CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-860

MEDICAL REVIEW(S)

Addendum to Medical Officer's NDA Review

NDA: 20-860 Trade Name: Levlite

"Intent-to-Treat" Population Pregnancy Rates

JUL 07 1998

Report AL 31/Protocol 94251 (German Study)

Subject number became pregnant after discontinuing the study medication and having withdrawal bleeding. When this pregnancy is included with the method failure that occurred in subject , the Pearl Index is 0.597.

Report 97035/Protocol 311-O1A (U.S. Study)

Subject became pregnant after discontinuing the study medication and subject became pregnant after failing to take 15 active tablets. When these two pregnancies are included with the three method failures that occurred, the Pearl Index is 1.8.

/S/

Ridgely C. Bennett, M.D., M.P.H. 7/7/98

Concur - MD

7-7-98

Medical Officer's NDA Review

NDA: 20-860

Applicant: Berlex Laboratories, Inc.
340 Changebridge Road
PO Box 1000
Montville, New Jersey 07045-1000
(973) 276-2000

JUN 17 1998

Date Completed: May 8, 1998

1. General Information

   a. Name of Drug
      1) Generic: Levonorgestrel and ethinyl estradiol
      2) Trade: Levlite (Micro-levlen)
      3) Chemical: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, 17∝(-)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17∝)-
   b. Pharmacologic Category: Oral Contraceptive
   c. Proposed Indication: Prevention of Pregnancy
   d. Dosage Form and Route of Administration:

      Tablets for oral administration, 21 and 28 day packages, one tablet each day as directed in instructions.

      21 days round, unscored, coated, pink "active" tablets consisting of 0.10 mg of levonorgestrel and 0.02 mg of ethinyl estradiol (followed by 7 days round, unscored, coated, white "reminder" tablets, for 28-day regimen).

   e. Related Drugs:
      IND

      Marketed Drugs:

Levlen:	Levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg
Nordette:	Levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg
Lo/ovral:	Norgestrel 0.3 mg and ethinyl estradiol 0.03 mg
Alesse:	Levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg

2. Manufacturing Controls
   Please refer to chemist's review.

3. Pharmacology

Please refer to pharmacologist's review. In addition, the pharmacology and toxicology of levonorgestrel and ethinyl estradiol are well-documented in the literature.

4. Clinical Background

Several low dose oral contraceptives containing levonorgestrel (or its racemic mixture, norgestrel) and ethinyl estradiol are currently marketed in the United States and elsewhere. Berlex has marketed Levlen (higher dose combination of levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg with LNG/EE in the same 5-to-1 ratio as the product that is the subject of this NDA) since 1986. The product that is the subject of this NDA has been marketed in Germany since April, 1996 under the trade name, Miranova.

The purported reason for marketing Micro-levlen (levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg) is to increase the margin of safety by reducing the amount of progestin and estrogen to 2/3 that of Levlen while maintaining good cycle control and contraceptive efficacy.

IND

The sponsor met with FDA staff May 14, 1996 to discuss their proposed phase III clinical development plans.

5. Clinical Studies

Three uncontrolled clinical studies are presented. The first (Report AG 43/Protocol 93102) is an uncontrolled phase II inhibition of ovulation study. The second (Report AL31/Protocol 94251) is the phase III pivotal clinical study. The third (Protocol 311-01A) is a supporting clinical study. In addition, two published studies are mentioned, for which there are no protocols, case report forms, or study reports. These two studies were not conducted or sponsored by the applicant.

a. Report AG43/Protocol 93102. Uncontrolled Clinical Study on the Inhibition of Ovulation by an Oral Contraceptive Containing 0.020 mg Ethinyl Estradiol and 0.100 mg Levonorgestrel During Three Treatment Cycles

1) Investigator and Site:

Prof. W. Feichtinger, Investigator and Study Director
Dr. M. Bruner, Co-Investigator
Dr. C. Kindermann, Co-Investigator
Prof. J. Spona, Head of Hormone Laboratory
All investigators were located at the
Institute of Sterility Treatment
A-1130 Wien, Austria

2) Objectives of the Study: To demonstrate the ovulation inhibiting effect of the study preparation and allow an assessment of the residual ovarian activity (follicular maturation) under its application.

3) Rationale for the Study: Reliable inhibition of ovulation was expected with the study preparation on the basis of the available data on the ovulation inhibiting effect of levonorgestrel alone (0.050 mg to 0.060 mg). The study was intended to confirm the expected reliable inhibition of ovulation.

4) Experimental Design:

a) Patient Population:

i. Demography

The study included 25 healthy, female volunteers who were prepared to adhere to the study conditions.

ii. Clinical Characteristics for Inclusion

- nonsmokers aged 19 to 35 years
- smokers (maximum 10 cigarettes per day) aged 19 to 30 years
- regular cycle pattern
- wish for contraception over 3 cycles
- willingness to accept 1 pre- and 1 post -cycle without hormonal contraception.

iii. Exclusion Criteria

- usual criteria for oral contraceptive studies

b) Procedure:

i. Clinical and Laboratory Studies

During the pre-cycle, a history including information on demographic data, gynecological history and previous contraceptive treatment was obtained. Additionally, a general medical examination and gynecological examination including the breasts was conducted. A pap smear and serum pregnancy test were also done.

ii. Adverse Event Recording

The investigator was instructed to document the occurrence of every adverse event in the case report forms. Details were given of severity, extent, site, temporal

progress, assessment of the causal association with the study preparation, and special measures. The severity of an adverse event was classified as mild, moderate, or severe and the causal association between the administration of the study preparation and the occurrence of an adverse event was classified as none, improbable, possible, probable, definite, or unclassifiable.

iii. Indications for Withdrawal of Subjects from Study

Volunteers had the right at all times to refuse to participate in the study any further without giving a reason. If the volunteer withdrew because of an adverse event, however, the volunteer had to provide the appropriate data. Furthermore, the investigator had the right at all times to exclude a volunteer from the study should he consider this advisable for health reasons or because of infringements of the study protocol.

d) Efficacy Considerations

The frequencies of the effectiveness variables (ovulation, follicular maturation, and luteinizing unruptured follicles) were assessed using ultrasound examinations and hormone concentrations of 17β-estradiol, progesterone, LH, and FSH.

5) Results of the Study

a) Sponsor's Evaluation:

The sponsor concludes that the study preparation reliably inhibits ovulation while exhibiting an adequate suppression of ovarian activity. Cycle control was good and the incidence of adverse events was low.

b) Reviewer's Evaluation:

i. Demographics

Twenty-five volunteers entered the first treatment cycle. Volunteer number 9 stopped treatment after taking 1 tablet of the study preparation because she did not fulfill the relevant criteria. No data was available for this volunteer. Of the 24 volunteers with data, the age varied between years with a mean age of 27.5 years, the height was between cm with a mean height of 167.4 cm, and the weight varied between kg with a mean weight of 61.2 kg. All volunteers were

Caucasians. Seven volunteers were smokers (2-10 cigarettes per day) and no alcohol abuse was documented. The characteristics of this study population are acceptable for this ovulation inhibition study.

ii. Adequacy of Sample Size

Empirical knowledge of the study of the ovulation-inhibiting effect of sex hormones shows that from the basis of just 10 demonstrable ovulatory volunteers with one treatment cycle, adequate conclusions about the central inhibitory effect of the study preparation can be drawn. In this study, it was planned to have 25 volunteers begin the first treatment cycle, with an estimated drop-out rate of 20%, so that 20 volunteers would complete 3 cycles of study. This is an ample sample size for this phase II ovulation inhibition study. A total of 24 volunteers actually completed three cycles of study.

iii. Efficacy

All volunteers ovulated during the pre-cycle. No ovulation occurred during the 3 treatment cycles and no pregnancies occurred. All but one volunteer ovulated in the post-cycle phase. This indicates that the study preparation may be a highly effective contraceptive.

