

4. Please provide the density of the tubing used in Compositions C and D and, if available, Pilot Composition D.

The density of the tubing batches is not available. A method of analysis for determining the density or specific gravity of the tubing has not been developed due to the anticipated technical difficulties in accurately measuring the required test parameters. Specifically, the ASTM standard used for determining the specific gravity of the _____ calls for the sample weight and volume to be a minimum of 1 gram and 1 cm³, respectively. One gram of tubing would correspond to approximately _____ of split tubing. After immersion of the sample in water, it would be nearly impossible to ensure that all trapped air bubbles are removed from the sample before the measurement is made.

For that reason, Leiras has instead utilized the specific gravity of the cured, unextruded elastomer. This parameter is routinely determined by the elastomer suppliers using the ASTM D792 standard, and has been reported for batches manufactured since 1988. Specific gravity results for the batches referenced in Report 1507 (see question #2), plus two additional tubing batches manufactured by _____ are provided below:

| Tubing Code | Tubing Batch No. ⁴ | Tubing Manufacturer | Product Composition | Supplier of _____ | Trade name of _____ | Specific gravity of _____ |
|-------------|-------------------------------|---------------------|---------------------|-------------------|---------------------|---------------------------|
| _____ | C98024 | Leiras | D | _____ | _____ | _____ |
| _____ | C98005 | Leiras | D | _____ | _____ | _____ |
| _____ | C96013 | Leiras | D (pilot) | _____ | _____ | _____ |
| _____ | C96014 | Leiras | D (pilot) | _____ | _____ | _____ |
| _____ | C98044 | Leiras | C | _____ | _____ | _____ |
| _____ | 60087 | Leiras | C | _____ | _____ | _____ |
| _____ | 60089 | Leiras | C | _____ | _____ | _____ |
| _____ | 94110171 | _____ | C | _____ | _____ | _____ |
| _____ | 906304 | _____ | C | _____ | _____ | _____ |

This data demonstrates that the specific gravity results for the _____ elastomers are comparable.

⁴ Tubing batches C98024 and C98005 were used in the primary stability batches, and tubing batch C96013 was used in the pilot Composition D stability batches; long-term dissolution data for these batches, and for three Composition C batches manufactured from _____ tubing batch 94110171, are provided in the NDA (see Item 4.1.2.6.7). Tubing batch 906304 was used in the clinical supplies utilized in one of the pivotal studies described in the NDA (Report AV97).

⁵ Only _____ elastomer is used for the US commercial formulation, Composition D

5. Please provide information pertaining to the DMF for the _____ used in the _____ that is referenced on page 24 in volume 6.

Please refer to the _____ Type III Drug Master File No. _____ for information pertaining to the _____ used in the _____. A letter authorizing FDA to refer to this DMF on behalf of Berlex Laboratories is provided in Item 4 as Attachment C.

6. Please provide information pertaining to the safety of the ink used for the scale of the insertion tube.

The printing ink, _____, is manufactured by _____. The composition of the ink is considered to be proprietary information by the manufacturer; however, printed insertion tubes manufactured using the same _____ and printing method have been commercially distributed in Europe for the past five years, i.e., along with the marketed copper intrauterine devices manufactured by Leiras Oy.

The printing ink manufacturer has stated that the ink corresponds to the European standard EN71-3, "Safety of toys Part 3: Specification for migration of certain elements" that determines migration limits for heavy metals. The _____ which is a _____ The scale on the insertion tube is pad printed onto the tube by _____, the manufacturer of the inserter.

Information pertaining to the toxicological risk evaluation of the insertion tubes is provided in Item 4, Volume 6, pages 96-97⁶. As described on page 96, the insertion tubes (printed) are subjected to cytotoxicity testing each time a new lot of raw material _____ is used to manufacture the tubes⁷. Furthermore, the printed tubes are tested _____ according to the manufacturing procedure for the product; therefore, the possible effects of _____ on the cells is considered. The cytotoxicity testing is performed in accordance with ISO 10993-5. Please refer to the inserter specification provided in the NDA for additional information pertaining to the cytotoxicity test (Item 4, Volume 6, page 30).

7. With reference to the regulatory methods for the drug product provided in Item 4, Volume 5: please explain the blank page on page 9; please provide a clear copy of the impurity information provided in Attachment 3 on page 24.

The regulatory methods for the drug product have been revised to address the reviewer's comments. In the updated version, which is provided in Item 4 as Attachment D, the blank page has been eliminated, and all three attachments have been replaced by clearer versions. There have been no other changes made to the methods except that the cover page has been revised to reflect that the method has been updated. Please note that the enclosed version of the regulatory methods replaces the version that was submitted in the CMC presubmission in Item 4.1.2.6 - Regulatory Methods (volume 5, page 1) and Item 4.3 -

⁶ We wish to clarify that the reference to "test articles with printed scales" on page 97 is not relevant for the current insertion tube because these samples were printed using different ink and printing method.

⁷ Please note that the insertion tubes that are subjected to cytotoxicity testing may be manufactured for use with either with copper IUDs or with Mirena and are printed at Leiras.

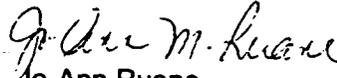
Methods Validation Package (volume 6, page 212). Therefore, two copies of the updated version of the regulatory methods are provided in Attachment D; three additional copies for Item 4.3 are also provided.

A Field Copy of this submission is being provided to the local FDA District Office. We are also providing Field Copies of all previously submitted responses to requests for CMC information, including our April 10, June 8, and July 11, 2000 submissions. A Field Copy Provision Certification, and a copy of the Field Copy Content Certification accompanying the Field Copies, are provided in Item 17.

We trust that our above responses satisfactorily address the reviewer's questions. Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES



Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copies (2): Ms. Jeanine Best

JMR/063

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| REVIEW'S COMPLETED | |
| CSO INITIALS | |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> MEMO |
| DATE | |

ORIGINAL

SCHERING

Susan Allen, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug
Products, HFD-580
Attention: Division Document
Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Schering AG
CRA Dossier Management FC/HT



Your Ref. _____ Your letter dated _____ Our Ref. (please indicate when replying) _____ Telephone: +49-30-468-11423 Date _____
+49-30-468-1111
R. Bragulla _____ Telefax: +49-30-468-18007 2000-08-02

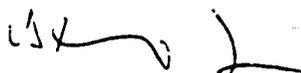
Re: NDA 21-225 Mirena (Levonorgestrel-releasing intrauterine system)
Drug Master File, Type II, No. _____ for _____ NEW CORRESP
Original Submission of May 21, 1981
Revised Version of February 22, 2000
Revised Annual Report dated August 01, 2000

Ladies and Gentleman,

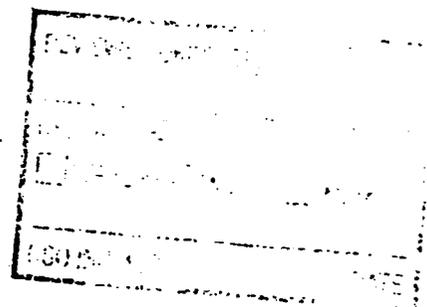
Enclosed please find two desk copies of the revised version of the annual report to the above-mentioned drug master file for the attention to Ms. Jeanine Best and Dr. Agarwal.

This revised version of the annual report with a detailed side-by-side comparison of the differences for two process steps of Levonorgestrel as requested by the FDA reviewing chemist Dr. Rajiv Agarwal replaces the previous annual report of the revised version of the DMF for Levonorgestrel dated February 22, 2000.

Yours sincerely,
SCHERING AKTIENGESELLSCHAFT


Dr. Fiedler
Group Leader Dossier Management FC/HRT


R. Bragulla
Dossier Management FC/HRT



enclosure
revised Annual Report

CC: Berlex Lab. Inc., Ms. Bray
Qualitätsmanagement, Herr Dr. Wozniowski
Corporate Quality Control, Frau Dr. Lehne
Betriebsleiter Bergkamen (über Ref. Technolog. Koordination, Dr. Peter)
Berlichem, Ms. Kaminski
PH-Chemikalien Vertrieb

Postal address: Schering AG, D-13342 Berlin, Germany · For visitors: Berlin-Wedding, Mülserstrasse 178 · Cable: Scheringchemie Berlin · Internet: <http://www.schering.de>

Executive board: Giuseppe Vita (Chairman), Klaus Pohle (Vice-Chairman), Hubertus Ertan, Ulrich Köstlin, Günter Stock · Chairman of the supervisory board: Klaus Subjetzki · Registered seat: Berlin · Trade register: AR Charlottenburg 93 HRB 283 · Commerzbank AG, Berlin, Account No. 108700800, Bank prefix No. 100 400 00 · Berliner Handels- und Frankfurter Bank.

