single Dose	Cycle 2	Cycle 4
% free	1.11(0.27)	0.79(0.22)	0.80(0.23)
% SHBG-bound	64.5(8.54)	75.6(6.59)	74.7(7.89)
% albumin-bound	34.4(8.28)	23.6(6.41)	24.5(7.67)

3. Bioavailability/Bioequivalence:

a) Absolute/Relative Bioavailability

The absolute bioavailability for this product was not determined in this NDA. The relative bioavailability of 3 tablets of MICRO-LEVLEN® (0.3 mg LNG and 0.06 mg EE2) was compared to a microcrystalline suspension (0.3 mg LNG and 0.06 mg EE2 in 100 mL of non-carbonated mineral water) in Study 94010. This study was a single dose, open-label, randomized two-period crossover comparison between the two formulations and it was done in healthy, female subjects not on hormonal contraceptives (N = 17). The results are shown in Table XI below.

Table XI. Summary of pharmacokinetic parameters (mean ± SD) for EE2 levels obtained from 17 women after single oral doses of 0.3 mg LNG/0.06 mg EE2 as a microcrystalline suspension and 3 coated tablets each containing 0.1 mg LNG/0.02 mg EE2.

Parameter	Suspension	Tablets (x 3)
C_{max} (pg/mL)	154.1(45.3)	153.2(52.2)
$^{*}T_{max}$ (hr)	1.0(0.4)	1.5(0.6)
$AUC_{0\text{-}24}$ (pg.hr/mL)	1377.6(327.3)	1380.1(422.3)
$AUC_{0\text{-}last}$ (pg.hr/mL)	1796.1(724.9)	1597.0(685.8)
Relative bioavailability, F (%)	(Reference)	99.0

Table XII. Summary of pharmacokinetic parameters (mean ± SD) for LNG levels obtained from 17 women after single oral doses of 0.3 mg LNG/0.06 mg EE2 as a microcrystalline suspension and 3 coated tablets each containing 0.1 mg LNG/0.02 mg EE2.

Parameter	Suspension	Tablets (x 3)
C_{max} (ng/mL)	6.9(2.0)	6.5(2.2)
$^{*}T_{max}$ (hr)	1.0(0.5)	1.3(0.4)
AUC_{0-24} (ng.hr/mL)	51.8(18.3)	50.5(16.6)
$AUC_{0-\infty}$ (ng.hr/mL)	92.7(32.3)	93.1(40.0)
$t_{1/2}$ (hr)	26.5(8.4)	26.7(8.6)
MRT (hr)	32.5(11.2)	33.1(11.6)
Cl/F (mL/min/kg)	0.9(0.4)	1.0(0.3)
Vd/F (L/kg)	2.1(0.7)	2.1(0.8)
Relative bioavailability, F (%)	(Reference)	98.6

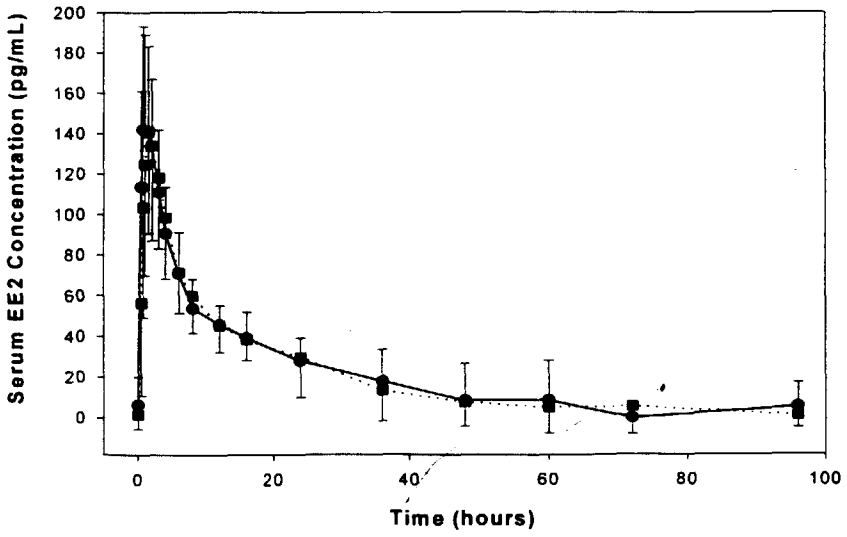


Figure 3. Mean (±SD) serum concentration of EE2 obtained from 17 women after single oral doses of 0.3 mg LNG/0.06 mg EE2 as a microcrystalline suspension (•) and 3 coated tablets (■) each containing 0.1 mg LNG/0.02 mg EE2.