The study preparation led to a more pronounced suppression of ovarian activity in the first treatment cycle as compared to the second treatment cycle which was followed by a decrease of residual ovarian activity in the third treatment cycle. This was not unexpected and is similar to findings with other low-dose contraceptives. This results from the fact that tablet intake in the first treatment cycle begins with the first day of the menstrual cycle. Tablet intake in the second treatment cycle begins seven days after the beginning of the pill-free interval which results in reduced suppression in the second and subsequent treatment cycles.

iv. Safety

No deaths or serious adverse events were recorded during the course of the study. The most frequently reported symptoms were headache, nausea, and breast tenderness. Intermenstrual bleeding was reported mainly in the first treatment cycle. In the first cycle, spotting was reported by 12 volunteers, breakthrough bleeding by one

volunteer, and spotting and breakthrough bleeding by 3 volunteers. During the second treatment cycle, there were 5 volunteers with spotting and none with breakthrough bleeding. During the third treatment cycle, 10 volunteers reported spotting and one volunteer reported spotting and breakthrough bleeding. The incidence of intermenstrual bleeding in cycles 1 and 3 was higher in this study than usually seen. Volunteer number 4 was withdrawn from study during the third treatment cycle because of four luteinized unruptured follicles considered possibly associated with the study preparation. No changes in laboratory values were documented as clinically important.

6) Discussion

This phase II study was completed in August, 1994. It was designed to look at the ovulation-inhibiting effect of the study preparation and to allow an assessment of the residual ovarian activity (follicular maturation) due to the study preparation.

7) Conclusions

Reliable inhibition of ovulation was demonstrated and suppression of ovarian activity was adequate. There was a high incidence of intermenstrual bleeding, but one which is acceptable for a product containing 20 micrograms of ethinyl estradiol.

b. Report AL31/Protocol 94251. Multicenter, Non-Controlled, Clinical Study of the Contraceptive Efficacy, Cycle Control, and Tolerance of MICRO 20 in 820 Women over 6 Treatment Cycles

1) Investigators and Sites:

Prof. J.P. Hanker; Trier, Germany; Coordinating Investigator plus 43 other investigators in Germany.

2) Objectives of the Study:

To demonstrate the contraceptive efficacy of the study preparation, MICRO 20, and to assess cycle control and tolerance under use of the study preparation.

3) Rationale for the Study:

Reduction of doses of ethinyl estradiol and levonorgestrel as utilized in this study could possibly result in a safer oral contraceptive.

4) Experimental Design:

a) Patient Population:

i. Demography

This study included 950 healthy women attending outpatient gynecology clinics seeking oral contraceptive counseling. During recruitment, an attempt was made to achieve an equal balance between de novo users and women switching from another oral contraceptive. (In actuality, switchers constituted ¾ of the subject population.) Switchers were not required to observe a wash-out period before beginning treatment.

ii) Clinical Characteristics for Inclusion

- nonsmokers aged 18 to 35 years
- smokers (maximum of 10 cigarettes per day) aged 18 to 30 years
- regular cycle pattern (28 ± 5 days)
- desire for oral contraception over 6 treatment cycles
- willingness to adhere to the study conditions
- ethnicity was not a factor for inclusion or exclusion

iii. Exclusion Criteria

- pregnancy and lactation
- liver disease
- vascular and metabolic diseases
- tumors, including all malignant tumors
- use of drugs that interact with oral contraceptives, e.g. barbiturates, phenytoin, phenylbutazone, rifampicin, ampicillin, and other antibiotics
- genital bleeding
- other usual criteria for oral contraceptive studies

b) Procedure:

i. Dosage Schedule

The first tablet in the first treatment cycle was taken on the first day of bleeding (menstruation in the case of de novo users and withdrawal bleeding in the case of switchers). One tablet was taken daily for 21 days. This was followed by a 7-day, tablet-free interval. At the end of the tablet-free interval, another course of 21 tablets was started. All subjects took the same study medication. The active tablets contained 20 micrograms of ethinyl estradiol and 100 micrograms of levonorgestrel in sugar-coated tablets. If the interval between two tablets exceeded 36 hours, the subject was to continue to take the study medication, but to also employ other non-hormonal means of contraception during the remainder of that cycle of use.

ii. Type of Experimental Controls

This was an open, uncontrolled, noncomparative study.

c) Safety Considerations

i. Clinical and Laboratory Studies

At recruitment, a thorough medical, gynecological, and medication history was elicited. The general medical examination was repeated at the end of the sixth treatment cycle (or upon premature discontinuation of the study). General clinical chemistry and hematology determinations were made in the pretreatment cycle and after the sixth treatment cycle. A pregnancy test was performed pretreatment and in the absence of withdrawal bleeding, before the next treatment cycle.

ii. Adverse Event Recording

Investigators recorded the nature, severity, and frequency of adverse events, association with the study medication, extent, site, start, duration, and course of the event,

including clinical laboratory findings, measures taken, and medical treatment, if any. Adverse events were coded according to the HARTS codes (Hoechst Adverse Reaction Terminology System) by body system.

iii. Indications for Withdrawal of Subjects from Study

Subjects had the right to withdraw from the study at anytime if they so desired, experienced an adverse event, or had a change of residence. In addition, subjects could be withdrawn at the discretion of the investigator.

d) Efficacy Considerations

Contraceptive efficacy was assessed assuming that all subjects were at risk of pregnancy in all medication cycles unless they used condoms for AIDS prophylaxis. Cycle control was determined by means of requiring subjects to keep a record of bleeding days and tablet intake during treatment. Subjects recorded days of bleeding by intensity, days without bleeding, and days of tablet taking. Bleeding which started on cycle days 18-21 and continued up to the tablet-free interval without a day void of bleeding was considered withdrawal bleeding and was documented as such. Intermenstrual bleeding was classified as either scanty, normal, or heavy. Scanty bleeding was considered as spotting. Normal (the intensity of a normal menstrual period) and heavy (heavier bleeding than a normal menstrual period) bleeding were considered to be breakthrough bleeding. Cycle length, duration of withdrawal bleeding, intensity of withdrawal bleeding and amenorrhea were determined for all subjects, for all subjects who completed 6 treatment cycles, and for new users and switchers.

5) Results of Study

a) Sponsor's Evaluation:

The sponsor concludes that the study medication is an effective oral contraceptive that is safe and well tolerated with good cycle control during the six

treatment cycles. Adverse events observed during the trial were those commonly encountered in clinical trials of oral contraception.

b) Reviewer's Evaluation:

i. Demographics

The mean age of subjects was 25.6 years with a range from years. A total of 140 subjects (17.1%) were ≤20 years, 529 subjects (64.5%) were between 21 and 30 and 151 (18.4%) were between years. The mean height was 167.1 cm with a minimum of cm and a maximum of cm. The mean weight was 62.7 kg with a range from kg. A total of 807 subjects (98.4%) were Caucasians. No blacks were enrolled. This population does not represent the ethnic distribution of the U.S. population. The mechanism of action of the study preparation (inhibition of ovulation) however, is such that one would not anticipate differences in efficacy between ethnic groups.

ii. Adequacy of Sample Size

The number of subjects was originally set at 1000 without biometrical considerations. The goal was to collect data from 5000 cycles of treatment in order to obtain valid data on the contraceptive efficacy, cycle control, and tolerance of the study preparation under practical conditions. The number of subjects studied and number of cycles completed satisfies FDA guidelines which state that when there is a total dose reduction of an approved combination oral contraceptive which retains the same estrogen: progestin ratio, no safety data would be required and reasonable proof of efficacy could be determined from studies of 600 subjects treated for 6 cycles. The approved combination oral contraceptives Levlen, Nordette, and Lo/Ovral have had the amounts of estrogen and progestin contained in them reduced by one third and have maintained the

same estrogen: progestin ratio. Therefore, the resulting contraceptive, Micro-levlen, can be evaluated for efficacy based on 600 subjects treated for 6 cycles. A total of 950 subjects were recruited. There were 130 subjects who received no medication. Of the remaining 820 subjects, 211 (26%) were starters and 594 (74%) were switchers. A summary of the disposition of subjects is given below:

Table 1
Summary of Disposition of Subjects
(Sponsor's Table TT3)

	Number
Subjects Admitted	950
Subjects who received no medication	130
Safety population	820
No evaluations during treatment	15
ITT population	805
Relevant protocol violations	12
Valid case population	793
Subjects with no valid treatment cycles	5
Subjects with one or more valid cycles	788

A total of 680 subjects completed all 6 treatment cycles.

iii. Efficacy

Two pregnancies occurred during this clinical trial. Subject 1005 had an enlarged uterus and sonographic evidence of a pregnancy at the conclusion examination. She discontinued the study medication of her own volition after taking medication for 2 cycles. Her last pill was taken July 15 and she had withdrawal bleeding July 19-23. The investigator determined that her conception date was August 1 based on the vertex-breech length, which was after she discontinued the study medication. This pregnancy, therefore, most likely represents the patient's noncompliance rather than study drug failure.