Drug Development & Technology
Division of Berlex Laboratories, Inc.

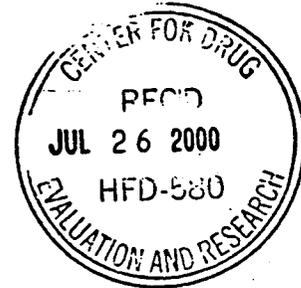
UPS OVERNIGHT

ORIGINAL

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

July 25, 2000

ORIG AMENDMENT



Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-225

Mirena[®] (levonorgestrel-releasing intrauterine system)
Amendment to Pending Application: Labeling, CMC
Other: Response to Request for Product Sample

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena[®] (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

Reference is also made to our letter dated June 30, 2000, in which we described Berlex's plans to amend the NDA to provide for changes to the Chemistry, Manufacturing and Controls information. In that letter, three planned changes were described: (1) a modification of the secondary packaging for the drug product; (2) a change in the site at which the T-Body is manufactured, and; (3) the use of an alternate assay method for barium sulfate USP, which is a component of the T-Body. We also indicated in the June 30 letter that revised labeling would be provided in the amendment.

Reference is also made to a July 6, 2000 voice mail message left by Ms. J. Best of the Division for the undersigned (Ms. J. Ruane) in which Ms. Best conveyed a request from the reviewing chemist for a sample of the drug product packaged in the modified secondary packaging that was described in the June 30 letter.

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| REVISED COMPLETED |
| CSG ACTION: |
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| COPIES DATE |

This submission amends NDA 21-225 to provide for the labeling and CMC changes to the NDA that were described in the June 30 letter. It also responds to the Division's July 6 request for a product sample. Provided below is a description of the information provided in this submission. A detailed Table of Contents is provided immediately following this letter.

Item 2- Labeling

Four copies of the each of the following:

- **Blister Pack Label:** Updated labeling for the primary package (i.e., a blister package with peelable lid) is provided.
- **Foil Pouch Label:** Labeling for the new Tyvek®/aluminum foil pouch that is described in this submission is provided. Also included is a mock-up drawing of the pouch showing the location of the lot number and expiration date.
- **Follow-up Reminder Card:** Labeling is provided for a new Follow-Up Reminder Card, which will be packaged in the secondary carton. Information pertaining to the date of insertion and the follow-up appointment schedules is to be recorded on this card and provided to the patient by the physician.
- **Carton Label:** Updated labeling for the secondary carton is provided.
- **Pocket Copy:** Labeling is provided for an pocket that is affixed to the inside lid of the secondary carton. Please note that we have included two versions of the labeling for this pocket (i.e., "option 1" and ——— that provide for placement of the Follow-Up Reminder Card either in the envelope or in the bottom of the carton beneath the foil pouch.
- **Physician Insert:** The draft physician insert has been updated to incorporate reference in the insertion instructions to the secondary pouch. The description of the package in the "how supplied" section has also been updated. No other changes in the package insert have been made.

Please note that updated patient labeling will be submitted in August '00.

A diskette (3.5 inch) containing electronic copies of the updated labeling in Word 97, SR 1 format is included in this submission. This diskette has been scanned for viruses using VirusScanNT 4.0.3a, which is produced and distributed by Network Associates, Inc., and is virus free. The diskette is located in a binder labeled "Electronic Copies of the Updated Labeling".

Item 4.1 – Chemistry, Manufacturing and Controls

- Information supporting the modification to the secondary packaging:
 - Introduction
 - Updated Packaging Processes and In-Process Controls Information
 - Updated Container-Closure System Information
 - Updated Stability Commitment

- information supporting the change in the site at which the T-body is manufactured:
 - Introduction
 - Copy of the cover letter to the updated _____ Type III Drug Master File No. _____ (Annual Update), which refers to the change in _____ and describes other minor revisions to the previously submitted information.
- Information supporting the use of an alternate assay method for barium sulfate, USP:
 - Introduction
 - Alternate assay method for barium sulfate USP
 - Information demonstrating the suitability of the method for use as an alternate to the USP assay method

Item 17 – Field Copy Certification

A statement certifying that a field copy has been sent to the local FDA district office is provided.

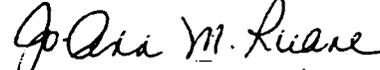
Sample of Packaged Product

Enclosed please find a sample of the drug product, which is packaged in the planned commercial packaging components. Please note that the primary container-closure system is unchanged from that described in the December 16, 1999 presubmission of Item 4. The foil pouch and secondary carton, including the envelope, are samples of those described in this amendment. These components are unlabeled, except that the primary container-closure system includes a label to enable identification of the product. This label is not intended to represent the labeling that will be used for the commercial product. In addition, it should be noted that, while the foil pouch has been left unsealed in this sample, the pouch used for the commercial product will be sealed during the packaging operation. Samples of the physician insert, patient information, and Follow-up Reminder Card are not yet available; however, we have included a sample of the booklet as an illustration of the format that will be used for the physician insert and patient information.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES



Jo-Ann Ruane

Manager

Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/061

Drug Development & Technology
Division of Berlex Laboratories, Inc.

UPS OVERNIGHT

ORIGINAL

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

July-18, 2000

ORIG AMENDMENT

BM



Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: **NDA 21-225**
Mirena® (levonorgestrel-releasing intrauterine system)
Amendment: Clinical Information

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Enclosed herein is an amendment containing new clinical information for 15 additional subjects from Study 8216 (Protocol 61540-8216) in whom the insertion was attempted but was not successful. Data from Study 8216 were *re-evaluated* under Protocol LE 102-98042 (Report AY99).

This amendment includes overview information on Protocol 61540-8216 and Protocol LE 102-98042 (Report AY99), the protocol under which the insertion information for these 15 subjects was collected. Also included in this amendment is an evaluation of the impact of this additional data on safety and efficacy, including pregnancy rate, continuation rates, discontinuation rates, extent of exposure, and adverse events.

Pertinent information for the 15 subjects with failed insertions, including subject number, study site number, whether the study site was qualified or nonqualified under the Protocol LE 102-98042, subject age, and the reason for the failed insertion is presented in Text Table 1. A copy of the CRF for each of the 15 subjects with failed insertions is included in Appendix 1.

Mirena (levonorgestrel-releasing Intrauterine sytem)

Amendment: Clinical Information

NDA 21-225

July 18, 2000

Page 2 of 2

We trust that the information contained in this amendment will not affect the NDA action date.

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, PharmD

Brenda Marczi, PharmD

Associate Director

Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best
Dr. Leslie Anne Furlong

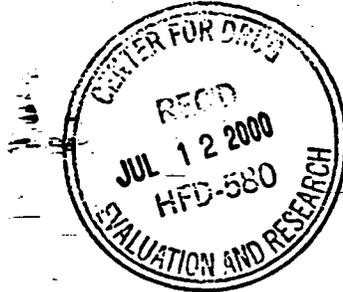
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*7/24/2000
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| REVIEWS COMPLETED | |
| CSO ACTION: | |
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| <input type="checkbox"/> MEMO | |
| ED | 7/24/00 |
| CSO-INITIALS | DATE |

BERLEX

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

July 11, 2000

ORIGINAL

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

BC

Re: **NDA 21-225**
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Response to Request for Information (CMC)

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Reference is also made to a June 16, 2000 voice mail message left by Ms. J. Best of the Division for the undersigned (Ms. J. Ruane) in which Ms. Best conveyed two requests for additional information from the reviewing chemist. Provided herein are our responses to those requests. For convenience, the requested information (as paraphrased by the undersigned) is provided in bold face type; Berlex's response is provided immediately thereafter.

