CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-860

ADMINISTRATIVE DOCUMENTS

Group Leader Memorandum JUN 17 1998

NDA:	**20-860**
Drug and Indication:	**Levlite ™ (levonorgestrel 0.10 mg and ethinyl estradiol 0.02 mg combined as one tablet)**
Dose:	**one tablet daily for 21 days followed by 7 days of placebo tablets daily**
Applicant:	**Berlex Laboratories, Inc.**
Original Submission Received:	**June 13, 1997**
Major Amendment Received:	**December 8, 1997**
Safety Update Received:	**April 29, 1998**
Date of Memorandum:	**June 16, 1998**

Background

Berlex Laboratories has an approved oral contraceptive product known as Levlen® (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg). This product has been marketed since 1986. They have now completed studies with a lower dose oral contraceptive which maintains the same ratio of levonorgestrel to ethinyl estradiol, now given at lower doses of 0.10 mg and 0.02 mg respectively. This product has been marketed under the trade name Miranova® in Germany since April of 1996, and is now proposed as a NDA in the United States, under the trade name Levlite™. The desire to use the lowest effective dose of hormonal contraceptives is obvious in an attempt to decrease the potential for adverse events in theory, however this actual claim of enhanced safety was not formally investigated.

FDA guidelines for the study of oral contraceptives which contain reduced amounts of estrogen and progestin, but which maintain the same ratio of estrogen and progestin, require that 600 subjects complete 6 treatment cycles, and that be demonstrated. These were the goals of this NDA.

Results of Studies

Three studies provided the support for this NDA. These are summarized briefly below.

1. "Uncontrolled Clinical Study on the Inhibition of Ovulation by an Oral Contraceptive Containing 0.02 mg of Ethinyl Estradiol and 0.1 mg Levonorgestrel During Three Treatment Cycles"

Efficacy Summary

This study enrolled 25 healthy female volunteers with the objective of confirming that ovulation was inhibited when study drug was taken. Twenty-four volunteers successfully completed the three month study. All volunteers ovulated during the pre-treatment cycle. No ovulation occurred during the three treatment cycles for any volunteer, and no pregnancies occurred. All but one volunteer resumed ovulation during the post-treatment observation cycle. The degree of suppression of ovarian activity was most pronounced during the first treatment cycle and diminished somewhat over the second and third cycles, but this is a known effect of oral contraceptive therapy. This study effectively demonstrated that the study drug (levonorgestrel 0.10 mg plus ethinyl estradiol 0.02 mg) prevented ovulation for three months.

Safety Summary

No deaths or serious adverse events occurred in this study. Breakthrough bleeding or spotting occurred in about 50% of the subjects, but no one discontinued the study due to this. One volunteer was withdrawn during the third treatment cycle due the development of four ovarian cysts which were possibly associated with the study drug.

2. "Multicenter, Non-Controlled, Clinical Study of the Contraceptive Efficacy, Cycle Control, and Tolerance of MICRO 20 in 820 Women over 6 Treatment Cycles"

Efficacy Summary

This study enrolled 950 healthy women, but 120 of these subjects received no study medication. Of the remaining 820 subjects, 211 were "starter" (i.e. newly starting oral contraceptive therapy) and 594 were "switchers" (i.e. women who switched from an earlier contraceptive therapy). Thus, despite an attempt to achieve an equal balance between de novo users and "switchers," this study enrolled approximately 75% switchers. A total of 680 subjects (83% of those who received any study medication) completed all six treatment cycles. Two pregnancies occurred during the trial: one of the pregnancies resulted from noncompliance with study drug while the second was a method failure. Follow-up regarding the outcome of these two pregnancies is unknown. The calculated Pearl Index was 0.299, which is acceptable.

Safety Summary

No deaths were reported, but two subjects reported serious adverse events: one subject had nephrolithiasis during the second treatment cycle and required lithotripsy. A second subject was diagnosed with malignant melanoma after the first cycle of therapy and was withdrawn from the study. Again, intermenstrual bleeding was common, with an incidence of about 30% in the first cycle, dropping to about 12% during cycle 6.

3. "An Open-Label, Multicenter Study to Evaluate the Efficacy of a Monphasic Oral Contraceptive Preparation Containing Levonorgestrel 100 ug and Ethinyl Estradiol 20 ug"

Efficacy Summary

This study enrolled 770 subjects, of whom 755 took study drug and were therefore evaluable for efficacy. Of these 755, 44% were "starters" and 56% were "switchers," representing a fairly balanced patient population. A total of 558 subjects (74% of those who received any study medication) completed all six cycles of treatment. Five pregnancies occurred during the trial. Two of these 5 pregnancies were felt to reflect noncompliance: one patient missed three consecutive days of therapy and one patient missed a week of therapy, had withdrawal bleeding, and then incorrectly resumed therapy with placebo tablets. Three pregnancies, however, were deemed method failures: two occurred in compliant patients with no obvious cause for failure, and the third occurred in a patient who was compliant, but had taken nitrofurantoin concomitantly. The outcome of the five pregnancies included: healthy baby (n=2), unknown outcome (n=2), and induced abortion (n=1). The calculated Pearl Index for this trial was 1.08, with three method failures in 3612 valid cycles. This study confirmed the efficacy of this combination oral contraceptive.

Safety Summary

No deaths were reported, but four patients had a total of five serious adverse events. The first subject had a history of kidney stones due to a congenital stenosis, and developed a kidney stone requiring lithotripsy. The second subject developed cholecystitis and required surgery for this. The third subject experienced vaginal and abdominal pain which was fairly severe, and had a degenerating uterine fibroids diagnosed laparoscopically. She was treated with Depot Lupron, but continued to be symptomatic and had an exploratory laparatomy which revealed a rectus abdominus muscle hematoma with an associated hemoperitoneum as a complication of her original surgery. The final subject returned for her final visit with a new scar in the right upper abdominal quadrant which appeared to have resulted from a cholecystectomy, but the patient refused to give any details. The incidence of intermenstrual bleeding in this trial was again relatively high (37% in the first cycle, dropping to about 20% by the end of six cycles).

Conclusions:

There is adequate data to support the efficacy of this low-dosage estrogen-progestin combination oral contraceptive drug product. Levlite™ was well-tolerated with the exception of a relatively high incidence of intermenstrual bleeding. It is notable that despite a relatively high incidence of intermenstrual bleeding (average of about 30-40% starting therapy and still 10-20% after six cycles), most patients (83% in one

pivotal study and 74% in the second study) remained on drug for a full six cycles. Serious adverse events were rare and did not appear to be a direct consequence of taking Levlite™ the drug product. Although the margin of safety of this low dose product is theoretically better than that of higher dose products, this was not demonstrated in any clinical trial and should not be a labeling claim. Finally, the sponsor should be encouraged to obtain information on the outcome of all pregnancies.

This NDA review supports the approval of Levlite™ for prevention of pregnancy. The labeling is acceptable with the exception of minor changes noted in the medical officer review by Ridgely Bennett, M.D.

/S/ 6/16/98

Marianne Mann, M.D.
Deputy Director, HFD-580

cc:
NDA 20-860
HFD-580/Rarick/Bennett/Mann

NDA 20-860
Levlite™
Berlex Laboratories Inc.

Division Directors Memo

This application will be signed in the Division, therefore a Division Directors Memo is not required.

NDA 20-860
Levlite (levonorgestrel and ethinyl estradiol) Tablets
Berlex Laboratories

Environmental Assessment

An environmental assessment is ~~not required at~~ per the revised regulation published in the Federal Register on July 29, 1997.

categorically excluded
MMiller 7/7/98

NDA 20-860
Levlite™
Berlex Laboratories Inc.

Microbiology Review

A Microbiology Review is not required for this application.

NDA 20-860
Levlite™
Berlex Laboratories Inc.

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee.

NDA 20-860
Levlite™
Berlex Laboratories Inc.

Federal Register Notice

This application was not the subject of a Federal Register Notice.

NDA 20-860
Levlite™
Berlex Laboratories Inc.

Advertising Materials

Advertising Materials have not yet been submitted for review for this application.

14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to this New Drug Application for LEVLITE™ Tablets [levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets, USP], NDA 20-860.

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel, Intellectual Property
US Representative of Schering AG

July 2, 1998
Date

16. DEBARMENT CERTIFICATION

CERTIFICATION UNDER SECTION 306(k)(1) OF THE FD & C ACT

This is to certify that neither Berlex Laboratories, Inc. ("Berlex") nor any person employed by Berlex in connection with this New Drug Application for LEVLITE™ [Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP] has been debarred under Section 306(a) or (b) of the Federal Food Drug and Cosmetic Act. and that Berlex will not employ any debarred person in connection with NDA 20-860 for LEVLITE™.

BERLEX LABORATORIES, INC.