The post-treatment examination of subject after completion of the sixth treatment cycle revealed a pregnancy in the seventh week of gestation. She denied missing any tablets. She did not take any medication that would have affected bioavailability. She had no illness that would have affected absorption. This pregnancy represents study drug failure. Follow-up outcomes of both pregnancies should be requested.

In all, 805 subjects were included in the ITT analysis of effectiveness and 4400 cycles were valid for the ITT analysis. Cycles in which subjects used alternative methods of contraception (n = 48 cycles) were excluded from the calculation of the Pearl Index. The calculated Pearl Index was 0.299.

$$\text{P.I.} = \frac{\text{No. of pregnancies x 13 cycles x 100}}{\text{Total number of cycles}} =$$

$$\frac{1 \times 13 \times 100}{4400\text{-}48} = \frac{1300}{4352} = 0.299$$

This Pearl Index indicates that the study preparation is a highly effective contraceptive.

Cycle control was considered to be another efficacy parameter. This can best be looked at by observing the percentage of cycles in which intermenstrual bleeding (breakthrough bleeding, spotting, or both) occurred.

Table 2
Incidence Rates of Intermenstrual Bleeding (ITT Analysis)
(Sponsor's Table TT5)

Cycle Number	No. of Subjects Completing	No. of Subjects with Bleeding	(%) of Subjects with Bleeding
1	805	246	30.6
2	777	165	21.2
3	743	138	18.6
4	710	107	15.0
5	686	66	9.6
6	681	83	12.2

The incidence of intermenstrual bleeding in each cycle is higher than that seen in contraceptives containing 0.05 mg of ethinyl estradiol. Overall, there was some intermenstrual bleeding in 18.3% of all six cycles, bleeding occurred most frequently in the first two cycles, an tended to be reduced to approximately 10% by cycles 5 and 6.

iv. Safety

There were no deaths during this clinical trial. Two subjects reported serious adverse events. Subject had nephrolithiasis diagnosed during the second treatment cycle. Lithotripsy was performed and she continued in the study. Subject had a malignant melanoma diagnosed after one cycle of treatment and was withdrawn from the study. Neither event was related to study drug.

A total of 69 (8.4%) subjects discontinued the study because of adverse events. The most common adverse event leading to discontinuation was intermenstrual bleeding and metrorrhagia. This occurred in 33 subjects. Most other adverse events were those commonly seen in clinical studies of oral contraceptives, such as headache, breast pain, nausea, and acne.

There were no abnormal laboratory parameters that were considered clinically significant during the study.

6) Discussion

This clinical trial was planned as a non-controlled, open, non-comparative, multicenter study in Germany to determine the efficacy of the study preparation. By reducing the amount of progestin and estrogen to 2/3 that of Levlen, Nordette, and Lo/ovral, the margin of safety of this study preparation is theoretically increased, but the study was not designed to prove this. It fulfills the FDA guidelines for the study of oral contraceptives containing reduced amounts of estrogen and progestin in the same ratio, namely 600 subjects completing 6 treatment cycles. Safety, as such, is not an issue; only contraceptive efficacy and cycle control, primarily intermenstrual bleeding, are of major concern. This clinical trial reveals that the contraceptive efficacy of this product is excellent. The Pearl Index was 0.299. Cycle control parameters were as expected for an oral contraceptive containing 20 micrograms of ethinyl estradiol. It is the pivotal trial for this NDA. Outcomes of the two pregnancies occurring in this study should be requested from the sponsor.

7) Conclusion

Micro-levlen is an effective and safe contraceptive with satisfactory cycle control. No data is submitted to conclude that this product is safer than those containing higher doses of estrogen.

c. Report 97035/Protocol 311-01A. An Open-Label, Multicenter Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation Containing Levonorgestrel 100 µg and Ethinyl Estradiol 20µg.

1) Investigators and Sites:

Table 3
Investigator Information and Subject Enrollment
(Sponsor's Table TT2)

		Number of Subjects	
Center No.	Investigator's Name and Address	Enrolled	Evaluated
101	Jeff Adelglass, MD Dallas, Texas	50	49
102	Bruce Bowling, MD Endwell, New York	25	25

		Number of Subjects	
Center No.	Investigator's Name and Address	Enrolled	Evaluated
103	Steven Bowman, MD Clearwater, FL	58	57
104	Marc Clanchko, MD Paramus, New Jersey	56	53
105	Jeffrey Frank, MD West Reading, PA	31	30
106	Stephen Gordon, MD Atlanta, GA	41	41
107	Dan C. Henry, MD Salt Lake City, UT	52	52
108	William Koltun, MD San Diego, CA	79	79
109	Robin Kroll Seattle, WA	33	33
110	John Lenihan, Jr, MD Tacoma, WA	40	40
111	John Mattox, MD Phoenix, AZ	17	17
112	Dennis Morrison, DO Springfield, MO	46	42
113	David Watson, MD Littleton, CA	49	49
114	Ernie Riffer, MD Phoenix, AZ	47	45
115	Jeffrey Rosen, MD Coral Gables, FL	34	34
116	John Schoenberger, MD Redwood City, CA	60	57
117	Barbara Soltes, MD Chicago, IL	41	41
118	Mark Weinstein, MD East Brunswick, NJ	11	11
	Total	770	755

2) Objectives of the Study:

To evaluate contraceptive efficacy of the study preparation and secondarily, to evaluate the effects of the study preparation on cycle control.

3) Rationale for the Study:

Reducing the dose of the contraceptive steroids as utilized in this study could possibly result in a safer oral contraceptive.

4) Experimental Design:

a) Patient Population:

i. Demography

This study included 770 healthy women attending private practices or investigational institutions experienced in the conduct of clinical studies in female health care in the United States. A total of 339 subjects (44%) were starters and 431 subjects (56%) were switchers.

ii. Clinical Characteristics for Inclusion

- 18 to 35 years old and at risk of becoming pregnant
- regular cycle pattern (21-35 days)
- willingness to use a low-dose oral contraceptive
- if post-abortal or post-partum, had 3 consecutive normal menstrual cycles immediately preceding treatment
- signed a written informed consent
- complied with the protocol
- negative pregnancy test within 2 weeks prior to first dose

iii. Exclusion Criteria

- pregnancy, lactation, or desired pregnancy
- diabetes mellitus
- smoked more than 10 cigarettes per day
- was over 30 years of age and currently smoking
- currently using an oral contraceptive containing ≥ 50 µg EE
- use of injectable hormones during prior 3 month period
- other usual criteria for oral contraceptive studies

b. Procedure:

i. Dosage Schedule

One tablet per day at the same time every day throughout the treatment period, beginning on the first day of menses for a 28-day dosing schedule. After all 28 pills

from the first package were taken (21 active and 7 placebo), the first tablet from the next package was taken the next day, and the 28-day dosing schedule was continued. The start day was the same for each package for all cycles. Each active pill contained 100 μg of levonorgestrel and 20 μg of ethinyl estradiol.

ii. Type of Experimental Controls

This was an open-label, non-comparative study.

c. Safety Considerations

i. Clinical and Laboratory Studies

A complete medical, surgical, and gynecological history was taken at baseline. A complete physical examination was performed at baseline and after the end of cycle 6 or the final visit. General hematology and clinical chemistry determinations were made at baseline and cycle 6 or final visit. A pregnancy test was performed at baseline, cycle 6 or final visit, and at the 2 week follow-up visit or at additional visits as deemed necessary by the investigator.

ii. Adverse Event Recording

Investigators recorded the nature, severity, and frequency of adverse events associated with the study medication, outcome of the adverse event, and an opinion of drug relationship or attribution, including clinical laboratory findings.

iii. Indications for Withdrawal of a Subject from the Study

Subjects could withdraw if they so desired or if they failed to comply with the protocol.

d. Efficacy Considerations

The primary efficacy variable was the pregnancy rate. Efficacy was assessed using the Pearl Index (number of pregnancies per 100 women years) and life table methods. Cycles in which additional contraceptive methods were used were deleted from the computation of the Pearl Index and from all subsequent cycles for the life table method analysis. The secondary efficacy variables were measures of cycle control and intermenstrual bleeding. Intermenstrual bleeding was summarized by duration and type. Bleeding which was not withdrawal bleeding and described as light bleeding in the subject's diary was considered as

spotting. Normal or heavy bleeding which was not withdrawal bleeding was considered as breakthrough bleeding. Withdrawal bleeding was defined as the continuous bleeding from day 18 onward into the placebo pill period (days 21 - 28), or from the placebo pill period to the third day of the next pill cycle.