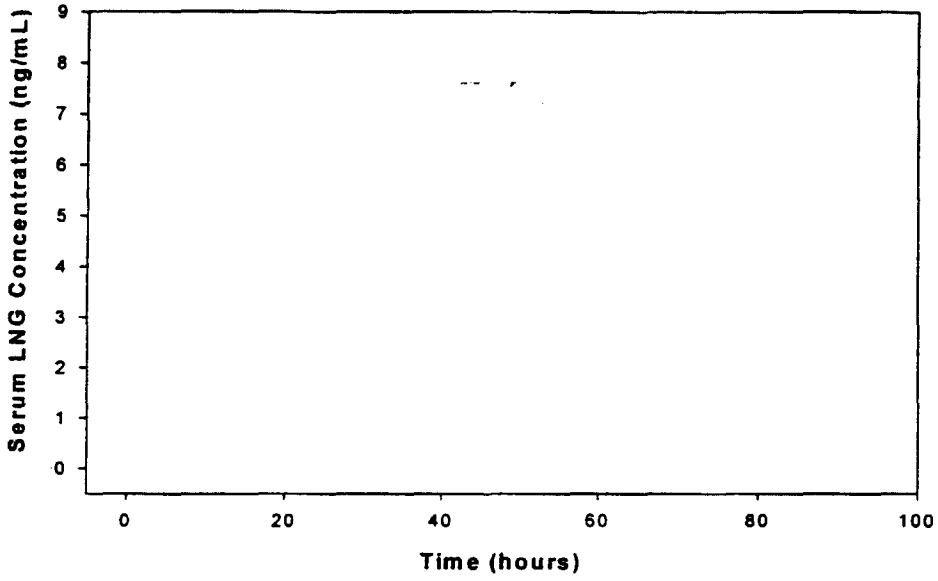


Figure 4. Mean (±SD) serum concentration of LNG obtained from 17 women after single oral doses of 0.3mg LNG/0.06mg EE2 as a microcrystalline suspension (•) and 3 coated tablets (■) each containing 0.1 mg LNG/0.02 mg EE_2.

Reviewer Comments:

1. The study design was adequate to determine the relative bioavailability of 3 coated tablets each containing 0.1 mg LNG/0.02 mg EE_2 compared with 100 mL volume of microcrystalline suspension containing 0.3 mg LNG/0.06 mg EE2.

2. The bioavailability of the tablets was greater than 98% relative to the suspension, suggesting complete absorption of LNG and EE2.

b) Bioequivalence, Effect of Food, Dose Proportionality

No studies were needed to demonstrate bioequivalence. No studies were done to look at the effect of food. Only one dose will be marketed, no dose proportionality studies were needed.

4. Special Populations

No studies were performed in Special Populations.

5. Metabolism

The metabolism of LNG and EE2 is well defined and no new studies were needed.

6. Drug Interactions

No studies were done to evaluate drug interactions.

7. PK/PD Relationships and Population Pharmacokinetics

No studies were done to examine PK/PD relationships or population pharmacokinetics.

VIII. Labeling Comments

The sponsor's proposed labeling is included in Attachment A. Recommended changes to the proposed labeling are listed below:

5. Other sections of the labeling appear to be appropriate, and no changes are recommended.

Attachment A

NDA 20-860

Proposed Labeling

Redacted 13

pages of trade

secret and/or

confidential

commercial

information

Attachment B

NDA 20-860

Review of Individual Studies

Study No. : 94010

Study Title:

Relative bioavailability of a combination tablet formulation containing 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol in comparison to a microcrystalline suspension in 17 healthy, young, female volunteers.

