CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-225

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-225

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

DEC 0 6 2000

Dear Ms. Ruane:

Please refer to your new drug application (NDA) dated January 31, 2000, received February 7, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirena® (levonorgestrel-releasing intrauterine system).

We acknowledge receipt of your submissions dated December 16, 1999; and February 14, March 17 (2), April 10, 19 and 20, May 23, June 8, 27 and 30, July 11, 18 and 25, August 7, 21, 25 and 28, October 6, 13 and 26 (2), November 8, 14 (2), 16, 17 (3), 21 (2), 24, 27, 28 and 30, December 1, 5 (2) and 6(2), 2000.

This new drug application provides for the use of Mirena® (levonorgestrel-releasing intrauterine system) for intrauterine contraception.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert submitted December 6, 2000) and submitted draft labeling (immediate container and carton labels submitted November 17, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-225." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your submissions dated November 16, 21, 27 and 28 and December 5 and 6, 2000. These commitments, along with any completion dates agreed upon, are listed below.

Clinical:

1. Submit the completed study report for Study 102-96502 entitled "Incidence of Complications Requiring Hospital Treatment in Lenonova Users in 1990-95" in the year 2001.

2. For postmarketing safety reports of pregnancy, follow up cases through delivery or termination to obtain information regarding outcome of spontaneously reported cases of pregnancy including live births, premature births, miscarriages, (spontaneous abortions), septic abortions, and congenital anomalies. 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.

Clinical Pharmacology:

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

2. The ongoing long-term dissolution studies with Compositions C and D will be continued up to five years, and the five-year data will be submitted to the Division.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

12/6/00

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

NDA 21-225

Mirena®

Berlex Laboratories, Inc.

NAME	SIGNATURE
Susan Allen, M.D. M.P.H. Director Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)	/S/ 12/6/00
Daniel Shames, M.D. Deputy Director DRUDP (HFD-580)	/S/ 12/6/00
Dena Hixon, M.D. Team Leader DRUDP (HFD-580)	/S/
Lesley Furlong, M.D. Medical Officer DRUDP (HFD-580)	/S/
Alexander Jordan, Ph.D Pharmacology Team Leader DRUDP (HFD-580)	/S/
Moo-Jhong Rhee, Ph.D. Chemistry Team Leader Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)	/S/
Rajiv Agarwal, Ph.D. Chemist DNDC II @ DRUDP (HFD-580)	/S/
Ameeta Parekh, Ph.D. Pharmacokinetic Team Leader Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)	/S/
D. J. Chatterjee, Ph.D. Pharmacokinetics Reviewer OCPB @ DRUDP (HFD-580)	/S/
Lisa Kammerman, Ph.D Biometrics Team Leader Division of Biometrics II (DB II) @ DRUDP (HFD-580)	/S/
Kate Meaker, M.S. Statistician DB II @ DRUDP (HFD-580)	/S/

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Mirena®
Berlex Laboratories, Inc.

Peter Cooney, Ph.D. Director, Microbiology DNDC (HFD-160)	ET	
David Hussong, Ph.D. Microbiologist DNDC (HFD-160)	ET	
Terri Rumble, B.S.N. Chief, Project Management Staff DRUDP (HFD-580)	ET	12/6/00
Jeanine Best, M.S.N., R.N. Regulatory Project Manager DRUDP (HFD-580)	ET	