

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-225**

**ADMINISTRATIVE DOCUMENTS**

**BERLEX**

Laboratories, Inc.

NDA 21-225

LNG-Releasing Intrauterine System

**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 Mirena® [Levonorgestrel-releasing Intrauterine System (LNG-IUS)], NDA 21-225.

BERLEX LABORATORIES, INC.

*Ted Ikeda*

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

*Jan. 27, 2000*

Date

**BERLEX**

Laboratories, Inc.

NDA 21-225

LNG-Releasing Intrauterine System

**13. PATENT INFORMATION**

Pursuant to 21 CFR 314.50(h)(ii), there are no patents that claim the Levonorgestrel-releasing Intrauterine System (LNG-IUS) on which the investigations that are relied upon in this New Drug Application, NDA 21-225, were conducted, nor are there any relevant patents that claim the use of the Levonorgestrel-releasing Intrauterine System that is the subject of NDA 21-225.

BERLEX LABORATORIES, INC.

Ted Ikeda

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

Jan. 27 2000

Date

**EXCLUSIVITY SUMMARY for NDA # 21-225**

SUPPL #     

Trade Name Mirena® Generic Name levonorgestrel intrauterine system

Applicant Name Berlex Laboratories, Inc. HFD- 580

Approval Date December 6, 2000

**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 questions about the submission.

a) Is it an original NDA? YES / X / NO /      /

b) Is it an effectiveness supplement? YES /      / NO / X /

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 / X / 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 /X\_/ NO /\_\_\_/

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

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /X\_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /X\_/

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /\_\_\_/ NO /X\_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # \_\_\_\_\_

Levonorgestrel is an active moiety in many approved contraceptive products.

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 # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 /X/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 /X\_/ 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 9:**

\_\_\_\_\_

- (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 /X\_/ 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 /X\_/

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 /X/

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:

Investigation #1, Study # Report AY99, Protocol 98042

Investigation #2, Study # Report Bo78, Protocol 89532

Investigation #3, Study # Report AV97, Protocol 92533

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 /X\_/

Investigation #2 YES /\_\_\_/ NO /X\_/

Investigation #3 YES /\_\_\_/ NO /X\_/

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

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (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 / X /

Investigation #2                      YES / \_\_\_ /                      NO / X /

Investigation #3                      YES / \_\_\_ /                      NO / X /

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

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (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"):

Investigation # 1 , Study # Report AY99, Protocol 98042

Investigation # 2 , Study # Report B078, Protocol 99532

Investigation # 3 , Study # Report AV97, Protocol 92533

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.



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 / X /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

         
Signature of Preparer  
Title: Regulatory Project Manager

         
Date

         
Signature of Office of Division Director

         
Date 12/6/00

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**Request for Three Years Marketing Exclusivity**

Pursuant to 21 U.S.C. 355(j)(4)(D)(iii) and 21 U.S.C. 355(c)(3)(D)(iii), and with reference to 21 CFR 314.50(j)(1) and to 21 CFR 314.108(b)(4)(iv), Berlex Laboratories, Inc. hereby requests a period of 3 years marketing exclusivity for Mirena® [Levonorgestrel-releasing Intrauterine System (LNG-IUS)], the subject of NDA 21-225. This request for a three-year exclusivity period is based upon the following criteria:

1. The Levonorgestrel-releasing Intrauterine System (LNG-IUS), the subject of NDA 21-225, has not been previously approved by the Food and Drug Administration.
2. The results of the three new clinical investigations included in NDA 21-225, and identified below, to support a finding of substantial evidence of effectiveness of the Levonorgestrel-releasing Intrauterine System (LNG-IUS) for intrauterine contraception.
  - A. Report AY99, Protocol 98042, Re-evaluation of the Levonorgestrel-releasing Intrauterine System (LNG-IUS) users of Leiras Study 8216. Report AY99 can be found in Item 8, Volume 7, Page 4 of NDA 21-225.
  - B. Report B078, Protocol 89532, Five-year clinical performance of the new formulation of the Levonorgestrel Intrauterine System and serum Levonorgestrel concentration with the new formulation compared to that with the original one. Report B078 can be found in Item 8, Volume 78, Page 1 of NDA 21-225.
  - C. Report AV97, Protocol 92533, Clinical performance of LNG-IUS versus combined oral contraceptive in young nulliparous women. Report AV97 can be found in Item 8, Volume 94, Page 22 of NDA 21-225.
3. A determination that the three aforementioned clinical investigations are essential to the approval of Levonorgestrel-releasing Intrauterine System (LNG-IUS) for intrauterine contraception. Berlex Laboratories, Inc. certifies that there are not sufficient published studies or publicly available reports of clinical investigations, other than those sponsored by Leiras Oy, Turku, Finland, to support the approval of NDA 21-225. Leiras Oy, like Berlex Laboratories, Inc., is a wholly owned subsidiary of Schering AG, Berlin, Germany. Schering AG acquired Leiras Oy in 1996.
4. IND \_\_\_\_\_ was originally submitted to the Food and Drug Administration by The Population Council on August 31, 1983. All rights and responsibilities for IND \_\_\_\_\_ were transferred to Berlex Laboratories, Inc. on March 6, 1998. Information pertaining to the three aforementioned studies, which are essential to the approval of NDA 21-225, was submitted to IND \_\_\_\_\_ copy of the letter from FDA, Division of Reproductive and Urologic Drug Products [HFD-580], dated April 9, 1998, acknowledging the transfer of ownership of IND \_\_\_\_\_ to Berlex is provided herewith.

