CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-225

CHEMISTRY REVIEW(S)
Summary of Chemistry Review of NDA 21-225

A. Drug Substances:

Levonorgestrel is a synthetic progestin, which has been widely used in the contraceptive drug products. It is marketed by three separate Schering AG facilities in Germany (DMF) and they are all in compliance with cGMP.

The quality of levonorgestrel is controlled by specifications such as [details not provided]. The tests and limits are considered to be adequate for assuring the quality of the drug substance.

B. Drug Product:

The drug product is intra-uterine system (IUS) which is composed of T-body, elastomer core containing levonorgestrel, membrane tubing, and removal thread. The vertical stem of the T-body is covered with the elastomer core, which is further covered with the membrane tubing. The drug substance in the elastomer core is to be continuously released through the membrane tubing for five years in-vivo. The IUS has removal thread tied to the low-end part of the vertical stem, which is made of [details not provided].

The elastomer core is made of [details not provided] which contains 52mg of levonorgestrel. The membrane tubing is also made of [details not provided] although it is flexible. Both elastomer core and membrane tubing are manufactured by [details not provided].

Leiras (DMF) using the [details not provided] supplied by [details not provided]. Those elastomer core and membrane tubing had been made and supplied by [details not provided]. However, since dropped those products, Leiras and [details not provided] have been replaced for producing those products with demonstration of the equivalency to the deceased products.

The T-body made of polyethylene and barium sulfate is manufactured by [details not provided] the IUS is manufactured by Leiras Oy, Finland; the system is packaged by [details not provided]. and the product release testing is to be done by Berlex Laboratories, Inc. Analytical testing of inactive ingredients as well as in-vitro release testing of the product are to be done by [details not provided]. They are all deemed in compliance with cGMP.

The quality of the drug product, IUS, is controlled by specifications including [details not provided] they are deemed adequate for assuring the quality of the product. The IUS is sterilized by [details not provided] after primary packaging is done, and sterility assurance is deemed satisfactory by Microbiology reviewer.

One of the critical attributes of the product is in-vitro release rate and the following specifications are established based on clinical as well as stability batches:

Total mean value of release rate measured in a medium of should be within [details not provided] and at least out of 12 tested samples should be ±10% of the range without any sample outside ±15% of the range.
The IUS loaded in an inserter made of ______ package in a: ______ blister tray with a peelable lid. The tray is further packaged in a pouch made of polyester and laminated aluminum foil. The pouch is not intended to provide additional protection of the product, but rather for commercial reasons.

Based on available real time data up to ______ and ______ accelerated data and inherent stability of the drug substance as well as previously approved similar product, 24-month of expiry date is granted.

The tradename, Mirena, was accepted by OPDRA.

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA may be approved.

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-225
DATE REVIEWED: 12/06/00
REVIEW #: 3
REVIEWER: Rajiv Agarwal

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
ORIGINAL 12-16-1999 12-17-1999 01-03-2000
FAX 12-06-2000

NAME & ADDRESS OF APPLICANT:
Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

DRUG PRODUCT NAME
Proprietary: Mirena®
Established: Levonorgestrel USP
Code Name/#: Levonorgestrel-releasing intrauterine system, LNG IUS
Chem Type/Ther Class: 3 S

PHARMACOL CATEGORY/INDICATION:
Contraception

DOSAGE FORM:
Intrauterine system

STRENGTHS:
.52 mg

ROUTE OF ADMINISTRATION:
Rx/OTC:

SPECIAL PRODUCTS:
Yes No

('If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (-)-13-Ethyl-17-hydroxy-18, 19- dinor-17 α -pregn-4 en-20-yn-3-one

Molecular Formula: C24H29O2
Molecular weight: 312.45

Structural Formula:
SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): See Chem. Rev. # 1-# 12

CONSULTS: See Chem. Rev # 2

COMMENTS/REMARKS:

- Sponsor is accepting all comments made on the Blister Pack labeling, Carton Labeling, Pocket Copy-Option 1, Follow-Up Reminder card and Pouch labeling with the exception that the lot number will be included with the Consent Form, which is intended to be kept with the patient's records by the health care provider, rather than with the Follow-Up reminder Card, which is intended to be kept by the patient (see amendment on 12-05-2000).

