CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-098

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-098

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your new drug application (NDA) dated May 14, 1999, received May 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yasmin® 28 Tablets (drospirenone 3 mg/ethinyl estradiol 0.030 mg).

We acknowledge receipt of your submissions dated July 8, September 14, 22 and 30, October 22, November 1, 18, 19 and 24, and December 3, 1999; January 6, 7, 14, 18 and 28, February 2, 3, 4, 7, 10, 15, 17, 18, 23 March 2, 3, 9, 15, 16, and 29, April 4, 20 and 27, May 4, 8 (2), 9 and 24, June 12, 14, 15 (3), 16 (2), 19, 20, 21 and 22, July 7 and 21, August 18, September 8, 15 and 19, November 6 (2), 9, 14 and December 20, 2000; January 5 and 16, February 12, March 9, 12 (2), 16, 27 and 30, April 4 (2), 9 (2), 16, May 7 (2), 9 and 11, 2001. Your submission of November 9, 2000 constituted a complete response to our July 10, 2000 action letter.

This new drug application provides for the use of Yasmin® 28 Tablets (drospirenone 3 mg/ethinyl estradiol 0.030 mg) for oral 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), and to the immediate container and carton labels submitted November 14, 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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-098." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated June 7, 2000, and modified May 11, 2001. These commitments are listed below.

1. Develop an educational outreach program for health care providers and patients, focusing on Yasmin®'s contraindications in patients with renal or hepatic impairment and in patients predisposed to hyperkalemia.

- Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports. Submit a final report within 6 months after completion of the program.
- Include educational outreach for patients, which is not described in the November 6, 2000 proposal.
- Educate healthcare providers to the importance of reporting all serious adverse events (especially cardiac events) that occur in Yasmin® users.
- Provide healthcare providers with a mechanism to facilitate the reporting of serious adverse events in Yasmin® users.

Protocol Submission:	Within 3 months of the date of this letter
Study Start:	Within 6 months of the date of this letter
Final Report Submission:	Within 6 months of the completion of the program

2. Develop a surveillance program to a) evaluate the prescribing of Yasmin to contraindicated patients with underlying renal or hepatic impairment using a database of Yasmin users. The database would provide a list of all Yasmin® users, and these patients would then be screened carefully for any past or recent diagnoses of renal and/or hepatic impairment. Submission of full case report summaries of all such contraindicated prescriptions, including patient outcome, would be required, and to b) evaluate compliance of healthcare providers with the serum potassium measurements in the first cycle of Yasmin® use in patients receiving long-term treatment with medications that may increase serum potassium

   - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives. Submit a final report within 6 months after completion of the program.
   - Set acceptable limits approved by FDA for contraindicated prescribing of Yasmin® and describe the corrective actions that will be taken if the limits are exceeded.

Protocol Submission:	Within 3 months of the date of this letter
Study Start:	Within 6 months of the date of this letter
Final Report Submission:	Within 6 months of the completion of the program

3. Use a database to evaluate all patients prescribed Yasmin® for the subsequent outcomes of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc. (other search terms may also be considered appropriate); patients taking Yasmin® and experiencing these types of events (or taking Yasmin® within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients.

   - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives. Submit a final report within 6 months after completion of the program.
   - Ensure that the surveillance program based on the United Healthcare database will identify Yasmin® users who are hospitalized, receive emergency treatment, or who experience other serious adverse events.

Protocol Submission:	Within 3 months of the date of this letter
Study Start:	Within 6 months of the date of this letter
Final Report Submission:	Within 6 months of the completion of the program

4. Analyze more carefully pregnancy outcomes that occur in patients exposed to Yasmin®. This could be done in the same cohort of Yasmin® users described in the database described above. In addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin® exposure. A pregnancy exposure registry is an alternative. Outcome on as many patients as possible is desired and may require several years of follow-up. Finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended. Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives.

Protocol Submission:	Within 3 months of the date of this letter
Study Start:	Within 6 months of the date of this letter
Final Report Submission:	Within 6 months of the completion of the program

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

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 send one copy to the Division of Reproductive and Urologic Drug Products 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,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-098

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 10 2000

NDA 21-098

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ. 07045-1000

Dear Ms. Velez:

Please refer to your new drug application (NDA) dated May 9, 2000, received May 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yasmin® 28 Tablets (drospirenone/ethinyl estradiol).