Objectives:

- Determine the relative bioavailability (%) of ethinyl estradiol (EE_2) and levonorgestrel (LNG) in comparison to that in a microcrystalline suspension

Study Design:

This was a single dose, open-label, randomized two-period crossover design. The study was carried out in healthy, female subjects not on hormonal contraceptives (N = 17).

The treatments were as follows:

A. Three coated tablets (0.1 mg LNG/0.02 mg EE2) for a total dose of 0.3 mg LNG/0.06 mg EE2, administered orally (test product)

B. Levonorgestrel and ethinyl estradiol microcrystalline suspension (100 mL), total dose = 0.3 mg LNG/0.06 mg EE2, administered orally (reference product)

Blood Sampling and Analysis : (hours)

Baseline: 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96.

Serum levels of LNG and EE2 were measured at each time point using Additionally, sex hormone binding globulin (SHBG) levels were determined from the serum taken immediately before every administration (0 hr).

Pharmacokinetic Analysis:

Non-compartmental analysis was performed on LNG and EE2 serum concentrations to estimate C_{max}, T_{max}, AUC_{0-24}, $AUC_{0-t(last)}$, $AUC_{0-\infty}$ and apparent $t_{1/2}$.

C_{max} and T_{max} were determined by visual inspection of the data; AUC_{0-24} and $AUC_{0-t(last)}$ were calculated by the linear trapezoidal rule. $AUC_{0-\infty}$ was calculated by:

$$AUC_{0-\infty} = AUC_{0-t(last)} + C_{last}/\lambda_z$$

where C_{last} is the last measurable drug concentration and λ_z is the slope of regression. The terminal half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \ln 2/\lambda_z$$

Apparent clearance (CL/f) and the apparent volume of distribution (V_z/f) were calculated according to:

$$CL/f = Dose/AUC_{0-\infty} \text{ and } V_z/f = CL/\lambda_z$$

Mean residence time (MRT) was calculated by:

MRT = AUMC/AUC, where AUMC = area under the moment curve

Statistical Analysis:

Single dose pharmacokinetic parameters were examined using analysis of variance (ANOVA) of log transformed serum concentrations of LNG and EE_2. The variance model included sequence, patient within sequence, treatment, and period effect. The sequence effect was tested using the "subject (sequence)-mean square error" at a significance level of 10%.

Results:

Table I. Summary of pharmacokinetic parameters (mean ± SD) for EE2 levels obtained from 17 subjects after single oral doses of 0.3 mg LNG/0.06 mg EE2 as a microcrystalline suspension and 3 coated tablets each containing 0.1 mg LNG/0.02 mg EE2.

Parameter	Suspension	Tablets (x 3)
C_{max} (pg/mL)	154.1(45.3)	153.2(52.2)
$^{*}T_{max}$ (hr)	1.0(0.4)	1.5(0.6)
AUC_{0-24} (pg.hr/mL)	1377.6(327.3)	1380.1(422.3)
$AUC_{0-tlast}$ (pg.hr/mL)	1796.1(724.9)	1597.0(685.8)
Relative bioavailability (%)	(Reference)	99.0

Table II. Summary of pharmacokinetic parameters (mean ± SD) for LNG levels obtained from 17 subjects after single oral doses of 0.3 mg LNG/0.06 mg EE2 as a microcrystalline suspension and 3 coated tablets each containing 0.1 mg LNG/0.02 mg EE2.

Parameter	Suspension	Tablets (x 3)
C_{max} (ng/mL)	6.9(2.0)	6.5(2.2)
*T_{max} (hr)	1.0(0.5)	1.3(0.4)
AUC_{0-24} (ng.hr/mL)	51.8(18.3)	50.5(16.6)
$AUC_{0-\infty}$ (ng.hr/mL)	92.7(32.3)	93.1(40.0)
$t_{1/2}$ (hr)	26.5(8.4)	26.7(8.6)
MRT (hr)	32.5(11.2)	33.1(11.6)
Cl/f (mL/min/kg)	0.9(0.4)	1.0(0.3)
Vd/f (L/kg)	2.1(0.7)	2.1(0.8)
Relative bioavailability (%)	(Reference)	98.6