- An Amendment on 12-06-2000 was submitted with a revised version of Schematic drawing of Mirena in Physician Insert.

- A correspondence (via FAX) on 12-06-2000 from the sponsor also provides the mock-up drawings (also see amendment on 11-17-2000) of the Blister Pack Labeling, Carton Labeling, Pouch labeling, Pocket Copy-option 1 and Follow up Reminder Card.

CONCLUSIONS & RECOMMENDATIONS:

Sponsor has made the requested change in the labeling and NDA 21-225 may be approved from a chemistry, manufacturing and controls point of view.

cc: Org. NDA 21-225
HFD-580/Division File
HFD-580/RAgarwal
HFD-580/JBest
HFD-580/MRhee
R/D Init by:

Rajiv Agarwal, Ph.D
Review Chemist
WITHHOLD PAGE (S)
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-225
REVIEW #: 2

DATE REVIEWED: 12/04/00
REVIEWER: Rajiv Agarwal

SUBMISSION TYPE DOCUMENT DATE
ORIGIINAL 12-16-1999
AMENDMENT 10-26-2000 12-17-1999
AMENDMENT 10-31-2000 10-31-2000
AMENDMENT 11-09-2000 11-09-2000
AMENDMENT 11-17-2000 11-17-2000
AMENDMENT 11-20-2000 11-20-2000
AMENDMENT 11-20-2000 11-24-2000
AMENDMENT 11-30-2000 11-30-2000
FAX 12-01-2000 12-01-2000

NAME & ADDRESS OF APPLICANT:
Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

DRUG PRODUCT NAME
Proprietary: Mirena®
Established: Levonorgestrel USP
Chem. Name/#: Levonorgestrel-releasing intrauterine system
Chem. Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION:
Contraception

DOSE FORM:
Intrauterine system

STRENGTHS:
52 mg

ROUTE OF ADMINISTRATION:
Intrauterine

Rx/OTC:
X Rx OTC

SPECIAL PRODUCTS:
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (-)-13-Ethyl-17-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one
Molecular Formula: C_{21}H_{28}O_{3}
Molecular weight: 312.45
Structural Formula:

SUPPORTING DOCUMENTS:

CONSULTS:

- The EER is requested on 2/2/00, an “acceptable” recommendation was received from the Office of Compliance on 11-30-2000 (see attached EER report on pages 26-29 of this review).
- The consult for sterility assurance was sent to Microbiologist, review was completed and deficiencies were communicated to the sponsor. A satisfactory review on the responses from the sponsor (amendment dated 11-14-2000 and Fax dated 12-1-2000) was received from the microbiologist on 12-1-2000.
- A satisfactory review on Mirena IUS was received on 11-17-2000 from CDRH.

COMMENTS/REMARKS:

- An Amendment on 10-26-2000 was submitted to update and clarify manufacturing information that was submitted in the original NDA. This submission addresses some minor differences in the manufacturing process of primary stability batches and commercial batches.
- Another Amendment on 10-26-2000 was submitted to address the two deficiencies (point # 11 and 12) delineated in the Draft Deficiency letter dated 10-19-2000.
- An Amendment on 11-14-2000 is provided in response to the labeling comments made on pouch and Blister pack labels. Sponsor is asking to use the unchanged version of the label text for the pouch and Blister pack for the first commercial batch of drug product being produced for the US. This request was withdrawn by the sponsor on 11-27-00 via an Amendment.
- An Amendment on 11-14-2000 was submitted to address the deficiencies (Microbiology) delineated in the Deficiency letter dated 11-06-2000.
- Labeling deficiencies in the Patient Insert are described in the Chemistry review #1 of this NDA, and they are no longer relevant as the sponsor replaced the entire section with the new information. From the chemistry point of view, no changes are needed in the final version of the patient insert. However,
the Physician Insert, blister pack, Pouch, and Carton labelings were revised in accordance with our request except for the Schematic drawing of Mirena.

