

WITHHOLD 4 PAGE (S)

BEST
A61

MEMORANDUM OF TELECON

DATE: 9-20-00

APPLICATION NUMBER: DMF

BETWEEN:

Name: Ms. Jo Ann Ruane/Ms June Bray
Phone: 973-276-2343
Representing: Berlex

AND

Name: Dr. Rajiv Agarwal
DRUDP, HFD # 580

SUBJECT:

Page 913 was blank in DMF

BACKGROUND:

- The last page of the method validation of release control test methods in vol 5.3 of the DMF was left blank.

TELEPHONE CONVERSATION:

The above concern was communicated to the Ms Jo Ann Ruane and Ms. June Bray on 9/20/00 at 10 AM. Ms. Ruane will FAX the missing information to this reviewer.

BSI
Dr. Rajiv Agarwal
Review Chemist

cc:

Archival DMF
HFD-580/Division Files
HFD-580 /AgarwalR/RheeM/BestJ
Drafted by: RA/9/7/00
Initialed by:
Final: RA/9/7/00
Filename: TC

TELECON

BEST 6.1 Mark Cym

MEMORANDUM OF TELECON

DATE: 9-7-00

APPLICATION NUMBER: NDA 21-225

BETWEEN:

Name: Ms. Jo Ann Ruane
Phone: 973-276-2343
Representing: Berlex

AND

Name: Dr. Rajiv Agarwal
DRUDP, HFD # 580

SUBJECT:

- Discrepancies in the Trade names of _____ used to manufacture "Plunger"
- CMC and various USP tests on "Flange" were not provided in the original submission.

BACKGROUND:

- The trade name of _____ used to manufacture the "plunger" of Insertion tube is different (_____ , in table on page 29 of vol. 1.6) from what has been described in the DMF (Trade name _____). A clarification is required from the sponsor.
- The flange is made of _____ and contains _____. The flange will have some contact with the uterine cervix of the subjects, therefore, the CMC section and results of USP tests (Physico-chemical <661> and biological tests <87>, <88>) were requested.

TELEPHONE CONVERSATION:

The above concerns were communicated to the Ms Jo Ann Ruane on 9/7/00 at 2 PM. Ms. Ruane will call the DMF holder for the answers.

151

Dr. Rajiv Agarwal
Review Chemist

cc:

Archival IND/NDA 21-225
HFD-580/Division Files
HFD-580 /AgarwalR/RheeM/BestJ
Drafted by: RA/9/7/00
Initialed by:
Final: RA/9/7/00

WITHHOLD 6 PAGE (S)

D/F

Teleconference Minutes

Date: August 10, 1999 **Time:** 11:30-12:20 PM **Location:** Parklawn; 17B-43

IND **Drug:** Levonorgestrel-Releasing Intrauterine System

Indication: Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Guidance

AUG 31 1999

Meeting Chair: Ameeta Parekh, Ph.D.

External Lead: Herman Ellman, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

John Hunt – Deputy Director, Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-860)

Ameeta Parekh, Ph.D. – Team Leader, OCPB @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Herman Ellman, M.D. – Director, Endocrinology and Fertility Control, Clinical Research and Development

Rolf Krattenmacher, Ph.D. – Associate Director of Project Management, Female Health Care

Brenda Marczi, Ph.D. – Associate Director, Drug Regulatory Affairs

Armen Meilikian, Ph.D. – Associate Director, Clinical Pharmacology

Jo-Ann Ruane - Manager, Drug Regulatory Affairs

Hannu Allonen, M.D., Ph.D. – Director, R&D Project Management

Pasi Merkkü, Ph.D. – Product Development Manager, Head of Pharmaceutical Development

Pirjo Sallinen – Project Manager

Heikki Voipio – Director, Regulatory Affairs

Meeting Objective: To discuss the IVTC submission dated May 24, 1999.

Discussion:

- the sponsor has linked formulation changes from Composition B to Composition C
- the sponsor is now using Composition D as the to-be-marketed formulation because they are no longer able to obtain the polymer from
- the IVTC data submitted in the May 24, 1999 submission is attempting to link Composition C to Composition D

- the sponsor plans to begin a clinical study using the to-be-marketed product following submission of the NDA; during that time, the sponsor will collect some dry blood levels as additional data to validate the IVIVC
- blood samples will be monitored, in addition to *ex-vivo* release information from removed IUS; this pattern can be compared to previously submitted data to strengthen the IVIVC
- the new information can be submitted within the review cycle and would not be considered a filing issue
- the sponsor is reminded that information submitted less than 90 days before the action date would result in the extension of the clock


Decisions made:

- the sponsor will submit additional data during the review clock for validation of the IVIVC
- the sponsor will submit the protocol for the study prior to initiation

Unresolved decisions: None

Action Items:

- Fax meeting minutes to sponsor within 30 days


Minutes Preparer


Concurrence, Chair

cc:

Original IND

HFD-580/DivFile

HFD-580/Rumble/Mercier

HFD-580/Rarick/Mann/Rhee/Parekh

HFD-860/Hunt

drafted: August 11, 1999

concurrence: Rumble8.13.99/Parekh8.15.99/Rhee8.13.99/Hunt8.27.99

final: August 30, 1999

MEETING MINUTES

- D/F

Teleconference Minutes

Date: July 19, 1999

Time: 12:00 - 1:00 PM

Location: Parklawn; 17B-43

IND

Drug: Levonorgestrel-Releasing Intrauterine System

Indication: Contraception

Sponsor: Berlex Laboratories, Inc.

AUG 17 1999

Type of Meeting: Guidance

Meeting Chair: Lisa Rarick, M.D.

External Lead: Herman Ellman, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Susan Allen, M.D. - Team Leader, DRUDP (HFD-580)

Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)

Kate Meaker, Ph.D. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Terri Rumble, B.S.N. - Chief, Project Management Staff, DRUDP (HFD-580)

External Attendees:

Berlex Participants

Herman Ellman, M.D. - Director, Female Health Care - Clinical Research & Development

Brenda Marczl, Pharm.D. - Associate Director, Drug Regulatory Affairs

Jo-Ann Ruane - Manager, Drug Regulatory Affairs

Rolf Krattenmacher, Ph.D. - Associate Director Project Management - Female Health Care

Marja Oinonen - Statistical Scientist - Clinical Research & Development

Leiras Participants

Ilkka Rauramo, M.D., Ph.D. - Senior Research Manager, Clinical Research & Development

Pirjo Sallinen - Project Manager

Britt-Marie Lindstroem, M.S. - Biostatistician

Heikki Voipio - Director, Regulatory Affairs

Meeting Objective: To discuss the fileability of the NDA.

Background: The sponsor submitted a pre-NDA packet in April, 1999 and additional supporting information on June 17 and July 16. This information has been reviewed by the Division.

Discussion Points:

1. Primary endpoint (pregnancy)

- pregnancy tests were not performed uniformly at entry, during follow-up or at study discontinuation
- the sponsor will need to provide rationale to justify the lack of routine pregnancy test data in the submission
- documentation will also be needed regarding complete follow-up information for the pregnancies which occurred during the trial
- a lack of this data would be a review issue

2. Lack of complete and valid safety data

- per information contained in the packet there is a lack of bleeding and spotting data from the studies performed
- hemoglobin data is the only information available to measure these effects; routine blood work was performed
- there is lack of complete information regarding the severity of adverse events in study AY 99
- there is incomplete information on the insertion date of the IUD for all study participants

3. Sites

- According to the 4/99 information, many of the sites for Study B075 would not qualify as valid sites due to:
 - a lack of valid source documents
 - a lack of informed consents documentation
- regarding the nine remaining clinical trial sites
 - information would have to be provided on the exact number of patients who had informed consent at those qualified sites
 - it appears that approximately 500 subjects participated at sites that may not qualify as "valid"
 - sponsor states that all patients were given informed consent, but not all were documented; the sponsor also opted to provide a retrospective statement for these sites that have no documented informed consent

Decisions Made:

NDA requirements for this application include:

- the exact number of patients who completed 5 years of product use at valid sites
- a minimum of 200 women who completed 5 years of product use will be required if the sponsor seeks a 5-year use indication
- at least 35-40,000 women months of data

The sponsor had not planned to conduct another study for this product.