- The DMF number should be provided for the ~~_____~~ manufactured at ~~_____~~

The Drug Master File number for the ~~_____~~ used to ~~_____~~ manufactured at ~~_____~~ is DMF No. ~~_____~~

Please refer to our April 10, 2000 response to the Division's requests for information, which included additional information regarding this Drug Master File. In that submission, we clarified that the reference to DMF No. ~~_____~~ in the submitted ~~_____~~ DMF

authorization letter (Item 4, Volume 1, Page 333) was intended to specify that the information is located in Item No. 32 within DMF No. [redacted] We also provided information to clarify that the current holder of DMF No. [redacted] is [redacted]

- **Results for the USP Physicochemical tests for [redacted] tubing and [redacted] should be provided.**

USP Physicochemical tests for [redacted] are not applicable for [redacted] These tests are specified for [redacted]

The [redacted] Type IV Drug Master Files for [redacted] that are referenced in the NDA (DMF Nos. [redacted] respectively) contain comparative studies in which tests were carried out according to modified [redacted] for [redacted] This testing was performed based on an FDA guidance for testing of materials that were intended to replace [redacted] materials¹. Included in both Leiras DMFs are [redacted] Please refer to the following reports for detailed information from these studies:

- Report 1470, "Summary of Comparative Study for [redacted] DMF No. [redacted] Vol. II, pg. 428
- Report 1340, [redacted] in [redacted] DMF No. [redacted] Vol. II, pg. 434 (addendum)
- Report 1469, "Summary of Comparative Study for [redacted] DMF No. [redacted] Vol. I, pg. 233
- Report 1339, [redacted] DMF No. [redacted] Vol. I, pg. 239 (addendum)

APPEARS THIS WAY
ON ORIGINAL

¹ Please refer the FDA guidance entitled [redacted]

NDA 21-225
July 11, 2000
Page 3

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane

Manager

Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/056

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|---------------------------------|---------------------------------|
| REVIEWS COMPLETED | |
| CSO ACTION: | |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. |
| <input type="checkbox"/> MEMO | |
| CSO INITIALS | DATE |

BERLEX

ORIGINAL

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

June 30, 2000

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

NEW CORRESP

NC

Re: NDA 21-225

Mirena® (levonorgestrel-releasing intrauterine system)
General Correspondence re: Future NDA Amendment

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Reference is also made to a June 16, 2000 telephone conversation between Ms. Jeanine Best of the Division and the undersigned (Jo-Ann Ruane) in which the latter described Berlex's plans to amend the NDA to provide for changes to the Chemistry, Manufacturing and Controls information. During the telephone conversation, two planned changes were described: (1) a modification of the secondary packaging for the drug product, and; (2) a change in the site of the manufacture of the T-body. In accordance with Ms. Best's recommendation, we are providing herein a detailed description of these changes and the information that we intend to include in the NDA amendment, targeted for submission in mid-July, 2000.

1. The secondary packaging of the drug product will be modified to include a aluminum pouch as an additional secondary package, and the existing secondary carton, which is intended to provide only physical protection of the primary package, will be modified to accommodate the pouched product. There will be no changes to the primary container-closure system.

This modification to the secondary package is being made for commercial reasons only; it is intended to render the U.S. commercial packaging significantly different in appearance from the packages produced for the non-U.S. markets. This differentiation will reduce the potential for illegal sale in the U.S. of goods that have been produced for other countries. The pouch is not intended to contribute to the stability of the drug product, and the pouch materials have been selected to ensure that the existing stability data for the drug product remain applicable.

The pouch will be constructed as follows: one side will consist of the same material that is used for the primary container-closure system (), as described in the NDA); the other side of the pouch will consist of a aluminum foil. () will supply prefabricated pouches (i.e., sealed on three sides) to Leiras Oy, the drug product manufacturer¹.

Packaging of the primary package into the foil pouch will be performed by Leiras. The primary package will be inserted into the pouch and sealed such that the () surfaces face each other. Thus, the overall permeability of the primary package will not be affected by the presence of the pouch. The foil pouch, as well as the physician insert and patient information, will be placed in a carton, which has been modified to accommodate the foil pouch. There are no changes in the packaging sites that are described in the NDA.

The NDA amendment, which we plan to submit in the middle of July, will include labeling for the pouch, and updated physician, patient, and carton labeling. A disk containing all labeling as MS Word files will be included. As recommended by Ms. Best, we will also provide a mock-up drawing of the pouch, and will specify the location of the lot number and expiration date. We will also submit the following CMC information, which we expect to consist of fewer than 100 pages:

Information regarding Packaging Processes and In-Process Controls:

- updated flow chart and description of the production process and in-process controls
- updated proposed master batch record for labeling and secondary packaging
- updated proposed in-process control records for the labeling and secondary packaging processes

Information regarding the Container-Closure-System

- updated description of the container-closure system
- information regarding the new packaging components, including:
 - names and addresses of the pouch and component suppliers
 - pouch supplier's technical data for the pouch components
 - Confirmation that the pouch components meet the 21 CFR requirements for indirect food additives
 - Leiras specifications and test methods for the pouch

We will also update the stability commitment to specify that the commercial stability samples will be stored in a secondary carton without the pouch.

¹ Leiras Oy and Berlex Laboratories are subsidiaries of Schering AG, Berlin, Germany.

NDA 21-225

June 30, 2000

Page 3

2. _____ the manufacturer of both the T-body and the inserter, will change the site of manufacture of the T-body from _____ to the same site at which the inserter is manufactured, _____ has informed us that preparation of the documents for submission to the _____ Type III DMF No. _____ is underway and is expected to be completed by the end of June. Transfer of the production equipment and validation will occur during July and August of this year. It is planned that the site will be ready to be inspected in the end of August or early September, 2000.

The NDA amendment planned for mid-July will include a letter authorizing FDA to refer to the update _____ Type III DMF No. _____ on behalf of Berlex Laboratories.

Based on the telephone conversation with Ms. Best, we understand that an amendment submitted in mid-July to provide for the above changes will not affect the NDA goal date.

Please note that, in the upcoming amendment, we also intend to provide for an additional change that was not discussed with Ms. Best, i.e., the use of an alternate assay method for barium sulfate USP, a component used in the manufacture of the T-body. The alternate assay, which has been shown to be equivalent to the USP method, was used to test the barium sulfate used in the manufacture of the T-bodies described in the NDA. The upcoming NDA amendment will include the alternate test method as well as method validation information. We trust that inclusion of this alternate method in the amendment will also not affect the NDA action date.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane
Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/047

| | |
|---------------------------------|---|
| REVIEWS COMPLETED | |
| CSC ACTION: | |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS | DATE |

Drug Development & Technology
Division of Berlex Laboratories, Inc.

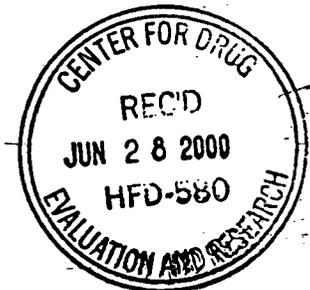
UPS OVERNIGHT

ORIGINAL

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

June 27, 2000

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857



ORIG AMENDMENT

BM

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Response to Request for Information - Clinical

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception.

Reference is also made to June 12 and 13, 2000 telephone conversations between Ms. Jeanine Best of the Division and the undersigned (Jo-Ann Ruane) in which Ms. Best conveyed requests for additional information on behalf of the Medical Officer. Provided herein are our responses to the Division's requests for information. For convenience, the requested information (as paraphrased by the undersigned) is provided in bold face type; Berlex's response is provided immediately thereafter.

- **A copy of the study report for Leiras study 102-96502, a post-marketing surveillance study, should be provided if available.**

Study 96502 involves obtaining information from a central registry that is maintained by the Finnish Health Ministry. Although the collection of information regarding Mirena® users is complete, Leiras has determined that a meaningful analysis should include data from a control group. Leiras is currently in the process of applying for permission to obtain the hospital registry results from a control group. The final report, which will include data from both the Mirena® and control groups, is expected to be available in 2001.