Geri A. Besta
Manager, Regulatory Submissions
and Information

July 9, 1998
Date

GAB\ debarmt.050

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-760 **SUPPL #**_____

Trade Name: Levlite **Generic Name:** levonorgestrel 0.100mg + Ethinyle Estradiol 0.020mg

Applicant Name: Berlex **HFD #** 580

Approval Date If Known: 7/13/98

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. **An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.**

   a) **Is it an original NDA?**

   YES/ ✓ **/ NO /__/**

   b) **Is it an effectiveness supplement?**

   YES /__/ NO / ✓ **/**

   If yes, what type? (SE1, SE2, etc.) _____

   c) **Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")**

   YES / ✓ **/ NO /__/**

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

   d) **Did the applicant request exclusivity?**

YES /✓/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. **Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)**

   YES /__/ NO /✓/

   If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. **Is this drug product or indication a DESI upgrade?**

   YES /__/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. **Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. **Combination product.**

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-668 Nordette 20-693 Alesse

NDA# _____ _____

NDA# _____ _____
19-192 Triphasil 21 pk

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. **Does the application contain reports of clinical investigations?**
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. **A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.**

   (a) **In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?**

   YES /✓/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   _____

   (b) **Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?**

   YES /✓/ NO /___/

(1) **If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.**

YES /___/ NO /✓/

If yes, explain:

(2) **If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?**

YES /___/ NO /✓/

If yes, explain:

(c) **If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:** 12-351 & 311-014

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. **In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.**

a) **For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")**

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) **For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?**

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

(c) **If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):**

AL-31 _____

311-01A _____

4. **To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.**

a) **For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?**

Investigation #1

IND # _____ YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /✓/ NO /___/ Explain: _____

b) **For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?**

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) **Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)**

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Signature:

Date: 5/6/98

Title: Project Manager

Signature of Office/Division Director

Signature: /S/

Date: 7/6/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-760 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 580 Trade and generic names/dosage form: Levlite (levonorgestrel & Ethinyl estradiol) Tablets Action: AP AE NA

Applicant Berlex Therapeutic Class 5

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate __

Proposed indication in this application Contraception

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from The medical officer (e.g., medical review, medical officer, team leader)

/S/
Signature of Preparer and Title

3/17/98
Date

Orig NDA/BLA # 20-760
HFD-580 Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Kish

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date October 21, 1997 /S/

From Lisa D. Rarick, M.D. 10/24/97
Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject Identification of Protocols for Inspection
NDA: 20-860
Sponsor: Berlex laboratories
Drug Name: Micro-Levlen (levonorgestrel and ethinyl estradiol)
Dosage Form: Tablets

To Dr. Gurston Turner, CIB Reviewer
Clinical Investigations Branch, HFD-344

We have identified the protocols listed below as being important to the approval of this application.

Protocol # Report AL31

As Discussed with you, the sites identified in and around the city of Frankfurt will be acceptable for auditing.

The contact person at the sponsor's site is Ms. Nancy Velez, Manager, Drug Regulatory Affairs, at (973) 276-2305.

The reviewing Medical Officer (MO) for this application is Dr. Ridgely Bennett.

The Project Manager/CSO is Ms. Christina Kish at 301-827-4260.

The User Fee Goal Date is June 13, 1998.

The Division Action Goal Date is May 13, 1998.

cc:
NDA 20-860
HFD-580
HFD-580/RBennett/Kish
HFD-344/GTurner/CCourier/MTarosky

MEMORANDUM

JUL 1 19

Date: June 31, 1998
To: NDA 20-860
From: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader
Subject: Firm's Commitments

7/1/98

After a telephone conference on June 12, 1998, the firm submitted an amendment dated June 17, 1998, reflecting their commitment to:

Should there be any difficulties in meeting these requirements, the firm will notify the Division and submit a prior approval supplement for the changes with justification.

cc: NDA 20-860
HFD-580 Division File
HFD-580/MRhee/Ckish
HFD-180/AAlhakim

Memorandum

To: Division Document Room
From: Christina Kish
Date: February 11, 1998

Re: NDA 20-860

Tanya:

The Chemist reviewing NDA 20-860 has been reassigned. The new Reviewing Chemist for NDA 20-860 is Dr. Ali Al-Hakim.

Please make this change to the COMIS system.

/S/

Christina Kish 2/11/98

B44

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention : Dan Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Reproductive and Urologic Drug Products. HFD-580
Attention: K. Srinivasachar, Ph.D. Phone: 827-4248

Date: 22 July 1997

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: MICRO-LEVLEN NDA #: 20-860

Established name, including dosage form: levonorgestrel and ethinyl estradiol tablets, USP

Other trademarks by the same firm for companion products: LEVLEN and TRI-LEVLEN 21 and 28

Indications for Use (may be a summary if proposed statement is lengthy): low dose oral contraceptive

Initial comments from the submitter (concerns, observations, etc.)
This is a proportionate dose reduced variant of the currently marketed product, LEVLEN. The strength of the MICRO-LEVLEN tablet is 0.100 mg levonorgestrel and 0.020 mg ethinyl estradiol whereas LEVLEN is 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol. A concern was raised by the Div. Deputy Dir. about the prefix MICRO-- this could imply that the product is only a tiny fraction of the currently marketed product in strength (in reality the strength is only reduced by a third).

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 1993

Consult 938

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention : Dan Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Reproductive and Urologic Drug Products. HFD-580
Attention: K. Srinivasachar, Ph.D. Phone: 827-4248

Date: 8 Jan.1998

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: LEVLITE NDA #: 20-860

Established name, including dosage form: levonorgestrel and ethinyl estradiol tablets, USP

Other trademarks by the same firm for companion products: LEVLEN and TRI-LEVLEN 21 and 28

Indications for Use (may be a summary if proposed statement is lengthy): low dose oral contraceptive

Initial comments from the submitter (concerns, observations, etc.)
This is a proportionate dose reduced variant of the currently marketed product, LEVLEN. The original tradename proposed by the firm, MICRO-LEVLEN, was found unacceptable by the L & N Committee and the Division. They have now proposed the new tradename, LEVLITE

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 1993

CONSULT #938

LNC TRADEMARK REVIEW

TO: HFD-580

ATTN: K. Srinivasachar, Ph.D.

PROPOSED NAME(S): LEVLITE

ESTABLISHED NAME: levonorgestrel and ethinyl estradiol tablets

COMMITTEE'S COMMENTS:

A review one name which sound like or look like the proposed name: Prevalite (cholestyramine for oral suspension). Due to differences in dosage forms, the Committee does not believe there is a significant potential for confusion with these two names.

The Committee has no reason to find the proposed name unacceptable.

/S/ 3/1/98

Dan Boring, Ph.D., Chairman
Labeling and Nomenclature Committee

Consult #844 (HFD-580)

MICRO-LEVLEN levonorgestrel and ethinyl estradiol tablets

LEVLEN is already in use for other products in this line, therefore it was not evaluated by the Committee. However the following look-alike/sound-alike conflicts were noted with MICRO-LEVLEN: MICRONEPHRIN, MICRONASE, and MICROLIPID. Although "MICRO" has appeared in proprietary names it is not recommended by the Committee due to the imprecise nature of the term.

The Committee finds the proposed proprietary name unacceptable.

/S/ 9/9/97, Chair
CDER Labeling and Nomenclature Committee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-680

JUN 26 1998

Berlex Laboratories, Inc.
Attention: Ms. Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your pending June 13, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levlite (levonorgestrel and ethinyl estradiol) Tablets.

We have completed our review of the Clinical section of your submission and have the following Labeling comments:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely.

/S/

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE
1998 Trussell Table

Kish

NDA 20-860

JUN 9 1998

Berlex Laboratories, Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

We acknowledge receipt on May 28, 1998, of your May 26, 1998, amendment to your new drug application (NDA) Levlite (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets.

We consider this a major amendment received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 13, 1998.

If you have any questions, please contact Ms. Christina Kish Project Manager, at (301) 827-4260.

Sincerely yours,

/S/

Marianne Mann, M.D.
Deputy Director
Division of Reproductive
and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-580
HFD-580/LPauls/CKish
DISTRICT OFFICE
HFD-580/CKish/5.27.98/n20860ex
concurrence:LPauls 5.28.98

REVIEW EXTENSION

Kish

NDA 20-860

JUN 8 1998

Berlex Laboratories, Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your pending June 13, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levlite (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets.

We have completed our review of the Clinical Pharmacology section of your submission and have identified the following comments and information requests:

1. Your proposed dissolution release specifications are not justified by the dissolution data presented in the application. Please revise the release specification for levonorgestrel and ethinyl estradiol to Q '% at minutes.

2. The analytical methods used for the estimation of ethinyl estradiol and levonorgestrel concentrations are less sensitive than currently available assays.

3. The section, subsection should be modified as detailed in the attachment entitled "Labeling Comments".

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments have been reviewed only to the level of the discipline team leader. They do not reflect division director input or concurrence and should not be construed to do so. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle, we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

If you have any questions, contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 6/3/98

Lisa Rarick, M.D
Director
Division of Reproductive
and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/ADorantes/Shaidar
HFD-580/CKish/5.27.98/n20860bph
concurrence: SHaidar 6.2.98/ADorantes 6.2.98/LRarick 6.3.98

INFORMATION REQUEST (IR)

KIS/

MAY 1 1 1998

NDA 20-860

Berlex Laboratories Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your pending June 13, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levlite (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets.

To complete our review of the chemistry manufacturing and control section of your submission, we request the following information:

1. Please note that ethinyl estradiol has five chiral centers, not six as reported in your NDA.

2. Information on the holding time and acceptance testing for the bulk drug product tablets received from Schering AG should be provided. The type of testing (if any) performed on the stored tablets should be indicated.

3. All necessary information relating to the safety of or citation of the appropriate references (should be submitted.

4. Information regarding any major differences in equipment, manufacturing process and controls of the product between the Wedding and Weimar facilities should be submitted.

5. Information regarding the reprocessing operation (section 3.2.5.5) in the drug product manufacturing process should be submitted, if it exists.

6. Information on the temperature of the column for testing Appearance, Assay and Content Uniformity should be provided.

7. The following information regarding the decomposition method should be provided:

   a. integration data (area under the peak) for individual decomposition products;

b. identification of the two degradation products, shown as additional peaks at 18 and 21 minutes (Figure 5), if these products are consistent unknown degradation products and they exceed %; and

c. clarification regarding why decomposition product Δ6-ethinyl estradiol is not being monitored during stability studies.