Arrows to define the dimensions of T-body must be better aligned c - i must be closer to the T-body. This change has been incorporated on the N: drive and will be conveyed to the sponsor.

- An Amendment on 11-17-00 was submitted further to address the deficiencies (points 7 and 8) communicated to the sponsor via teleconference on 11-13-00 while reviewing the amendment dated 11-8-2000.
- An Amendment on 11-17-2000 was submitted for an additional (total 30°C/60%RH) of the stability data.
- A consult was sent to LNC on 10-31-00 for using IUS terminology instead of IUD. This issue was also discussed with Dr. Dena Hixon, MO, Team leader. Dr. Hixon has no objection in using IUS terminology.
- A teleconference was made on 11-16-2000 with the sponsor to tighten the current release rate specifications (set in 1 day) from ____________ µg/day to ____________ µg/day with an average release rate of ____________ day and an Amendment on 11-24-2000 was submitted to include some new release data for ____________ product batches including clinical and stability data to support their new regulatory release rate specifications (__________ µg/day). This report amends the original in vitro release rate justification report that was provided in the CMC section of the NDA (page 323, vol. 1.4).
- An Amendment on 11-27-2000 was submitted to provide a new regulatory specifications for in vitro release rate.
- Sponsor is accepting 24 months of shelf life, which was based on ____________ 30°C/60%RH and ____________ 10°C/75% RH) of real time stability data on primary stability batches (see amendment on 11-30-2000).
- A correspondence (via FAX) on 12-01-2000 from the sponsor provides a commitment to discontinue the practice of multiplying colony counts by a correction factor to yield an estimated bioburden.

CONCLUSIONS & RECOMMENDATIONS:

From chemistry, manufacturing and controls point of view, this NDA may be approved pending resolution of the Labeling issues.

cc:
Org. NDA 21-225
HFD-580/Division File
HFD-580/RAgarwal
HFD-580/JBest
HFD-580/MBhee
R/D Init by:  
filename: NDA 21-225
WITHHOLD PAGE (S)
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-225
DATE REVIEWED: 8/30/00
REVIEW #: 1
REVIEWER: Rajiv Agarwal

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
ORIGINAL 12-16-1999 12-17-1999 01-03-2000
Correspondence 06-30-2000 07-03-2000 07-10-2000
AMENDMENT 07-11-2000 07-12-2000 07-21-2000
AMENDMENT 08-21-2000 08-22-2000 08-23-2000
AMENDMENT 08-25-2000 08-28-2000 08-30-2000

NAME & ADDRESS OF APPLICANT:
Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-2000

DRUG PRODUCT NAME
Proprietary: Mirena®
Established: Levonorgestrel USP
Code Name/#: Levonorgestrel-releasing intrauterine system, LNG IUS
Chem. Type/Ther. Class: 3 S

PHARMACOL. CATEGORY/INDICATION:
Contraception

DOSAGE FORM:
Intrauterine system

STRENGTHS:
52 mg

ROUTE OF ADMINISTRATION:
Intrauterine

Rx/OTC: __Rx ___OTC

SPECIAL PRODUCTS:
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

Yes  No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: (-)-13-Ethyl-17-hydroxy-18, 19-dinor-17 α -pregn-4 en-20-yn-3-one
Molecular Formula: C_{31}H_{30}O_{3}
Molecular weight: 312.45

Structural Formula:
### SUPPORTING DOCUMENTS:

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<th>Type/Number</th>
<th>Subject</th>
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<td>Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland</td>
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<td>Reviewer: Rajiv Agarwal</td>
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**RELATDO DOCUMENTS (if applicable):** None