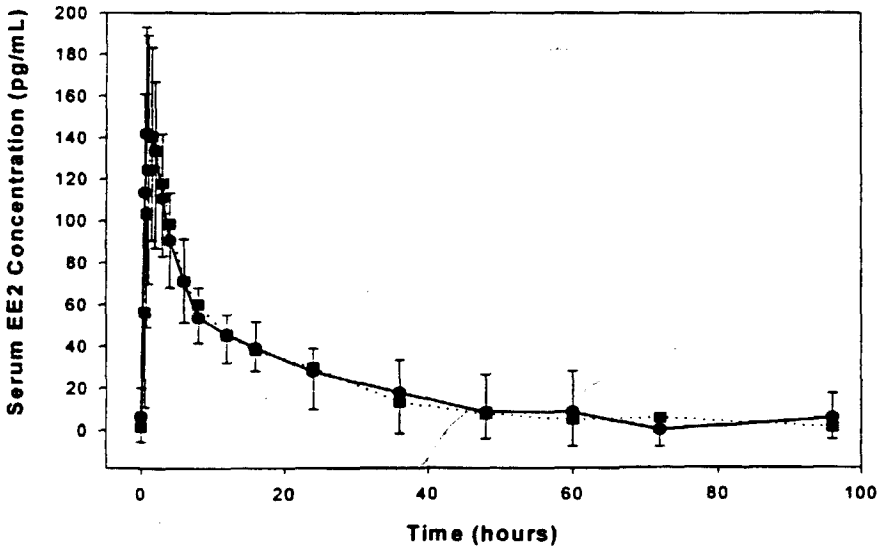


Figure 1. Mean (±SD) serum concentration of EE2 obtained from 20 women after single oral doses of 0.3 mg LNG/0.06 mg EE2 as a microcrystalline suspension (•) and 3 coated tablets (■) each containing 0.1 mg LNG/0.02 mg EE2.

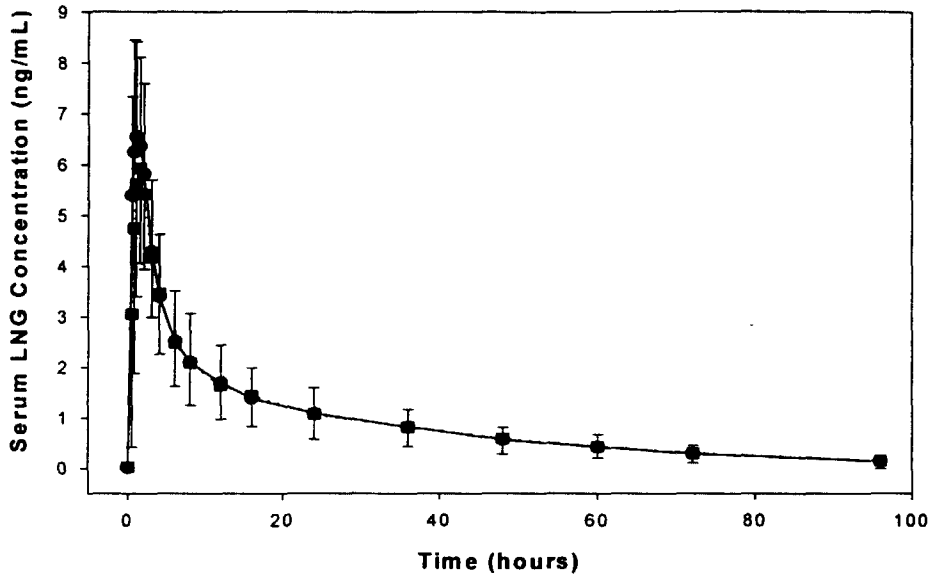


Figure 2. Mean (±SD) serum concentration of LNG obtained from 20 women after single oral doses of 0.3mg LNG/0.06mg EE2 as a microcrystalline suspension (•) and 3 coated tablets (■) each containing 0.1 mg LNG/0.02 mg EE2.

Reviewer Comments:

1. The study design was adequate to determine the relative bioavailability of 3 coated tablets each containing 0.1 mg LNG/0.02 mg EE_2 compared with 100 mL volume of microcrystalline suspension containing 0.3 mg LNG/0.06 mg EE2.