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) [View Word Document](#)

NDA Number: 021225 Trade Name: MIRENA(LEVONORGESTREL RELEASING INTRA-UT  
 Supplement Number: 000 Generic Name: LEZONORGESTREL RELEASING INTRA-UTERINE S  
 Supplement Type: N Dosage Form:  
 Regulatory Action: OP COMIS Indication: CONTRACEPTION TREATMENT  
 Action Date: 2/1/00

Indication # 1 Intrauterine Contraception  
 Label Adequacy: Does Not Apply  
 Formulation Needed: NO NEW FORMULATION is needed  
 Comments (if any):

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
Adult	Adult	Waived	
Comments: Not indicated for pediatric usage, Indicated for parous women who desire long-term contraception			

This page was last edited on 12/6/00

*LS*

12/6/00

Signature

Date

**BERLEX**

Laboratories, Inc.

NDA 21-225

LNG-Releasing Intrauterine System

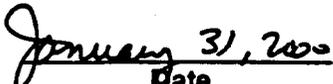
**16. Debarment Certification**

**Certification Under Section 306(k)(1) of the FD & C Act**

Berlex Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-225 for LNG-Releasing Intrauterine System.

**BERLEX LABORATORIES, INC.**

  
Joan Mutascio  
Regulatory Submissions &  
Information Associate

  
Date

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-225</u> / SE _____	
Drug <u>Mirena® (levonorgestrel intrauterine system)</u> Applicant <u>Berlex Laboratories, Inc.</u>	
RPM <u>Jeanine Best, M.S.N., R.N.</u> Phone <u>7-4260</u>	
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) _____	
Application classifications: Chem Class <u>3S</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>December 7, 2000</u> Secondary <u>February 7, 2001</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:
  - User Fee Paid
  - User Fee Waiver (attach waiver notification letter)
  - User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
  - FDA revised labeling and reviews..... X
  - Original proposed labeling (package insert, patient package insert) ..... X
  - Other labeling in class (most recent 3) or class labeling..... X
  - Has DDMAC reviewed the labeling? .....  Yes (include review)  No (no written review)
  - Immediate container and carton labels ..... X
  - Nomenclature review..... X
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.
  - Exception for review (Center Director's memo)..... \_\_\_\_\_
  - OC Clearance for approval..... \_\_\_\_\_

◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	■ Materials requested it: AP letter
◆ Post-marketing Commitments	X
Agency request for Phase 4 Commitments.....	X
Copy of Applicant's commitments.....	X
◆ Was Press Office notified of action (for approval action only)?.....	■ Yes <input type="checkbox"/> No
Copy of Press Release or Talk Paper.....	
◆ Patent	
Information [505(b)(1)].....	X
Patent Certification [505(b)(2)].....	
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	NA
◆ Exclusivity Summary.....	X
◆ Debarment Statement.....	X
◆ Financial Disclosure	
No disclosable information.....	
Disclosable information – indicate where review is located.....	X
◆ Correspondence/Memoranda/Faxes.....	X
◆ Minutes of Meetings.....	X
Date of EOP2 Meeting <u>NA</u>	
Date of pre NDA Meeting <u>January 27, 1998, June 21, 1999</u>	
Date of pre-AP Safety Conference <u>NA</u>	
◆ Advisory Committee Meeting.....	NA
Date of Meeting.....	
Questions considered by the committee.....	
Minutes or 48-hour alert or pertinent section of transcript.....	
◆ Federal Register Notices, DESI documents.....	NA

**CLINICAL INFORMATION:**

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo).....	X
◆ Clinical review(s) and memoranda.....	X

- ◆ Safety Update review(s) .....  X
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver) □ Deferred Pediatric Page.....  X
  - Pediatric Exclusivity requested? □ Denied □ Granted ■ Not Applicable
- ◆ Statistical review(s) and memoranda .....  X
- ◆ Biopharmaceutical review(s) and memoranda.....  X
- ◆ Abuse Liability review(s) .....  NA 
  - Recommendation for scheduling ..... \_\_\_\_\_
- ◆ Microbiology (efficacy) review(s) and memoranda .....  NA
- ◆ DSI Audits .....  X 
  - Clinical studies □ bioequivalence studies .....  X

**CMC INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda .....  X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability .....  NA
- ◆ DMF review(s) .....  X
- ◆ Environmental Assessment review/FONSI/Categorical exemption .....  NA
- ◆ Micro (validation of sterilization) review(s) and memoranda .....  X
- ◆ Facilities Inspection (include EES report)
  - Date completed \_\_\_\_\_ □ Acceptable □ Not Acceptable
- ◆ Methods Validation ..... □ Completed ■ Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda .....  X
- ◆ Memo from DSI regarding GLP inspection (if any) .....  NA

- ◆ Statistical review(s) of carcinogenicity studies ..... NA
- ◆ CAC/ECAC report ..... NA

WITHHOLD 2 PAGE (S)

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** March 21, 2000

**DUE DATE:** September 7, 2000

**OPDRA CONSULT #:** 00-0104

**TO:** Susan Allen, M.D.  
Director, Division of Reproductive and Urologic Drug Products  
HFD-580

**THROUGH:** Jeanine Best, Project Manager  
HFD-580

**PRODUCT NAME:** Mirena™  
(levonorgestrel-releasing intrauterine system)

**NDA SPONSOR:** Berlex Laboratories, Inc.  
Wayne, New Jersey 07470

**NDA #:** 21-225

**SAFETY EVALUATOR:** Carol Pamer, R.Ph.

**SUMMARY:** In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Mirena" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:** OPDRA does not object to the use of the name "Mirena".