8. A microbial test and specifications should be included in the analytical testing of the drug product.

9. Dissolution specifications should be established with available dissolution profiles from production batches and submitted for review.

10. There are significant differences in the degradation products profile between pilot and production scale batches with respect to 6-α-hydroxy ethinyl estradiol. The production scale batches have a higher content of this degradation product. Therefore, a 24 month expiry date will be recommended rather than the 36 months proposed.

11. Specifications for degradation products should be revised as follows:

a. no more than % for individual known and unknown decomposition products; and

b. no more than % for total known and unknown decomposition products.

12. A justification for the deletion of the microbial contamination test from the specifications for production scale batches should be submitted.

13. An explanation regarding why the decomposition method did not account for the decomposition product Δ6-ethinyl estradiol should be submitted. The method should also provide the percentage ratio data (area percent) for all detectable decomposition products.

Additionally, although the Clinical Pharmacology review has not been completed, we have the following comments and questions:

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

2. The dissolution data submitted do not justify the proposed dissolution specifications of Q % at minutes; a revised release specification of Q % at minutes for levonorgestrel and ethinyl estradiol should be submitted.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

/S/ 5/7/98

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/MRhee/ADorantes/SHaidar
HFD-180/AAlHakim
HFD-580/CKish/4.30.98/n20860.ir3
concurrence:AAlHakim 5.4.98/MRhee 5.4.98/SHaidar 5.4.98/ADorantes 5.5.98

INFORMATION REQUEST (IR)

KJSh

MAR 12 1998

NDA 20-860

Berlex Laboratories Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your pending June 13, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levlite (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets.

To complete our review of the statistical section of your submission, we request the following information:

1. Please clarify which datasets and variables were used to calculate the pregnancy rates of 0.158 for the German study and 0.543 for the US study.

2. For both studies please provide electronic files, if possible in SAS or ASCII, containing the following variables:

   a. subject ID;
   b. site ID;
   c. study ID (e.g., German or US);
   d. treatment group (e.g., new user/switcher);
   e. date on which the first tablet is taken;
   f. did the subject become pregnant (1=pregnant/0=not pregnant), if she did then provide:

      1. the cycle in which conception occurred;
      2. whether the subject use another type of contraceptive method;
      3. if the subject used another type of contraceptive method; in which cycle was the alternative contraceptive used;
      4. the date the pregnancy was diagnosed;
      5. the outcome of the pregnancy; and
      6. the days from the first tablet taken to the cycle of conception.

   g. the date on which the last tablet was taken;
   h. the days from the first tablet taken to the last tablet taken;
   I. the date of discontinuation from the study;
   j. the reason for discontinuation from the study; and
   k. the days from the first tablet taken to the date of discontinuation.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

/S/

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/LKammerman
HFD-715/MNg
HFD-580/CKish/3.4.98/n20860.ir2
concurrence:LKammerman 3.9.98/MNg 3.9.98/LRarick 3.9.98

INFORMATION REQUEST (IR)

Kish

NDA 20-860

OCT 14 1997

Berlex Laboratories Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your pending June 13, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Micro-Levlen (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets.

The Labeling and Nomenclature Committee has completed their review of your proposed tradename and has found it unacceptable for the following reasons:

Please propose an alternate tradename so that it can be forwarded to the committee for review.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

/S/ 10/14/97

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/MRhee/KSrinivasachar/HJolson
HFD-580/CKish/10.3.97/n20860.gc
concurrence:LPauls 10.7.97/KSrinivasachar 10.7.97/MRhee 10.7.97

GENERAL CORRESPONDENCE (GC)

Kish

NDA 20-860

SEP 15 1997

Berlex Laboratories Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your pending June 13, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Micro-Levlen (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets.

To complete our review of the Clinical, Chemistry Manufacturing and Controls, and Human Pharmacokinetics and Bioavailability sections of your submission, we request the following information:

Clinical

Please indicate the status of your U.S. clinical study report, including a proposed time-line for submission of the study report.

Chemistry

The final rule (FR29JY97-16) amending the environmental assessment regulation was published in the Federal Register July 29, 1997. This rule affects all applications still pending on August 28, 1997. You may, if appropriate, submit an amendment to your application claiming categorical exclusion in accordance with 25.31(b) of the final rule and withdrawing your environmental assessment.

Human Pharmacokinetics and Bioavailability

1. The subsection of the section of your proposed labeling should be reformatted according to the internal Division guidelines (see enclosed format).

2. Please submit a summary of the human PK/bioavailability section, individual study report summaries and the revised package insert on disk, if possible in MS Word, version 7.

3. Raw data of individual studies should be submitted on disk, preferably in Excel, version 7.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

/S/ 9-15-97

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE
Internal Division Labeling Guidance

Orig. NDA
HFD-580
HFD-580/RBennett/KSrinivasachar/SHaidar
HFD-580/CKish/8.21.97/n20860.ir
concurrence:LPauls 8.28.97/RBennett 8.29.97/KSrinivasachar 9.3.97/SHaidar 9.3.97/GBarnette 9.11.97

INFORMATION REQUEST (IR)

NDA 20-860

JUN 23 1997

Berlex Laboratories, Inc.
Attention: Ms. Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Micro-Levlen (levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg) Tablets
Therapeutic Classification:	Standard
Date of Application:	June 13, 1997
Date of Receipt:	June 13, 1997
Our Reference Number:	20-860

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 12, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Christina Kish, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

/S/

for Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA 20-860
HFD-580
HFD-580/HJolson/LRarick/MRhee/AJordan
DISTRICT OFFICE
HFD-580/CKish/6.17.97/n20860.ac
concurrence:

ACKNOWLEDGEMENT (AC)

Teleconference Meeting Minutes

Date: June 12, 1998 **Time:** 2:00 PM - 2:30 PM **Location:** Parklawn C/R 17B-43

NDA: 20-860 **Drug Name:** Levlite (levonorgestrel and ethinyl estradiol) Tablets

External Participant: Berlex Laboratories

Type of Meeting: Chemistry discussion

Meeting Chair: Moo-Jhong Rhee, Ph.D.

External Participant Lead: Nancy Velez

Meeting Recorder: Christina Kish

FDA Attendees:
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ali Al-Hakim, Ph.D. - Chemistry Reviewer (DNDC II) @ Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)
Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:
June Bray - Director of Drug Regulatory Affairs
Nancy Velez - Manager, Drug Regulatory Affairs
Monika Wolff, Ph.D. - Section Head, Technical Services
Paul Van der Berg, Ph.D. - Director of Quality Affairs
Ronald Wohl, Ph.D. - Director of Strategic Chemistry Manufacturing and Controls

Meeting Objectives:
The sponsor has submitted a proposal for dissolution specifications. In an internal meeting it was decided that the proposed specifications are unacceptable and must be tightened. This teleconference is to discuss this decision with the sponsor.

Discussion Points:

- Expiration Date
  - the sponsor has stability data to support 18 months of stability, of the bulk tablets
  - the sponsor should submit information regarding the expected time bulk tablets are stored and under what conditions these tablets are stored
  - the proposed expiration date (24-months) should include the storage time of the bulk tablets
  - the sponsor believes the shelf-life to commence at the time of tablet compression but will confirm this

- Degradation Specifications
  - the specifications for degradation products should be limited to % for individual known and unknown products
  - the total known and unknown degradation products should not exceed %
  - the Divisions recommended degradation product specifications are supported by the sponsors submitted stability data
  - should later stability data indicate that these specification should be changed, a prior approval supplement can be submitted to change them
- Dissolution Specifications
  - the data submitted for the original manufacturing site suggest that a specification of Q % at minutes is warranted
  - initial data from the new manufacturing plant indicate that there may be an issue of subpotency at that manufacturing site which should be investigated
  - should later dissolution data show that this specification should be changed, a prior approval supplement can be submitted to change them
- Sponsor Issues
  - the sponsor is interested in completing this review cycle quickly
  - there is concern that should the specifications be too stringent, a product recall will be required
  - a potential reason that the data from the second manufacturing plant appear to show a subpotent product is because the product assay and the dissolution assay are two different assays

Decisions Reached:

- the sponsor should submit an amendment with the following information:

- the sponsor will fax theses commitments to the Division within 24 hours
- if, after further stability data is obtained, specifications must be revised, the sponsor will notify the Division as soon as possible and submit a prior approval supplement

Unresolved Issues: none

Action Items: see decisions reached

/S/

Minutes Preparer 6/26/98

/S/ 6/26/98

Concurrence, Chair

cc:
Orig. IND
HFD-580
MEETING ATTENDEES
HFD-580/JMercier/LPauls
HFD-580/CKish/6.17.98/n20860.ctc
Concurrence:MRhee6.19.98
no response:AAl-Hakim

MEETING MINUTES

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Date: July 14, 1997

Place: PKLN 17B-43

From: Sam H. Haidar, R.Ph., Ph.D. /S/ 7/14/97

Through: Angelica Dorantes, Ph.D., Team Leader (HFD 870) /S/ 7/14/97

To: HFD-580

RE: 21-Day Filing Meeting, **NDA 20-860, MICRO-LEVLEN™**
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets)

Background:

NDA 20-860 for MICRO-LEVLEN™ (Levonorgestrel/Ethinyl Estradiol) 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". According to the sponsor, the dissolution profiles of LNG and EE of the two lots were superimposable.

Comments:

1. A was used to determine LNG and EE levels in the blood; assay validation data were included in the reports of the pharmacokinetic studies.

2. Dissolution methods provided by the sponsor comply with the requirements of USP 23 <711>, Q % minutes for levonorgestrel and ethinyl estradiol.