NDA 21-225

June 27, 2000

Page 2

- A copy of the following reference, which was cited in Item 8, Vol. 7, Page 96, should be provided: Keith LG, Berger GS: The aetiology of pelvic inflammatory disease. In: Zathuchni GE (ed)

A copy of the requested reference is attached.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo Ann M. Ruane

Jo-Ann Ruane

Manager

Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/048

| | |
|---------------------------------|---|
| REVIEWS COMPLETED | |
| CSO ACTION: | |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS | DATE |

Drug Development & Technology
Division of Berlex Laboratories, Inc.

UPS OVERNIGHT

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

June 8, 2000

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857



ORIG AMENDMENT

BC

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Response to Request for Information (CMC)

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Reference is also made to telephone conversations on April 18, 25 and 26, 2000 between Ms. J. Best of the Division and the undersigned (Jo-Ann Ruane) during which Ms. Best conveyed several questions from the reviewing chemist. Provided below are our responses pertaining to those questions. The requested information (as paraphrased by the undersigned) is provided in bold face type; Berlex's response is provided immediately thereafter.

- **A tabulation of the specifications and test results for the polymers used in the Composition B, C, and D clinical lots should be provided.**

Provided in Attachment 1 is a tabulation of the specifications and test results for the unfilled elastomer used in the Composition B, C and D batches described in Item 4 of the NDA. Tabulated specifications and test results for the tubing used for these drug product batches is provided in Attachment 2.

The tabulations include the lot numbers of the component, as well as the drug product batches in which those components were used. Cross-references to the pages in the NDA on which the corresponding certificates of analysis can be found is also provided.

Please note that, additional comparative information for these components was provided in the introduction to Item 4 in the NDA (CMC presubmission, Item 4, Vol. 1, Pages 21-32).

- The [redacted] DMF for the [redacted], refers to the [redacted]. The [redacted] DMF differ from those provided in the Mirena NDA. A letter from the DMF holder for the [redacted] describing the [redacted] for Mirena, as well as the [redacted], should be provided.

The drug product is marketed outside of the US as Levonova[®] and Mirena[®]. The [redacted] manufactured by [redacted] for both Mirena[®] and Levonova[®] are identical, as indicated in the [redacted] DMF authorization letter provided in the NDA (Item 4, Volume 1, Page 148). In addition, [redacted] has also provided us with a copy of a certificate of compliance which was submitted as page 30 in their DMF No. [redacted] (Attachment 3). This certificate refers both to the part name as [redacted] and the customer part number as [redacted]. Part number [redacted] corresponds with the code number for the [redacted] that is specified in the batch documentation submitted in the NDA (e.g., Item 4, Vol. 1, Page 298 and Vol. 2, Page 141).

The [redacted] specifications for the [redacted] (as submitted in the [redacted] / Type III Drug Master File No. [redacted] and the corresponding [redacted] specifications (as submitted in the NDA on Item 4, Volume 1, P. 149) are listed below:

| Dimensions | Specifications | Specifications |
|------------|----------------|----------------|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

The [redacted] specifications for the [redacted] are more restrictive than the corresponding Leiras specifications. It is common practice at Leiras to require suppliers to adopt more restrictive specifications than are necessary for the manufacture of a drug product. Furthermore, [redacted] measures the [redacted] dimension of the [redacted] using a device capable of measurements to the hundredth of a millimeter (i.e., 1.55 ± 0.05 mm). Leiras checks this dimension during routine receiving controls using a device that enables measurements to one tenth of a millimeter. Measurements to one tenth of a millimeter precision is sufficient to ensure that the [redacted] are suitable for use in the manufacture of Mirena[®].

Please note that [redacted] are [redacted] and are not [redacted]

NDA 21-225
June 8, 2000
Page 3

Reference is also made to our response to the Division's request for addition information that was submitted on April 10, 2000. In that submission, we indicated that we would respond in the future to the following request for additional CMC information

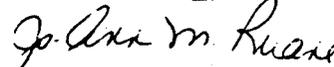
- The manufacturing/production information for the _____ used for the T-body should be provided.

We now wish to respond to this comment by referring to the submission made by _____ to the Division on April 19, 2000. A copy of the cover letter which accompanied that submission is provided as Attachment 4.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES



Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/042

BERLEX

UPS OVERNIGHT

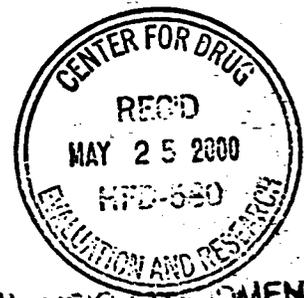
ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

May 23, 2000

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857



DRUG DOCUMENT

BM

Re: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Correction to NDA 21-225

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system) which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Enclosed is a correction to an Appendix in Study Report AY99 in Item 8 of the subject NDA. There were some problems with the electronic file for this Appendix resulting in illegible or misplaced words on the pages. The corrected pages include Item 8 Volume 27 Page 1 to Item 8 Volume 27 Page 93. We apologize for any inconveniences that may occur as a result of this correction.

NDA 21-225
May 23, 2000
Page 2

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, Pharm D.

Brenda Marczi, Pharm D.
Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

BM/letter/lius/003

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| REVIEWS COMPLETED | |
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| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
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BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

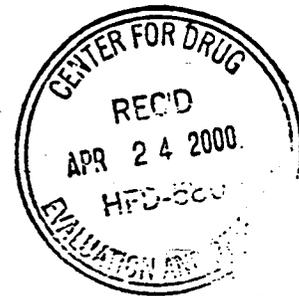
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ORIG AMENDMENT

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

April 20, 2000

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857



Re: **NDA 21-225**
Mirena[®] (levonorgestrel-releasing intrauterine system)
Other: Response to Request for Information

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena[®] (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Reference is also made to a April 12, 2000 telephone conversation between Ms. Jeanine Best of the Division and Jo-Ann Ruane of Berlex, in which Ms. Best conveyed a request for information for the Medical Officer who is reviewing the NDA. Provided herein are the questions (in bold), responses and the appropriate attachments.

1. **Item 8, Volume 126, Report B085: This is a large post-marketing study with a high questionnaire response rate³ - where is the safety information for this study? What do the two referenced publications relating to (1) snoring in men, and (2) the Finnish twin registry, have to do with Mirena?**

In Report B085, the two publications are references to the report regarding the effect of socio-economical status on response rates in epidemiological population surveys in general. These two published studies are used as examples of surveys showing such results. One of the authors of these publications (Professor Markku Koskenvuo, MD) was a member of the team working with

the Mirena study and therefore the methods in these two publications were familiar to the team, and thus they were chosen to be referenced.

Results on safety of the study reported in B085 has recently been published in March 2000. A copy of the publication (Backman et al. Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nation-wide study of 17,360 users. Br J Obstet Gynaecol 2000;107:335-9) is attached. (Attachment 1)

- 2. Report AV97: Patient No. 234 suffered some sort of infection complication. The CRF indicates that the patient was hospitalized for 1 month; the narrative indicates that hospitalization was for two days. The Medical Officer asks that we resolve this discrepancy.**

The patient number 234 in Report AV97 was hospitalized for two days (from 10 Jun 94 to 11 Jun 94), not one month. Page 23 of CRF listed the date as 10-06-94 to 11-06-94. As further explanation, the dates used in individual study reports, in all the CRFs, and in any other study material prepared in Europe are in European format, ie, ddmmyy, whereas the dates used elsewhere in the NDA application and in narratives are in US format, ie, mmddyy unless the first three letters of the month shown, ie, dd Mon yy.

- 3. Item 8, Volume 184, page 372: An article describes 3 cases of Group A streptococcus sepsis in Sweden. Included in the article is a statement that an investigation by the Medical Products Agency was ongoing in 1995. The Medical Officer asked whether the investigation has been completed and, if so, she requested that we submit the results.**

In the article (Ottander et al. Sepsis in connection with levonorgestrel IUD. Läkartidningen 1995;92:4555-7), the investigation that was mentioned to be on-going was on sepsis cases among women of childbearing age in Sweden in general, not related to IUD use. The investigation was started because the number of sepsis cases in this age group had been increasing since 1992 in the national register. The authors mentioned that based on the results of this investigation a risk assessment would be possible. We conducted a literature search on sepsis in Sweden and no results of such investigation have been reported or published so far. Based on the separate search looking for the publications written by the authors of the article, no further reports have been published nor is available on the three cases described in the article. This was also confirmed by the the Medical Products Agency (MPA) of Sweden who was contacted by Schering Nordiska AB (Sweden) on 17 Apr 2000.