Unresolved decisions: None

Action Items:

- Fax meeting minutes to sponsor within 30 days
- Sponsor should provide justification for lack of pregnancy testing
- Sponsor should provide justification for using Hgbs as parameter for bleeding assessment
- Sponsor should provide information regarding the source data, valid sites and number of patients that are included with this criteria

LSI
Minutes Preparer

LSI
Concurrence, Chair

IND
Meeting Minutes
Page 4

cc:

Original IND

HFD-580/DivFile

HFD-580/PM/Rumble/Pauls/Mercier

HFD-580/Rarick/Mann/Allen/Meaker/Kammerman

drafted: August 3, 1999

concurrence: Rumble 8.3.99/Allen 8.9.99/Rarick 8.13.99/Meaker 8.4.99

final: August 17, 1999

MEETING MINUTES

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DIF

Teleconference Minutes

MAR 31 1999

Date: March 10, 1999 Time: 10:00 AM - 11:30 AM Location: Parklawn C/R 17B-43

IND Drug Name: levonorgestrel intrauterine system

External Participant: Berlex Laboratories

Type of Meeting: biopharmaceutic guidance

Meeting Chair: Marianne Mann, M.D.

External Participant Lead: Jo-Ann Ruane

Meeting Recorder: Christina Kish

FDA Attendees:

- Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
- Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics; Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
- Sam H. Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
- Johnny Lau, R.Ph., Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
- John Hunt - Deputy Director, DPE II (HFD-870)
- Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

- Berlex
- Herman Ellman, M.D. - Director, Endocrinology and Fertility Control, Clinical Research and Development
- Rolf Kattermacher, Ph.D. - Associate Director of Project Management, Female Health Care
- Brenda Marczi, Pharm.D. - associate Director, Drug Regulatory Affairs
- Armen Melikian, Ph.D. - Associate Director, Clinical Pharmacology
- Jo-Ann Ruane - Manager, Drug Regulatory Affairs
- Mukul Singh, M.D. - Senior Associate Medical Director, Female Health Care

Leiras Participants

- Hannu Allonen, M.D., Ph.D. - Director, Research and Development Project Management
- Heikki Lyytikainen, M.Sc. - Senior Scientist, Product Development
- Pasi Merkku, Ph.D. - Product Development Manager, Head of Pharmaceutical Development
- Ikka Rauramo, M.D., Ph.D. - Senior Research Manager, Clinical Research and Development
- Heikki Voipio - Director, Regulatory Affairs

Consultants

IND
levonorgestrel IUS
March 10, 1998

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Meeting Objectives:

To discuss the sponsor's request for an *in vitro/in vivo* correlation waiver for their contraceptive levonorgestrel containing intrauterine system.

Discussion Points:

• **Background**

- the sponsor is currently developing an IUS for contraception
- the formulation for the IUS has changed four times, such that there has been an IUS formula A, B, C, and a newly proposed to-be-marketed formulation D
- clinical trials have been performed primarily with formulation B, although there are some clinical data for formulation C
- the sponsor proposes submitting *in vitro/in vivo* correlation data equating release rate with efficacy in order to link formulations B and C
- *in vitro/in vivo* correlations are generally used to link changes in oral dosage formulation changes, it is unusual to use this type of correlation to support formulation changes in an IUS where *in vivo* serum levels of drug may not be relevant

• **Formulation Changes**

- changes in manufacture between formulations C and D are minimal according to the sponsor, and include:
 - a change in raw material supplier from _____
 - a change in membrane manufacture, although qualitatively the membranes are the same
 - changes in the manufacturing process
 - the sponsor proposes that it is the change from formulation B to C that is relevant, and they intend to support this by demonstrating similar release rate of each

• ***in vitro/ex vivo* testing**

- a custom apparatus is utilized in dissolution testing of the IUS
- different media yield different dissolution results
- the current dissolution media chosen is _____ this media was chosen because it was the dissolution media used successfully for Norplant; although some studies may exist in which _____ was used
- current release rate specifications are based on the variability of the manufactured product, which range from _____ release rate
- the sponsor will provide information on the release rates of the lots used in clinical trials
- clinical trials carried out by the World Health Organization utilized systems with a lower release rate of _____ which was deemed ineffective, however Berlex does not have access to that data
- Leiras has carried out a small clinical trial with a system having a release rate of 10 ug/day which returned an unacceptable pregnancy rate, this information can be provided for review although the release rate testing method may not be the same as that currently used

IND

levonorgestrel IUS
March 10, 1998

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- if information is available for two formulations with the same release rate in which one proved efficacious and one did not, the sponsor should provide that information
- the sponsor has submitted information which indicates that formulation B may have a more rapid release rate than formulation C, although Berlex statisticians have indicated that the difference in release rate is not statistically significant, this may be of clinical relevance and may become a review issue
- *Ex vivo* release rates
 - ex vivo release rates are based on a single clinical trial in which formulations B and C were both used (in 50 and 340 women respectively)
 - release rates were determined based upon residual drug levels in the system after removal at the end of the trial (approximately 1800 days) or earlier if the woman requested early removal
 - the sponsor will review their data to determine whether there is any additional release rate data from other clinical trials in which formulations B or C were used
 - the sponsor should submit all information on the correlation, or lack of correlation, between the serum concentrations and efficacy rates
 - three pregnancies occurred in the Phase 3 clinical trials, the sponsor will determine when during the trial these pregnancies took place and provide that information

Decisions Reached:

- the sponsor will provide the following information
 - literature and data evidence that serum levels and pregnancy rates do not correlate
 - additional data points of residual drug levels in the IUS after removal from subjects for formulations B and C
 - a complete list of all changes, both formulation and manufacturing, between B, C and D formulations
- the sponsor will provide the requested information within 30 - 45 days

Unresolved Issues: acceptability of *in vivo/in vitro* correlation

Action Items: see decisions reached

ISA
Minutes Preparer

3/31/98

ISA
Concurrence, Chair

3/31/98

IND
levonorgestrel IUS
March 10, 1998

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cc:

Orig.

HFD-580

MEETING ATTENDEES

HFD-580/CKish/3.16.99/ ————^{tc}

Concurrence: SHaidar 3.18.99/MMann 3.19.99/JHunt 3.25.99

No response: AParekh/JLau

MEETING MINUTES

BEST POSSIBLE COPY

Meeting Minutes

Date: January 27, 1998 Time: 9:00 AM - 10:30 AM Location: Parklawn C/R 'C'

NDA pre-NDA Drug Name: levonorgestrel intrauterine system

External Participant: Berlex Laboratories, Inc.

Type of Meeting: pre-NDA

Meeting Chair: Lisa Rarick, M.D.

External Participant Lead: Suzanne Hampton, Ph.D.

Meeting Recorder: Christina Kish

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)

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

Kasturi Srinivasachar, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Alexander Jordan, Ph.D. - Pharmacology Team Leader, DRUDP (HFD-580)

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

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

~~REGULATORY AFFAIRS~~

Herman Ellman, M.D. - Director, Endocrinology and Fertility Control, Clinical Research

Suzanne Hampton, Ph.D. - Associate Director, Drug Regulatory Affairs

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

Lou Mylecraine, Ph.D. - Section Head, Toxicology

Marja Oinonen - Statistical Scientist

Thomas Proske, Ph.D. - Director, Project Management

Ronald Wohl, Ph.D. - Director, Chemistry, Manufacturing and Controls Administration

~~REGULATORY AFFAIRS~~

Hannu Allonen, M.D., Ph.D. - Director, Research and Development Project Management

Ilkka Rauramo, M.D., Ph.D. - Senior Research Manager, Clinical Research and Development

Heikki J. Voipio, M.Sc., M.B.A. - Director, Regulatory Affairs

~~REGULATORY AFFAIRS~~

Meeting Objectives:

To gain concurrence with regard to the acceptability of the upcoming NDA submission.