3. The proposed labeling currently has no pharmacokinetics section.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) is of the opinion that the provided information is appropriate to support the filing of NDA 20-860. The following comments, however, should be communicated to sponsor as appropriate:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-860

CORRESPONDENCE

BERLEX

TELEFAXED
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

ORIG AMENDMENT
32

July 6, 1998

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated October 14, 1997 which stated that the Labeling and Nomenclature Committee found the original proposed Berlex trade name MICRO-LEVLEN unacceptable. On March 4, 1998, Ms. Christina Kish of the Division informed Berlex that the Labeling and Nomenclature Committee approved the trade name LEVLITE (submitted to the Division on December 23, 1997) for this product.

Additional reference is made to a telephone conversation on June 29, 1998 between Ms. Christina Kish and the undersigned during which Ms. Kish asked that labeling components with the LEVLITE™ name be submitted to the Division. On July 2, 1998, DRAFT copies of our proposed labeling components for LEVLITE™ 21 tablets (21s) and LEVLITE™ 28 tablets (28s) were telefaxed to Ms. Kish. Included were blister labeling and carton labeling.

Per Ms. Kish's request in a telephone conversation on July 2nd, attached please find the required two DRAFT hard copies of the proposed labeling components to be amended to NDA 20-860. Per Ms. Kish's request, an additional copy is included for her use. As stated in the telefax on July 2nd, these labeling components are exact copies of those submitted in the original NDA on June 13, 1997 except that the trade name has been changed from MICRO-LEVLEN™ to LEVLITE™. As also stated in the July 2nd telefax, please note that subsequent to the original NDA submission and as described in our March 4, 1998 amendment, the foil pouch is no longer part of the final market presentation and is, therefore, not included in this submission. In addition, although included in the original NDA, Berlex has decided that units of 6 slidecases will not be marketed at launch, therefore, they have not been included in this submission.

Please contact the undersigned immediately at (973) 276-2305 with any questions or comments that you may have regarding this submission. The telefax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/levlt125

BERLEX

TELEFAXED
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

July 2, 1998

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to Ms. Christina Kish's message to the undersigned on July 1, 1998. Ms. Kish stated that she was preparing the action package for our NDA and asked that the patent information statement provided in the initial NDA be revised by removing the phrase

Reference is also made to telephone conversations between Ms. Kish and the undersigned on May 5 and 6, 1998 during which the undersigned verbally communicated that Berlex was claiming a period of 3 years of marketing exclusivity for LEVLITE™.

In response to and in accordance with Ms. Kish's request of July 1st, attached please find Items 13 (PATENT INFORMATION, page 13 00001) and 14 (PATENT CERTIFICATION, pages 14 00001 and 14 00002) which have been revised. The phrase
has been removed from both items. In addition, Item 14 has been updated to reflect that a patent certification is not applicable to our NDA. Please also note, in follow-up to the May 6th conversation with Ms. Kish and for documentation purposes, that a "Statement of Claimed Exclusivity" for a period of 3 years has been included in Item 14.

Please contact the undersigned immediately at (973) 276-2305 with any questions or comments that you may have regarding this submission. The telefax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/levlt122

BERLEX

TELEFAXED
UPS OVERNIGHT

DUPLICATE

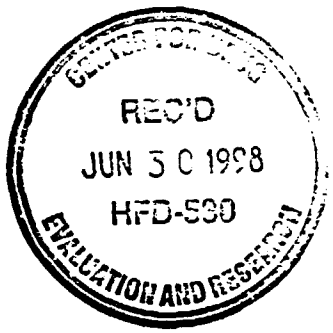
ORIG AMENDMENT
B2

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

June 29, 1998

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the telefax from the Division dated June 26, 1998 which states that the review of the Clinical section of the NDA has been completed. (A copy of the telefax is provided for your convenience in Attachment 1.) The following Labeling comments, identified here in bold, were provided:

Prescribing Information

1. **Table 1 should be updated to Trussell et al., 1998. A copy is enclosed for your reference.**

2. **The date of last revision should be added to the end of this insert.**

3. **A *Pediatric Use* subsection should be added to the PRECAUTIONS section of this insert, suggested wording is as follow:**

Detailed Patient Insert

1. **Table 1 should be updated to Trussell et al., 1998.**

2. **The date of the last revision should be added to the end of this insert.**

3. **The proprietary name and established name of this product should be printed on the first page of this insert.**

Brief Patient Insert

The "Instruction to Patients" located in the Detailed Patient Insert should be included in the Brief Patient Insert.

All of these comments, with the exception of footnotes 9 and 10 from Table 1 (Trussel et al., 1998), have been incorporated into the revised DRAFT labeling for LEVLITE™ which is provided on a 3.5 inch diskette in Attachment 2. The diskette is labeled **"LEVLITE™ Labeling"**, is dated June 29, 1998 and is provided in MS Word 6.0 format. Included on the diskette are the Physician Insert, the Detailed Patient Insert and the Brief Summaries for Levlite 21 and 28. Please note that the graphics for the structural formulas and the slidecase do not appear in this electronic copy of the labeling. Berlex Laboratories certifies that the diskette has been scanned for viruses and is virus free using McAfee VirusScan for Windows created May 15, 1998.

A hard copy of the revised DRAFT labeling is provided for your convenience in Attachment 3.

Please note that Clinical Pharmacology Labeling comments were also communicated to Berlex in the May 20, 1998 telefax and June 8, 1998 letter from the Division. In our June 2, 1998 response to the May 20th telefax, we agreed to incorporate the comments into the final printed labeling for LEVLITE™. The Clinical Pharmacology comments have also been incorporated into the attached revised DRAFT labeling.

Please contact the undersigned immediately at (973) 276-2305 with any questions or comments that you may have regarding this submission. The telefax number is (973) 276-2016.

Although the approval goal date for LEVLITE™ was officially extended beyond June 13th, Berlex will make every effort possible to address your concerns in order to receive approval of LEVLITE tablets as close as possible to that date.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/levlt119

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Berlex Laboratories, Inc.	June 29, 1998
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(973) 276 - 2305	(973) 276 -2016

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
340 Changebridge Road P.O. Box 1000 Montville, New Jersey 07045 -1000	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Levonorgestrel and Ethinyl Estradiol Tablets, USP	LEVLITE™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α(-)-and 19 Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Coated Tablet	0.100 mg levonorgestrel and 0.020 mg ethinyl estradiol	Oral

(PROPOSED) INDICATION(S) FOR USE:
Oral Contraception

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION RESPONSE TO TELEFAX OF June 26, 1998 (Clinical Review comments)

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached pages

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF	DMF	DMF	DMF	DMF	DMF
DMF	DMF	DMF	DMF	DMF	DMF
DMF	DMF				

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Nancy F. Velez	Nancy F. Velez Manager	June 29, 1998

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
340 Changebridge Road P.O. Box 1000 Montville, New Jersey 07045 - 1000	(973) 276 -2305

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please DO NOT RETURN this form to this address.

TELEFAXED
UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

June 17, 1998

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
LETTER OF UNDERSTANDING

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to our amendment dated May 26, 1998 which provided responses to the Division's letter of May 11, 1998 that contained Chemistry, Manufacturing and Controls comments as well as two preliminary Clinical Pharmacology comments.

Additional reference is made to a teleconference held on June 12, 1998 between the following FDA and Berlex representatives during which the May 26th amendment was discussed:

FDA Representatives
Dr. Moo-Jhong Rhee, PhD, Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII)
Dr. Ali Al-Hakim, PhD, Chemistry Reviewer, DNDCII
Dr. Sam Haidar, PhD, Division of Pharmaceutical Evaluation II
Ms. Christina Kish, Consumer Safety Officer, Division of Reproductive And Urologic Drug Products

Berlex
Dr. Paul Vandenberg, PhD, Director, Quality Affairs

Dr. Ron Wohl, PhD, Director, Strategic CMC

Dr. Monika Wolff, PhD, Section Head, Technical Services
Ms. June Bray, Director, Drug Regulatory Affairs

Ms. Nancy Velez, Manager, Drug Regulatory Affairs

Final reference is made to teleconference on June 16, 1998 between Ms. Kish, Ms. Bray and Ms. Velez during which Berlex verbally communicated the following commitments resulting from the June 12th teleconference. These commitments are documented below for your review:

Although the approval goal date was officially extended beyond June 12th, we will make every effort to address any of your concerns in order receive approval of LEVLITE tablets as close as possible to that date. Please contact the undersigned immediately at (973) 276-2161 or Nancy Velez at (973) 276-2305 with any questions or comments that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

June K. Bray
Director
Drug Regulatory Affairs

Desk Copies: Dr. Moo-Jhong Rhee
Dr. Ali Al-Hakim

NFV/letter/levlt114

BERLEX

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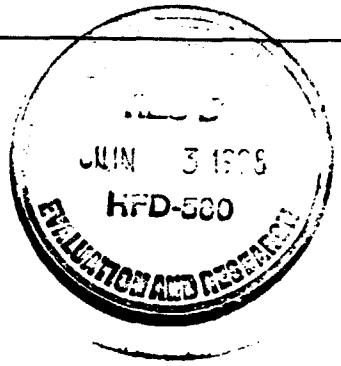
Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

June 2, 1998



Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to our amendment dated May 26, 1998 which provided responses to the Division's letter of May 11, 1998 that contained Chemistry, Manufacturing and Controls comments as well as two preliminary Clinical Pharmacology comments.

Additional reference is made to our telefax of May 29, 1998 and to telephone conversations on May 29th and June 1st, between Dr. Sam Haidar of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and Dr. Armen Melikian and the undersigned of Berlex. The subject of these communications was the telefax from the Division dated May 20, 1998 which is discussed further below.