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**  
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**  
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS**  
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

51  
Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

51  
Peter Honig, M.D.  
Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Jan 1 8/11/00

# Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

## PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** August 1, 2000  
**NDA NUMBER:** 21-225  
**NAME OF DRUG:** Mirena (levonorgestrel-releasing intrauterine system)  
**NDA SPONSOR:** Berlex Laboratories, Inc.  
Wayne, New Jersey 07470

### I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the tradename *Mirena*. Mirena is a levonorgestrel-releasing intrauterine system that is indicated for intrauterine contraception and is effective for up to 5 years following its insertion. The device releases levonorgestrel at a rate of 20 mcg per day.

### II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>i,ii,iii</sup> as well as several FDA databases<sup>iv</sup> for existing drug names which sound alike or look alike to Mirena to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's (USPTO) Text and Image Database was also conducted<sup>v</sup>. An Expert Panel discussion was conducted to review all findings from the searches.

#### A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Mirena. Potential concerns regarding drug marketing and promotion related to the proposed trade name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The consensus reached by the Expert Panel was that name comparison should be made with proprietary names of other intrauterine devices (IUDs). As with other IUDs, Mirena will have limited channels of distribution, all IUDs require that the patient read and sign informed consent

forms provided by the manufacturer prior to insertion, and all IUDs require insertion by a physician at the location where the product is dispensed (e.g., physician's office or contraceptive clinic). Two other intrauterine contraceptive devices are marketed in the U.S. *ParaGard® T380A* (Ortho-McNeil) is a copper-releasing intrauterine system that is effective for up to 10 years following its insertion. *Progestasert®* (Alza) is a progesterone-releasing intrauterine system that is effective for 12 months following its insertion. Neither of these proprietary names was believed to have look-alike, sound-alike properties relative to Mirena.

### B. SAFETY EVALUATOR RISK ASSESSMENT

The consensus reached by the Expert Panel was that the products with which Mirena should be compared were other IUDs. Neither of the names for products currently marketed in the U.S., *ParaGard T380A* and *Progestasert*, were considered likely to be confused with the proprietary name "Mirena".

For these reasons, we do not object to the use of the proprietary name "Mirena".

### III. RECOMMENDATIONS

OPDRA has no objections to use of the proprietary name "Mirena".

If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

BP

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Carol Pamer, R.Ph.  
Safety Evaluator  
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

BP

8/10/00

---

Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-225

FD-580: Division Files/Jeanine Best, Project Manager

FD-580: Susan Allen, Division Director

HFD-400: Jerry Phillips, Associate Director, OPDRA

HFD-400: Carol Pamer, Safety Evaluator, OPDRA

Electronic only cc:

HFD-002: Murray Lumpkin, Deputy Center Director for Review Management

HFD-400: Peter Honig, Director, OPDRA

HFD-040: Patricia Staub, Senior Regulatory Review Officer, DDMAC

HFD-440: Mary Dempsey, Project Manager, OPDRA

HFD-400: Sammie Beam, Project Manager, OPDRA

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<sup>i</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

<sup>ii</sup> American Drug index, 42<sup>nd</sup> Edition, 1999, Facts and Comparisons, St. Louis, MO.

<sup>iii</sup> Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

<sup>iv</sup> COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

<sup>v</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

APPEARS THIS WAY  
ON ORIGINAL

7  
**MEMORANDUM OF TELECON**

DATE: December 5, 2000

APPLICATION NUMBER: NDA 21-225

**BETWEEN:**

Name: Jo-Ann Ruane, Manager, Regulatory Affairs  
Phone: (973) 276-2343  
Representing: Berlex Laboratories, Inc.

**AND**

Name: Jeanine Best, M.S.N. R.N., Regulatory Project Manager  
Division of Reproductive and Urologic Drug Products

**SUBJECT:** Biopharmaceutical Phase 4 Commitments

The sponsor was asked to accept two Phase 4 Commitments in a November 16, 2000 teleconference. The sponsor submitted their agreement to the two Phase 4 Commitments on November 16, 2000 and the requested revision on November 27, 2000.. The Division requests that the first Phase 4 Commitment be revised to read:

"The ongoing (12-month) Phase 1 study (Protocol 303700) will be completed, and the study results including the *in vivo* and *ex vivo* data will be submitted to the Division within one year of approval of the product."

The sponsor will submit acceptance to this revised Phase 4 Commitment.

151  
\_\_\_\_\_  
Jeanine Best, R.N., M.S.N.,  
Regulatory, Project Manager

cc:

Archival NDA 21-225  
HFD-580/Division Files  
HFD-580/Parekh

Drafted by: JAB/December 5, 2000  
Final: JAB/December 5, 2000  
Filename: N21225tcon120500.doc  
**TELECON**

**MEMORANDUM OF TELECON**

**DATE:** November 30, 2000

**APPLICATION NUMBER:** NDA 21-225

**BETWEEN:**

**Name:** Jo-Ann Ruane, Manager, Drug Regulatory Affairs  
**Phone:** (973) 276-2343  
**Representing:** Berlex Laboratories, Inc.