Discussion Points:

● **General**

- the product is a levonorgestrel intrauterine device (IUD) to be used for contraception
- the sponsor does not currently hold an IND for this product
- the sponsor is currently in the process of obtaining IND from the Population Council through transfer of the IND
- all clinical studies and drug development have been completed outside of the U.S.
- the sponsor anticipates submitting an NDA for this application in 1999

● **Chemistry Manufacturing and Controls**

- a formulation change has been made to the product due to discontinuation of the original polymer material by outside manufacturers
- the sponsor claims the replacement materials in the reformulation are equivalent to the discontinued materials
- new elastomers to be used show virtually identical release characteristics
- the sponsor does not plan to measure residual monomers for each batch, this may be a review issue

● **Clinical Pharmacology and Biopharmaceutics**

- the sponsor has data on levonorgestrel blood plasma levels for the 0 - 3 month time point and will provide this information
- an initial blood plasma spike is not present with this product
- in general, blood plasma levels of levonorgestrel are very low as it is hoped to be a local rather than systemic delivery
- subject weight is not expected to impact efficacy of the system; data have been collected on this issue and will be included in the upcoming application
- an explanation should be submitted with the sponsor's *in vitro/in vivo* correlation data regarding the absence of significant levonorgestrel blood plasma levels
- the proposed *in vitro/in vivo* correlation should be validated
- the sponsor claims that formulations B, C and D are essentially identical
- if the *in vitro/in vivo* correlation is established for B and C the sponsor would like to submit dissolution data only for formulations C and D .

● **Clinical**

- eleven studies performed abroad are proposed to provide the basis for the safety and efficacy of this system
- of those studies, approximately 342 women have completed 5 years with the system

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Pre-NDA
levonorgestrel IUD
Berlex Laboratories

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- only studies which meet good clinical practices, are auditable and have documentation of patient consent are included as pivotal trials
 - study designs across the eleven studies vary slightly
 - the case report forms will be rewritten to a common study report for submission
 - all women enrolled in these eleven studies will be included in one of the intent-to-treat analysis
 - the integrated summary of safety will include studies in which other indications for this product were examined (e.g., _____)
 - the sponsor is encouraged to submit the protocols used for the pivotal studies prior to submission of a new drug application
 - from a statistics perspective, the proposed package is not fileable due to the lack of statistical information at present, the sponsor is encouraged to submit a statistical analysis plan for review prior to submission of a new drug application
- **Sponsor Chemistry Questions**
 - Q1. Are the drug product specifications adequate?
 - A1. The sponsor should supply the following additional information in their upcoming NDA submission:
 - content uniformity data
 - more specific information the drug product specifications
 - characterization of the degradation products over 0.1 %
 - methods validation
 - sterility
 - Q2a. Is the *in vitro* characterization of Composition D acceptable?
 - A2a. The *in vitro* data must be reviewed by the Division before such a determination can be made.
 - Q2b. Are _____ stability data acceptable for the initial NDA submission?
 - A2b. Although a _____ shelf-life will be requested, if the sponsor submits _____ of stability data at the time of submission and supplements the submission with further stability data during the review, the final amount of stability data would likely support a 2 year shelf-life.
 - Q2c. Is the proposed matrix design for the stability study acceptable?
 - A2c. The proposed matrix design for the stability study is acceptable, however the sponsor should also obtain data at the _____ time point for all batches at 45°C.
 - Q2d. Is the 5-year long term dissolution testing plan acceptable?
 - A2d. The proposed plan is acceptable, however we recommend that the dissolution testing be performed on _____ batches instead of _____ batch as proposed.

Q2e. Is a 6-month dissolution profile acceptable for initial NDA submission?

A2e. Yes.

Q3. Does the CMC section overall appear to be sufficient for filing?

A3. Yes.

● Sponsor Toxicology Questions

Q4. Have the components in this IUD been adequately qualified with regard to pre-clinical information?

A4. Yes.

Q5. Is the ongoing monkey study sufficient to support an indication for 5 years of use?

A5. Yes.

Q6. Do the monkey studies provide sufficient nonclinical information for evaluation of the comparative local and systemic absorption profiles and pharmacodynamics of the active component delivered locally?

A6. Yes.

Q7. Are the ongoing local and systemic toxicological study of subcutaneous implants in rats sufficient to qualify the component material for use in the final marketed product?

A7. Yes.

Q8. Does the nonclinical Pharmacology and Toxicology appear to be sufficient for filing?

A8. Yes.

● Sponsor Clinical Pharmacology Questions

Q9. Does the Human Pharmacokinetics and Bioavailability information appear to be sufficient for filing?

A9. The application appears to be fileable, however individual data should be submitted with the application

Q10. Has an *in vitro/in vivo* correlation been established for the IUD?

A10. The Division must review the data before such a determination can be made.

- Q11. Can composition D be approved without further clinical testing for bioavailability?
- A11. If the *in vitro/in vivo* correlation is found to be acceptable, further clinical bioavailability testing for composition D will not be required.
- Q12. Will 600 days of dissolution profile for Composition D prototype IUD and 6 months of manufactured Composition D be sufficient to support filing of an NDA?
- Q12. Yes, however the sponsor is encouraged to supplement their application with further data during the review period.

• Sponsor Clinical Questions

- Q13. Does the clinical section appear to be sufficient for filing?
- A13. The amount of data is adequate for filing, if the *in vitro/in vivo* correlation data is acceptable. However, until a detailed protocol is submitted for review a determination of the appropriateness of the data cannot be made.

Decisions Reached:

- the sponsor should submit copies of clinical protocols, statistical analysis plans and the *in vitro/in vivo* correlation data

Unresolved Issues: whether the *in vitro/in vivo* correlation is acceptable

Action Items: see decisions reached

BT
Minutes Preparer

2/4/78

BT 2/5/78
Concurrence, Chair

NDA 21-225

Mirena® (levonorgestrel-releasing intrauterine system)

Berlex Laboratories, Inc.

There was no Advisory Committee Meeting held for this drug product.

**APPEARS THIS WAY
ON ORIGINAL**

Division of Reproductive and Urologic Drug Products
ADMINISTRATIVE REVIEW OF APPLICATION

APR 03 2000

Application Number: 21-225

Name of Drug: Mirena® (levonorgestrel-releasing intrauterine system)

Sponsor: Berlex Laboratories, Inc.

Material Reviewed: NDA Summary Volumes

Submission Date: January 31, 2000

Receipt Date: February 1, 2000

Filing Date: April 7, 2000

User-Fee Goal Date(s): December 7, 2000 (10-month), February 7, 2001 (12-month)

Proposed Indication: Contraception

Other Background Information: The CMC section of the NDA was presubmitted to the Division on December 16, 1999.

Review

PART I: OVERALL FORMATTING*

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Vol. 1
2. Form FDA 356h (original signature)	X		Vol. 1
a. Reference to DMF(s) & Other Applications	X		Cross-referenced on Form FDA 356h
3. Patent information & certification	X		Vol. 1, P. 1
4. Debarment certification (note: must have a definitive statement)	X		Vol. 1, P. 1

5. Financial Disclosure	X	Vol. 1, P. 7
6. Comprehensive Index	X	Vol. 1
7. Pagination	X	Confusing, data can be located
8. Summary Volume	X	Vol. 1, Items 1,2, and 3
9. Review Volumes	X	
10. Labeling (PI, container, & carton labels)	X	Vol. 1
a. unannotated PI	X	Vol. 1
b. annotated PI	X	Vol. 1
c. immediate container	X	Draft Vol. 1
d. carton	X	Draft Vol. 1
e. foreign labeling (English translation)	X	Vol. 185, P. 37
11. Foreign Marketing History	X	Vol. 185, P. 1
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X	Located in multiple volumes, based on study #
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X	Electronic

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^b

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Vol. 1, P. 47
2. Summary of Each Technical Section	X		
a. Chemistry, Manufacturing, & Controls (CMC)	X		Vol. 1, P. 49
b. Nonclinical Pharmacology/Toxicology	X		Vol. 1, P. 68
c. Human Pharmacokinetic & Bioavailability	X		Vol. 1, P. 76
d. Microbiology	X		Vol. 1, P. 75
e. Clinical Data & Results of Statistical Analysis	X		Vol. 1, P. 133
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Vol. 1, P. 264
4. Summary of Safety	X		
5. Summary of Efficacy	X		

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS*

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Vol. 1, P. 45
2. Controlled Clinical Studies	X		Multiple Volumes
a. Table of all studies	X		Multiple Volumes
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Multiple Volumes
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Vol. 189, P. 1
4. Integrated Summary of Safety (ISS)	X		Vol. 193, P.1
5. Drug Abuse & Overdosage Information	X		Vol. 207, P. 153
6. Integrated Summary of Benefits & Risks of the Drug	X		Vol. 207, P. 154
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	Special Population Studies Vol. 1. P.75

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y = Yes (Present), N = No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Request for waiver in NDA cover letter
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0		X	Requested
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format	X		Item 10
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorenicity study data in SAS data set format		X	
3. User-fee payment receipt		X	

Y = Yes (Present), N = No (Absent)

^a"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^b"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

^c"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:

Conclusions: NDA is acceptable for filing.