Furthermore, based on this contact, Schering Nordiska got a fax (Attachment 2) from the Medical Products Agency (MPA) containing all the information compiled on sepsis cases in LNG IUS users in their files so far. According to the latest information 4 cases have been reported to MPA in Sweden. For two of the three cases published in the article mentioned above, supplemental information has changed the causality assessment to be unlikely and in one case the assessment has remained unclassifiable due to a lack of information. The one additional case occurred in 1997 in a 41-year-old woman and with the available information, the causality assessment is unclassifiable. The narrative of this case is included in the fax received from Swedish MPA as the last case. These cases did not prompt MPA to request a change in the product labelling in Sweden.

NDA 21-225
April 20, 2000
Page 3

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, Pharm D.

Brenda Marczi, Pharm D
Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

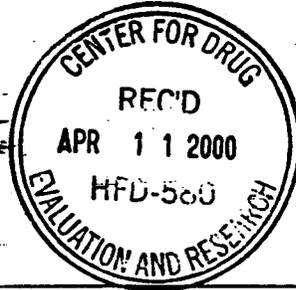
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| REVIEWS COMPLETED | |
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| CSO INITIALS | DATE |

ORIGINAL

BERLEX

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

April 10, 2000

ORIG AMENDMENT

BZ

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: **NDA 21-225**
Mirena® (levonorgestrel-releasing intrauterine system).
Other: Response to Request for Information

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Reference is also made to several telephone conversations on March 21, 2000 between Ms. J. Best of the Division and the undersigned (Jo-Ann Ruane) during which Ms. Best conveyed the outcome of the Division's 45-day review meeting for NDA 21-225. Ms. Best indicated that, while no filing issues had been identified, the Division had requests for additional information. Provided below are our responses to the Division's requests for information related to the Chemistry, Manufacturing and Controls, Human Pharmacokinetics and Bioavailability, and Clinical sections of the NDA. The requested information (as paraphrased by the undersigned) is provided in bold face type; Berlex's response is provided immediately thereafter.

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| REVIEWS COMPLETED |
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| <input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS _____ DATE _____ |

Chemistry, Manufacturing and Controls:

1. The manufacturing/production information for the _____ used for the T-body should be provided.

We are working with _____ to obtain the requested manufacturing information and will provide a separate response to this question in the near future.

2. The DMF number for the _____ DMF provided in the NDA, DMF No. _____ is not correct; the correct DMF number for the _____ DMF should be provided.

_____ has clarified that the reference to DMF No. _____ in their authorization letter (provided in Item 4, Volume 1, Page 333 in the CMC presubmission) is meant to specify that the information on their _____ can be found in Item No. 32 within DMF No. _____.

In addition, DMF No. _____ is listed by FDA as being held by _____ has provided a copy of a March 24, 1997 letter in which they informed FDA that the company name was changed from _____.

A copy of this letter is provided as Attachment 1.

Human Pharmacokinetics and Bioavailability:

1. The protocol (or location of the protocol in IND _____ for the ongoing in vivo study with the commercial Composition should be submitted.

An outline of the protocol for the Phase 1 study, as well as the finalized Protocol 303700 and amendments, have been submitted to our IND _____ for levonorgestrel-releasing intrauterine system. The submission dates and amendment serial-numbers for these submissions were provided verbally by the undersigned to Ms. Best during the conversations on March 21, 2000. During the conversations, Ms. Best confirmed Berlex's understanding that sparse blood sampling and ex vivo testing are considered sufficient for evaluating the in vivo performance of the commercial formulation, Composition D, under Protocol 303700.

2. An electronic copy of the reports containing the PK/IVIVC information should be submitted.

The information supporting the in vivo/in vitro correlations (IVIVCs) for the formulations used in the pivotal clinical trials (Compositions B and C) was originally submitted as an amendment to our IND _____ for levonorgestrel-releasing intrauterine system [_____ submitted November 2, 1998]. A second amendment containing additional IVIVC information was submitted on May 24, 1999 _____ in response to the Division's request for additional information that was conveyed during a March 10, 1999 teleconference. Both amendments included the relevant raw data in electronic format.

The information provided in the two IND amendments, as well as updated in vitro data, were presented in the Human Pharmacology and Bioavailability section of NDA 21-225 (Item 6). Although a separate report containing the IVIVC information is not available, the PK/IVIVC information presented in Item 6 is available electronically. Provided herein is a diskette _____.

containing selected information from Item 6¹ in electronic format. The file was produced using CoreDossier® 4.0.2 Assembler and a companion module, CDER Compiler 2.0. These applications are produced and distributed by ESPS, Fort Washington, PA. The diskette has been scanned for viruses using Virus Scan NT 4.0.3a, which is produced and distributed by Network Associates, Inc., and is virus free.

3. The analytical validation reports, or location in the NDA, should be provided.

Four study reports containing serum data are described in the Mirena NDA: B336, B073, B078, and B089. All serum levonorgestrel data were generated using radioimmunoassay (RIA) methods. For each of the study reports, information pertaining the available assay validation information is provided below.

Please note that assay validation information relevant for the ongoing clinical study using the commercial formulation (Composition D)² will be submitted along with the interim data from this study during the NDA review period, i.e., not less than 90 days prior to the primary user feel goal date of December 7, 2000.

Report No. B336

In this study, an early development formulation (Composition A) was used, and serum levonorgestrel levels were determined over 6 months. The study results were published in 1982.³ The assays were performed at the _____

_____ An assay validation report is not available; however, the assay used is described by Stanczyk et al (Contraception 1975;12:279-295). A copy of this publication is provided as Attachment 2.

Report No. B073

Report No. B073 describes the serum levonorgestrel levels measured over a 6.5 year period for women using a development formulation (Composition B). As in Report No. B336, the assays described in Report No. B073 were performed at the _____ however, at the time the samples from this study were tested, a new RIA method was in place. This method is described by Weiner and Johansson (Contraception 1976;14:81-92). A copy of this publication, which was provided in the NDA (Item 6, Volume 16, Pages 245-56), is provided as Attachment 3 for the convenience of the reviewer. The assay validation report for this method is provided as Attachment 4. This report includes data showing a good correlation between the results obtained by the new and former methods.

¹ Excluding Items 6.24-Study Reports, 6.25-Publications, and 6.26-Previous Correspondence with Agency

² Protocol 303700-Amendment 2 under Berlex IND for levonorgestrel-releasing intrauterine system.

³ Heikkilä M et al. Immediate postabortal insertion of a levonorgestrel-releasing IUD. Contraception 1982;26:245-59. A copy of this publication can be found in the Mirena NDA (Item 6, Volume 11, Page 305)

Report No. B078

In this study, development Compositions B and C were used, and serum levels were determined over a 5-year period. The assays were performed at the _____ using the same _____ procedure described for Report B073.

Report No. B089

This report describes the serum levonorgestrel levels over 56 weeks in women who received Mirena (Composition C) in combination with oral estradiol as hormone replacement therapy. The assays were performed by Leiras Oy⁴, the manufacturer of the drug product. A copy of the assay validation report, which was included in Item 8 as an appendix to a related report (Report No. AW96, Appendix 16.1.10.1) is provided as Attachment 5.

Clinical:

1. Investigator name(s) and full address for the following sites:

Provided below is the full address for the requested study sites, the names of the investigators who participated in the pivotal clinical trials at those sites, and the report number(s) in which the investigator is named.

| Clinical Site Name and Address | Investigator Name | Report Number(s) |
|--------------------------------|-------------------|--|
| _____ | | AV97/LE102-92533-01 B078/102-89532-07 |
| _____ | | AY99/LE102-98042-01 |
| _____ | | AY99/LE102-98042-01 B078/102-89532-07 |

The complete List of Investigators can be found in the NDA in Item 8, Volume 1, Page 45.