2. The bioavailability of the tablets was greater than 90% relative to the suspension, suggesting complete absorption.

Study No. : 94011

Study Title:

Pharmacokinetics of levonorgestrel (LNG) and ethinyl estradiol (EE2) after a three-month administration of the low dose oral contraceptive SH D 593 A (Miranova) in 20 young women

Objectives:

- Determine the pharmacokinetics of EE2 and LNG after repeated administration over three treatment cycles

Study Design:

This was an open-label, intra-individual comparison; single dose (0.1 LNG + 0.02 EE2) administration in the precycle, additional drug administration over 3x21 days. The study was carried out in healthy, young female subjects between the ages of 18 and 35 and who are not taking hormonal contraceptives (N = 18).

Blood Sampling and Analysis : (hours)

Baseline: 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96.

Serum levels of LNG and EE2 were measured at each time point using Additionally, sex hormone binding globulin (SHBG) levels were determined from the serum taken immediately before every administration (0 hr).

Pharmacokinetic Analysis:

Non-compartmental analysis was performed on LNG and EE2 serum concentrations to estimate C_{max}, T_{max}, AUC_{0-24}, $AUC_{0-t(last)}$, $AUC_{0-\infty}$ and apparent $t_{1/2}$.

C_{max} and T_{max} were determined by visual inspection of the data; AUC_{0-24} and $AUC_{0-t(last)}$ were calculated by the linear trapezoidal rule. The terminal half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \ln 2/\lambda_z$$

where λ_z was the slope of terminal phase. Apparent clearance (CL), clearance of fraction unbound (CL_u) for LNG, and the apparent volume of distribution (V_z/f) were calculated according to:

$$CL = f^*Dose/AUC_{0-\infty} \text{ and } V_z/f = CL/\lambda_z$$

$$CL_u = CL/f_u$$

where f is bioavailability, and which was assumed to equal 1, f_u is the fraction of LNG unbound.

Mean residence time (MRT) was calculated by:

MRT = AUMC/AUC, where AUMC = area under the moment curve

The accumulation factor R_1 was calculated according to:

$$R_1 = AUC_{(0\text{-}24)day21}/AUC_{(0\text{-}24)day1}$$

and the mass balance factor R^{**} was calculated according to:

$$R^{**} = AUC_{(0\text{-}24)SS}/ AUC_{(0\text{-}24)single\ dose}$$

Results:

Table I. Summary of pharmacokinetic parameters (mean ± SD) for EE2 levels obtained from 18 subjects after single dose (0.1 LNG + 0.02 EE2), and following administration (once daily) over 3x21 days.

Parameter	Single Dose	Day 1 Cycle 2	Day 21 Cycle 2	Day 1 Cycle 4	Day 21 Cycle 4
C_{max} (pg/mL)	49.5(13.4)	50.1(14.9)	66.2(29.5)	48.9(12.5)	58.1(19.3)
$^{*}T_{max}$ (hr)	1.5(0.4)	1.4(0.7)	1.4(0.4)	1.5(0.5)	1.4(0.3)
$AUC_{0\text{-}4}$ (pg.hr/mL)	143(47)	132(50)	203(103)	129(40)	178(59)
$AUC_{0\text{-}24}$ (pg.hr/mL)	298(215)	203(145)	596(494)	231(166)	417(289)
$AUC_{0\text{-}tlast}$ (pg.hr/mL)	224(153)	163(117)	629(802)	167(107)	362(288)

Table II. Summary of pharmacokinetic parameters (mean ± SD) for LNG levels obtained from 18 subjects after single dose (0.1 LNG + 0.02 EE2), and following administration (once daily) over 3x21 days.