BT

3/31/00

Regulatory Health Project Manager

BT

4/3/00

Concurrence

cc:
Original NDA 21-225
HFD-580/Div. Files
HFD-580/PM/Best
HFD-580/Allen/Mann
Final: JAB/March 31, 2000

ADMINISTRATIVE REVIEW

DEC 06 2000

Group Leader Memorandum
NDA 21-225

Drug	Mirena®
Generic Drug Name	Levonorgestrel intrauterine system
Dose	Intrauterine system containing 52 mg levonorgestrel, released at a rate of 20 µg /day
Indication	Pregnancy prevention for up to 5 years
Applicant	Berlex Laboratories, Inc.
Date of Submission	February 1, 2000
Date of Memorandum	December 6, 2000

Background

Mirena® is an intrauterine system (IUS) consisting of a T-shaped intrauterine device (IUD) that releases a low dose of levonorgestrel (LNG) from a reservoir surrounding the stem of the T like a sleeve. LNG, a well-characterized and widely used contraceptive progestogen, is delivered directly into the uterus to provide long-term (5-years) contraception. Berlex Laboratories, Inc. the sponsor of this NDA, proposes that Mirena® is a highly effective method of contraception that, unlike the currently available oral contraceptives, does not require continued motivation for optimal effectiveness and has minimal systemic side effects. Unlike sterilization, it is reversible and does not require surgical intervention for effectiveness. The currently available copper releasing IUD is longer acting (10 years) and highly effective without systemic effects, but it may increase the amount and duration of menstrual bleeding.

As with other IUDs, the contraceptive mechanism of action has not been conclusively demonstrated. The majority of women continue to ovulate with Mirena® use. However they have some disturbance in follicular development and rupture and a decrease in progesterone production. Fertilization may be prevented by inhibition of sperm capacitation or survival or thickening of cervical mucus preventing passage of sperm. The high LNG concentrations in the endometrium produce progestogenic changes that may prevent implantation.

Three different prototypes of Mirena® (Compositions A, B, and C) have been used in clinical trials, and a fourth (Composition D) is to be marketed. Composition A did not maintain stable serum LNG concentrations beyond 3 months and was not studied further. Composition B, made with elastomer _____, contained _____ LNG released at a rate of 20 µg/day. Composition C, made with elastomer _____ contained 52 mg LNG released at a rate of 20 µg /day. Protocol 89532 (Report B078) supported the clinical and pharmacokinetic equivalence of Compositions B and C. The proposed "to-be-marketed" product, Composition D, differs from Composition C only in the manufacturer of the unfilled elastomer, and it is not expected to perform differently. Acceptability of Composition D for marketing is based on long term in vitro dissolution data, Level A IVIVC and composition similarity.

The LNG IUS was first approved for marketing in Finland in 1990. It is registered and marketed in 28 countries, and as of September 1999 had been approved in 14 additional countries but not yet marketed. It has not been withdrawn from the market in any country.

Efficacy of Mirena

The total exposure to LNG IUS in the pivotal studies was 92,129 woman-months of which 64,136 woman-months were in qualified sites (with verifiable informed consent and source documents). 633 subjects completed 5 years of treatment at qualified sites.

Pivotal studies

1. Report AY99 is a reanalysis of Protocol 61540-8216 (using Composition B), which was conducted before the first 2 Pan-European standards of Good Clinical Practices (GCP) were established in the late 1980s. Deficiencies in available data included lack of informed consent verification or auditable data sources. Therefore, this study was re-evaluated to include only qualified, auditable sites (those with verifiable informed consent and auditable source documents). The qualified study centers enrolled 1110 LNG IUS subjects, and 523 subjects completed 5 years of treatment. The Pearl Index (PI) for pregnancy was 0.10 at one year and 0.06 at 5 years (cumulative PI) for qualified centers.

The original Protocol 61540-8216 (Report B075) was a 5-year multisite, randomized, open-label parallel-group study conducted in Denmark, Finland, Norway, Sweden, and Hungary from 1982 to 1989. A total of 1821 women received the LNG IUS and 937 received the Nova T copper IUD (not available in the U.S.). The cumulative 5-year gross pregnancy rate was 5.9% for the copper IUD and 0.5% for the LNG IUS ($p < 0.0001$). The ectopic pregnancy rate was 0.25 per 100 woman-years for the copper IUD and 0.02 per 100 woman-years for the LNG-IUS. The LNG IUS was removed more often for amenorrhea (6% vs. 0%) and hormonal side effects (12% vs. 2%). The copper IUD was removed more often for bleeding problems (21% vs. 14%). Removals for pain were similar (6%). Adverse events with LNG IUS use were reported more often in the first 3 months and decreased over time. Menstrual problems were the most frequently reported adverse event.

2. Report B078 described a 5-year multisite randomized open-label study of contraceptive efficacy and safety of the LNG IUS in 390 women aged 20 to 38 years with at least 1 previous pregnancy. 340 women received Composition C and 50 received Composition B. 219 women completed 5 years of treatment. During 5 years of treatment, 3 ectopic pregnancies were detected in Composition C users (5 year cumulative Pearl Index 0.24) and no pregnancies in Composition B users.
3. Report AV97 described a one-year, multisite, randomized, open-label study comparing LNG IUS (94 subjects) with a low-dose oral contraceptive (OC) containing 150 µg desogestrel and 30 µg ethinyl estradiol (99 subjects) in young, nulliparous women ages 18-25. Seventy-five IUS users and 72 OC users completed the study. There were no pregnancies reported in either treatment group.

Data from the 3 pivotal studies (Reports AY99, B078, and AV97) were pooled to evaluate the pregnancy rates, continuation rates, and discontinuation rates for various reasons. Over 5 years, there were a total of 10 pregnancies in the LNG IUS subjects in these studies. Five were ectopic pregnancies, 2 resulted in spontaneous abortions, and 3 were terminated. The Pearl Index was 0.14 at 1 year and 0.10 at 5 years (cumulative PI) in the qualified sites. In study reports with an OC or copper IUD comparator, the Pearl Index at 1 year was 0 for the OC and 0.98 for the copper IUD, and at 5 years the cumulative PI was 1.26 for the copper IUD. Pearl Indices were similar for the subjects who were no older than 35 years at enrollment.

Reviewer's Comments:

The following characteristics of the clinical trial population may have introduced bias for lower pregnancy rates. However, the data have shown Mirena® to be a highly effective method of contraception for the target population of older parous women with the added benefit of sustained long-term effectiveness without the need for daily pill taking or periodic injections.

- *In the qualified sites of contraceptive studies, 21% of subjects were at least 36 years old at enrollment (at least 41 years old after 5 years of use), and another 39% were 31-35 years old at enrollment (36-40 years old after 5 years of use). The increasing age of subjects may have presented a bias in favor of lower pregnancy rates.*

- *Women who used Mirena® in the contraception studies had menstrual cycles at baseline ranging from 14 to 70 days (median 28 days), and duration of menstrual bleeding ranged from 1 to 14 days at baseline (median 5 days). 14% of Mirena® users reported intermenstrual bleeding/spotting at baseline. Mirena® users who did not have regular menstrual cycles of 25-35 days may not have been ovulating regularly and may have therefore been at reduced risk of pregnancy.*
- *Over 70% of LNG IUS users in the pivotal trials had previously used IUDs. Therefore, applicability of this data to the population of U.S. women seeking contraception is uncertain, and there is some bias in favor of lower pregnancy rates because previous successful IUD users would be expected to have less adverse events and less failures than new users.*

The overall efficacy results suggest a statistically lower failure rate with the LNG IUS than with the copper IUD comparator. However, the copper IUD comparator that was used in the pivotal trials is not the same as the copper IUD currently marketed in the U.S. The published 1-year pregnancy rate with the Copper T 380A available in the U.S. is 0.8 per 100 women-years. With combined OCs, the perfect-use pregnancy rate is 0.1 per 100 woman-years, and the typical use pregnancy rate is 5 per 100 woman-years.

The Kaplan-Meier estimates of the continuation rates of the LNG IUS per 100 women at all sites were 78.45 at 1 year and 45.31 at 5 years.

Reviewer's Comment

These continuation rates are similar to those seen in other contraceptive trials.