5) Results of the Study -- ,

a) Sponsor's Evaluation:

The sponsor concludes that the study medication appears to be an effective oral contraceptive which is safe and well tolerated. Adverse events observed were similar in type and frequency to those commonly encountered with marketed oral contraceptives. Cycle control was acceptable.

b) Reviewer's Evaluation

i. Demographics

The mean age was 27 years, with a range of years. The mean height was 167 cm with a minimum of cm and a maximum of cm. The mean weight was 63 kg with a range from kg. A total of 616 subjects (82%) were Caucasians. A total of 44 subjects (6%) were black, 61 subjects (8%) were Hispanic, 22 subjects (3%) were Asian, and 12 subjects (2%) were classified as "other". This racial distribution of subjects comes closer to reflecting the ethnic distribution of the U.S. population.

ii. Adequacy of Sample Size

A total of 770 subjects were enrolled at 18 U.S. study centers in order to ensure that at least 600 subjects completed 6 months of treatment in order to satisfy FDA's guidelines for study of this type of oral contraceptive (total dose reduction of an approved combination oral contraceptive which retains the same estrogen:progestin ratio). A total of 558 subjects completed all 6 cycles. The sample size of this clinical trial is, therefore, adequate. Fifteen subjects did not take any study medication. Therefore, the total number of subjects evaluated was 755. The number of subjects enrolled per center ranged from a minimum of 11 subjects to a maximum of 79 subjects. Fifteen centers enrolled ≥30 subjects.

iii. Efficacy

Five pregnancies occurred during this clinical trial. Subject missed the first tablet of cycle 6 and took two tablets on day 2. She omitted taking tablets on days 3, 4, and 5 of the same cycle and

contacted the investigator who told her she was no longer qualified for the study (in accordance with the protocol). The subject decided not to take any more tablets and became pregnant in the same cycle (confirmed by ultrasound). The pregnancy resulted in the birth of a healthy baby. This pregnancy was not due to study drug failure.

Subject went on vacation from day 13 to day 20 of cycle 5 and forgot to take her study medication. She did not take any medication during these days and had withdrawal bleeding days 15 - 20. She resumed pill intake upon her return home from vacation. She started, however, with the placebo tablets for seven days, which was incorrect. Subsequently withdrawal bleeding did not occur after cycle 6. Pregnancy was confirmed by both the beta hCG test and ultrasound examination showing a pregnancy length corresponding to a conception date during the treatment-free weeks. This pregnancy resulted from interruption of treatment by the subject who was without active treatment for 14 consecutive days. The subject completed the study unaware of her pregnancy. The outcome of the pregnancy is unknown as the subject relocated. This pregnancy was not a method failure.

Subject became pregnant during the first treatment cycle. She did not report missing any tablets and did not have any concomitant disease or medication. The subject discontinued the study and delivered a healthy baby. This pregnancy is a method failure.

Subject had no withdrawal bleeding at the end of cycle 5. She missed tablets on days 8 and 18 of cycle 5. In addition, she was treated with nitrofurantoin capsules for a urinary tract infection from day 19 to day 25 of cycle 5. After the second week of cycle 6, the beta hCG test was positive. The subject discontinued the study and was subsequently lost to follow-up. This pregnancy was a method failure.

Subject had no withdrawal bleeding after the fourth cycle. Pregnancy was confirmed. Her diary showed no missed pills. No concomitant diseases or medication were reported. The subject discontinued the study and had an induced abortion. The pregnancy was a method failure.

The Pearl Index, calculated on the basis of three method failures in 3612 valid cycles without other contraceptive use, was 1.08. This indicates that the study preparation is an effective oral contraceptive.

Intermenstrual bleeding was a secondary efficacy variable.

Table 4
Incidence Rates of Intermenstrual Bleeding

Cycle Number	No. of Subjects Completing	No. of Subjects with Bleeding	(%) of Subjects with Bleeding
1	675	250	37
2	634	171	27
3	610	146	24
4	573	126	22
5	567	108	19
6	558	117	21

Overall, there was some intermenstrual bleeding in 25% of all cycles and occurred mostly in the first cycle.

iv. Safety

There were no deaths during the clinical trial. Four subjects reported five serious adverse events. Subject had a history of kidney calculus due to congenital uteropelvic junction stenosis with hydronephrosis, and had undergone a pyeloplasty. She developed right lower quadrant pain and was admitted to the hospital for lithotripsy. The subject completed the study. The drug relationship was classified as "unrelated".

Subject developed severe pain in the upper right quadrant of the abdomen during cycle 5. Gallstones were diagnosed and she underwent laproscopic cholecystectomy. The subject completed the study. The drug relationship was classified as "probable" and was probable related to increased cholesterol concentrations in bile due to the study drug.

Subject reported two serious adverse events. A uterine fibroid was not detected during the gynecological examination at the beginning of the study. Beginning in cycle 1, the subject complained of abdominal pain. From cycle 2 onwards, she also experienced vaginal pain during intercourse. At the end of study visit after cycle 6, the subject presented with severe vaginal pain and abdominal pain and was admitted to the hospital for laparoscopic exploration of the abdomen. A diagnosis of a degenerating fibroid at the back of the uterus was made. The investigator considered the fibroid to be probably related to the study drug and was reported as a serious adverse event. The subject was treated with Depot Lupron. The subject continued to feel ill. An exploratory laparotomy

was performed. A rectus abdominus hematoma was found that had leaked into the perioneal cavity causing a hemoperioneum. After evacuating the hematoma and irrigating the perioneal cavity, the fibroid was removed. The hemoperitoneum was considered to be a complication of the initial diagnostic laparoscopy and was reported as a serious adverse event unrelated to the study drug.

Subject did not return for her visit at the end of cycle 3. She apparently had discontinued pill intake without notifying the investigator. At the request of the investigator, the subject returned for the final visit. A scar was noticed on the subject's upper right abdomen which appeared to have resulted form a cholecystectomy. The subject refused to give any information or details regarding the scar. This serious adverse event was considered by the investigator to be unlikely related to the study drug.

Of the 755 subjects evaluated in the clinical trial, a total of 35 subjects (4.6%) discontinued the study because of adverse events. The most common adverse event leading to discontinuation was intermenstrual bleeding and menorrhagia. This occurred in 13 subjects. Most adverse events were those commonly seen in clinical studies of oral contraceptives.

There were no abnormal laboratory parameters of clinical significance that were attributed to the study drug.

Twenty subjects had clinically significant abnormalities in one or more physical examination parameters at cycle 6 which were not present at baseline. None of these were considered to be study-drug related.

Twenty-three subjects had transitions in one or more gynecological examination parameters at cycle 6 which were not present at baseline. With the exception of one subject (number discussed above in the "Safety" section), none of these changes were considered to be study-drug related.

The most frequently reported adverse events are listed below.

Table 5
Frequency of the Most Commonly Occurring Adverse Events
(Sponsor's Table 48)

Adverse Event	%
Headache	20.3
Flu syndrome	9.3
Abdominal pain	6.6
Nausea	6.6
Breast Pain	5.4
Sinusitis	5.2
Vaginal moniliasis	4.9
Acne	4.5
Dysmenorrhea	4.0
Upper respiratory infection	4.0

No clinically significant changes in mean systolic or diastolic blood pressure were observed during the clinical trial. Only minor changes in body weight were noted during the study.

6) Discussion

This supporting clinical trial was planned as a non-controlled, open, non-comparative, multicenter study in the United States to confirm the efficacy of the study preparation found in Germany. By reducing the amount of progestin and estrogen to 2/3 that of Levlen, Nordette, and Lo/ovral, the margin of safety of this study preparation is theoretically increased, but the study was not designed to prove this. It fulfills the FDA guidelines for the study of oral contraceptives containing reduced amounts of estrogen and progestin in the same ratio, namely 600 subjects completing 6 treatment cycles. Contraceptive efficacy and cycle control, primarily intermenstrual bleeding, were acceptable. This clinical trial reveals that the contraceptive efficacy of this product is good. The Pearl Index was 1.08. Cycle control parameters were as expected for an oral contraceptive containing 20 micrograms of ethinyl estradiol. Adverse reactions reported were similar in both nature and incidence with those known to occur with oral contraceptives.

7) Conclusion

Micro-levlen is an effective and safe oral contraceptive with acceptable cycle control. No data is busmitted to conclude that this product is safer than oral contraceptives containing higher amounts of ethinyl estradiol.

d. Published Report. "Clinical Evaluation of a Low-Dosage Estrogen-Progestin Combination (100 mcg of d-Norgestrel and 20 mcg of Ethinyl Estradiol)". Sartoretto, J.N. and OrtegaRecio, J.C. Rev. Bras. Clin. Terap.;1974; 3:399-404.