The telefax from the Division dated May 20, 1998 contains the review of our NDA from the OCPD (a copy of the telefax is provided for your convenience in Attachment 1). OCPD finds the NDA acceptable, however, two recommendations and labeling comments are provided. This submission amends NDA 20-860 to provide responses to all of the comments in the telefax of May 20th. The Division's comments are provided first in bold, followed by our 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:

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.

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

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.**

Berlex agrees to change the Arabic numeral 1 for Table 1 to the Roman numeral I. A legend will be added under Table 1 defining the pharmacokinetic parameters listed in the Table. These changes will be reflected in the final printed labeling for LEVLITE.

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.**

Please contact the undersigned immediately at (973) 276-2305 with any questions or comments that you may have regarding this submission. Berlex will make every effort possible to address your concerns in order to receive approval of LEVLITE tablets as close as possible to the original approval goal date of June 13, 1998.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk Copy: Dr. Sam Haidar

NFV/letter/levlt105

ORIGINAL

BERLEX

TELEFAXED
HAND DELIVERED

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

ORIG AMENDMENT
BC

May 26, 1998

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®. In a telephone conversation on May 6, 1998 between Ms. Christina Kish of the Division and the undersigned, Ms. Kish confirmed that the approval goal date for the NDA is June 13, 1998.

Reference is also made to the letter from the Division dated May 11, 1998 (a copy of the letter is provided for your convenience in Attachment 1) which requests information to enable the reviewer to complete his review of the Chemistry, Manufacturing and Controls section of the NDA. This submission amends NDA 20-860 to provide responses to the comments in the letter of May 11th. The Division's comments are provided first in bold, followed by our responses.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

1. **Please note that ethinyl estradiol has five chiral centers, not six as reported in your NDA.**

Berlex agrees that ethinyl estradiol has five chiral centers. This was an error in the original NDA submission.

2. **Information on the holding time and acceptance testing for the bulk drug product tablets received from Schering AG should be provided. The type of testing (if any) performed on the stored tablets should be indicated.**

Full stability testing has been for production scale bulk tablets. Twelve month controlled room temperature (CRT) stability data for bulk tablets (Berlex Analytical Report M197-247 for Lot Nos. 9603033, 9603034, 9603035) was submitted as an amendment to this NDA on March 4, 1998.

A report of 18 month data (Berlex Analytical Report M198-109) is provided in Attachment 2. Based on these 18 month data, we are requesting a maximum holding period of 18 months for bulk tablets.

3. **All necessary information relating to the safety of or citation of the appropriate references should be submitted.**

supplier of confirms that the specifications meet the requirements of 21 CFR § 178.3770 [Polyhydric alcohol esters of oxidatively refined A letter from to Schering AG documenting this information has been translated into English and is provided in Attachment 3.

4. **Information regarding any major differences in equipment, manufacturing process and controls of the product between the Wedding and Weimar facilities should be submitted.**

The manufacturing process is essentially the same for product produced in Weimar and Wedding. The equipment used at both sites (fluid bed granulator, rotary tablet press, coating pan) are of the same design and operating principle. The equipment capacities are comparable, and the same in process controls are used at both sites. Attachment 4 provides a summary of the differences.

5. **Information regarding the reprocessing operation (section 3.2.5.5) in the drug product manufacturing process should be submitted, if it exists.**

At this time we do not intend to reprocess the drug product. Should a decision be made to reprocess the product in the future, information will be submitted for review prior to implementation.

6. **Information on the temperature of the column for testing Appearance, Assay and Content Uniformity should be provided.**

Testing is performed under ambient laboratory conditions which typically range from °C.

7. **The following information regarding the decomposition method should be provided:**

   a. **integration data (area under the peak) for individual decomposition products;**

      Data in the NDA were provided for all potential decomposition products. Peaks present in any chromatograms and not reported as decomposition products were determined to be impurities of the drug substance or products of decomposition of the placebo matrix, consistent with ICH guidelines. Each decomposition product is calculated by comparison with the 1% external standard solution of the corresponding active ingredient. Consequently, the results are presented as weight percentage as specified in the monograph.

   b. **identification of the two degradation products, shown as additional peaks at 18 and 21 minutes (Figure 5), if these products are consistent unknown degradation products and they exceed 1%; and**

      Figure 5 (Original NDA Vol. 9, page 3 02725), a decomposition product chromatogram at 242 nm, is an expanded view of the chromatogram (detector response or y-axis) and may have been misleading as to the amount of impurities present.

      The peaks mentioned at about 18 and 21 minutes are present at 0.09% and 0.07 %, respectively. We have determined that the two peaks mentioned are impurities of levonorgestrel, not decomposition products and are thus not routinely determined on stability. These peaks have always been present in chromatograms of the levonorgestrel drug substance and, therefore, also the drug product. The peaks did not increase in size when stored for 6 months at 40 °C / 75 % RH and were thus determined to be impurities and not decomposition products. These two impurities at about 18 and 21 minutes have been identified as

   c. **clarification regarding why decomposition product is not being monitored during stability studies.**

      is now known to be an impurity of the ethinyl estradiol drug substance. During early studies it was thought that may also be a decomposition product. However, since we now know that this is not a decomposition product, it should not have been included in the table on p. 3 02720-25 in original NDA Vol. 9.

8. A microbial test and specifications should be included in the analytical testing of the drug product.

The Microbiological testing monograph for the drug product is provided in Attachment 5.

Specifications* : Total Aerobic Microbial Count - cfu/g

Total Yeast and Mold Count - cfu/g

*Proposed <61> Microbial Limit Tests specifications for oral solid dosage form in the USPF.

9. Dissolution specifications should be established with available dissolution profiles from production batches and submitted for review.

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. Dissolution profiles for six lots are provided in Attachment 6.

10. There are significant differences in the degradation products profile between pilot and production scale batches with respect to 6-α-hydroxy ethinyl estradiol. The production scale batches have a higher content of this degradation product. Therefore, a 24 month expiry date will be recommended rather than the 36 months proposed.

Pilot scale stability data was generated on blisters packaged in a thick foil pouch. Packaging using the thick foil pouch has been discontinued. Since the original NDA submission, 18 month stability data on production scale batches on unpouched blisters have been generated (Berlex Analytical Report M198-108) and are provided in Attachment 7. Berlex will accept a 24 month expiration date at this time. Berlex plans to extend the expiration date to 36 months in accordance with our stability protocol, when acceptable 36 month CRT data become available.

Although 6α-hydroxy ethinyl estradiol did increase significantly at 40 °C / 75 % RH, it did not increase significantly over 18 months under CRT conditions. Therefore, 6-α-hydroxy estradiol is not limiting the expiration dating when the product is stored under the recommended storage conditions.

11. Specifications for degradation products should be revised as follows:

We are concerned with meeting your proposed specifications. In our recently completed report of 18 month stability data for packaged tablets (see Attachment 7) at 25 °C / 60 % RH, we report values up to % for individual decomposition products and up to % for total decomposition products. These data indicate a greater than 1 % increase might be expected for individual decomposition products over the intended expiration dating period. These data also indicate

small amounts of degradation products may occur during stressed shipping conditions. In view of these data, we have tightened our specifications as follows: individual unknown - not more than (NMT) %, individual known - NMT %, and total - NMT %.

12. A justification for the deletion of the microbial contamination test from the specifications for production scale batches should be submitted.

Berlex proposes to conduct microbiological testing of all lots of tablets received for the first 12 months of distribution (consisting of approximately 36 lots of active tablets and 12 lots of placebo tablets). These data will be used as part of the release specifications during this time period. The requirement for continued microbiological testing as a release specification will then be evaluated based on all of the accumulated data for the above noted lots of drug product (see also response to Comment 8).

13. An explanation regarding why the decomposition method did not account for the decomposition product ethinyl estradiol should be submitted. The method should also provide the percentage ratio data (area percent) for all detectable decomposition products.

We provided in the original NDA data on all potential decomposition products. It was subsequently determined that ethinyl estradiol is not a decomposition product (see also response to Comment 7c.).

Additionally, although the Clinical Pharmacology review has not been completed, we have the following comments and questions:

1. Your proposed in vitro dissolution method is acceptable.

We acknowledge that you have found our proposed in vitro dissolution method acceptable.

2. The dissolution data submitted do not justify the proposed dissolution specifications of Q: % at minutes; a revised release specification of Q % at minutes for levonorgestrel and ethinyl estradiol should be submitted.

As also stated in the response to Comment 9, 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 6).

Please contact the undersigned immediately at (973) 276-2305 with any questions or comments that you may have regarding this submission. Berlex will make every effort possible to address your concerns in order to receive approval of LEVLITE tablets by the approval goal date of June 13, 1998.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk Copy: Dr. Ali Al-Hakim

NFV/letter/levlt098

DUPLICATE

BERLEX

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

May 6, 1998

ORIG AMENDMENT
BM

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®. On March 4, 1998, Ms. Christina Kish of the Division informed Berlex that the Labeling and Nomenclature Committee approved the trade name LEVLITE for this product.

Reference is also made to the first Safety Update Report submitted on April 28, 1998 to NDA 20-860 and to a conversation today between Ms. Christina Kish of the Division and the undersigned regarding this update. The undersigned informed Ms. Kish that in the original "Table of All Studies" (attachment designated as page 1 in the update) the column for "Start Date/Duration/Status" had been inadvertently omitted.

Attached please find a corrected "Table of All Studies" which incorporates the "Start Date/Duration/Status" column. None of the other information has been changed from the original table. This corrected page was also telefaxed to Ms. Kish today.