Parameter	Single Dose	Day 1 Cycle 2	Day 21 Cycle 2	Day 1 Cycle 4	Day 21 Cycle 4
C_{max} (ng/mL)	2.36(0.79)	2.43(0.78)	4.04(2.08)	2.47(0.88)	4.53(1.94)
T_{max} (hr)	1.3(0.4)	1.1(0.3)	1.0(0.3)	1.1(0.3)	1.0(0.3)
$AUC_{0-\infty}$ (ng.hr/mL)	29.2(10)	-	100.2(64.3)	-	116.2(78.6)
AUC_{0-24} (ng.hr/mL)	15(5.8)	15.3(6.4)	43.8(22.4)	16.5(7.3)	49.5(24.5)
$t_{1/2}$ (hr)	25.4(9.7)	-	27.7(6.7)	-	28.6(7.4)
MRT (hr)	30.6(13.2)	-	37.3(9.8)	-	38.4(10.6)
CL (mL/min/kg)	1.0(0.3)	-	0.73(0.34)	-	0.65(0.33)
CL_s (mL/min/kg)	100(27.5)	-	89.2(24.6)	-	78.7(22.9)
Vd (L)	129(46)	-	106(0.42)	-	96(35)

Table III. Protein binding (mean ± SD) of LNG in pools of serum samples collected from 18 subjects after single dose (0.1 LNG + 0.02 EE2), and following administration (once daily) over 3x21 days.

Parameter	Single Dose	Cycle 2	Cycle 4
% free	1.11(0.27)	0.79(0.22)	0.80(0.23)
% SHBG-bound	64.5(8.54)	75.6(6.59)	74.7(7.89)
% albumin-bound	34.4(8.28)	23.6(6.41)	24.5(7.67)

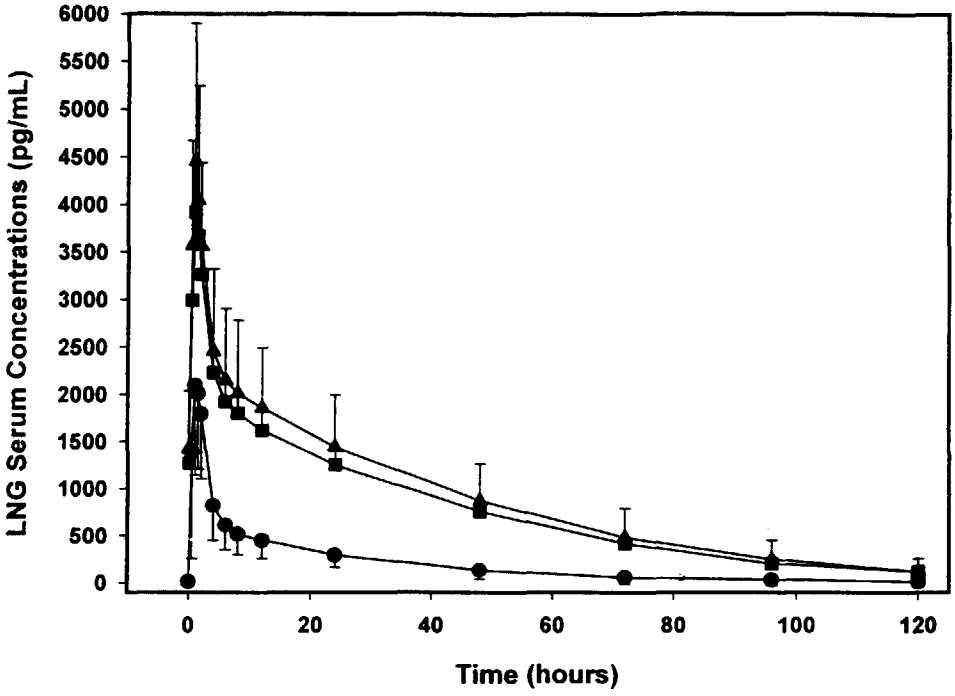


Figure 1. Mean (SD) LNG serum concentrations following single dose administration (•), and following administration at day 21 during cycle 2 (■) and cycle 4 (▲).

Reviewer Comments:

1. The study design appears to be adequate to determine the pharmacokinetics of Micro-levlen® after single dose, and following administration (once daily) over 3x21 days.

2. As expected, the increase in SHBG levels following administration Micro-levlen® led to an increase in the levels of LNG (as a result of protein binding and decreased clearance) in cycles 2 and 4. This is consistent with what has been observed with other formulations containing EE2 and LNG.