**AND**

**Name:** Jeanine Best, M.S.N., R.N.  
**Division of Reproductive and Urologic Drug Products, HFD-580**

**SUBJECT:** Microbiologist's comment to sponsor's November 14, 2000 response to Microbiology deficiencies.

The following comment was conveyed to the sponsor:

The sponsor will commit to discontinuing the use of \_\_\_\_\_  
s and will implement by the first annual report after approval of this NDA.

LSI  
Jeanine Best, M.S.N., R.N., Regulatory Project Manager

**cc:**

Archival NDA 21-225  
HFD-580/Division Files  
HFD-580/Rhee/Agarwal/Rumble

Drafted by: JAB/December 1, 2000  
Final: JAB/December 1, 2000  
Filename: 21225telecon113000.doc  
**TELECON**

MEMORANDUM OF TELECON

DATE: November 28, 2000

APPLICATION NUMBER: NDA 21-225

BETWEEN:

Name: Jo-Ann Ruane, Manager, Regulatory Affairs  
Phone: (973) 276-2343  
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N.  
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Clinical Phase 4 Commitments

Three Clinical Phase 4 Commitments were discussed in November 20, 2000 teleconference and agreed upon and submitted on November 21, 2000. The Division requests revision of the commitments as follows:

1. "Submit the completed study report for Study 102-96502 entitled "Incidence of Complications Requiring Hospital treatment in Lenonova Users in 1990-95" in the year 2001."
2. "For postmarketing safety reports of pregnancy: follow up cases through delivery (or termination) to obtain information regarding outcome of spontaneously reported cases of pregnancy including live births, premature births, miscarriages, (spontaneous abortions), septic abortions, and congenital anomalies. Also, obtain information about duration of fetal exposure."
3. "In periodic safety reports: provide a separate line listing of U.S. safety reports and an estimation of U.S. patient exposure to Miren<sup>a</sup>"

151  
\_\_\_\_\_  
Jeanine Best, M.S.N., R.N.  
Regulatory Project Manager

cc:

Archival NDA 21-225  
HFD-580/Division Files  
HFD-580/Hixon/Furlong

Drafted by: JAE/November 28, 2000  
Final: JAB/November 28, 2000  
Filename:telecon21225112800.doc

TELECON

**MEMORANDUM OF TELECON**

DATE: November 27, 2000

APPLICATION NUMBER: NDA 21-225

**BETWEEN:**

Name: Jo-Ann Ruane, Manager, Regulatory Affairs  
Phone: (973) 276-2343  
Representing: Berlex Laboratories, Inc.

**AND**

Name: Jeanine Best, M.S.N. R.N., Regulatory Project Manager  
Division of Reproductive and Urologic Drug Products

SUBJECT: Biopharmaceutical Phase 4 Commitments

The sponsor was asked to accept two Phase 4 Commitments in a November 16, 2000 teleconference. The sponsor submitted their agreement to the two Phase 4 Commitments on November 16, 2000. The Division requests that the first Phase 4 Commitment be revised from:

To:

"The ongoing (12-month) Phase 1 study (Protocol 303700) will be completed, and the study results including the *in vivo* and *ex vivo* data will be submitted to the Division."

The sponsor will submit acceptance to this revised Phase 4 Commitment.

  
\_\_\_\_\_  
Jeanine Best, R.N., M.S.N.,  
Regulatory, Project Manager

cc:

Archival NDA 21-225  
HFD-580/Division Files  
HFD-580/Parekh

Drafted by: JAB/November 27, 2000

Final: JAB/November 27, 2000

Filename:

TELECON

## Teleconference Meeting Minutes

**Date:** November 20, 2000    **Time:** 9:00-9:50 AM    **Location:** Parklawn; 17B-45

**NDA** 21-225                      **Drug:** Mirena® (levonorgestrel-releasing intrauterine system)

**Indication:** Contraception

**Sponsor:** Berlex Laboratories, Inc.

**Type of Meeting:** Teleconference

**Meeting Chair:** Dr. Dena Hixon

**Meeting Recorder:** Jeanine Best

**External Lead:** Dr. Brenda Mardzi

**FDA Attendees:**

Dena Hixon, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

**External Participants:**

Berlex Laboratories, Inc. **BERLEX TO PROVIDE LIST OF NAMES**

Brenda Mardzi, Pharm. D., Associate Director, Drug Regulatory Affairs

Dr. Vladimir Yankov, Senior Associate Medical Director (Female Health Care)

**Leiras**

Dr. Faru Blom, Core Clinician for Mirena

Dr. Christer Stromberg, Director of Regulatory Affairs

**Meeting Objective:** To discuss Phase 4 Commitments for postmarketing of this drug product

**Background:**

Mirena® was developed by Leiras Oy, Turku, Finland, as an intrauterine contraceptive with a 5-year period of use. Mirena® is comprised of a T-shaped frame on which a reservoir containing 52 mg of levonorgestrel USP, is mounted. The reservoir is covered with a membrane that regulates the release of levonorgestrel (LNG) from the system at a nominal initial rate of 20 µg/day. The product has undergone four formulation changes; dose-finding studies were done with formulation "A"; one pivotal trial was done with formulation "B"; another pivotal trial was done with formulation "C", which included the manufacturing change within \_\_\_\_\_ and formulation "D" is the to-be-marketed product, which represents a change in the manufacturer of the reservoir and membrane.