Please feel free to contact the undersigned at (973) 276-2305 with any questions or comments that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/levlt082

ORIGINAL

BERLEX

UPS OVERNIGHT

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

April 28, 1998

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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Lisa Rarick, MD, Director
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UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
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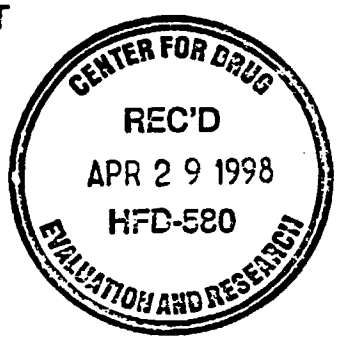
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
SU



Dear Dr. Rarick:

Re: NDA 20-860 - LEVLITE™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
SAFETY UPDATE REPORT

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®. On March 4, 1998, Ms. Christina Kish of the Division informed Berlex that the Labeling and Nomenclature Committee approved the trade name LEVLITE for this product.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), attached please find the first Safety Update Report submitted for NDA 20-860. This update is being submitted approximately 9 months after the initial NDA submission rather than at the 4 month timepoint referenced in the regulations based on a recommendation by Ms. Christina Kish of the Division during a conversation with the undersigned on August 27, 1997. Ms. Kish recommended that the first update be submitted about 9 months after the initial NDA submission because if it were submitted at 4 months, the Division would ask for another update a few months later to determine if anything else had occurred.

The reporting interval for this Safety Update is January 10, 1997 - September 1, 1997. These dates correspond to the cut-off date for inclusion of data into the NDA and the cut-off date established for inclusion of data into this update, respectively.

US Supportive Study (Report 97035, Protocol 311-01A)
Please note that at the time of the initial NDA submission, the data from the supportive US study (Report 97035, Protocol 311-01A) were still undergoing analysis, however, Berlex provided pregnancy rate data and serious adverse events (AEs) from women who had completed the study as well as other preliminary data. This agreement was reached during a meeting on May 14, 1996 between representatives of the Division of Metabolism and Endocrine Drug Products and Berlex Laboratories. Also as agreed during the May 14th meeting, the final US study report was submitted as an amendment to the NDA when it was completed, on December 5, 1997.

Although the final data from Report 97035 became available during the reporting interval of this Safety Update, it is not included because it does not differ significantly from the preliminary data submitted in the NDA. For your reference, an introduction to the final study report in the December 5th amendment identifies the most noteworthy differences between the preliminary data submitted in the NDA and the final study report data.

1. SAFETY UPDATE

Four foreign clinical studies as well as one post marketing trial (identified below, see also Page 1) conducted by our parent company, Schering AG, Berlin, Germany were

Clinical Studies

1. Study #96007: "Randomised, Controlled, Open, Multicenter Clinical Study Of Cycle Control And Tolerance Comparing Micro 20 And Eve 20 With A Reference Of Microgynon";

2. Study #96038: "Single Center, Double-Blind, Randomized Study For Bone Mineral Density Under Long-Term Treatment With MIRANOVA (SH D 637 A) In Comparison With MICROGYNON (SH 7.1155 A) In Contraceptive Use In 100 Healthy Women Over 36 Treatment Cycles";

3. Study #96045: "Multicenter, Double-Blind, Randomized Study Of Cycle Control Comparing SH D 637 A (20 µg Ethinyl Estradiol/100 µg Levonorgestrel) And SH 7.1155 A (MICROGYNON) In Contraceptive Use In 1,000 Healthy Women Over 7 Treatment Cycles";

4. Study #96050: "Single-Center, Open, Randomized Study Of Hemostatic And Lipid And Carbohydrate Metabolism Parameters Comparing SH D 637 A (20 µg EE2/100 µg LNG) And SH 7.1155 A (MICROGYNON) In Contraceptive Use In 60 Healthy Women Over 13 Treatment Cycles".

Post Marketing Trial

Report No. AV31: "Post marketing surveillance observational trial regarding contraceptive efficacy, cycle control and tolerance of Miranova(R) (levonorgestrel 100 µg + ethinylestradiol 20 µg) in 13085 women over 6 treatment cycles".

As described in the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (July 1988), this Safety Update refers only to new data obtained during the interval. These additional data are relatively few and all come from foreign sources; therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less

serious event, subjects who died and subjects who failed to complete a clinical study due to an AE are described. Commercial marketing experience, foreign regulatory actions and the results of literature searches are also provided for your information.

It was concluded that there is no new safety information learned about levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets, USP, that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

1.1 Serious Or Potentially Serious AEs (SAEs)

The table below identifies SAEs that occurred in Studies 96007, 96038 and 96045. Please note that some of the SAEs received fell outside the reporting interval but are included in this report for completeness. Please also note that Studies 96038 and 96045 are double blind studies; therefore, it is not known for these AEs which active drug the subject received. No SAEs have been reported in Study 96050.

STUDY NO.	SUBJECT NO.	DATE OF ONSET (During reporting interval)	DATE OF ONSET (After reporting interval)	DESCRIPTION OF SAE
96007		7/28/97	–	Hospitalization July 28 - July 30, 1997 due to hypoplasia of right mamma, known since puberty
		–	09/13/97	Hospitalization, appendectomy
		–	10/04/97	Hospitalization, unclear abdominal pain, subject recovered
		–	10/21/97	Hospitalization, suicide, subject survived
96038*		–	12/29/97	Erythema nodosum
96045*		5/4/97	–	Fracture of ankle joint prior to treatment
		8/14/97	–	Gastroenteritis
		9/97	–	Salpingitis
		–	11/97	Pneumonia
		–	11/97	Tinnitus
		–	12/97	Appendicitis
		–	1/98	Rectal bleeding

*These are double blind studies, drug codes have not been broken; therefore, it is not known which active drug the subject received.

1.2 Unusually High Frequency Of A Less Serious Event

There was not an unusually high frequency of a less serious event in any of the studies that were

1.3 Subjects Who Died Or Discontinued A Clinical Study Due To An AE

1.3.1 Deaths

No subjects died in the four clinical studies that were

1.3.2 Discontinuations Due to AEs

Because Studies 96038 and 96045 are double blind and an interim evaluation is not being performed, data is not yet available regarding discontinuations due to AEs. No subjects discontinued due to AEs in open Study 96050 during the reporting interval.

In Study 96007, 45 (6.3%) of 719 subjects with data during treatment discontinued due to AEs. Fourteen (2%) of these subjects received levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets. This information was obtained from a DRAFT interim biometrical report and may be revised upon issuance of a final study report. A table identifying the HARTS coded AEs and the number of subjects that discontinued for each AE in each treatment group is provided on Page 2. Case Report Forms for the 45 subjects will be available upon request.

1.4 Commercial Marketing Experience And Foreign Regulatory Actions

Levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets have been marketed in Germany as MIRANOVA since April 1996.

1.4.1 List Of Countries In Which The Drug Has Been Approved

Levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets have not been approved in any country during the reporting interval.

1.4.2 List Of Countries In Which The Drug Has Been Submitted For Approval And The Applications Are Pending

During the reporting interval, applications were submitted for approval in Great Britain (02/11/97), Ireland (06/09/97) and Australia (08/07/97).

1.4.3 Reports from Foreign Regulatory Authorities, Foreign Affiliates, Licensors or Licensees of the Applicant

There are no reports of, or analyses of, AEs, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other

experience with levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets from foreign regulatory authorities, foreign affiliates, licensors or licensees of the applicant.

1.4.4 Epidemiological Studies

There are no reports of epidemiological studies or studies underway with levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets.

1.4.5 Spontaneous Reports From Foreign Marketing Experience

During the reporting interval, two serious AEs were reported with levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets. These AEs occurred in the post marketing observational trial described in section 1 and are summarized in the table provided on Page 3.

1.5 Reports From Literature

Nonclinical and clinical literature searches for levonorgestrel 0.100 mg and ethinyl estradiol 0.020 mg tablets were performed for the reporting interval. The searches revealed that there is no new safety information in the literature that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

Please feel free to contact the undersigned at (973) 276-2305 with any questions or comments that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/levlt067

ORIGINAL

BERLEX

CERTIFIED MAIL
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Drug Development & Technology
Division of Berlex Laboratories, Inc.

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March 4, 1998

ORIG AMENDMENT

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - MICRO-LEVLEN™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated October 14, 1997 which states that the Labeling and Nomenclature Committee found the original proposed Berlex trade name MICRO-LEVLEN unacceptable. On December 23, 1997, Berlex submitted to the Division a new proposed trade name, LEVLITE, which was forwarded to the Committee as an expedited review request. To date, no response has been received from the Committee. Please note that the MICRO-LEVLEN name appears throughout this submission. A new trade name will be used in future submissions when it is approved.

Reference is also made to the teleconference on September 24, 1996 during which Berlex representatives discussed with Ms. Christina Kish and Dr. Srinivasachar (Division of Metabolism and Endocrine Drug Products) the proposed NDA stability data filing plan for MICRO-LEVLEN. During the teleconference, Berlex agreed to submit and subsequently submitted in the NDA , 6-month data for 3 primary (full-scale production) stability batches and 36-month supportive data for 3 pilot-scale batches. Berlex committed to amend the NDA with 12-month controlled room temperature stability data on the 3 primary batches.

This submission amends Item 3 of NDA 20-860 to provide for 12-month controlled room temperature stability data on the 3 primary batches. These batches were manufactured in the full-scale tablet production facility of Schering AG, Wedding (W1), Berlin, Germany described in the initial NDA submission. The facility underwent a successful pre-approval inspection in September of 1997. The following stability reports on bulk and packaged tablets are provided in Attachment 1:

MI97-247: Twelve Month Stability Report For Bulk Micro-Levlen Sugar-Coated Tablets (Levonorgestrel and Ethinyl Estradiol Tablets) Manufactured at the Wedding Facility;

MI97-235: Twelve Month Stability Report For Packaged Micro-Levlen Sugar-Coated Tablets (Levonorgestrel and Ethinyl Estradiol Tablets) Manufactured at the Wedding Facility.