⁴ Please note that in the initial NDA submission, we noted incorrectly that this assay was performed at the _____

⁵ The following non-pivotal studies were also conducted at this center: B080/1205, B086/102-90528-01, B075/1208, B330/102-89532-08, B090/1227, AW96/LE118-90513-04, B080/1205, B075/1208, B072/1204

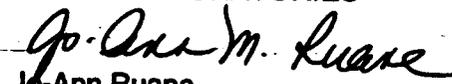
⁶ The following non-pivotal studies were also conducted at this center: B080/1205, B075/1208, B086/102-90528-01, B080/1205, B075/1208

NDA 21-225
April 10, 2000
Page 5

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES



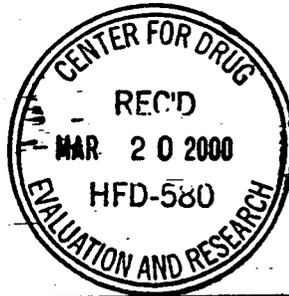
Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/030

BERLEX

FACSIMILE
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

March 17, 2000

Susan Allen, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG. ASSIGNMENT
RB

Re: **NDA 21-225**
Mirena® (levonorgestrel-releasing intrauterine system)
Other: Response to Request for Information
(Biopharmaceutics)

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception. The Chemistry, Manufacturing and Controls Information (NDA Item 4) was presubmitted on December 16, 1999.

Reference is also made to a March 10, 2000 telephone conversation between Ms. Jeanine Best of the Division and the undersigned in which Ms. Best conveyed a request for information related to the Biopharmaceutics review of the NDA. Specifically, Ms. Best requested that Berlex provide a table correlating the development formulations (Compositions) with the clinical studies. In addition, the information about when each of the Compositions was developed was requested.

Provided herein is a summary table which in the requested information is provided. Please note that this table refers to the Table of All Studies, which was submitted in the NDA as component of the Integrated Summary of Safety, for more detailed information. A copy of the Table of All Studies from Item 8 is included for the convenience of the Reviewer.

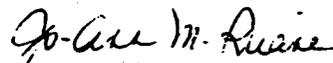
Please note that, as previously agreed with the Division, interim (3-month) in vivo data from the ongoing Phase 1 study with the commercial product (Composition D) will be submitted not less than 90 days prior to the primary user fee goal date of December 7, 2000.

NDA 21-225
March 17, 2000
Page 2

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES



Jo-Ann Ruane
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jeanine Best

JMR/021

BERLEX

FACSIMILE
UPS OVERNIGHT

March 17, 2000



Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Susan Allen, M.D, MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIGINAL

ORIGINAL DOCUMENT

BM

Dear Dr. Allen:

Re: **NDA 21-225 Mirena (levonorgestrel-releasing Intrauterine system)**
OTHER: Response to Request for Information

Reference is made to **NDA 21-225** submitted on January 31, 2000 for Mirena (levonorgestrel-releasing intrauterine system), a contraceptive product.

Reference is also made to phone conversations between **Berlex** and the Division on March 8 and March 9, 2000 during which information was requested, as presented in bold below.

Responses follow each of the bolded items listed below.

1. **For studies AY99 and B078, please calculate the efficacy data for women who were 35 years old or under. Please present the data from qualified sites, nonqualified sites and total.**

The requested efficacy data is presented in Attachment 1.

2. **For Study Reports AY99 and B078, how many women were 35 yrs old or under at the end of 5 years in the studies? Please present the number from qualified and nonqualified sites. Also, please provide the number of women who were 35 years old or under at the start of the studies (Reports AY99 and B078).**

For Study Reports AY99 and B078, a total of 277 subjects were 35 years old or less and completed 5 years; there were 170 subjects from qualified sites and 107 subjects from nonqualified sites. This data is presented in Table 2 of Attachment 1.

As additional information, a total of 662 subjects were 35 years or less at the start of the studies in Reports AY99 and B078 who also completed 5 years. Of these subjects, 457 were from qualified sites and 205 were from nonqualified sites. This data is presented in Table 1 of Attachment 1.

3. Is the inserter that was used in B083 the same as the to-be-marketed inserter? If not, what are the differences?

The function, dimensions, and raw materials of the inserter used in B083 were essentially the same as the properties of the current, to-be-marketed inserter, but it is not the exact to-be-marketed inserter. The critical parts of the inserter, like the insertion tube diameters and materials that are in direct contact with the IUS or the uterus, are unchanged. However, some minor adjustments have been made in the to-be-marketed inserter:

- The printed scale on the insertion tube has been added.
- The length of the inserter shaft has been shortened for easier handling.
- The [] flange has been replaced with a re-designed [] flange, for environmental reasons.

4. How wide is the inserter with device in it?

The IUS does not have an effect on the dimensions (width) of the inserter at the insertion. When the IUS is pulled into the insertion tube according to the insertion instructions, the knobs at the ends of the IUS arms are pressed together by the insertion tube and the total width remains smaller than the outer diameter of the insertion tube. Specification for the tube outer diameter is _____

5. Please provide a list of protocol deviations for Study Report B078.

The list of protocol deviations for this study is provided in Attachment 2.

We trust that the information provided in this submission satisfies your request. If you have any questions regarding this submission, please contact the undersigned at (973) 276-2240.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, Pharm D.

Brenda Marczi, Pharm D
Associate Director
Drug Regulatory Affairs

Desk copy: Ms. Janine Best (cover letter only)
Dr. Leslie Furlong



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-225

FEB 08 2000

Berlex Laboratories, Inc.
Attention: Jo-Ann M. Ruane
Manager, Drug Regulatory Affairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Ruane:

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: Mirena (levonorgestrel, USP) Intrauterine System

Therapeutic Classification: Standard (S)

Date of Application: January 31, 2000

Date of Receipt: February 1, 2000

Our Reference Number: NDA 21-225

We are adjusting your performance goal dates because one of your affiliate companies did not submit their annual product and establishment fees until February 7, 2000. This letter supercedes the acknowledgement letter dated February 4, 2000.

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 April 7, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 7, 2000 and the secondary user fee goal date will be February 7, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

151

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-225

Page 3

cc:

Archival NDA 21-225

HFD-580/Div. Files

HFD-580/JBest

DISTRICT OFFICE

Drafted by: JAB/February 8, 2000

Initialed by: Rumble, 02.08.00

final: JAB/February 8, 2000

filename: N21225ACKsupltr0200.doc

ACKNOWLEDGEMENT (AC)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-225

Berlex Laboratories, Inc.
Attention: Jo-Ann M. Ruane
Manager, Drug Regulatory Affairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

FEB 04 2000

Dear Ms. Ruane:

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: Mirena (levonorgestrel, USP) Intrauterine System
Therapeutic Classification: Standard (S)
Date of Application: January 31, 2000
Date of Receipt: February 1, 2000
Our Reference Number: NDA 21-225

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 April 1, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 1, 2000 and the secondary user fee goal date will be February 1, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case,

however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

LSI

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-225

Page 3

cc:

Archival NDA 21-225

HFD-580/Div. Files

HFD-580/JBest

DISTRICT OFFICE

Drafted by: JAB/February 4, 2000

Initialed by: Rumble, 02.04.00

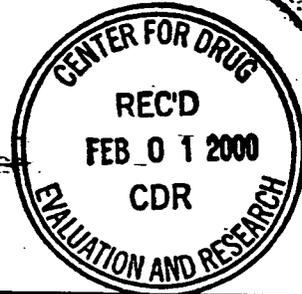
final: JAB/February 4, 2000

filename: N21225ACKltr0200.doc

ACKNOWLEDGEMENT (AC)

BERLEX

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

January 31, 2000

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
Parklawn Building, Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: **NDA 21-225**
Mirena[®] (levonorgestrel-releasing intrauterine system)
— ORIGINAL NEW DRUG APPLICATION

Dear Dr. Rarick:

Pursuant to 505 (b) (1) of the Federal Food, Drug and Cosmetic Act and to 21 CFR 314.50, Berlex Laboratories, Inc. is submitting herewith a New Drug Application for Mirena[®] (levonorgestrel-releasing intrauterine system) for intrauterine contraception. The Chemistry, Manufacturing and Controls (CMC) section of this-NDA (Item 4) was presubmitted to the Division on December 16, 1999.