**Discussion:**

- the Agency now has an increased emphasis on risk management activities especially pertaining to the postmarketing period of drug products
- the Agency is attempting to improve pregnancy labeling in all drug labels
- the Division proposes the following three Clinical Phase 4 Commitments:
  - Berlex to submit the final study report LE102-96502 in 2001 that will include data on insertion complications resulting in hospitalization. Study LE102-96502 was a large postmarketing study of 26,000 Mirena users in Finland that evaluated length of use, safety, and efficacy of Mirena
  - Berlex to follow-up on adverse events reports related to pregnancy for as much outcome information as possible. Pregnancy reports must be followed up for birth defects, septic abortions, premature deliveries, and duration of the exposure to Mirena, whenever this information can be obtained
  - Berlex to provide a separate section (a brief synopsis) in the periodic safety update reports for U.S. adverse event data and estimates of exposure to Mirena (intrauterine devices (IUDs) are not widely used in the U.S. and it is possible that the lack of experience will adversely affect the safety profile of Mirena, i.e., perforations may be a greater problem in the U.S. than elsewhere)
- the sponsor reported that they accept the Phase 4 Commitment # 1, but need to discuss #'s 2 and 3 with their Drug Safety Unit before providing an acceptance

**Action Items:**

- the sponsor will notify the Division in writing with their decision regarding acceptance of the proposed Phase 4 Commitments
- Meeting Minutes to the sponsor within 30 days

151

Minutes Preparer

BT

Concurrence, Chair

**Note to Sponsor:**

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes

**NDA 21-225**  
**Meeting Minutes**  
**Page 3**

**cc:**

**Original NDA 21-225**

**HFD-580/DivFile**

**HFD-580/PM/BEST**

**HFD-580/Hixon/Furlong/Rumble**

**drafted: JAB/November 20, 2000/N21225Tcon112000.doc**

**concurrence: Rumble, 11.20.00/Furlong, 11.20.00/Hixon, 11.27.00**

**Final: JAB/November 27, 2000**

**MEETING MINUTES**

## Teleconference Meeting Minutes

**Date:** November 16, 2000    **Time:** 9:00-9:50 AM    **Location:** Parklawn; 17B-45

**NDA 21-225**                      **Drug:** Mirena® (levonorgestrel-releasing intrauterine system)

**Indication:** Contraception

**Sponsor:** Berlex Laboratories, Inc.

**Type of Meeting:** Teleconference

**Meeting Chair:** Dr. Moo-Jhong Rhee

**Meeting Recorder:** Jeanine Best

**External Lead:** Jo-Ann Ruane

### **FDA Attendees:**

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD 580)

Rajiv Agarwal, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

DJ Chatterjee, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

### **External Participants:**

#### **Berlex Laboratories, Inc:**

Jo-Ann Ruane, Manager, Drug Regulatory Affairs

Adela Karera, Associate Director, Clinical Pharmacology

Konald Wohl, Director, Strategic CMC

#### **Consultant**

#### **Leiras**

Hannu Allonen, Director of Project Management

Pasi Merkkü, Head of Pharmaceutical Development (Fertility Control/Hormone Therapy)

Merja Wester, Laboratory Manager, Analytical Development (Fertility Control/Hormone Therapy)

Christer Stromberg, Director of Regulatory Affairs

Heikki Lyytikäinen, Senior Scientist (Fertility Control/Hormone Therapy)

Jyrki Pihlaja, Scientist (Fertility Control/Hormone Therapy)

**Meeting Objective:** To discuss dissolution specification proposal, Phase 4 Commitment proposal, and shelf-life expiry date.

**Background:**

Mirena® was developed by Leiras Oy, Turku, Finland, as an intrauterine contraceptive with a 5-year period of use. Mirena® is comprised of a T-shaped frame on which a reservoir containing 52 mg of levonorgestrel USP, is mounted. The reservoir is covered with a membrane that regulates the release of levonorgestrel (LNG) from the system at a nominal initial rate of 20 µg/day. The product has undergone four formulation changes; dose-finding studies were done with formulation "A"; one pivotal trial was done with formulation "B"; another pivotal trial was done with formulation "C", which included the manufacturing change within \_\_\_\_\_ and formulation "D" is the to-be-marketed product, which represents a change in the manufacturer of the reservoir and membrane.

**Discussion:****Dissolution Specifications**

- setting specific dissolution specifications are necessary for completing the NDA review process; setting correct specifications for a controlled release product such as Mirena is critical for contraceptive efficacy
- the Division has applied concepts from ICH guidelines and proposed specifications based on a mean of presented historical data  $\pm 3$  standard deviations (SD); the sponsor presented two histograms in their NDA; one presenting minimum values and the other presenting maximum values; the Division took an average of this histogram data \_\_\_\_\_, and applied the sponsor's proposed SD (\_\_\_\_\_ mcg/day) to set the dissolution specification range between \_\_\_\_\_ mcg/day; the product will, therefore, have an average release of \_\_\_\_\_ µg/day with the range of release between \_\_\_\_\_ mcg/day; these specifications are tight because the Division needs to ensure that the individual product will provide sufficient drug to the patient for contraceptive efficacy
- the sponsor believes that these proposed specifications are too tight, and not warranted based on clinical study information, and that many individual products will fall out of this range; the sponsor also reports that based on these specifications the clinical batch used for the pivotal efficacy trial would fail; the Division responded that these specifications were set based on data that the sponsor submitted in their NDA, and must be based on U.S. clinical study batch data; the sponsor may compile and submit additional data today, if available, to support looser dissolution specifications; the sponsor may submit a supplement, post-approval, to change the specifications, if in the future they are experience failures based on current specifications; the sponsor would also need to perform bioavailability studies to support any changes; the Division reminded the sponsor of the Stage I and Stage II requirements for stability and release methods
- the Division recommends that the sponsor accept the current proposed specifications as interim specification at this time due to review-clock constraints and then provide an additional data base with accumulated U.S batch data and rationale to propose new specifications