1) Investigators and Sites

Jose Paixao de Souza and
Roberto Bruce da Luz
Juiz de Fora, Brazil

Aguinaldo A. Cantuaria
Uberaba, Brazil

Eduardo Lana
Campias, Brazil

2) Objectives of the Study

Not stated, but it may be inferred that the objectives were to evaluate contraceptive efficacy and the effects of the study preparation on cycle control.

3) Rationale for the Study

The development of low-dosage progestogen-estrogen combinations may offer both efficacy and good cycle control without the inconvenience of the estrogen dosages then in use.

4) Experimental Design:

a) Patient Population:

i. Demography

This study included 438 healthy women attending three hospital clinics in Brazil.

ii. Clinical Characteristics for Inclusion

- aged 45 years or less
- motivated to appear for monthly visits to the clinic
- proven fertility by previous pregnancies
- regularly sexually active
- literate to fill in data charts

iii. Exclusion Criteria

- over age 45 years
- medical conditions contraindicating oral contraceptives

b) Procedure:

i. Dosage Schedule

Twenty-one active tablets consisting of d-norgestrel 100 μg and ethinyl estradiol 20 μg which was administered from the fifth day of the first cycle in cycles of 21 days of medication and 7 days without the drug for a period of 12 cycles.

ii. Type of Experimental Controls

This was an open-label, non-comparative, multicenter study.

c) Safety Considerations

i. Clinical and Laboratory Studies

Careful general and gynecological examinations designed to rule out the existence of medical conditions that would contraindicate the use of oral contraceptives were performed. Laboratory studies were not performed. Monthly visits to the hospital clinics were required.

ii. Adverse Event Recording

Breakthrough bleeding and spotting were recorded. There is no mention of other adverse events being recorded, but discontinuances for medial reasons (unspecified) were tabulated.

iii. Indications for Withdrawal of a Subject from the Study

No indications for withdrawal of subjects are mentioned. However, subjects were discontinued from study for personal reasons, medical reasons, and one subject for pregnancy.

d) Efficacy Considerations

Presumably, the primary efficacy variable was the pregnancy rate. Efficacy was calculated in accordance with the "life table method". A 1972 reference is given for the method by P. Bergsjo. The presumed secondary efficacy variables were measures of cycle characteristics.

5) Results of the Study

a) Sponsor's Evaluation:

The sponsor concludes that cycle control was good, but the report author concludes that cycle control was not perfect, spotting occurring in 3.1% of cycles and breakthrough bleeding occurring in 12.4% of cycles, but that fertility control can be achieved with the drug product.

b) Reviewer's Evaluation:

i. Demographics

Ages of subjects ranged from below 20 years (17.76%) to 45 years. Only 3 subjects had never been pregnant.

ii. Adequacy of Sample Size

A total of 438 subjects completed a total of 3424 cycles with 162 subjects completing 12 cycles. The sample size of this clinical trial is not adequate. It does not satisfy FDA's guidelines for either a 6 month study or a 12 month study.

iii. Efficacy

One pregnancy occurred during this clinical trial. This occurred in the second cycle in a subject who had taken tablets irregularly. The calculated Pearl index was 0.35. This indicates that the study preparation is a highly effective oral contraceptive.

Intermenstrual bleeding (breakthrough bleeding and spotting) was a secondary efficacy variable.

Table 6
Incidence Rates of Intermenstrual Bleeding

Cycle Number	No. of Subjects Completing	No. of Subjects with Bleeding	(%) of Subjects with Bleeding
1	438	114	26.0
2	405	79	19.5
3	372	60	16.1
4	330	53	16.0
5	306	48	15.7
6	280	41	14.7
7	260	31	11.9
8	241	31	12.9
9	228	21	9.2
10	210	19	9.0
11	191	22	11.5
12	163	14	8.6

iv. Safety

Severe adverse events were not observed. A description of adverse events is not given (other than breakthrough bleeding and spotting). Medical reasons, presumably adverse events, were the reason for discontinuation of 8.9% of subjects and occurred mostly in cycles 3, 4, and 5.

6) Discussion

This old clinical report was published in a Brazilian medical journal in 1974. The authors are not any of the clinical investigators, but employees of the then sponsoring drug company. Berlex has no access to the protocol, case report forms, or report of this study. The Pearl Index of 0.35 would be indicative of a highly effective oral contraceptive if based on larger numbers of subjects for longer periods of time. The incidence of spotting (3.1% of cycles) and breakthrough bleeding (12.4% of cycles) was rather high. The percentage of subjects that discontinued the study because of bleeding problems is not given. No severe adverse events occurred. A detailed description of adverse events is not given (except for breakthrough bleeding and spotting). My calculation of incidence rates of intermenstrual bleeding (Table 6) confirms the high rate of annoying bleeding that occurred. The numbers of subjects (438) and cycles completed (3424) are too small to serve as a definitive basis on which to reach a firm conclusion regarding a confident delineation of an efficacy

rate. This small study does add a little more information regarding the expected safety of the drug product.

7) Conclusion

Micro-levlen has a high incidence of intermenstrual bleeding, but one which is acceptable for a product containing 20 micrograms of ethinyl estradiol.

e.) Published Report. "Clinical Trials with a Combination Contraceptive Containing 100 mcg of d-Norgestrel and 20 mcg of Ethinyl Estradiol." Aquinaldo, A. Cantuaria and Sartoretto, J.N. A. Folha Medica; 1974; 69: 537-542.

1) Investigator and Site
Aquinaldo A. Cantuaria
Bemfam Hospital
Uberada, Brazil

2) Objectives of the Study
The objectives of the study were not stated, but it may be inferred that the objectives were to evaluate contraceptive efficacy and the effects of the study preparation on cycle control.

3) Rationale for the Study
Theoretically, the benefit of including as low a hormone dose as possible in estrogen-progestin preparations used for fertility control in women may result in a safer product.

4) Experimental Design

a) Patient Population:

i. Demography
This study included 87 healthy women attending the Bemfam Hospital Clinic in Uberaba, Brazil.

ii. Clinical Characteristics for Inclusion
- aged 35 years or less
- motivated to appear for monthly visits to the clinic

- proven fertility by previous pregnancies
- literate to fill in data charts

iii. Exclusion Criteria
- over age 45 years
- medical conditions contraindicating oral contraceptives

b) Procedure:

i. Dosage Schedule

Subjects were advised to take the tablets from the fifth day of the first cycle for a period of 21 days. The treatment was then interrupted for 7 days and recommenced with a new series of 21 tablets.

ii. Type of Experimental Controls

This was an open-label, noncomparative, single center study.

c) Safety Considerations

i. Clinical and Laboratory Studies

Careful general and gynecological examinations designed to rule out the existence of medical conditions that would contraindicate the use of oral contraceptives were performed. Monthly visits to the hospital clinic were required. Laboratory studies were not required.

ii. Adverse Event Recording

Subjects were issued cards on which they noted adverse events including breakthrough bleeding and spotting.

iii. Indications for Withdrawal of a Subject from the Study

No indications for withdrawal of subjects from study are mentioned. However, subjects were discontinued from

study for personal reasons and secondary effects (medical reasons).

d) Efficacy Considerations

Presumably, the primary efficacy variable was the pregnancy rate and the secondary efficacy variables were measures of cycle control.

5) Results of the Study

a) Author's Evaluation:

The author concludes that the study preparation had a high incidence of abnormal bleeding and that no pregnancies occurred.

b) Reviewer's Evaluation:

i. Demographics

Ages of subjects ranged from below 20 years (18.39%) to 35 years. None of the subjects were nulliparous. All had regular menstrual cycles.

ii. Adequacy of Sample Size

A total of 87 subjects completed a total of 673 cycles with 16 subjects completing 12 cycles. The sample size of this study is inadequate to yield meaningful data on efficacy or safety.

iii. Efficacy

No pregnancies occurred, but the number of subjects studied is too small to make a conclusion about efficacy. Intermenstrual bleeding (breakthrough bleeding and spotting) was a secondary efficacy variable.