Mirena[®] (levonorgestrel-releasing intrauterine system) is comprised of a T-shaped frame on which a reservoir containing 52 mg levonorgestrel USP is mounted. The reservoir is covered with a membrane which regulates the release of levonorgestrel from the system at a nominal initial rate of 20 µg/day. Mirena[®] was developed by Leiras Oy, Turku, Finland, as an intrauterine contraceptive with a 5-year period of use. Schering AG, Berlin, Germany is the parent company of Leiras Oy and Berlex Laboratories. Leiras currently markets a levonorgestrel-releasing intrauterine system in Europe under the trade names Mirena[®] and Levonova[®]. Berlex plans to use the trade name, Mirena[®], for the U.S. commercial product.

The IND for Mirena (IND _____) was previously held by The Population Council, New York, NY, and was transferred to Berlex on March 6, 1998. However, a pre-IND meeting between Berlex and the Division took place on January 27, 1998. The purpose of this meeting was to discuss Berlex's plans to submit an NDA based solely on data from clinical trials conducted in Europe, i.e., in essence, the meeting served as a pre-NDA meeting, and the discussion topics included the proposed contents of the CMC, nonclinical, human pharmacokinetics and bioavailability, and clinical sections of the NDA. A copy of the Division's minutes from this meeting is provided immediately following this letter.

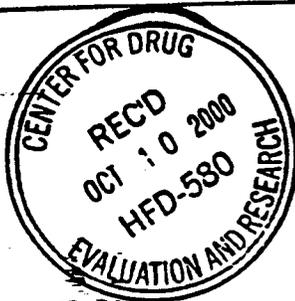
UPS OVERNIGHT

ORIGINAL

BERLEX

Item 2 - Labeling

October 6, 2000



Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Susan Allen, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

Re: **NDA 21-225**
Mirena® (levonorgestrel-releasing intrauterine system)
AMENDMENT TO PENDING APPLICATION - LABELING

Dear Dr. Allen:

lease refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception.

This submission amends Item 2 of NDA 21-225 to incorporate updated patient labeling. Attached please find four copies of the updated version of the draft patient insert. This version replaces the draft patient insert submitted in the original application. An electronic copy of the updated patient insert is provided as a MS Word 97, SR 1 file on the enclosed 3.5 inch diskette. This diskette has been scanned for viruses using VirusScanNT 4.0.3a, which is produced and distributed by Network Associates, Inc., and is virus free.

Please call the undersigned at (973) 276-2343 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Jo Ann M. Ruane
Jo-Ann Ruane
Manager
Drug Regulatory Affairs

10/16/2000
Noted
1/31

Desk Copy: Ms. Jeanine Best, MSN, RN

JMR/106

| | |
|---------------------------------|---|
| REVIEWS COMPLETED | |
| CSO ACTION: | |
| <input type="checkbox"/> LETTER | <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO |
| CSO INITIALS | DATE |

ORIGINAL

BERLEX

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

August 28, 2000

ORIG AMENDMENT

Susan Allen, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Re: **NDA 21-225**
Mirena® (Levonorgestrel-Releasing Intrauterine System)
Other: Periodic Safety Update Report

Dear Dr. Allen:

Please refer to New Drug Application 21-225 for Mirena® (levonorgestrel-releasing intrauterine system), which was submitted on January 31, 2000 for the indication, contraception, and to the Chemistry, Manufacturing and Controls Information (NDA Item 4), which was presubmitted on December 16, 1999.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), attached please find the first Safety Update Report submitted for NDA 21-225.

After analysis of the information in this report, it was concluded that there is no new safety information learned about LNG IUS that may reasonably affect the statement of contraindications, warning, precautions and adverse reactions in the draft labeling. Therefore, new draft labeling is not needed for this safety update. The following components are included:

Attachment 1: Periodic Safety Update Report (PSUR) for Reporting Period of September 28, 1999 to March 27, 2000

Provided in Attachment 1 is the PSUR from our parent company, Schering AG. It summarizes the Mirena® (levonorgestrel-releasing intrauterine system) safety data received from worldwide sources during this time period and provides a detailed analysis of this new data. All available adverse drug reaction reports have been collected, summarized and incorporated into this PSUR

for the reporting period. It covers all indications for which Mirena is marketed and it includes an update of the worldwide marketing authorization status.

Attachment 2: Medwatch Forms for Serious Adverse Events for Reporting Period of September 28, 1999 to March 27, 2000.

Please refer to Table 3 of Appendix III of the PSUR (provided in Attachment 1 of this submission). Table 3 includes a line listing of serious adverse events that occurred in the reporting period of the PSUR. Details of these listed serious adverse events in the format of Medwatch forms are provided in Attachment 2.

Attachment 3: Addendum to the Table of All Studies for Reporting Period of May 31, 1999 to March 27, 2000.

This table provides updated information for studies that were ongoing as of the previous cut-off for the Table of All Studies in the Integrated Summary of Safety of the NDA. New studies, which have been initiated since the last cut-off date, are also included. No new study reports have been completed, so this Safety Update does not include any new clinical study reports.

Attachment 4: Literature References for Reporting Period of September 28, 1999 to March 27, 2000.

There are 5 new literature references included in Attachment 4 for this reporting period.

Attachment 5: Case Report Forms for Subjects who Dropped Out of the Ongoing US Study "An Open-Label, Non-Randomized Trial With A Levonorgestrel-Releasing Intrauterine System in Young Women to Evaluate the Short Term Dosage Form Performance Characteristics", Protocol Number 303700.

Since the submission of the NDA, a new study was initiated under the Mirena[®] (levonorgestrel-releasing intrauterine system) IND ~~_____~~. This was the only study being conducted under the U.S. IND as of the cut-off date of March 27, 2000. Included herein are case report forms for 5 subjects who dropped out of this study. The cut-off date for the provision of these case report forms was June 1, 2000.

Attachment 6: IND Safety Reports for Unexpected, Serious Adverse Events for Reporting Period of March 28, 2000 to August 28, 2000

Since the initiation of Protocol 303700, Berlex started submitting IND safety reports for unexpected, serious adverse events to IND ~~_____~~. Copies of these are included herein Attachment 6.

Attachment 7: Clinical Study Report AY98, "Quality of Life with LNG IUS among former OC and Progestasert Users"

A new study report is provided which was not included in the initial NDA. However, the subjects from this study report are the same subjects discussed in study report AY08 that was included in the initial NDA. Therefore the total number of subjects in the safety database for the Integrated Summary of Safety remains unchanged.

NDA 21-225
August 28, 2000
Page 3

Please call the undersigned at (973) 276-2240 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

Brenda Marczi, PharmD

Brenda Marczi, PharmD
Associate Director
Drug Regulatory Affairs

bm/015

Desk copy: Dr. Furlong

| |
|-----------------|
| REVIEW COMPLETE |
| DATE |
| CSB |

Since the January 27, 1998 meeting, and subsequent to the transfer of IND _____ to Berlex Laboratories, there have been numerous interactions with the Division related to this NDA. Overviews of the relevant and significant interactions with the Division can be found in the introductions to the related Items in this NDA; where appropriate, copies of related minutes and/or submissions are also provided.

NDA Format

This NDA has been formatted in accordance with 21 CFR 314.50 and the FDA "Guideline on Formatting, Assembling and Submitting New Drug and Antibiotic Applications" (February 1987). The assignment of item numbers is consistent with the application outline in the current version of the Form FDA 356h (7/97). The archival and review copies of this NDA are being submitted only in paper, with the exception of Item 12 (Case Report Forms), which is being submitted only in electronic format in accordance with the January 1999 FDA "Guidance for Industry: Providing Regulatory Submissions In Electronic Format - NDAs".

This application is comprised of a 370-volume Archival Copy and a 369-volume Review Copy and includes 6 technical sections.

The CMC section of this NDA (Item 4) was presubmitted on December 16, 1999 (6 volumes); Item 4 of this submission includes a very limited amount of CMC information which is intended to amend the information that was provided in the presubmission.