**Phase 4 Commitment**

- the sponsor reports that they are currently conducting long-term (5-year) comparative dissolution studies for Compositions "C" and "D", and that they are collecting *ex vivo* data for Composition "D" for 12-months to compare to Composition "C"
- the Division requests the following Phase 4 Commitments:
  1. Collect data on 5-year comparative dissolution profiles for Compositions "C" and "D"
  2. Collect *ex vivo* release information on Composition "D"
- the Division requests that the above data be submitted to the FDA for review when available

**Shelf-Life Expiry Date**

- the sponsor is requesting a \_\_\_\_\_ expiry date for their product but has only submitted \_\_\_\_\_ of real-time data and \_\_\_\_\_ of accelerated data in their NDA, data that would support an \_\_\_\_\_ expiry date; the sponsor reports that they will have \_\_\_\_\_, real-time data to submit next week to support a 24-month expiry date
- the Division told the sponsor that the data can be submitted but may not be reviewed during this review-cycle; if the data constitutes a major amendment, then the Division will either extend the review-clock for three months or, defer review during this review-clock since the Division is ready to take an Action

**Action Items:**

- the sponsor will notify the Division by 11/17/00 with their decision regarding acceptance of the proposed dissolution specifications
- the sponsor will submit their acceptance to the Phase 4 Commitments by COB today
- Meeting Minutes to the sponsor within 30 days

LSI

\_\_\_\_\_  
Minutes Preparer

LSI

\_\_\_\_\_  
Concurrence, Chair

**Note to Sponsor:**

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes

NDA 21-225  
Meeting Minutes  
Page 4

cc:

Original NDA 21-225

HFD-580/DivFile

HFD-580/PM/BEST

HFD-580/Rhee/AgarwalParekh/Chatterjee

drafted: JAB/November 16, 2000/N21225Tcon111600.doc

concurrence: Rumble, 11.20.00

Final: JAB/November 27, 2000

MEETING MINUTES

**NDA 21-225**

**Mirena® (levonorgestrel-releasing intrauterine system)  
Berlex Laboratories, Inc.**

**Original Carton Labeling**

**APPEARS THIS WAY  
ON ORIGINAL**

5 pages redacted from this section of  
the approval package consisted of draft labeling

**NDA 21-225**

**Mirena® (levonorgestrel-releasing intrauterine system)  
Berlex Laboratories, Inc.**

**There was no Chemistry/Statistical review for this drug product.**

**APPEARS THIS WAY  
ON ORIGINAL**

**NDA 21-225**  
**Mirena® (levonorgestrel-releasing intrauterine system)**  
**Berlex Laboratories, Inc.**

**Sponsor Updated Patient Insert, October 6, 2000**

**APPEARS THIS WAY  
ON ORIGINAL**

14 pages redacted from this section of  
the approval package consisted of draft labeling

**NDA 21-225**  
**Mirena® (levonorgestrel-releasing intrauterine system)**  
**Berlex Laboratories Inc.**

**Original Patient Insert**

**APPEARS THIS WAY  
ON ORIGINAL**

9 pages redacted from this section of  
the approval package consisted of draft labeling

**NDA 21-225**

**Mirena® (levonorgestrel-releasing intrauterine system)**

**Berlex Laboratories, Inc.**

**Original Physician Insert**

APPEARS THIS WAY  
ON ORIGINAL

25 pages redacted from this section of  
the approval package consisted of draft labeling

**3.2 Pharmacologic class, scientific rationale, intended use, and potential clinical benefit**

**3.2.1 Pharmacologic class**

Drug delivery system delivering progestin hormone (levonorgestrel) locally (intrauterine)

**3.2.2 Scientific rationale**

Although progestins can have contraceptive efficacy by local or systemic means, the levonorgestrel in the levonorgestrel-releasing intrauterine system (LNG IUS) has mainly local progestogenic effects in the uterine cavity. Some or all of the following effects are the basis of the contraceptive efficacy of LNG IUS. The high levonorgestrel concentrations in the endometrium inhibit the endometrial synthesis of estrogen receptors, making the endometrium insensitive to the circulating estradiol and a strong antiproliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction are observed during use of LNG IUS. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. The local milieu of the uterus and of the ovarian tubes inhibits sperm mobility and function, preventing fertilization. Although acting predominantly locally, ovulation is inhibited in some women.

**3.2.3 Intended use**

Long-term (5 years) contraception

**3.2.4 Potential clinical benefits**

The LNG IUS is a highly effective contraceptive. Once inserted, no further action such as daily pill intake or monthly injection is required on the part of the woman or her physician for 5 years. As a result, the failure rate approximates that achieved by sterilization. Bleeding, a problem which characterizes IUDs, is usually not a problem with LNG IUS. In fact, some women become amenorrheic due to the local effects of the progestin and this will be viewed by some as a benefit.

**3.3 Foreign marketing history**

The levonorgestrel-releasing intrauterine system (LNG IUS) is registered and marketed in 28 countries. As of September 27, 1999, LNG IUS has been approved in 14 additional countries, but not yet marketed. There is no country in which LNG IUS has been withdrawn from the

market for any reason. Text Table 1 lists the countries where LNG IUS is approved, the tradename under which it is marketed, and the date of approval.