Supportive contraception studies

In 13 supportive contraception studies, 5 controlled and 8 uncontrolled, pregnancy rates/100 women ranged from 0 to 2.5 at 3 years and from 0.4 to 1.1 at 5 years.

Reviewer's Comment

Due to small numbers of subjects, the higher pregnancy rates seen in some studies are not significantly different than the rates seen in the pivotal studies.

Safety and Tolerance of Mirena®

Safety of Mirena® is supported by both the pivotal and supporting contraceptive studies. In addition, 10 menorrhagia studies and 8 endometrial protection studies provided reassuring safety information for older women. Women in the menorrhagia studies had a mean age of 40.4 years, and women in the endometrial protection studies were perimenopausal or postmenopausal.

The following adverse events seen with Mirena® use are similar to those previously reported with use of other IUDs. Unlike the currently available copper IUDs, Mirena® does not appear to increase menstrual blood loss. In fact, 10 supporting studies (5 controlled and 5 uncontrolled) using a LNG IUS in the treatment of menorrhagia showed a reduction in menstrual bleeding with LNG IUS use similar to that seen with the comparators in the controlled studies (endometrial resection, tranexamic acid, flurbiprofen, or norethisterone, commonly accepted medical treatments for menorrhagia in Sweden and Finland).

Ectopic Pregnancy

Ectopic pregnancy occurred in 5 women in the pivotal contraception studies (0.09 per 100 women at 1 year and 0.034 per 100 women at 5 years). A large European post-marketing study reported 52 ectopic pregnancies in 26,630 women (0.2%). This incidence is similar to that in sexually active women using no contraception.

Reviewer's Comment

Half of the pregnancies reported in the pivotal studies were ectopic. While the incidence of ectopic pregnancy with Mirena® use is similar to that in women using no contraception, the possibility of ectopic pregnancy should be considered for any pregnancy that does occur with Mirena® use.

Pelvic Inflammatory Disease (PID)

PID was reported in 22 women and salpingitis in 43 women in the pivotal contraception studies. PID/salpingitis led to discontinuation in 28 women (1.2%). The incidence of PID/salpingitis is similar to that in sexually active women using no contraception. Of a total of nine cases requiring hospitalization in the pivotal trials, 3 occurred in the first month of use.

Reviewer's Comment

Published literature indicates that the highest risk of PID occurs shortly after IUD insertion (usually within the first 20 days thereafter). This information was incorporated into the final label.

Ovarian Cysts

Ovarian cysts occur with increased frequency in Mirena® users, but most resolve without surgical intervention. One study designed specifically to evaluate ovarian cyst formation with daily ultrasound revealed cysts in 42% of 26 ovulatory cycles in women using the LNG IUS for more than 7 years. However, only 8 ovarian cysts were listed as serious adverse events in the 3 pivotal trials, an incidence of 148/100,000, compared to the U.S. incidence of hospitalization for ovarian cysts of 327/100,000 in 1988-1990.

Difficult or painful insertion

A disadvantage of Mirena®, as with other IUDs, is the need for insertion by a qualified medical professional. Investigators characterized insertions as "easy" in 85.5% of subjects and "difficult" in 14.5%. However, 4% of subjects reported severe pain with insertion and 21% reported moderate pain. Pain with insertion was described as severe more often in the young nulliparous women in AV97.

Perforation

No perforations occurred during the 2339 insertions attempted in the pivotal contraception studies. Overall, 7 perforations in LNG IUS users were reported, 2 in the 20 clinical studies reviewed in this NDA and 5 in the publications.

Expulsion

Discontinuation due to expulsion occurred in a total of 70 of the 2339 subjects (3.21 per 100 women) in the 3 pivotal trials during the first year, and in an additional 27 subjects by 5 years.

Irregular bleeding and amenorrhea

Menstrual pattern changes were typically seen in LNG IUS users. In the first 3 months of use, the number of spotting and bleeding days increased, and the bleeding was irregular. After the third month of use, the bleeding and spotting days constantly decreased to an average of 0 bleeding days and 1 to 3 days of spotting per month at the end of the first year. Amenorrhea occurred in 13% to 28% of women in the first year of use.

Drug Interactions

The effect of systemic hormonal contraceptives may be impaired by drugs that induce liver enzymes. The influence of these drugs on the contraceptive efficacy of Mirena® has not been studied, but it is not believed to be of major importance due to the mainly local mechanism of action.

Return to Fertility

Mirena® can be removed easily, and there was no delay in return to fertility after discontinuation of use of LNG IUS. Conception occurred within 1 year for 79% and within 2 years for 86 to 88% of women who discontinued treatment. This rate of conception is similar to that of the general population.

Fetal Exposure

Because of the high local concentrations of LNG in the endometrium with Mirena® use, there is potential for significant fetal exposure in cases of unintended pregnancy. The number of pregnancies identified in the clinical studies was small. Approximately half of them were ectopic pregnancies, and the others were electively terminated or ended in spontaneous abortion. Postmarketing reports have identified 35 births following Mirena® exposure, including 3 infants with congenital abnormalities. One was a pulmonary

artery hypoplasia. One was a partial labial fusion. The other was a cystic hypoplastic kidney in an infant whose sibling had renal agenesis without Mirena® exposure.

Comment

Due to this limited pregnancy outcome data showing no pattern of birth defects, it is unknown whether Mirena® exposure results in adverse long-term effects on a fetus. The primary and secondary reviewers have requested the sponsor to collect outcome information for all reports of pregnancies occurring with Mirena® use. The sponsor has agreed to a Phase IV commitment to follow-up all reports of pregnancy for duration of Mirena® exposure and pregnancy outcome.

Clinical Assessment and Recommendations

The data in this submission support the safety and efficacy of Mirena® for marketing in the U.S. The efficacy appears to be at least as good as that seen with the currently available IUDs and comparable to perfect use efficacy of OCs. The bleeding profile appears to be better than that of currently available IUDs, as menstrual flow usually decreases after the first 3 months of Mirena® use.

Most of the subjects in clinical trials were previous users of IUDs. Currently, IUD use in the U.S. is relatively uncommon. Therefore, applicability of the data to the U.S. population is uncertain. Also, high concentrations of LNG in the endometrium present an unknown risk to a fetus in the event of contraceptive failure. Therefore, the following phase 4 commitments were requested and the sponsor agreed to them in fax letters dated November 28, 2000 and December 6, 2000:

1. Submit the completed study report for LE102-96502 entitled "Incidence of Complications Requiring Hospital Treatment in Levonova Users in 1990-95" (a large postmarketing study of 26,000 Mirena® users in Finland evaluating length of use, safety, and efficacy) in the year 2001.
2. For postmarketing safety reports of pregnancy, follow-up cases through delivery (or termination) to obtain information regarding outcome of spontaneously reported cases of pregnancy, including live birth, premature birth, miscarriages (spontaneous abortions), septic abortions and congenital anomalies. In addition, obtain information about the duration of exposure of each fetus to Mirena®.
3. In periodic safety reports: provide a separate line listing of U.S. safety reports and an estimation of U.S. patient exposure to Mirena®.

I agree with the primary medical reviewer's recommendation for approval with the above phase IV commitments.

Non-Clinical Assessments

Pharmacotoxicology

No genotoxicity or systemic or local intolerance was observed. The expected local pharmacologic effects of LNG on the endometrium were observed in cynomolgus and Rhesus monkeys. No evidence of reproductive toxicity was observed. Some rabbits with exposures 3X human had an increased incidence (not given) of uterine cysts and papillary hyperplasia. Considering the safety profile of LNG in animals and humans, the inert behavior of the device components, and the tolerance in rats and cynomolgus monkeys, the primary pharmacotoxicology reviewer concluded that there were no nonclinical findings that should preclude use in humans. The primary reviewer recommended that the carcinogenicity section of the label include the following:

However, the pharmacotoxicology team leader found that the evidence for this statement is not convincing and is of doubtful relevance to humans. He therefore recommended that it not be included in labeling.

I agree with the final recommendation for approval and the labeling recommendation of the team leader.

Chemistry, CDRH, and Microbiology

- Expiration date: The requested expiration date is 36 months. Data submitted to date justify only 24 months. This was communicated to the sponsor on 11/30/00, and the sponsor agreed to accept the 24 month expiration date.