**CONSULTS:**
- The EER inspection is requested on 2/2/00, inspections pending.
- The OPDRA consult was sent on 3/21/00, OPDRA does not object to the use of the name “Mirena”.
- The consult for Devices was sent on 11/10/99, review pending.
- The consult for sterility assurance was sent to Microbiologist on 11/10/1999, review pending

**COMMENTS/REMARKS:**
Levonorgestrel-releasing intrauterine system (LNG IUS) consists of a T-shaped polyethylene frame (T-body) with a cylindrical steroid reservoir (hormone-elastomer core) and membrane mounted on the vertical stem. The polyethylene in the T-body is compounded with barium sulfate for radio-opaency. The steroid core is composed of a mixture of 52 mg levonorgestrel (by weight) and polydimethylsiloxane. The core is covered by a polydimethylsiloxane membrane, which regulates the release of levonorgestrel to achieve a nominal initial release rate of 20 μ g/day. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body.

The to be marketed product is identified as Composition D (production). Earlier, Composition B and C were used in the pivotal clinical trials and Composition C is currently marketed in the Europe. The [supplier of the “key” components] has ceased the production and distribution of the materials and components used to manufacture the membrane and hormone core of the Composition B and C. Therefore, Leiras of Finland is manufacturing the key components (membrane and unfilled elastomer) from the raw material (polymer) provided from [supplier]. Earlier, was also the supplier of the polymers.

Similarly, the chemicals also discontinued the production of in late 1995. This was earlier used in the manufacturing of Composition D and composition C batches. Composition D now utilizes the...
The following table will explain the suppliers used to provide the "other" material and components for Composition B, C and D. Bold face suppliers under composition D are indicative of "different" suppliers from the suppliers of Composition B and C formulations. The information on physico-chemical properties and other specifications from the different suppliers are provided in the NDA and addressed in this review.

<table>
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<tr>
<th>Component/Description</th>
<th>Composition B</th>
<th>Composition C</th>
<th>Composition D</th>
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</table>

- An Amendment on 4-19-00 is provided for Composition of the base polymers MED) manufactured by (information was requested by this reviewer).

- An Amendment on 6-8-00 is provided for a comparative specifications and test results for unfilled elastomer and tubing batches used in Composition B, C, and D. The other information is provided for the dimensions of mentioned in DMF ( ) for because the DMF addressed only an European, product (information was requested by this reviewer).

- Correspondence on 6-30-00 describes the intention to amend the NDA with mostly new secondary packaging and change in site of manufacturing of T-body to (manufacturing site of ) from.

- An Amendment on 7-11-00 is provided for the DMF number for that the manufactured at for the USP physicochemical tests for and (information was requested by this reviewer).

- An Amendment on 7-25-00 is provided for the information committed in the correspondence dated 6-30-00 and provided the following information.
  
  - Modification of the secondary packaging for the drug product.
  - A change in the site at which the T-body is manufactured.
The use of alternate assay method for barium sulfate USP.

It also contains most of the "updated" labeling information but lacks the updated patient labeling information. Commitment is made to provide this information in August 2000.

An Amendment on 8-21-00 is provided for the following new information, which were requested by this reviewer.

- Discrepancy in trade names used for membrane elastomer.
- Composition of elastomer used in composition C.
- Comparative specific gravity of elastomer used in C and D compositions (originally, comparative densities of membrane were requested).
- Information on used for the scale of the insertion tube.
- DMF # for is provided.

An Amendment on 8-25-00 is provided for a long term (360 days) dissolution data on composition C and D batches using dissolution medium.

An Amendment on 10-13-00 is provided for the following new information, which were requested by this reviewer.

- Discrepancy in the tradename of the that is used in the plunger.
- USP physico-chemical and biological reactivity tests on flange.