**Text Table 1: Worldwide Approval and Marketing Status of  
Levonorgestrel-Releasing Intrauterine System  
(Status as of September 27, 1999)**

Country	Trademark <sup>a</sup>	Approval Date	Remarks
Austria	Mirena	July 10, 1996	
Belgium	Mirena	July 28, 1995	
Brazil	Mirena	August 20, 1999	Not yet launched
Bulgaria	Mirena	November 5, 1998	Not yet launched
China	Mirena	March 5, 1998	Not yet launched
Colombia	Mirena	May 4, 1999	Not yet launched
Czech Republic	Mirena	May 14, 1997	
Denmark	Levonova	April 5, 1993	
Estonia	Mirena	January 10, 1996	
Finland	Levonova	May 9, 1990	
France	Mirena	July 21, 1995	
Germany	Mirena	September 30, 1996	
Greece	Mirena	May 15, 1997	Not yet launched
Hong Kong	Mirena	August 13, 1996	
Hungary	Mirena	March 31, 1998	
Iceland	Levonova	April 1, 1994	
Iraq	Mirena	May 9, 1999	Not yet launched
Ireland	Mirena	August 28, 1998	
Israel	Mirena	August 1, 1997	
Italy	Mirena	January 19, 1996	
Korea, Republic Of	Mirena	September 30, 1998	
Lithuania	Mirena	June 2, 1998	
Luxembourg	Mirena	February 2, 1994	
Malaysia	Mirena	August 6, 1998	
Mexico	Mirena	June 21, 1999	Not yet launched
New Zealand	Mirena	April 2, 1998	
Norway	Levonova	December 7, 1993	
Peru	Mirena	September 9, 1999	Not yet launched
Philippines	Mirena	May 5, 1999	Not yet launched
Poland	Mirena	May 30, 1997	
Portugal	Mirena	December 12, 1996	
Russian Federation	Mirena	September 6, 1996	Not yet launched
Saudi Arabia	Mirena	July 15, 1998	Not yet launched

<sup>a</sup>Mirena and Levonova are registered trademarks of Leiras Oy.

**8.5.7.3 Package Inserts from Other Countries and Disclosure of Differences in Labeling**

The Berlex package insert proposed in this NDA was compared to our parent (Schering AG) company's corporate core text (CCT). This comparison starts on the next page. The CCT was also compared to foreign package inserts and these are provided in table format starting on Item 8, Volume 185, page 5.

The corporate core text is provided on Item 8, Volume 185, page 24.

Translations of foreign package inserts and copies of the inserts in the original language are provided as follows:

Country	Item, Volume and Page Number
Austria	Item 8 Volume 185 page 37
Belgium	Item 8 Volume 185 page 54
Denmark	Item 8 Volume 185 page 69
Finland	Item 8 Volume 185 page 88
France	Item 8 Volume 185 page 103
Germany	Item 8 Volume 185 page 114
Ireland	Item 8 Volume 185 page 149
Italy	Item 8 Volume 185 page 155
Netherlands (The)	Item 8 Volume 185 page 171
New Zealand	Item 8 Volume 185 page 192
Portugal	Item 8 Volume 185 page 201
South Africa	Item 8 Volume 185 page 222
Sweden	Item 8 Volume 185 page 227
United Kingdom	Item 8 Volume 185 page 245

## 1. Comparison of US and Foreign Labeling

The proposed US labeling for Mirena differs in some respects from the approved labeling which this product carries in other countries. The different foreign labelings are based on a Corporate Core Text (CCT). The differences between the CCT and the individual approved national labelings is discussed in Section 2 of this document.

There are many differences between the CCT and US labeling because the 2 documents have different structures. However, in most cases, these differences are due to different organization of essentially the same content.

This section will summarize the important differences between the proposed US labeling and the CCT. The first part will discuss elements found in the CCT but omitted from the proposed US labeling. The second part will discuss elements which are included in the proposed US labeling but not present in the CCT.

### 1.1 Elements found in CCT but omitted from US labeling

#### 1.1.1 Additional Indications

The LNG IUS is approved in some countries for

\_\_\_\_\_

\_\_\_\_\_

#### 1.1.2 Use

As per the format of the EU Summary of Product Characteristics (SmPC), the CCT states that there is

\_\_\_\_\_

No such statement is included in the proposed US labeling.

#### 1.1.3 Description of Adverse Events

The adverse events described in the CCT are those which had occurred in the clinical trials program which led to the European approvals. The AEs described in the proposed US labeling are those which occurred in the studies included in the Integrated Summary of Safety Data.

#### 1.1.4 Dysmenorrhea

The CCT states that the LNG IUS, \_\_\_\_\_ This statement is not included in the proposed US labeling.

**1.2 Elements found in CCT but omitted from US labeling****1.2.1 Elements based on approved US labeling of IUDs**

The proposed labeling for the LNG IUS includes several items which are modeled on the approved labeling for Paragard® and/or Progestasert®.

**1.2.1.1 Indication and Usage Section**

A Recommended Patient Profile is included.

**1.2.1.2 Contraindication section**

A history of PID, as well as active PID, is considered a contraindication.

Multiple sex partners is considered a contraindication.

**1.2.1.3 Warnings section**

Septic abortion and treatment of PID (as per CDC recommendations) are discussed in a manner different from the CCT but analogous to the approved US labeling for Paragard®.