- Final labeling recommendations were conveyed to the sponsor on 12/5/00.
 - The sponsor submitted data from clinical trial batches and stability batches to justify release rate specifications of _____, which the chemistry reviewer found acceptable.
 - A CDRH consult found the IUD inserter acceptable for introducing Mirena® into the uterus.
 - Microbiology consult found the sponsor's proposal to _____, and the sponsor agreed in a fax letter dated 12/1/00 to delete the _____ and implement the change by the first annual report after approval. This response was acceptable to the microbiology reviewer.
- I agree with the final recommendation for approval and the release rate specifications of _____

Clinical Pharmacology

The Clinical Pharmacology and Biopharmaceutics Review found this NDA acceptable. The to-be-marketed formulation of the IUD (Composition D) is different than that used in the clinical trials (Compositions B and C). There is limited *in vivo* data available for Composition D. The difference between Compositions C and D is negligible, and a difference in clinical performance is not expected. An IVIVC analysis was submitted, incorporating the following:

- *in vitro* dissolution profiles of formulations C and D and a comparison of the two
- *in vivo* serum levels of LNG following use of the to-be-marketed formulation D at 1, 2, and 3 months
- *ex vivo* release rate comparisons between formulations C and D

Limited (3-month) clinical data has been provided.

The primary reviewer concluded that although no true external validation is possible with this limited data, this data provides assurance that formulation D releases the drug in comparable amounts as compared to composition C in the first 3 months. To assure that release of the drug remains comparable to Composition C with prolonged use, the following Phase IV Commitment was requested, and the sponsor agreed in letters dated November 16, 2000, November 27, 2000, and December 5, 2000:

- a) to collect data on 5-year comparative dissolution profiles for compositions C and D
- b) to complete the ongoing (12 month) Phase I study (Protocol 303700) with the final formulation (composition D) and submit study results, including *in vivo* and *ex vivo* data, within 1 year of the approval date.

Consideration of Release Rate Specifications

The primary clinical pharmacology reviewer initially recommended tighter release rate specifications because one pregnancy was reported after 12 months of use of Composition A with *ex vivo* release rate determined to be _____. After further discussion between clinical and chemistry reviewers, the proposed release rate specifications of _____ in _____ medium were found to be acceptable.

I agree with the reviewer's recommendation for approval with the above Phase IV commitment and with the recommended release rate specifications of _____

DSI

Inspections are completed and are satisfactory.

Tradename

OPDRA and the Division concur that the proposed tradename is acceptable.

Facilities Inspection

All sites have been inspected and are satisfactory.

Labeling

Final labeling was received from the sponsor on 12/6/00, incorporating all of the recommended changes from all disciplines.

Conclusions and Recommendations

I agree with the recommendations of the primary and secondary reviewers of all disciplines that this application for Mirena® be approved with the following phase IV commitments as agreed to by the sponsor on 11/16/00, 11/27/00, 11/28/00, 12/5/00 and 12/6/00:

1. Submit the completed study report for LE102-96502 entitled "Incidence of Complications Requiring Hospital Treatment in Levonova Users in 1990-95" (a large postmarketing study of 26,000 Mirena® users in Finland evaluating length of use, safety, and efficacy) in the year 2001.
2. For postmarketing safety reports of pregnancy, follow-up cases through delivery (or termination) to obtain information regarding outcome of spontaneously reported cases of pregnancy, including live birth, premature birth, miscarriages (spontaneous abortions), septic abortions and congenital anomalies. In addition, obtain information about the duration of exposure of each fetus to Mirena®.
3. In periodic safety reports: provide a separate line listing of U.S. safety reports and an estimation of U.S. patient exposure to Mirena®.
4. Collect data on 5-year comparative dissolution profiles for compositions C and D
5. Complete the ongoing Phase 1 study (Protocol 303700) and submit study results, including *in vivo* and *ex vivo* data to the Division within 1 year of the approval date.

LS

Dena R. Hixon, M.D., FACOG /
Team Leader/DRUDP

Ames

LS

Daniel A. Shames, M.D.
Deputy Director/DRUDP

Cc: HFD-580/J. Best/ S. Allen /D. Shames/D. Hixon/L. Furlong

4.1.3 Environmental Assessment

The drug product provided for in this application, levonorgestrel-releasing intrauterine system, is indicated for contraception. The system includes a reservoir containing 52 mg levonorgestrel USP and has a 5-year period of use.

For the purpose of assessing whether approval of this application will result in increased use of the drug substance, it is assumed that all levonorgestrel is released over the 5 year use period. This corresponds to an average daily release of 28 μg levonorgestrel into the environment, which is significantly lower than for other approved products containing the same active ingredient for the same indication (e.g., a monophasic oral contraceptive product containing 150 μg levonorgestrel has an average introduction rate of approximately 112 $\mu\text{g}/\text{day}$). Furthermore, it is expected that this product will substitute directly for other approved products.

Based on the above information, and pursuant to 21 CFR 25 - Subpart C pertaining to actions that are categorically excluded from the requirement to prepare an Environmental Assessment, a categorical exclusion is claimed under §25.31(a) for NDA where approval of the application will not increase the use of the active moiety. To the best of our knowledge, no extraordinary circumstances, as described under §25.21, exist with respect to this application.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM
SERVICES

DEPARTMENT OF HEALTH AND HUMAN

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

RESEARCH

Date: February 17, 2000

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products
(HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 21-225)

I have reviewed the financial disclosure information submitted by Berlex Laboratories in support of NDA 21-225.

Three studies were conducted to support the safety and efficacy of the levonorgestrel-releasing uterine system. The study numbers and their respective outcomes with regard financial disclosure obligations are summarized below:

Study No.	Disposition regarding Financial Disclosure
B078	Completed prior to February 2, 1999; appropriate documentation provided
AV97	Completed prior to February 2, 1999; appropriate documentation provided
AY99	Ongoing as of February 2, 1999; appropriate documentation provided

The study upon which AY99 was based is Study No. 8216/B075 (completed in September 1991). Although there was a financial relationship between the sponsor, and the conductor of this original study, it was not taken into consideration as the study to support the NDA (AY99) was a re-evaluation of this original study, and none of the original investigators participated.

Additional information considered in this review included the business relationship between the sponsor of the NDA, Berlex, and the sponsor of the clinical studies, Leiras Oy. The sponsor has submitted appropriate documentation regarding this relationship.

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

APPEARS THIS WAY
ON ORIGINAL

19 Financial Disclosure by Clinical Investigators

19.1 Introduction

Provided in this section is information pertaining to compensation to, and financial interests of, clinical investigators conducting certain clinical studies identified as "covered" clinical studies. This information is being provided in accordance with the requirements set forth in the final rule entitled "Financial Disclosure by Clinical Investigators" published in the Federal Register on February 2, 1998. The final rule was amended on December 2, 1998 and became effective on February 2, 1999. Further clarification of the requirements became available in a draft guidance document published in the Federal Register on October 26, 1999.

19.2 Background Information

Berlex Laboratories, Inc. has been a wholly owned subsidiary of Schering Berlin Inc., the U.S. management holding company for Schering AG, Germany, since 1979. Schering AG also manufactures the active drug substance, levonorgestrel USP, that is used in the drug product.

The sponsor of the covered clinical studies is Leiras Oy, Turku, Finland, the manufacturer of the drug product. Leiras Oy is also a wholly owned subsidiary of Schering AG, having been acquired by Schering in 1996. From 1992-1996, Leiras was incorporated as a wholly owned subsidiary of parent company, Huhtamaki Oy. There have been no individual shareholders in Leiras Oy since 1992.

Prior to 1992, Leiras was a department of a conglomerate corporation, Huhtamaki Oy, which was active in several industries; this corporation was publicly traded. Please note that at no time did any individual (investigator or otherwise) own a significant number of shares or more than a fraction of 1% of the shares of this corporation. Based on this information, the sponsor has concluded that no investigator of a covered clinical study held a significant equity interest (as defined in 21 CFR 54.2(b)) in Leiras Oy.

19.3 Identification of Covered Clinical Studies

As defined in 21 CFR 54.2(e) and in the context of this NDA, a "covered clinical study" means any study of the drug in humans submitted in a marketing application that the applicant or FDA relies upon to establish that the product is effective, or any study in which a single investigator makes a significant contribution to the demonstration of safety.