CONCLUSIONS & RECOMMENDATIONS:

The provided chemistry, manufacturing and control information is adequate to make this NDA approvable pending resolution of the following issues:

- resolution of the issues delineated in the Draft Deficiency Letter on 10-19-00
- satisfactory consulting reviews from CDRH and microbiologist.
- satisfactory site inspection results from the Office of Compliance.

Rajiv Agarwal, Ph.D
Review Chemist

cc:
Org. NDA 21-225
HFD-580/Division File
HFD-580/RAgarwai
HFD-580/JBest
HFD-580/MRhee
R/D Init by:
filename: NDA 21-225
WITHHOLD__PAGE (S)
NDA FILEABILITY CHECKLIST

NDA Number: 21-225  Applicant:  Berlex Laboratories Inc.,  
340 Changebridge Road,  
P. O. Box 1000, Montville,  
NJ 07045-1000

Stamp Date: Dec 20, 1999  
Drug Name: Mirena® (Levonorgestrel)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes _x_No ____)

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
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<td>1  On its face, is the section organized adequately?</td>
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<td>x</td>
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<tr>
<td>2  Is the section indexed and paginated adequately?</td>
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<tr>
<td>3  On its face, is the section legible?</td>
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<td>4  Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?</td>
<td></td>
<td>x</td>
<td>Full street addresses of the Drug Substance and Drug Product manufacturers are not provided.</td>
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<tr>
<td>5  Is a statement provided that all facilities are ready for GMP inspection?</td>
<td></td>
<td>x</td>
<td>No statement is provided whether the Schering AG (drug substance), Leiras Oy (drug product), Berlex Laboratories, NJ or (contract facility), facilities are ready for inspection.</td>
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<td>6  Has an environmental assessment report or <em>categorical exclusion been provided</em>?</td>
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<td>7  Does the section contain controls for the drug substance?</td>
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<tr>
<td>8  Does the section contain controls for the drug product?</td>
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<tr>
<td>9  Has stability data and analysis been provided to support the requested expiration date?</td>
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<td>See the stability section of Drug product.</td>
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<td>10 Has all information requested during the IND phase, and at the pre-NDA meetings been included?</td>
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<tr>
<td>11 Have draft container labels been provided?</td>
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<tr>
<td>12 Has the draft package insert been provided?</td>
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<td>13 Has an investigational formulations section been provided?</td>
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<td>14 Is there a Methods Validation package?</td>
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<td>15 Is a separate microbiological section included?</td>
<td></td>
<td>x</td>
<td>Relevant sterility test is performed.</td>
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If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

This application now meets the filing requirement from the CMC point of view. Earlier, several items were not included in the submission, therefore, a request was made and sponsors have provided all the requested material.
This application is now adequate to review from the CMC standpoint.

Review Chemist: Rajiv Agarwal, Ph.D. Date: 3/20/00

Team Leader: Moo-Jhong Rhee, Ph.D. Date: 3/20/00

cc:
Original NDA 21-225
HFD-580/Division File
HFD-580/Chem/RAgarwal/MRhee
HFD-580/PM/JMercier
HFD-580/DivDir/SAllen

Have all DMF References been Identified? YES

<table>
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<td>Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland</td>
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<td>Yes</td>
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<tr>
<td>(Type IV)</td>
<td>Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland</td>
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<td>(Type IV)</td>
<td>Leiras Oy Pansiontie 47 P.O. Box 415 FIN-20101 Turku Finland</td>
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<td>(Type III)</td>
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<tr>
<td>(Type I)</td>
<td>Bectax Laboratories, Inc.</td>
<td>300 Fairfield Road</td>
<td>Yes</td>
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<td>wayne, NJ 07420</td>
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SUMMARY

DRUG SUBSTANCE:

Information in NDA:

The active ingredient in the Mirena® is Levonorgestrel USP, formulated as an hormonelastomer core in intrauterine system. The core is composed of a mixture of 52mg levonorgestrel by weight and polydimethylsiloxane. The drug substance is manufactured by Schering AG of Berlin, Germany and detailed information regarding the synthesis and characterization of levonorgestrel is provided in the Schering AG Type II DMF no.