Table 7
Incidence Rates of Intermenstrual Bleeding

Cycle Number	No. of Subjects Completing	No. of Subjects with Bleeding	(%) of Subjects with Bleeding
1	87	40	46.0
2	82	16	19.5
3	79	18	22.8
4	69	22	31.9
5	60	13	21.7
6	59	17	28.9
7	54	12	22.2
8	50	11	22.0
9	46	11	23.9
10	41	8	19.5
11	31	10	32.3
12	15	3	20.0

The incidence of intermenstrual bleeding was high in all cycles.

iv. Safety

Of the 87 subjects evaluated in the clinical trial, a total of 4 subjects (4.6%) discontinued the study because of secondary effects (medical reasons) and another 4 subjects because of abnormal bleeding. Adverse events occurring during the study are similar to what is expected with oral contraceptives: headache, dizziness, frigidity, nausea, nervousness, anorexia, and sleepiness.

Laboratory parameters were not studied.

6) Discussion

This old clinical report was also published in a Brazilian medical journal in 1974. It is a report of a subset of the data (from one of the study centers, Uberaba) that was published by Sartoretto and Recio. The results represent 20% of the total experience (numbers of subjects and cycles completed) from the three center, multicenter clinical trial.
While no pregnancies occurred in this study, the numbers of subjects studied and cycles completed are insufficient to warrant any definitive statement regarding efficacy or safety. The incidence of intermenstrual

bleeding in cycles 3 through 12, by my calculations (Table 7) is considerably higher in this study than that reported in the published multicenter study that included this very small clinical trial. This is because of the much higher incidence of spotting in this subset. Despite the high incidence of abnormal bleeding, only 4.59% of subjects discontinued for this reason, all within the first four cycles. Subjects were to take pills on a 21 days on and 7 days off regimen, but many of them restarted a new series of pills on day 5 of the cycle instead of as instructed. Adverse reactions reported were those commonly occurring in oral contraceptive users.

7) Conclusion

Micro-levlen has a high incidence of intermenstrual bleeding, but one which is acceptable for a product containing 20 micrograms of ethinyl estradiol.

6. Postmarketing Clinical Studies

No postmarketing clinical trials are required.

7. Labeling Review

8. Overall Evaluation and Conclusions

Alesse, an oral contraceptive containing the same ingredients in the same strength as Levlite, has been approved for marketing in the United States since March 27, 1997. No unexpected adverse events have been reported with this product nor has an unusually high incidence of known and expected adverse events been reported with the use of Alesse.

The drug product that is subject of this NDA has been marketed in Germany since April, 1996 under the trade name, Miranova. The amount of levonorgestrel and ethinyl estradiol in Micro-Levlen is exactly 2/3 that of Levlen, an oral contraceptive marketed in the United States since 1986. Safety, per se, therefore, is not a critical issue. Efficacy of this drug product, contains reduced amounts of hormones, is, of course, a major issue. A phase II ovulation inhibition study was done. Ovulation did not occur in 24 of the

subjects followed for three treatment cycles. Thus, reliable inhibition of ovulation was demonstrated. Two phase III clinical studies (a single center study in Germany and a multicenter study in the United States) demonstrated that Micro-Levlen is an effective oral contraceptive with an Pearl Index of 0.299 in the German study and 1.08 in the U.S. study. These two studies also showed a high incidence of intermenstrual bleeding associated with use of the drug. This bleeding was not associated with a decrease in efficacy or a high discontinuation rate, however, the pivotal German study and the supporting U.S. study were similar in design. However, the German study utilized a 21 days on, 7 days off dosage regimen while the U.S. study utilized a 28 day dosage regimen (21 active pills followed by 7 placebo pills). This is acceptable. The German study included 98.4% Caucasians and no blacks while the U.S. study included 82% Caucasians, 8% Hispanics, 6% blacks, and 3% Asian subjects. The mechanism of action of the study preparation (inhibition of ovulation) is such that one would not expect to find differences in efficacy between different ethnic groups. Mean age, height, and weight were similar in both studies, but subjects in the U.S. study had a broader distribution for weight and height. The draft labeling follows the "Labeling Guidance Text for Combination Oral Contraceptives" which was revised in August, 1994. With a few revisions (please see Labeling Review section) the draft labeling will be acceptable. The drug is safe and effective.

9. Recommendation

Approval of the application is recommended.

The sponsor should be requested to submit follow-up information, if it can be obtained, on the outcomes of all pregnancies.

/S/ 6/17/98

Ridgely C. Bennett, MD, MPH

NDA 20,860 Berlex
Levlite (Micro-levlen)

Medical Officer's Review of Safety Update

JUN 17 1998

Date Submitted: April 28, 1998
Date Received: April 29, 1998
Date Assigned: May 1, 1998
Review Completed: May 28, 1998

The reporting interval for this Safety Update is January 10, 1997 - September 1, 1997.

Additional data available are relatively few and all come from foreign sources. Four foreign clinical studies conducted by Berlex's parent company, Schering AG, were reporting interval of this Safety Update. One post marketing trial, also conducted by Schering AG, was the reporting interval.

The largest source of information from a clinical trial comes from Study 96045 which is double blind study in which 1023 subjects have been enrolled. Seven serious or potentially serious adverse events have been reported, none of which seem to be caused by an oral contraceptive. These events were a fracture of the ankle joint prior to treatment, gastroenteritis, salpingitis, pneumonia, tinnitus, appendicitis, and rectal bleeding.

The next largest source of information from a clinical trial comes from Study 96007 which was a comparative trial of three oral contraceptives in which 817 subjects were enrolled. Four serious or potentially serious adverse events were reported, none of which seem to be caused by an oral contraceptive. These events were all hospitalizations, and included hypoplasia of the right breast (known since puberty), appendectomy, unclear abdominal pain (subject recovered), and attempted suicide. Twenty-five subjects discontinued drug use for a variety of reasons; the number taking each active drug is not given;

Study 96038 is an double blind study in which 40 subjects have been enrolled. There is one report of a serious or potentially serious adverse event, erythema nodosum. The blind has not been broken.

No serious adverse events have been reported in Study 96050 which has 23 subjects enrolled.

This product has been marketed in Germany since April 1996 under the tradename MIRANOVA. This foreign marketing experience yields another source of information, Report number AV31, which was an uncontrolled post marketing surveillance observational trial done for marketing purposes by Schering AG. The Schering AG sales force asked gynecologists throughout Germany if they would be interested in participating in the study. A total of 2,461 gynecologists expressed an interest. Each

gynecologist was given a booklet (combination description of the study/Case Report Form) with report forms for six subjects. A total of 2,192 booklets were returned. Each subject came in to the gynecologist's office monthly for six visits at which time the gynecologist completed the report form. Subjects were asked if they experienced any adverse events. (Specific adverse events were not identified in the booklet.) If they answered "yes", they were asked which ones. A total of 13,085 subjects were enrolled.

Two serious adverse events were reported during this observational trial. The first was an occipital lobe infarction, tension headache, and impaired vision occurring in a 32 year old subject who recovered after discontinuation of the oral contraceptive. This patient also had thrombocytosis as a risk factor for a cerebrovascular accident. The second was an iliopelvic venous thrombosis occurring in a 15 year old subject that required surgery and who recovered with sequela after discontinuation of the oral contraceptive. No risk factors, other than oral contraceptive use were reported. There are no reports of warning letters sent to physicians or revisions of the labeling in Germany.

There was not an unusually high incidence of a less serious event in any of the trials during the reporting interval.

During the reporting period, marketing applications were submitted to Great Britain, Ireland, and Australia.

There are no epidemiological studies in progress with this oral contraceptive.

Literature searches did not yield any new safety information that would suggest revision of any contraindications, warnings, precautions, or adverse reactions in the draft labeling.

Alesse, an oral contraceptive containing the same ingredients in the same strengths as Levlite, has been approved for marketing in the United States since March 27, 1997. No unexpected adverse events have been reported with this product and an unusually high incidence of known and expected adverse events has not been reported with the use of Alesse.

Reviewer's Conclusion:

The Safety Update Report submitted April 28, 1998 confirms the safety profile reported in the original NDA submission. The safety profile of Levlite did not change during this safety update reporting interval.

Reviewer's Recommendation:

Approval of this application is recommended provided draft labeling is revised as suggested in the Medical Officer's NDA Review completed May 8, 1998.

/S/ 6/16/98

Ridgely C. Bennett, MD, M.P.H.