This application relies on three Phase 3 adequate and well-controlled studies which establish the efficacy of levonorgestrel-releasing intrauterine system:

Report Nos.	Protocol No.	Title
B078 / 102-89532-07	89532	Five-Year Clinical Performance of the New Formulation of the Levonorgestrel Intrauterine System and Serum Levonorgestrel Concentration With the New Formulation Compared to that With the Original One
AV97 / 102-92533-01	92533	Clinical Performance of LNG IUS Versus Combined Oral Contraceptive in Young Nulliparous Women
AY99 / LE102-98042-01	LE102-98042	Re-evaluation of the Levonorgestrel Intrauterine System (LNG IUS) Users of Leiras Study 8216

No other single study makes a significant contribution to the demonstration of the safety of the drug product.

Additional information pertaining to the above covered clinical studies, as well as to the original study re-evaluated in Study AY99, is provided below:

Study B078

This study was completed prior to February 2, 1999. The first subject was enrolled in January, 1990, and the last subject completed the study in January, 1996. The study report was signed on July 1, 1996. A Form FDA 3454 certifying the absence of disclosable financial arrangements for this study (consistent with the requirements for studies completed as of February 2, 1999) is provided in Section 19.5.

Study AV97

This study was completed prior to February 2, 1999. The first subject was enrolled in October, 1993, and the last subject completed the study in February, 1996. The study report was signed on October 28, 1998. A Form FDA 3454 certifying the absence of disclosable financial arrangements for this study (consistent with the requirements for studies completed as of February 2, 1999) is provided in Section 19.5.

Study AY99

This study was ongoing as of February 2, 1999. The study was started in June, 1998 and was completed in December, 1999¹. The study report was signed on January 21, 2000. Study AY99 is a re-evaluation of an earlier clinical study, Study 8216. The clinical protocol for re-evaluating Study 8216 (Protocol LE102-98042) has been reviewed by the Division [submitted as amendments to IND Serial Nos. 004 and 007]. In the re-evaluation study (AY99), no subjects were treated or evaluated; only existing data were verified and evaluated. At sites where the investigator who participated in the original study was no longer available, another investigator participated in the re-evaluation study.

A Form FDA 3454 certifying the absence of disclosable financial arrangements for Study AY99 (consistent with the requirements for studies ongoing as of February 2, 1999) is provided in Section 19.5.

The original study, Study 8216, was started in December, 1982 and the report (B075) cut-off date was in December, 1990. Report B075 was signed on September 19, 1991. This study is not considered a covered clinical study as it is not an adequate and well-controlled study being relied upon to establish the efficacy of the drug product, and no single investigator made a significant contribution to the demonstration of safety. However, because data from Study 8216 are incorporated in a covered clinical study, i.e., AY99, some information regarding the compensation to the clinical investigators in the original study is provided below.

One of the 19 clinical investigators who participated in Study 8216, Dr. _____, (as well as two other investigators² who participated only in non-covered clinical studies²) was also

¹ These dates refer to the period during which data from the original study were re-evaluated. The start and end dates listed in Report AY99 refer to the enrollment date of the first subject and the date of the final visit of the last enrolled subject (unscheduled), respectively.

² Reference Study Reports AW96, B072, B073, B086, B090, B336 as well as publications listed in the Table of All Studies which is provided in Item 8.7 of this application.

involved in the invention and early development of the LNG IUS. On October 27, 1987, before the completion of Study 8216, these investigators concluded an agreement with Leiras in which all rights to the invention were transferred to Leiras in exchange for royalties paid to a company formed by the three scientists for _____ years from the year the product was first launched. The product was launched in 1990, and the payment of royalties will cease at the end of the year _____. The paid or accrued royalties as of the end of 1999 amount to an equivalent of approximately _____.

The potential for bias in Study 8216 was minimal based on the study design (i.e., multi-center and multi-national) as well as the statistical design. Dr. _____ site contributed only 200 of over 1800 subjects in Study 8216. Moreover, Dr. _____ did not participate in the re-evaluation study, AY99 (he had already retired by the time that study was conducted), and the re-evaluation of data in that study was performed by a different investigator (see Section 19.4).

19.4 Clinical Investigators Who Conducted the Covered Clinical Studies

Provided below is a list of the Clinical Investigators who conducted covered studies. None of the investigators listed below have been employees of Berlex Laboratories, our parent company, Schering AG, or the sponsor of the clinical studies, Leiras Oy. For the re-evaluation study (AY99), the investigator is the same as in the original study (B075) unless otherwise noted.

Report	Site	Investigator
B078	_____	_____
AV97	_____	_____
AY99	_____	_____
	_____	_____
	_____	_____
	_____	_____
	_____	_____
	_____	_____

³ In addition to _____ and _____ was an investigator in the original study (Report B075)
⁴ _____ was the investigator in the original study (Report B075)
⁵ _____ was also an investigator in the original study (Report B075)
⁶ _____ was the investigator in the original study (Report B075)

7

Report	Site	Investigator
AY99 (cont.)	[Redacted]	[Redacted]

19.5 Form FDA 3454 (Certification) and Form FDA 3455 (Disclosure)

Provided on the following page is a signed Form FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators," which applies to the three covered clinical studies, B078, AV97, and AY99. As the applicant who was not the sponsor of the covered clinical studies, Berlex Laboratories attests to the absence of disclosable financial arrangements for the investigators who participated in the covered studies based on information provided by the sponsor of the studies.

Form FDA 4355, "Disclosure: Financial Interests and Arrangements of Clinical Investigators," is not included as the study sponsor has informed Berlex that no investigator in a covered clinical study has disclosable financial arrangements.

APPEARS THIS WAY
ON ORIGINAL

⁷ In addition to Dr. [Redacted] Dr. [Redacted] and Dr. [Redacted] were investigators in the original study (Report B075)
⁸ Dr. [Redacted] and Dr. [Redacted] were the investigators in the original study (Report B075)
⁹ Dr. [Redacted] was the investigator in the original study (Report B075)
¹⁰ Dr. [Redacted] was also an investigator in the original study (Report B075)

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS****TO BE COMPLETED BY APPLICANT**

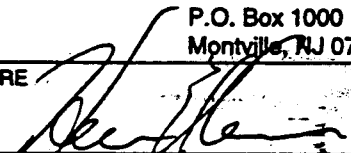
With respect to all covered clinical studies (or specific clinical studies listed below (if applicable)) submitted in support of this application, I certify to one of the statement below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- 1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator has a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- 2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)). **SEE ATTACHED PAGE**
- 3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Herman Ellman, M.D.	TITLE Director, Medical Science Liaison Female Health Care
FIRM / ORGANIZATION Berlex Laboratories, Inc. P.O. Box 1000 Montville, NJ 07045-1000	
SIGNATURE 	DATE January 28, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

WITHHOLD 1 PAGE (S)

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

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996

USER FEE COVER SHEET

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0297)
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

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

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Gerri A. Besta
Manager, Regulatory Submissions and Information
Berlex Laboratories, Inc.
[See Item 1 for Address]

3. TELEPHONE NUMBER (Include Area Code)

[973] 276-2157

4. PRODUCT NAME

Mirena® [Levonorgestrel-releasing Intrauterine System (LNG-IUS)]

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?

YES

NO

IF YOUR RESPONSE IS "NO" AND THIS IS A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

3856

7. LICENSE NUMBER/NDA NUMBER

NDA 21-225

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED BEFORE 9/1/92

THE APPLICATION IS SUBMITTED UNDER 505(b)(2)
(See reverse before checking box.)

AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

A CRUDE ALLERGENIC EXTRACT PRODUCT

BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

AN 'IN VITRO' DIAGNOSTIC BIOLOGIC PRODUCT
LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?

YES

NO

(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES

NO

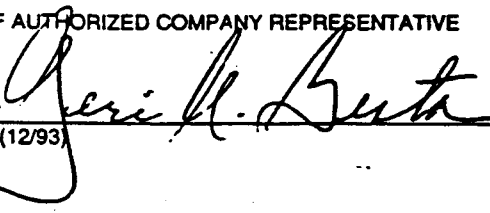
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Gerri A. Besta

FM FDA 3397 (12/93)



TITLE

Manager, Regulatory Submissions
and Information

DATE

January 24, 2000

WITHHOLD 19 PAGE (S)

1 Page(s) Withheld

WITHHOLD 3 PAGE (S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue
Rockville, MD 20850

Date: November 17, 2000

From: Colin M. Pollard
Chief, Ob/Gyn Devices Branch (HFZ-470)
DRARD/ Office of Device Evaluation

To: The Record

Subject: NDA 21-225
Device Consult Review from CDRH on Inserter for Mirena® IUS (Berlex Labs)

We have reviewed the information you supplied us on the inserter for the Mirena® IUS. The inserter is provided as sterile — single-use disposable device that is packaged with the Mirena® IUS itself. The device is intended to be within the uterus for up to 1-2 minutes during IUD insertion and deployment. The materials included a good description of the inserter, diagrams, functional description, a full set of design and material specifications. In general, I think the manufacturer has come up with a novel design for the inserter that should make insertion and IUD deployment easier (compared to the inserter used earlier in the European market experience). Component materials chosen for the inserter, e.g., _____ etc., are ones typically used for simple mechanical devices like this. Material safety of the chosen materials is documented with the results from as battery of tox studies, consistent with the guidance of ISO 10993, an FDA-recognized international standard for material safety testing. The essential requirements and the associated risk analysis are appropriate and consistent for this type of device.