Table of birth-related and method-related mortality identical to that in the approved US labeling for other products is included.

**1.2.1.4 Adverse Events/Clinical Studies**

Adverse events frequencies, bleeding frequencies, continuation and discontinuation rates, etc are based on the clinical data included in the integrated summaries on which this NDA is based and, therefore, differ slightly from the frequencies cited in the CCT. Comparative efficacy rates for different methods are based on data from Trussel, et al (as per other approved US products) and differ from the CCT.

**2. COMPARISON OF THE MIRENA® CCT AND 14 FOREIGN LABELING TEXTS**

The important differences between the CCT and the local MIRENA® labeling texts of 14 countries with respect to contraindications, warnings, precautions for use and adverse reactions are summarized below. The reference countries are: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, New Zealand, Portugal, South Africa, Sweden and the United Kingdom. Although Mirena is approved in an additional 42 countries, these 14 major countries are considered sufficiently representative.

There are obvious differences of the various labeling texts of MIRENA® caused by the different indications approved in the countries : MIRENA® can be used in contraception, treatment of menorrhagia and endometrial protection in connection with estrogen therapy, but all countries have not sought all these indications. The indications relevant for each country are mentioned. However, contraindication, warning and precaution information is included only as it pertains to the indication contraception.

APPEARS THIS WAY  
ON ORIGINAL

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# FACSIMILE TRANSMISSION RECORD

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Reproductive and Urologic Drug Products (HFD-580)  
Parklawn Building, Room 17B-45  
5600 Fishers Lane, Rockville, Maryland 20857

4 Number of Pages (including cover sheet)      Date: November 27, 2000

To: Jo-Ann Ruane  
Berlex Laboratories, Inc.  
Manager, Drug Regulatory Affairs

Fax Number: (973) 276-2016

Voice Number: (973) 276-2343

From: Jeanine A. Best, MSN, RN  
Regulatory Project Manager

Fax Number: 301-827-4267

Voice Number: 301-827-4260

Message: NDA 21-225, Meeting Minutes from 11/16/00

Please note that we do not consider this a formal communication.

NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

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Thank you.

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# Teleconference Meeting Minutes

OCT 26 2000

**Date:** October 20, 2000      **Time:** 11:00-11:30 AM      **Location:** Parklawn; 17B-43

**NDA** 21-225      **Drug:** Mirena® (levonorgestrel-releasing intrauterine system)

**Indication:** Contraception

**Sponsor:** Berlex Laboratories, Inc.

**Type of Meeting:** Teleconference

**Meeting Chair:** Dr. D.J. Chatterjee

**Meeting Recorder:** Jeanine Best

**External Lead:** Dr. Melikian

**FDA Attendees:**

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

DJ Chatterjee, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

**External Participants:**

**Berlex Laboratories, Inc.**

Jo-Ann Ruane, Manager, Drug Regulatory Affairs

Armen Melikian, Ph.D., Associate Director, Clinical Pharmacology

**Meeting Objective:** Discussion of IVIVC concerns.

**Background:**

Mirena® was developed by Leiras Oy, Turku, Finland, as an intrauterine contraceptive with a 5-year period of use. Mirena® is comprised of a T-shaped frame on which a reservoir containing 52 mg of levonorgestrel USP, is mounted. The reservoir is covered with a membrane that regulates the release of levonorgestrel (LNG) from the system at a nominal initial rate of 20 µg/day. The product has undergone four formulation changes; dose-finding studies were done with formulation "A"; one pivotal trial was done with formulation "B"; another pivotal trial was done with formulation "C", which included the manufacturing change within \_\_\_\_\_ and formulation "D" is the to-be-marketed product, which represents a change in the manufacturer of the reservoir and membrane.

**Discussion:**

**Clinical Pharmacology:**

**Questions:**

1. Please explain the IVIVC Graph (for formulations B and C) that relates dissolution profiles to amount of remaining LNG in the device. This graph shows a positive correlation and it appears to

demonstrate that the higher the dissolution rate, then a larger amount of LNG remains in the device. Is this true?

- the sponsor reported that they tried to predict the long-term dissolution from the amount of LNG left in removed devices; this graph demonstrates that products that were removed early had a greater amount of LNG remaining in the device, and therefore, a higher dissolution level
2. Does the sponsor have data on formulations C and D comparing the release rates in the two different dissolution media, \_\_\_\_\_ The release rates are different in the two media and the release specifications will be based on using \_\_\_\_\_ as the dissolution media.
- the sponsor has data on formulations C and D for initial release with a comparison in \_\_\_\_\_
  - all data on formulation D using \_\_\_\_\_ have been submitted in the NDA; it is located in the Chemistry section, Item 4, Volume 5, beginning on page 33
3. For IVIVC methodology, is the analysis of the LNG remaining in the devices based a chemical extraction method or a weight method? The weight method is not an acceptable analytical method. It can underestimate the release rate because of debris left on the device.
- the sponsor reported the analysis is done per the chemical extraction method

**Action Items:**

- Meeting Minutes to the sponsor within 30 days

ISA

\_\_\_\_\_  
Minutes Preparer

ISA

\_\_\_\_\_  
Concurrence, Chair

**Note to Sponsor:**

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes

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**cc:**  
**Original NDA 21-225**  
**HFD-580/DivFile**  
**HFD-580/PM/BEST**  
**HFD-580/Parekh/Chatterjee**  
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**MEETING MINUTES**