Concur - M Mann MD 6/17/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-860

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGICAL DRUG PRODTCS
HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-860 **CHEM.REVIEWEW #:** 3 **REVIEW DATE:** 6/18/1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL[1]	06/13/1997	06/13/1997	02/05/1998
Amendment[1]	10/31/1997	01/05/1997	02/05/1998
Amendment[1]	02/23/1997	02/30/1997	02/05/1998
Amendment[1]	03/04/1998	03/06/1998	03/15/1998
Amendment[2]	05/26/1998 (Fax)		05/27/1998
Correspondence[3]	06/17/1998 (Fax)		06/17/1998

[1] See Chemistry Review No. 1
[2] See Chemistry Review No. 2
[3] See Chemistry Review No. 3 (this review)

JUN 19 1998

NAME & ADDRESS OF APPLICANT:
Berlex Laboratories, Inc.
340 Changebridge Road
P.O.Box 1000
Montville, NJ 07045-1000

DRUG PRODUCT NAME

Proprietary: Micro-Levlen™ Tablets (new trade name, **Levlite** was proposed by the NDA applicant(amendment dated 12/23/97) and accepted by the agency(approved by the labeling and nomenclature committee on 1/1/98)

Nonproprietary/USAN: Levonorgestrel and Ethinyl Estradiol Tablets, USP

Code Name/#: SH D 593 A (active tablet)
SH D 593 P (inert tablet)

Chem.Type/Ther.Class: Oral Contraception

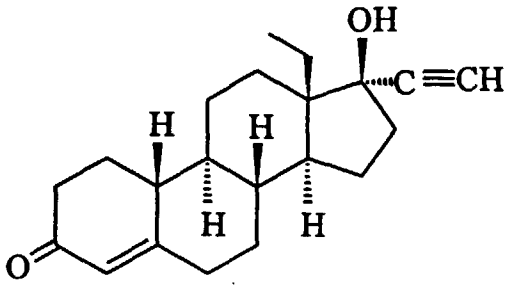
ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION:

DOSAGE FORM: Coated Tablet
STRENGTHS: Levonorgestrel: 0.100 mg
Ethinyl Estradiol: 0.020 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ✓ **Rx** ____ **OTC**

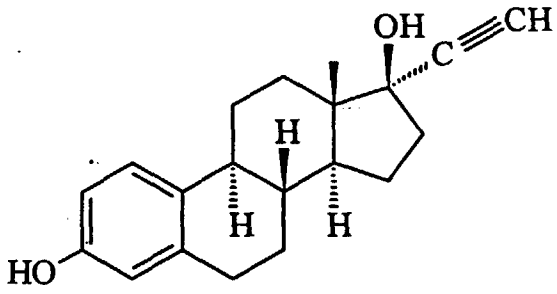
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

- **(-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.** (Levonorgesterl, USP)



Molecular Formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45

Levorotatory form of norgestrel; optically pure form with six asymmetric centers; corresponds to the stereochemistry of naturally occurring steroids



- **19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol** (Ethinyl estradiol, USP)

Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

This compound has five chiral centers; corresponds to the normal stereochemistry of naturally occurring steroids.

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND	CMC section	Berlex Laboratories	Adequate	3/7/97	N/A
DMF	Levonorgestrel USP drug substance	Schering AG Wedding	Adequate	4/21/98	N/A
DMF	Ethinyl Estradiol, USP drug substance	Schering AG Wedding Plant	Adequate	2/27/98	N/A
DMF	Manufacturing facilities.	Schering AG Wedding Site	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Manufacturing facilities.	Schering AG Wedding Site	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Opacode S-1-17711 Black		Adequate	4/21/98	N/A
DMF	Low density polyethylene		Adequate	3/06/98	N/A
DMF	Manufacturing Facilities	Schering AG Weimar Plant	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Blister packs		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Blister packaging, slidecasing and labeling	Berlex	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	pouching of slidecased blister packagers		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Polyethylene		The DMF is adequate	4/21/98	N/A

pe/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Mirrex rigid PVC film type 1025		The DMF remains adequate	3/06/98	N/A
DMF	Printed foil		The DMF remains adequate	9/8/95	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Facilities for Quality Controls	Schering AG Wedding Plant	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS:
Clinical Pharmacology

REMARKS/COMMENTS:

This correspondence (fax received from Berlex Laboratories dated 6/17/1998) was submitted in response to our Information Request letter dated May 11, 1998 and the teleconference with the firm dated 6/12/1998. The following responses were received from the firm:
(Queries no. 2, 7, 9, and 11 were described in details in chemistry reviews no. 1 and 2).

- Query No. 2.
  Regarding the expiration dating, the firm acknowledged that the expiration dating period for the tablets begins with the date of manufacturing (granulation).

- Query No. 7.
  With respect to the chromatograms, We reported in review no. 2 that the response for the above query is not satisfactory. However, after re-evaluated the firm's response (review no. 2), and considering that the content of the question does not have an impact on the approvability of the application, we do not have any concern regarding this query.

- Query no. 9.
  Regarding the dissolution specifications, Berlex accepted our revised dissolution specifications (Q= % at minutes).

- Query No. 11.
  Concerning the decomposition products specifications, the firm accepted our revise specifications with respect to the decomposition products (NTM % for individual known and unknown; NTM % for total known and unknown).

CONCLUSIONS & RECOMMENDATIONS:

Berlex Laboratories provided satisfactory responses to our information requests which were described in chemistry reviews no. 1 and 2 and during the teleconference between the firm and the agency on 6/12/1998. There are no outstanding issues relating to the chemistry, manufacturing and controls of the above application.
Approval

/S/ 6/19/1998

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

CC:
Orig. NDA 20-860
HFD-580/Division File
HFD-180/AAl-Hakim
HFD-580/CSO/MRhee/KSrinivasachar
R/D Init by: MJ Rhee
AA C:\Wordfiles\NDA\levlite\20860806.3aa

Khee

MAY 29 1998

DIVISION OF REPRODUCTIVE AND UROLOGICAL DRUG PRODTCS
HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-860 **CHEM.REVIEWEW #:** 2 **REVIEW DATE:** 5/27/1998 AA.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL[1]	06/13/1997	06/13/1997	02/05/1998
Amendment[1]	10/31/1997	01/05/1997	02/05/1998
Amendment[1]	02/23/1997	02/30/1997	02/05/1998
Amendment[1]	03/04/1998	03/06/1998	03/15/1998
Amendment[2]	**05/26/1998**		05/27/1998

[1] See Chemistry Review No. 1
[2] See Chemistry Review No. 2 (this amendment)

NAME & ADDRESS OF APPLICANT:

Berlex Laboratories, Inc.
340 Changebridge Road
P.O.Box 1000
Montville, NJ 07045-1000

DRUG PRODUCT NAME

Proprietary: Micro-Levlen™ Tablets (new trade name, **Levlite** was proposed by the NDA applicant(amendment dated 12/23/97) and accepted by the agency(approved by the labeling and nomenclature committee on 1/1/98)

Nonproprietary/USAN: Levonorgestrel and Ethinyl Estradiol Tablets, USP

Code Name/#: SH D 593 A (active tablet)
SH D 593 P (inert tablet)

Chem.Type/Ther.Class: Oral Contraception

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION:

DOSAGE FORM: Coated Tablet

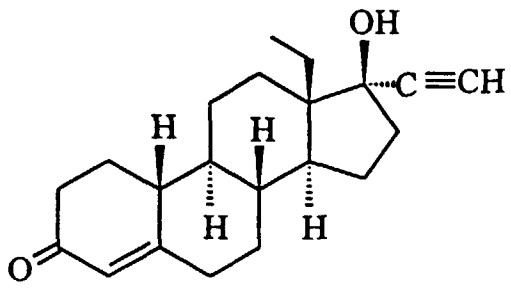
STRENGTHS: Levonorgestrel: 0.100 mg
Ethinyl Estradiol: 0.020 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: ✓ **Rx** ____ **OTC**

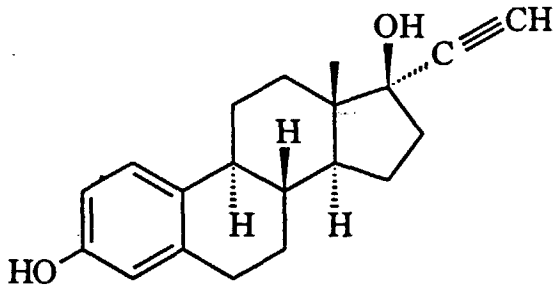
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

- **(-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.** (Levonorgesterl, USP)



Molecular Formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45

Levorotatory form of norgestrel; optically pure form with six asymmetric centers; corresponds to the stereochemistry of naturally occurring steroids



- **19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol** (Ethinyl estradiol, USP)

Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

This compound has five chiral centers; corresponds to the normal stereochemistry of naturally occurring steroids.