We acknowledge receipt of your submissions dated March 16 and 29, April 4, 20 and 27, May 4, 8 (2), 9 and 24, June 12, 14, 15 (3), 16 (2), 19, 20, 21 and 22 and July 7, 2000. Your submission of May 9, 2000 constituted a complete response to our March 17, 2000 action letter.

We have completed the review of this application as amended, including a reanalysis of the risk/benefit profile for Yasmin® 28 Tablets. Your application is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Additional clinical studies must be performed to assess the risk of hyperkalemia in women using Yasmin® 28 Tablets.

In addition, the following risk management issues related to Yasmin® 28 Tablets were discussed with you during a teleconference on July 5, 2000. You agreed to the following Phase 4 commitments in your submission dated July 7, 2000:

1. Develop an educational outreach program for health care providers and patients, focusing on Yasmin's contraindications in patients with renal and hepatic impairment and in patients predisposed to hyperkalemia.

2. Develop a surveillance program to evaluate the inappropriate prescribing of Yasmin to patients with underlying hepatic or renal dysfunction using a database of Yasmin users; the database would provide a list of all Yasmin users, and these patients would then be screened carefully for any past or recent diagnoses of hepatic and/or renal dysfunction; submission of full case report summaries of all such inappropriate prescriptions, including patient outcome, would be required.

3. Use a database to evaluate all patients prescribed Yasmin for the subsequent outcomes of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc (other search terms may also be considered appropriate); patients taking Yasmin and experiencing these types of events (or taking Yasmin within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients.

4. Analyze more carefully pregnancy outcomes which occur in patients exposed to Yasmin; this could be done in the same cohort of Yasmin users described in the database; in addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin exposure; a pregnancy exposure registry is an alternative; outcome on as many patients as possible is desired and may require several years of follow-up; finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended.

These risk management study program requirements may be changed depending on the results from additional studies conducted.

In addition, it will be necessary for you to submit draft labeling revised to reflect new data collected in additional studies performed.

Please also revise carton labeling as follows:

1. Delete the line separating the tradename and the established name in the labels

2. Place the dosage strength in the front panel of the carton label underneath the established name.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update must cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Div. Files
HFD-580/J.Best
HFD-580/Reviewers and Team Leaders
HFD-002/ORM
HFD-103/ADRA
HFD-42/DDMAC
HFD-820/DNDC Division Director
DISTRICT OFFICE
Drafted by: JAB/July 7, 2000
Initialed by:Allen/Mann/Rumble
final:JAB/July 10, 2000

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-098

MAR 17 2000

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

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We acknowledge receipt of your submissions dated July 8, September 14, 22, and 30, October 22, November 1, 18, 19, and 24, and December 3, 1999; January 6, 7, 14, 18, and 28, February 2, 3, 4, 7, 10, 15, 17, 18, and 23, and March 2, 3, 9, and 15, 2000.

We also refer to your submissions dated February 28 and 29, 2000. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Provide the final study results of the effects of Yasmin™ in renally-impaired patients. Results of the study in renally-impaired patients may affect several sections of the package insert. Therefore, we are deferring comments in the labeling at this time.

2. Submit revised draft labeling that includes appropriate information from the renal impairment study.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. This may include information on pregnancy outcome, ACE inhibitor interaction, and NSAID interaction.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus time of resubmission will certainly facilitate our review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

Florence Houn, M.D., M.P.H.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Div. Files
HFD-580/JBest
HFD-580/Reviewers and Team Leaders
HFD-002/ORM
HFD-103/ADRA
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: JAB/March 1, 2000
Initialed by: FHoun/SAllen/MMann/TRumble/BCollier
final:JAB/March 17, 2000
filename:

APPROVABLE (AE)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

23 pages draft labeling

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

TOTAL PAGES OF DRAFT LABELING

SECTIONS	PAGES	PAGES	
7		45	
28		45	155
18		52	142
37		142	297
25			
155			

297 pages

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

~22 pages
of Draft Guidance

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

43 pages of
foreign Labeling