Item 12 (Case Report Forms) is provided in electronic format on three CD-ROMs and is 746.9 MB in size. These CDs are provided in a separate, labeled binder immediately following the first volume in the Archival Copy of the NDA. Item 12 was produced using CoreDossier® 4.0.2 Assembler and a companion module, CDER Compiler 2.0. These applications are produced and distributed by ESPS, Fort Washington, PA. The CD has been scanned for viruses using Virus Scan NT 4.0.3a, which is produced and distributed by Network Associates Inc., and is virus free.

Item 19 (Other) includes information pertaining to Financial Disclosure by Clinical Investigators (21 CFR 54) and a Request for Three Years Marketing Exclusivity.

For the convenience of the reviewers, information pertaining to Item 12 (Case Report Forms) and Items 13-19 are provided in Volume 1 of this submission; all other sections of the NDA follow in numerical order.

New CMC Information and Response to the Division's Comments on the December 16, 1999 Presubmission of Item 4.

Included in Item 4 of this application is information intended to address the Reviewing Chemist's comments on the December 16, 1999 presubmission of Item 4 that were conveyed to Berlex (i.e., the undersigned) by the Regulatory Project Manager, Ms. J. Mercier, via telephone on January 13, 2000. Included is clarified information pertaining to the names and street addresses of the facilities involved in the manufacture and packaging of the drug substance and drug product. Also updated is the Attachment to Form FDA 356h which contains the requested establishment information for each of these facilities; this attachment confirms that all manufacturing facilities are ready for inspection. Please note that the draft package insert and container label, which were not included in the Item 4 presubmission, are provided in Item 2 of this application.

¹ Note: Items 9 and 15 are not provided as they are not applicable to this NDA.

Item 4 also includes a correction to previously submitted information pertaining to the stereochemistry of the drug substance and provides for additional sites for labeling and secondary packaging of the drug product.

Request for a Waiver from the Requirement to Assess the Safety and Effectiveness of New Drugs in Pediatric Patients

Berlex Laboratories requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of the drug product in all relevant pediatric subpopulations in accordance with 21 CFR 314.55(c)(2)(ii), i.e., Mirena[®] is indicated for women who have had at least one child; because the number of such patients in the pediatric population is very small, the necessary studies would be impossible or highly impractical. (This waiver request is also included in Item 6 of this NDA.)

Electronic SAS Datasets

For the convenience of the reviewer, a CD-ROM containing electronic copies of the integrated safety and efficacy datasets is provided at the beginning of Item 10 (Review Copy). Instructions for use and information pertaining to the content of these SAS datasets are provided in Item 10.9. Hard copies of the datasets will be provided upon request. The CD has been scanned for viruses using Virus Scan NT 4.0.3a, which is produced and distributed by Network Associates Inc., and is virus free.

NDA Application Fee

The Application Fee for NDA 21-225, totaling \$285,740.00, was sent to the FDA account at the Mellon Bank on January 24, 2000, via UPS Overnight delivery. This fee corresponds with the full amount required for an application submitted in Fiscal Year 2000 that requires clinical data.

Status of the Planned Phase 1 Clinical Study

As previously discussed with the Division (see Item 6 for detailed background information), Berlex is preparing to initiate a Phase 1 clinical study in order to evaluate the short-term dosage form performance characteristics of the proposed commercial formulation. This study is being conducted in order to further support the request for a waiver from the requirement to conduct a bioequivalence study to demonstrate the equivalence of the commercial formulation (Composition D) and the formulations that were used in the adequate and well-controlled efficacy trials (Compositions B and C). This waiver request is based on the Level A in vivo/in vitro correlations (IVIVCs) that have been established for Compositions B and C, comparative in vitro dissolution data, and the compositional similarity of the clinical and commercial Compositions. [Detailed information pertaining to the IVIVCs can be found in Item 6; composition and in vitro dissolution data can be found in Item 4 (presubmission).]

In accordance with the previously reached agreement with the Division, Berlex intends to submit interim results from this study not less than 90 days prior to the NDA action date.

Mirena® NDA 21-225

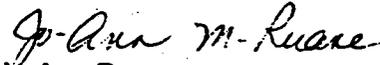
January 31, 2000

Page 4 of 4

Should you have any questions pertaining to this original NDA submission, please call the undersigned at (973) 276-2343.

Sincerely,

BERLEX LABORATORIES



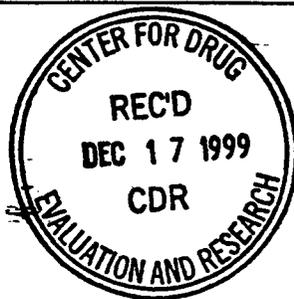
Jo-Ann Ruane

Manager

Drug Regulatory Affairs

BERLEX

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

December 16, 1999

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products, HFD-580
Office of Drug Evaluation II
U. S. Food and Drug Administration
Parklawn Building, Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: **NDA 21-225**
Levonorgestrel-releasing Intrauterine system
Presubmission of the Chemistry Section (Item 4)

Dear Dr. Rarick:

Pursuant to 21 CFR 314.50(d)(1)(iv), Berlex Laboratories, Inc. is presubmitting herewith the chemistry, manufacturing and controls section of NDA 21-225 for levonorgestrel-releasing intrauterine system for fertility control. Submission of all other sections of the NDA is planned for January, 2000.

Levonorgestrel-releasing intrauterine system (LNG IUS) was developed by Leiras Oy, Turku, Finland, as contraceptive intrauterine system with a 5-year period of use. Like Berlex Laboratories, Leiras Oy is a wholly owned subsidiary of Schering AG, Berlin, Germany. Leiras currently markets a levonorgestrel-releasing intrauterine system in Europe under the trade names Mirena[®] or Levonova[®]. Berlex plans to market drug product in the United States as Mirena[®].

Levonorgestrel-releasing intrauterine system has been the subject of numerous interactions between the Division and Berlex Laboratories. The initial interactions occurred on November 12, 1997, with the submission of a pre-IND meeting package in preparation for the pre-IND meeting, which took place on January 27, 1998. This meeting was considered a pre-IND meeting, although an IND for this product was currently on file (IND _____ however, transfer of this IND from the original owner, the Population Council, New York, NY, to Berlex Laboratories did not occur until March 6, 1998. Since the transfer of the IND to Berlex Laboratories, all interactions have been conducted under IND _____. A summary of the interactions with the Division that

pertain to the chemistry section is provided in the Introduction to the Chemistry, Manufacturing and Controls section.

Included in this submission is complete information for NDA Item 4 - Chemistry Section. Included are the following subsections:

| | |
|----------|---|
| Item 4 | Table of Contents |
| Item 4.1 | Chemistry, Manufacturing and Controls Information |
| Item 4.2 | Samples |
| Item 4.3 | Methods Validation Package |

In accordance with the FDA February 1987 "Guideline for Submitting Samples and Analytical Data for Methods Validation," one copy of the Methods Validation Package is submitted with the archival copy of Item 4 and three copies are submitted with the Item 4 review copy.

In accordance with a December 16, 1999 telephone conversation between Ms. J. Mercier of the Division and the undersigned, Berlex will submit a field copy of Item 4 to the FDA District Office at the time the original NDA application is submitted.

Should you have any question about this submission, please call the undersigned at (973) 276-2343.

Sincerely,

BERLEX LABORATORIES

Jo-Ann M. Ruane

Jo-Ann Ruane
Manager
Drug Regulatory Affairs

JMR/065



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

IND

Food and Drug Administration
Rockville MD 20857

APR - 9 1998

Berlex
Attention: Suzanne H. Hampton, Ph.D.
Associate Director
Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Maontville, NJ 07045-1000

Dear Dr. Hampton:

Please refer to the Investigational New Drug Application (IND) held by The Population Council for Levonorgestrel-releasing Intrauterine System, IND

We also refer to your communications of March 6, 1998 notifying us of the sponsorship transfer from The Population Council to Berlex, and providing the CV for the clinical Monitor.

The ownership is now considered transferred to Berlex. As sponsor of this IND, Berlex is responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any unexpected fatal or life-threatening experiences by telephone to this Agency no later than three working-days after receipt of the investigation (21 CFR 312.32). It also includes reporting annually on the progress of investigations (21 CFR 312.33).

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

Your cooperation is appreciated.

Sincerely,

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

Suzanne H. Hampton

APR 13 1998