The NDA stated that the use of a foil pouch over the slidecased blisters for the market presentation of Micro-Levlen tablets would be dependent on the results of these 12 month stability data for both pouched and unpouched product. These data indicate that the foil pouch is not necessary to maintain the stability of the product for the proposed expiration dating of three years. The foil pouch will not be part of the final market presentation.

Also included in this amendment, in accordance with our initial NDA commitment, are stability data on three full-scale production lots manufactured at an additional manufacturing facility described in the NDA, Schering GmbH und Co., Weimar, Germany. This facility recently underwent a successful pre-approval inspection in January of 1998. The following stability report is provided in Attachment 2:

MI97-292 Three Month Stability Report For Packaged Micro-Levlen Sugar-Coated Tablets (Levonorgestrel and Ethinyl Estradiol Tablets) Manufactured at the Weimar Facility.

Additional amendments to Item 3 of the initial NDA are described below:

1. The NDA stated that drug product manufactured at the Wedding facility will be imprinted by and drug product manufactured at the Weimar facility will be imprinted at Weimar. This submission amends Item 3 to allow for drug product manufactured at the Wedding facility also to be imprinted at the Weimar facility. A letter of authorization for the DMF for the Weimar facility was provided in the initial NDA in Volume 2, page 3 00150. For your convenience, a new NDA page 3 00147 reflecting this change is provided in Attachment 3.

2. This submission allows for the following additional alternate packaging subcontractors for secondary packaging:

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Drug Master File Nos.
facilities, respectively. Drug Master File No. Drug Master File No. facility. A new NDA page 3 00148 reflecting these changes, as well as copies of the letters of authorization for DMFs

are provided in Attachment 4. A new page 3 02668 has also been included in this attachment which now more accurately describes the primary and secondary packaging of the product.

3. , is being amended to the NDA to replace as the supplier of the slidecase, a secondary final packaging component. For your convenience, a new page 3 02669 reflecting this change is provided in Attachment 5. Please note that also on this page the supplier of the foil pouch has been deleted. As stated previously, the pouch will not be part of the final market presentation.

4. This submission amends the regulatory test methods with regard to decomposition. The correction factors for the drug related substances levonorgestrel and ethinyl estradiol are incorrectly identified on page 3 02720 (Regulatory Analytical Method as respectively. The correction factor for levonorgestrel should be and for should be For your convenience, a new page 3 02720 reflecting this change is provided in Attachment 6.

5. The decomposition specification provided in the stability commitment on page 3 02868 is incorrect and should be consistent with the regulatory specification provided on page 3 02703. The stability commitment specification has been corrected to read as follows:

   NMT % for known individual decomposition products, NMT % for unknown decomposition products, and NMT % for total known and unknown decomposition products relative to each drug substance

   For your convenience, a new page 3 02868 reflecting this change is provided in Attachment 7.

Please note that the amendment pagination appears on the lower right corner of each page except in the case of an NDA replacement page. In that case, the original NDA pagination appears in the lower right corner and the amendment pagination appears in the center.

Please feel free to contact the undersigned at (973) 276-2305 with any questions or comments that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro016

noted 1/7/98 RLB

ORIG AMENDMENT
BC

BERLEX

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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

December 23, 1997

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860
Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP, a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated October 14, 1997 which states that the Labeling and Nomenclature Committee found the original proposed Berlex trade name MICRO-LEVLEN unacceptable. Reference is also made to voice mail messages as follows:

1. the undersigned's message on December 19, 1997 to Ms. Christina Kish of the Division which communicated that Berlex had selected a new trade name. The undersigned asked if review of the name by the Labeling and Nomenclature Committee could be expedited and when the next meeting would be held.

2. Ms. Kish's message on December 22, 1997 to the undersigned which communicated that Ms. Kish had spoken to the chemists and that the next meeting of the Labeling and Nomenclature Committee would be held next month. Ms. Kish suggested that Berlex telefax the proposed name to her in the next two days and follow-up the telefax with an amendment to the Division. She said she would forward the proposal to the chemist as an expedited review request.

In accord with Ms. Kish's suggestion, this submission amends NDA 20-860 to provide for a new trade name for Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP. The new trade name is:

LEVLITE.

Two copies of this submission are included for the Division. One copy was telefaxed to Ms. Kish today.

Please feel free to contact the undersigned at (973) 276-2305 with any questions or developments that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro168

ORIGINAL

BERLEX

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NEW CORRESP

Drug Development & Technology
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noted 1/28/98 EB

December 12, 1997

noted KAmrhein 1-27-

HFJ 1/28/98

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D DEC 17 1997 HFD-580

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - MICRO-LEVLEN™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)

Reference is made to NDA 20-860 submitted on June 13, 1997 for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP), a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated October 14, 1997 which states that the Labeling and Nomenclature Committee has found the Berlex trade name MICRO-LEVLEN unacceptable. Berlex is currently evaluating this issue. Please note that the MICRO-LEVLEN™ name appears throughout this submission. A new trade name will be used in future submissions when it is approved.

Attached please find a submission addressed to Dr. Gurston Turner of the Division of Scientific Investigations dated December 12, 1997 regarding of the pivotal foreign study in NDA 20-860, Report AL31 (Study 94251). The submission contains the following documents requested by Dr. Turner:

1. One page which provides Study Site Information, i. e., the names of the four investigators that Dr. Turner has selected for the audit, the tentative schedule (order of sites) for the audit, and a complete address for each of the investigators' sites, including telephone and telefax numbers;

2. One page which provides Hotel Information;

3. Four separate 3.5 inch diskettes containing the electronic databases in Microsoft Excel format, Version 5.0, for the four investigators.

Two copies of the submission are included for the Division. One copy was hand delivered to Dr. Turner today.

Berlex is anxious to address all comments and requests in order to expedite the audit process and gain approval of MICRO-LEVLEN™ as soon as possible.

Please feel free to contact me at (973) 276-2305 with any questions that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro163

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

HAND DELIVER

ORIGINAL

ORIG AMENDMENT
32

December 5, 1997

Drug Development & Technology
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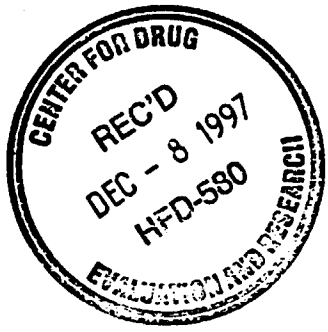

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
Parklawn Building, Room 17-B-45
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - MICRO-LEVLEN™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP), a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated October 14, 1997 which states that the Labeling and Nomenclature Committee has found the Berlex trade name MICRO-LEVLEN unacceptable. Berlex is currently evaluating this issue. The MICRO-LEVLEN™ name appears throughout this submission. A new trade name will be used in future submissions when it is approved.

This submission amends Items 8 and 10 of NDA 20-860 to provide for the recently completed final report of the supportive US clinical study, Report 97035 (Protocol 311-01A) entitled, "An Open-Label, Multicenter Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation Containing Levonorgestrel 100 µg and Ethinyl Estadiol 20 µg." Five hundred and fifty eight (558) women completed this 6 cycle study.

As agreed during a meeting on May 14, 1996 between representatives of the Division of Metabolism and Endocrine Drug Products and Berlex Laboratories to discuss the proposed Phase 3 program for MICRO-LEVLEN™, the final US study report is being submitted as an amendment to the NDA which will not be considered a major amendment and will not reset the

review clock (see "Letter of Understanding" submitted to IND and "Memorandum of Meeting" from the Division of Reproductive and Urologic Drug Products dated October 31, 1996).

The data from the US study were analysis at the time of the initial NDA submission, however, Berlex provided pregnancy rate data and serious adverse events (AEs) from women who had completed the study (as agreed at the May 14, 1996 meeting) as well as other preliminary data in the NDA. The final data in attached Report 97035 differ slightly, and insignificantly, from the data provided in the NDA. An Introduction immediately precedes the report in Item 8 which describes these differences in detail.

This submission consists of 17 volumes. An overall Table of Contents for the items in the submission, Items 8 (Clinical Data) and 10 (Statistical Section), immediately follows this cover letter. The page numbers cited refer to the numbers stamped in the lower right corner of each page, e.g.; page 8 01234. Report 97035 appears in Item 8. The overall Table of Contents refers the reviewer to the detailed Table of Contents within the study report. The page numbers cited in the report Table of Contents are located in the top right corner of each page (both portrait and landscape pages appear in the report) with one exception. In Appendix 16.3.1, Case Report Forms for Deaths, Other Serious AEs, and Withdrawals for AEs, the internal pagination appears in the lower middle of the page, e.g.; page 1234.

In accordance with the suggestion by Ms. Christina Kish of the Division of Reproductive and Urologic Drug Products in a conversation with the undersigned on November 21, 1997, Report 97035 is not being submitted in duplicate to Item 10. An internal cross reference page has been provided in Item 10 which refers the reviewer to the volume and page in Item 8 of this submission where the report is located.