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND	CMC section	Berlex Laboratories	Adequate	3/7/97	N/A
DMF	Levonorgestrel USP drug substance	Schering AG Wedding	Adequate	4/21/98	N/A
DMF	Ethinyl Estradiol, USP drug substance	Schering AG Wedding Plant	Adequate	2/27/98	N/A
DMF	Manufacturing facilities.	Schering AG Wedding Site	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Manufacturing facilities.	Schering AG Wedding Site	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Opacode S-1-17711 Black		Adequate	4/21/98	N/A
DMF	Low density polyethylene		Adequate	3/06/98	N/A
DMF	Manufacturing Facilities	Schering AG Weimar Plant	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Blister packs		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Blister packaging, slidecasing and labeling	Berlex	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	pouching of slidecased blister packagers		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Polyethylene		The DMF is adequate	4/21/98	N/A

›e/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Mirrex rigid PVC film type 1025		The DMF remains adequate	3/06/98	N/A
DMF	Printed foil		The DMF remains adequate	9/8/95	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Facilities for Quality Controls	Schering AG Wedding Plant	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS:
Clinical Pharmacology

REMARKS/COMMENTS:
This amendment was submitted in response to our Information Request letter dated May 11, 1998.

CONCLUSIONS & RECOMMENDATIONS:
Most of the responses were satisfactory. However, the following items need to be communicated to the firm.

- Query No. 2. The 16 months holding time for the bulk tablets are part of the 24 months expiry dating recommended for the drug product.
- Query No. 7. The firm did not explain or justify why it can not provide the integration peak area of the decomposition products.
- Query No. 11. The total decomposition product limit should be NMT %, as we recommended compared to NMT % reported by the firm. This limit supported by the decomposition data provided by the firm (tables 13-15).

/S/
5/29/98
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 5/29/98
Moo Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

cc:
Orig. NDA 20-860
HFD-580/Division File
HFD-180/AAl-Hakim
HFD-580/CSO/MRhee/KSrinivasachar
R/D Init by: MJ Rhee
AA C:\Wordfiles\NDA\levlite\20860805.2aa

ORIGINAL

DIVISION OF REPRODUCTIVE AND UROLOGICAL DRUG PRODTCS

HFD-580

Review of Chemistry, Manufacturing, and Controls

APR 23 1998

NDA #: 20-860 **CHEM.REVIEWEW #:** 1 **REVIEW DATE:** 3/3/1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	06/13/1997	06/13/1997	02/05/1998
Amendment	10/31/1997	11/05/1997	02/05/1998
Amendment	12/23/1997	12/30/1997	02/05/1998
Amendment	03/04/1998	03/06/1998	03/15/1998

NAME & ADDRESS OF APPLICANT:

Berlex Laboratories, Inc.
340 Changebridge Road
P.O.Box 1000
Montville, NJ 07045-1000

DRUG PRODUCT NAME

Proprietary: Micro-Levlen™ Tablets (new trade name, **Levlite** was proposed by the NDA applicant(amendment dated 12/23/97) and accepted by the agency(approved by the labeling and nomenclature committee on 1/1/98)

Nonproprietary/USAN: Levonorgestrel and Ethinyl Estradiol Tablets, USP

Code Name/#: SH D 593 A (active tablet)
SH D 593 P (inert tablet)

Chem.Type/Ther.Class: Oral Contraception

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION:

DOSAGE FORM: Coated Tablet

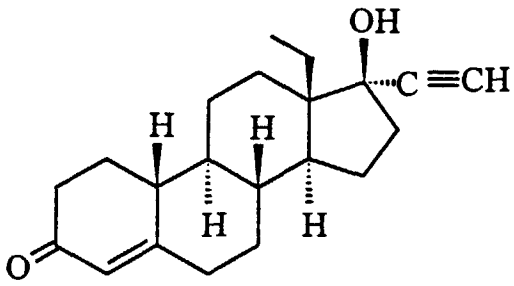
STRENGTHS: Levonorgestrel: 0.100 mg
Ethinyl Estradiol: 0.020 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: ✓ **Rx** ____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

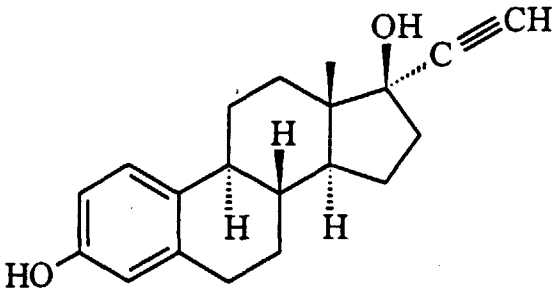
- **(-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.** (Levonorgesterl, USP)



Molecular Formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45

Levorotatory form of norgestrel; optically pure form with six asymmetric centers; corresponds to the stereochemistry of naturally occurring steroids

- **19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol** (Ethinyl estradiol, USP)



Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

This compound has five chiral centers; corresponds to the normal stereochemistry of naturally occurring steroids.

Comment: Please note that ethinyl estradiol has five chiral centers and not six as reported in the NDA (volume 1.2, P. 0006).

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND	CMC section	Berlex Laboratories	Adequate	3/7/97	
DMF	Levonorgestrel USP drug substance	Schering AG Wedding	Adequate	4/21/98	N/A
DMF	Ethinyl Estradiol, USP drug substance	Schering AG Wedding Plant	Adequate	2/27/98	N/A
DMF	Manufacturing facilities.	Schering AG Wedding Site	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Manufacturing facilities.	Schering AG Wedding Site	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Opacode S-1-17711 Black		Adequate	4/21/98	N/A
DMF	Low density polyethylene		Adequate	3/06/98	N/A
DMF	Manufacturing Facilities	Schering AG Weimar Plant	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Blister packs		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Blister packaging, slidecasing and labeling	Berlex	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	pouching of slidecased blister packagers		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Polyethylene		The DMF is adequate	4/21/98	N/A

e/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Mirrex rigid PVC film type 1025		The DMF remains adequate	3/06/98	N/A
DMF	Printed foil		The DMF remains adequate	9/8/95	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Facilities for Quality Controls	Schering AG Wedding Plant	CGMP as per 21 CFR(210 & 211)	N/A	N/A
DMF	Packaging Facility		CGMP as per 21 CFR(210 & 211)	N/A	N/A

RELATED DOCUMENTS (if applicable): None

CONSULTS: Statistics

REMARKS/COMMENTS:

- The Levlite™ Tablets NDA application is a lower dosage form of the currently marketed product, Levlen Tablets. The dosage form for the marketed Levlen tablets contains 0.150 mg/tablet of Levonorgestrel and 0.030 mg/tablet of Ethinyl Estradiol compared to the current application which contains 0.100 mg/tablet and 0.020 of Levonorgestrel and Ethinyl Estradiol respectively.

- Throughout the NDA, the name Micro-Levlen™ Tablets was used, however, the firm has submitted an amendment (amendment dated 12/23/97) proposing a new trade name, **Levlite** which was reviewed and accepted by the Labeling and Nomenclature Committee (letter signed by D. Boring and dated 3/1/98).

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from CMC point of view, however, the NDA applicant has to provide additional information regarding some issues/items related to the drug product. Although we listed many deficiencies and queries in the chemistry deficiencies and comments section, our major concern is the drug product specifications which seem to have wider ranges than the actual results obtained from the stability studies.
An information request letter should be sent to the firm detailing the deficiencies/queries and requesting appropriate responses.

/S/ 4/23/98
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/ 4/23/98
Moo Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

cc:
Orig. NDA 20-860
HFD-580/Division File
HFD-180/AAl-Hakim
HFD-580/CSO/MRhee/KSrinivasachar
R/D Init by: MJ Rhee 4/23/98
filename: C:\MSWord\NDA\20860803.1aa

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-860

PHARMACOLOGY REVIEW(S)

KLSH

NDA 20-860

August 6, 1997

Micro-Levlen
Berlex Labs
Montville, NJ

AUG - 6 1997

Pharmacology Review of the NDA

Drug: Micro-Levlen (levonorgestrel 0.100 mg and ethinyl estradiol 0,020 mg tablets.

This NDA is for a lower dose of an approved oral contraceptive. There are no pharm/tox issues.

Recommendation: The NDA is approvable for pharm/tox. There are no labeling issues.

/S/

Alex Jordan, PhD 8/6

NDA 20-860
HFD-580