Some information (appearance, melting range, specific rotation, partition coefficient and solubility) on the drug substance is also provided in the NDA submission.

CAS # 797-63-7
Molecular weight: C_{21}H_{28}O_{2}
Structural formula:

Chemical name: (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yne-3-one

Information in DMF:

DMF was earlier reviewed by Dr. Ali Al-Hakim on 4/23/98 in conjunction with the NDA 20-860 and found to be adequate. The DMF was last updated in 1997.

DRUG PRODUCT

Dosage form: Intrauterine system
Strength: 52 mg
Route of Administration: Intrauterine
Composition:
The unit composition of LNG IUS plus the inserer is provided below.

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
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</thead>
<tbody>
<tr>
<td>Hormone-Elastomer Core</td>
<td></td>
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<tr>
<td>Evonik Polymer USP</td>
<td></td>
</tr>
<tr>
<td>Endometrial Coating</td>
<td>50 mg</td>
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<tr>
<td>Tubing - polydimethylsiloxane</td>
<td></td>
</tr>
<tr>
<td>Insertion - polydimethylsiloxane</td>
<td></td>
</tr>
<tr>
<td>T-body - containing</td>
<td>1 unit</td>
</tr>
<tr>
<td>Removal Thread - containing</td>
<td></td>
</tr>
<tr>
<td>Inserter</td>
<td>1 unit</td>
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</tbody>
</table>

Manufacturers:

- Schering AG DMF — (Type II)- Complete address is not provided.

Drug Product:
a. The commercial product will be manufactured, packaged, labeled and tested (release and stability) at:

Leiras Oy
Pansiontie 45-47
P.O. Box 415
20101 Turku
Finland

b. The finished packaged product will be shipped to Berlex in NJ (USA) and inspection of a statistical sample of the product will be performed prior to release distribution.

Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470

c. The testing of the components used in the drug product may be used at:
Stability:
Primary and supportive stability data is provided in the submission and an expiration date is requested.

In primary stability data, included are ——— data on ——— production scale lots (composition D, US commercial product) which were kept at CRT (30°C/60% RH) and accelerated conditions (45°C/75% RH). A ——— data (CRT) with ——— accelerated data for ——— scale batch of composition is also provided.

In supportive data, a ——— CRT and accelerated data is provided for a second batch of composition D (——— scale lot).

Also provided as supportive data are ——— CRT and accelerated stability data and a ——— of accelerated and temperature cycling data for ——— batches used in the clinical trial formulation (composition C, different material and material suppliers). The inserter and container closure system is different than will be used for the US commercial market. Data needs to be reviewed in detail.

Review concerns:
Only ——— of stability data on Composition D is provided at the time of submission. Sponsors should supplement the submission with further stability data on Composition D during the review process to support at least a 2 year shelf-life (see pre-NDA minutes, dated January 27, 1998). The supportive data may not be enough to support a ——— shelf-life as requested.

In vitro release:
Following comparative long term dissolution tests on the composition D (US commercial product), with the composition C (different material and material suppliers than the US commercial product and used in the clinical trials), is used to evaluate the in vitro performance of the drug product over time, is provided in the submission.

1. Long term (first 180 days) in vitro levonorgestrel dissolution of ——— production vs ——— batches of composition D (report 1513).
2. Long term (first 180 days) in vitro levonorgestrel dissolution of ——— production of Composition D vs ——— production batches of Composition C (report 1512).
3. Long term (three years) in vitro levonorgestrel dissolution of a ——— batch of Composition D vs a clinically used production batch of Composition C (report 1500).
4. Long term (two years) in vitro levonorgestrel dissolution of a ——— batch of Composition D (report 1495).

All data needs to be reviewed in detail.