Should you have any additional questions regarding this amendment, please do not hesitate to contact me at (973) 276-2305.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro155

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIG AMENDMENT
BC

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DUPLICATE

BERLEX

Drug Development & Technology
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October 31, 1997

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

Re: NDA 20-860 - MICRO-LEVLEN™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP), a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated September 15, 1997 which contained preliminary comments on the Clinical, Chemistry Manufacturing and Controls, and Human Pharmacokinetics (PK) and Bioavailability (BA) items of the submission. A separate letter being submitted today provides responses to those comments. The September 15th letter requires that, in addition to the responses, a separate amendment be submitted to address the Chemistry comment (provided in bold below):

Chemistry

The final rule (FR29JY97-16) amending the environmental assessment regulation was published in the Federal Register July 29, 1997. This rule affects all applications still pending on August 28, 1997. You may, if appropriate, submit an amendment to your application claiming categorical exclusion in accordance with 25.31(b) of the final rule and withdrawing your environmental assessment.

In accordance with 25.31(b) of the final rule, Berlex qualifies for categorical exclusion and is submitting this amendment as official notification that it has decided to withdraw the

environmental assessment provided in the original NDA submission for MICRO-LEVLEN™. This decision was also communicated to Ms. Christina Kish of the Division in a telephone conversation with me on September 24, 1997.

Should you have any additional questions regarding the application, please do not hesitate to contact me at (973) 276-2305.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro142

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Berlex Laboratories, Inc.

DATE OF SUBMISSION
October 31, 1997

TELEPHONE NO. (Include Area Code)
(973) 276-2305

ADDRESS (Number, Street, City, State and ZIP Code)
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-860

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
Levonorgestrel and Ethinyl Estradiol Tablets, USP

PROPRIETARY NAME (If any)
MICRO-LEVLEN™

CODE NAME (If any)
SH D 593 A (active tablets)
SH D 593 P (inert tablets)

CHEMICAL NAME
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α(-)-
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-

DOSAGE FORM
coated tablet

ROUTE OF ADMINISTRATION
oral

STRENGTHS (S)
Levonorgestrel
0.100 mg
Ethinyl Estradiol
0.020 mg

PROPOSED INDICATIONS FOR USE
1 contraception

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND		
DMF	DMF	DMF
DMF	DMF	DMF
DMF	DMF	
DMF	DMF	
DMF	DMF	
DMF	DMF	

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIGINAL

BERLEX

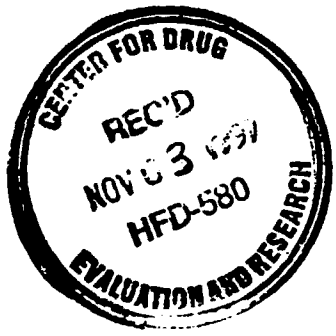
ORIG AMENDMENT

October 31, 1997

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Re: NDA 20-860 - MICRO-LEVLEN™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)
AMENDMENT TO PENDING APPLICATION

Reference is made to NDA 20-860 submitted on June 13, 1997 for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP), a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Reference is also made to the letter from the Division dated September 15, 1997 which contained preliminary comments on the Clinical, Chemistry Manufacturing and Controls, and Human Pharmacokinetics (PK) and Bioavailability (BA) items of the submission. This submission amends NDA 20-860 to provide responses to those comments. The Division's comment is provided first in bold, followed by our response.

Clinical

Please indicate the status of your US clinical study report, including a proposed time-line for submission of the study report.

The report for the supportive US study, Protocol 311-01A, is currently being prepared and will be undergoing final review in the next few weeks. We expect the report to be finalized and submitted to the Division by the end of November.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS: DATE:

Chemistry

The final rule (FR29JY97-16) amending the environmental assessment regulation was published in the Federal Register July 29, 1997. This rule affects all applications still pending on August 28, 1997. You may, if appropriate, submit an amendment to your application claiming categorical exclusion in accordance with 25.31(b) of the final rule and withdrawing your environmental assessment.

In accordance with 25.31(b) of the final rule, Berlex qualifies for categorical exclusion and has decided to withdraw the environmental assessment provided in the original NDA submission for MICRO-LEVLEN™. This amendment is being submitted today under separate cover.

Human Pharmacokinetics and Bioavailability

1. **The Pharmacokinetics subsection of the section of your proposed labeling should be reformatted according to the internal Division guidelines (see enclosed format).**

2. **Please submit a summary of the human PK/bioavailability section, individual study report summaries and the revised package insert on disk, if possible in MS Word, version 7.**

In response to Comment 1, the package insert (PI) which was submitted in the initial NDA submission has been revised in accordance with the Internal Division Labeling Guidance that was attached to the letter of September 15th. A subsection has been added to the section which includes the subheadings of In addition, a subsection has been added with subheadings of The suggested pharmacokinetic tables have also been included. The approved PI for Alesse™-28 Tablets was used as a guide for the incorporation of these new sections. Any differences from the Alesse PI, based on our product, have been annotated.

Disk #1, labeled **"LNG** (levonorgestrel) **0.100 mg and EE** (ethinyl estradiol) **0.020 mg Tablets, USP PI"** and dated October 31, 1997, contains the revised PI in MS Word 6.0 format. The file is identified as In a conversation on September 24, 1997 between Ms. Christina Kish of the Division and the undersigned, it was decided that the PI should be provided on a disk by itself. Please note that the graphics for the structural formulas and the slidecase do not appear in this electronic copy of the labeling.

A hard copy of the revised PI has been provided for your convenience in Attachment 1.

Please note that on October 3, 1997, Ms. Kish informed the undersigned that the Nomenclature Committee did not recommend the use of the trade name MICRO-LEVLEN™ for the product that is the subject of this NDA. Berlex subsequently received a letter from the Division dated October 14, 1997 which confirmed this fact. Berlex is currently investigating a new trade name for the product. In accordance with the recommendation by Ms. Kish during the conversation on October 3rd, please note that the MICRO-LEVLEN™ name appears throughout the revised PI but will be replaced when a new trade name has been approved.

In response to Comment 2, Disk #2, labeled **"LNG 0.100 mg and EE 0.020 mg Tablets, USP Human PK/BA Item"** contains the summary of the Human PK/BA item and the summaries of the two study reports, Reports A999 and AA00, which were included in the item. The disk is dated October 31, 1997, and contains the following three files:

During the conversation with Ms. Kish on September 24th, it was decided that the Human PK/BA Item summary and individual report summaries should be submitted together on a separate disk, and that MS Word 6.0 would be an acceptable format. Zip files were also considered acceptable.

3. **Raw data of individual studies should be submitted on disk, preferably in Excel, version 7.**

A hard copy of the raw data Excel worksheets has also been provided for your convenience in Attachment 2.

Berlex Laboratories certifies that the three 3.5 diskettes included in this submission have been scanned for viruses and are virus free using McAfee VirusScan for Windows created September 10, 1997.

We trust that the information provided in this submission addresses all of your concerns and will enable you to complete the review of our NDA. Should you have any additional questions regarding the application, please do not hesitate to contact me at (973) 276-2305.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro125

ORIGINAL

BERLEX

Attachment 1

Attachment 2

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

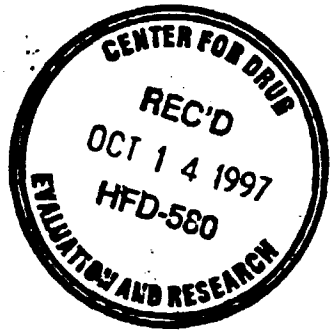
Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

ORIG AMENDMENT

October 9, 1997

Lisa Rarick, MD, Director
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Rarick:

Re: NDA 20-860 - MICRO-LEVLEN™
(Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP)

Reference is made to NDA 20-860 submitted on June 13, 1997 for MICRO-LEVLEN™ (Levonorgestrel 0.100 mg and Ethinyl Estradiol 0.020 mg Tablets, USP), a low dose oral contraceptive (OC) product that is a proportionate dose-reduced variant of the currently marketed Berlex product, Levlen®.

Attached please find a submission addressed to Dr. Gurston Turner of the Division of Scientific Investigations dated October 9, 1997 regarding
NDA 20-860, Report AL31 (Study 94251). The submission contains the following documents requested by Dr. Turner:

1. A sample of an electronic database in Microsoft Excel format, Version 5.0 (format requested by Dr. Turner), for one of the sites that participated in the study,
2. A blank Case Report Form for the study,
3. A copy of the protocol for the study.

Two copies of the submission are included for the Division. One copy was hand delivered to Dr. Turner today.

Attachment 1

Berlex is anxious to address all comments and requests in order to expedite the audit process and gain approval of MICRO-LEVLEN™ as soon as possible.

Please feel free to contact me at (973) 276-2305 with any questions that you may have regarding this submission.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/micro127

REVIEWS COMPLETED

CSO

MEMO

CSO IN

DATE

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

DUPLICATE

BERLEX

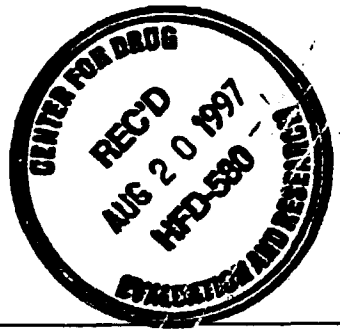
Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

August 15, 1997

NEW CORRESP

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane HFD-580, Room 17B-45
Rockville, Maryland 20857-1706



Re: NDA 20-860
MICRO-LEVLEN™ Tablets

Dear Dr. Rarick:

Please refer to New Drug Application 20-860 which was submitted on June 13, 1997. This NDA provides for a fixed combination of ethinyl estradiol and levonorgestrel tablets for use as an oral contraceptive.

Attached please find a letter addressed to Dr. Gurston Turner dated August 15, 1997 which provides information regarding

Please contact Ms. Nancy Velez at (973) 276-2305 if you have any additional questions.

Sincerely,

BERLEX LABORATORIES, INC.

Sharon W. Brown
Associate Director
Drug Regulatory Affairs

SWB/letter/micro113