Review of the packaging and _____ sterilization of the finished system identified no outstanding issues, _____ shelf life based on _____ accelerated aging and _____ real-time. It should be noted that the technical report (p63) states that the _____

_____ I presume that you also look carefully (or already have) at the sterilization information, in concert with the mfr inspectional findings.

Ergonomically, the design appears to allow for an easier pre-procedure preparation of the system, and easier insertion/deployment of the IUD for more accurate placement and easier assessment of 'seating' within the intrauterine cavity.

The manufacturer followed appropriate risk assessment procedures for designing the inserter, including design changes based on user feedback from clinical experience in Europe. As part of its design validation process, verification testing (_____ model) and clinical studies confirmed its safety and effectiveness. Presumably you have reviewed the three clinical studies with the earlier version, as well as the one study with the improved version. In the one clinical study with the improved inserter, the firm reported no uterine perforations with 199 insertions. There were three expulsions, one on insertion. These rates seem consistent to other IUD inserters, and should be acceptable.

It should be noted that from a device perspective, devices like these are exempt from 510(k) premarket notification, e.g., uterine curette, uterine sound, IUD remover, etc. We typically rely on postmarket regulatory controls such as labeling and the quality systems regulation.

From a design perspective, this IUD inserter is acceptable for introducing the Mirena® IUS into the uterus. Selection of materials and design are suitable, and the design approach taken by the mfr is very much in line with how we believe devices should be developed, i.e, risk analysis and design controls within a quality systems approach for the device. Just as, if not more, importantly however, there seems to be a large body of clinical experience with this and the previous version of the inserter from studies in Europe and the firm's market experience. I presume your reviewers have already carefully assessed that information as they reviewed the NDA. Unless their own reviews of that clinical data (not contained in the material supplied to us) identify problems with the inserter not described in what we have reviewed here, I think you should have no problem with the device. That is, your clinical reviewer should confirm from reviews of the clinical studies and the market experience in Europe that problems encountered during insertion or IUS deployment were minimal.

As far as the labeling goes, this also looks fine. Again, I would ask that the clinical reviewer ensure that the figures (not provided) accompanying the text in the labeling be assessed carefully to see that they are clear and not confusing, in terms of preparing the system and inserting & deploying it.

In addition, I also presume that your Office of Compliance, in concert with inspectional findings from the district office, has fully assessed the good manufacturing practices for this device.

I would like to acknowledge the help of Kathy Daws-Kopp (engineer) and Mike Kuchinski (microbiologist), reviewers within the branch, for their help on evaluating the submitted materials. If you have any questions, please feel free to call me, at 41180, x115.

LSI

_____)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21225/000**
Stamp: **01-FEB-2000** Regulatory Due: **01-DEC-2000**
Applicant: **BERLEX LABS**
340 CHANGEBRIDGE RD
MONTVILLE, NJ 070451000

Priority: **3S** Org Code: **580**
Action Goal: District Goal: **02-OCT-2000**
Brand Name: **MIRENA(LEVONORGESTREL**
RELEASING INTRA-UT
Established Name:
Generic Name: **LEZONORGESTREL RELEASING**
INTRA-UTERINE S
Dosage Form: **DBS (DRUG DELIVERY SYSTEM)**
Strength: **52 MG**

FDA Contacts: **J. BEST** (HFD-580) **301-827-4260**, Project Manager
R. AGARWAL , Review Chemist
M. RHEE (HFD-580) **301-827-4237**, Team Leader

Overall Recommendation:

ACCEPTABLE on 30-NOV-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **2243252** DMF No: _____
BERLEX LABORATORIES INC SUB S AADA No:
300 FAIRFIELD RD
WAYNE, NJ 074707358

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Establishment: _____ DMF No: _____
_____ AADA No. _____

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

Establishment: **9610938** DMF No: _____
LEIRAS OY AADA No:
TURKU 10,, FI

Profile: **GSP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE**
TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: 27-NOV-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION
 Profile: NEC OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 27-NOV-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

FINISHED DOSAGE LABELER
FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE
TESTER
FINISHED DOSAGE STABILITY
TESTER
FINISHED DOSAGE STERILIZER

Establishment:

DMF No:
AADA No:

Profile: NEC OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 08-MAR-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

Responsibilities:

Establishment: 9610131
 SCHERING AG
 D-13353
 BERLIN, , GM

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 05-SEP-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE RELEASE
TESTER

Establishment: 9611626
 SCHERING AG
 D-59179
 BERGKAMEN, , GM

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 01-MAR-2000
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment: 9611633

DMF No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

SCHERING AG
MAX DORN STRABE 8-10
CHARLOTTENBURG, BERLIN, GM D

AADA No:

Profile: CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-MAR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE

Establishment:

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-NOV-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

NDA 21-225

Mirena® (levonorgestrel-releasing intrauterine system)

Berlex Laboratories, Inc.

The Methods Validation is N/A at this time.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-225

Date: 11/22/00

Drug: Mirena

NOV 28 2000

Team Leader Labeling Memo

The NDA review by Dr. Davis-Bruno recommended adding information from _____ study to the carcinogenesis section of the label. Upon further review, we have determined that the information is not particularly convincing and of doubtful relevance to humans and should not be included in the label.

151

Alex Jordan, PhD

NDA 21225

HFD-580

AJordan/KDavisBruno/Jbest

REQUEST FOR CONSULTATION

Division/Office: Paul Cooney, Ph.D., Microbiology
Supervisor,
HFD-160, Rm. 18-B08

From: Jeanine Best, Project Manager, DRUDP, HFD-580

DATE February 4, 2000 IND NO. NDA NO. 21-225 TYPE OF DOCUMENT Microbiology Review Doc. DATE OF DOCUMENT January 31, 2000

NAME OF DRUG Mirena® (levonorgestrel, USP) Intrauterine System PRIORITY CONSIDERATION Standard CLASSIFICATION OF DRUG 3S DESIRED COMPLETION DATE October 15, 2000

NAME OF FIRM: ~~Alza Corporation~~ **Berlex Labs**

REASON FOR REQUEST

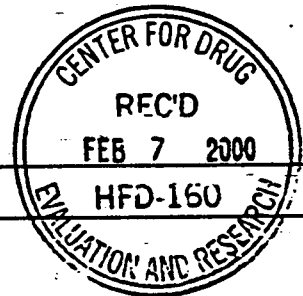
I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | • Microbiology Review |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

*To: D. Husson
Pik
2/15/00*



III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

Please forward all comments and reviews to Jeanine Best, Project Manager, DRUDP, HFD-580

SIGNATURE OF REQUESTER <i>[Signature]</i>	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF DELIVERER <i>[Signature]</i>	SIGNATURE OF DELIVERER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 6, 2000

TO: NDA 21-225 151

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

SUBJECT: Mirena® (levonorgestrel-releasing intrauterine system)

The following items are acceptable from Clinical Pharmacology and Biopharmaceutics perspective:

- Sponsor's response regarding the two Clinical Pharmacology Phase IV commitments (agreed to on 11/16/00, and revised on 11/27/00 and 12/5/00)
- Draft Labeling of Mirena® (NDA 21-225) submitted 12/5/00, incorporating requested revisions to the **Clinical Pharmacology** section

cc:

Archival NDA 21-225
HFD-580/Div. Files
HFD-580/PM/Best
HFD-580/Parekh/Chatterjee

Drafted by: AP/DECEMBER 6, 2000
Final: DECEMBER 6, 2000
Filename: Mirena MEMO.doc

MEMORANDUM