The paper copy of this information is located in Attachment 4A. The electronic data can be found on a compact disc located in Attachment 3 as a SAS transport file.

b) Paper and electronic versions of a listing of potassium (K) and sodium (Na) values in the following format:

Subject No.	Treatment	Potassium and Sodium Values		
		Visit A Date, K, & Na	Visit B Date, K, & Na	Visit Z Date, K, & Na
1	DRSP/EE	xx/yy/zz 4.9, 140	xx/yy/zz 4.3, 144	xx/yy/zz 4.5; 141
2	Placebo	xx//yy/zz 4/7, 145	xx/yy/zz 4.6,143	xx/yy/zz 4.6, 144
Etc				

- **List data by center, treatment, and subject as with other listings. Table need include only protocol scheduled visits if this simplifies formatting.**
- **Include only subjects who received study drug.**

The paper copy of this information is located in Attachment 4B. The electronic data can be found on a compact disc located in Attachment 3 as a SAS transport file. This file contains only the protocol scheduled visits.

5. **Questions to the Sponsor**

a) Can you explain why the number of subjects listed as using NSAIDs in Text Table 12 (pg 54) is larger than the number in Table 10 (pg 103)? One might expect the number of NSAID users in Table 10 to be larger since the number of subjects considered in generating Table 10 appears to be larger than that considered in Text Table 12.

Berlex agrees with your observation and has reanalyzed the numbers. An updated table reflecting revised numbers in Text Table 12 is provided in Attachment 5A. The number of subjects using NSAIDs in the placebo group is now 60 and in the DRSP 3mg/EE 30µg group is now 57. These revised numbers are not reflected in the electronic copy of the report on the compact disc provided in Attachment 3 as this compact disc is an exact copy of the text and text tables provided in the November 6, 2000 submission.

b) There appear to be instances in which a chemistry blood sample was obtained but no potassium value is reported. For example, the Subject No. 3601010 a chemistry blood sample is listed as being obtained (Listing 19 [Laboratory Data Dates], Date of 6/23/98) but there is no reported value for potassium for this date (Listing 16.2.8 [Laboratory Data]; only values for 2/27/98 and 8/22/98 are listed).

Attachment 5 contains a table providing an explanation as to the reasons why a blood chemistry sample was obtained but no potassium value was reported.

6. **Please provide an electronic version of data contained in Listing 6 (Chemistry, Vol. 30); maintain format of listing with chemistry values in columns by type of chemistry analysis.**

The electronic data can be found on a compact disc in Attachment 3 as a SAS transport file.

7. **Please provide the following new listings to include only subjects that received study drug:**

a) A listing of (1) medication start dates, (2) last dose date, and (3) compliance (%); these are the last 3 columns in Listing 16.2.5 (Vol. 23).

- Format in columns as shown below:

- "Investigator/Treatment/Subject No./Med start date/Last dose date/% compliance

The electronic data can be found on a compact disc in Attachment 3 as a SAS transport file. The paper copy is located in Attachment 7A.

b) Paper and electronic versions of a listing of potassium (k) and sodium (Na) values in the format described above under 4 b.

The electronic data can be found on a compact disc in Attachment 3 as a SAS transport file. The paper copy is located in Attachment 7B.

c) For Text Table 6: Concomitant use of Selected Medications (Vol. 19, Pg. 34)

- **Please provide a listing of the subjects by treatment group and concomitant medication who were taking the listed concomitant medications (Paper copy only).**

The paper copy is located in Attachment 7C. These listings are sorted by site, treatment, and subject number within a specified selected medication. There is no listing for concomitant medication 2 (Spironolactone, Aldactone or Aldactazide) since there were no subjects who took these medications.

d) For Table 17 (Vol. 20, Potassium data only, pg. 271, 279, 287, 295, 303)

- **Please provide a listing of the subjects and their K values in each of the respective groups that are represented in the Table for the entry of potassium.**

The electronic data can be found on a compact disc in Attachment 3 as a SAS transport file. The paper copy is located in Attachment 7D.

Berlex Laboratories certifies that the four compact disks provided herewith were scanned for viruses and are virus free using Network Associates VirusScanNT 4.0.3a created December 27, 2000.

Berlex believes that we have adequately addressed each response. Should you require any additional information or have any questions regarding today's submission, please call the undersigned immediately at (973) 487-2305. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy (cover letter): Ms. Jeanine Best

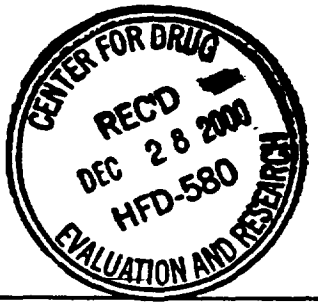
NFV/letter/drpoc001

APPEARS THIS WAY
ON ORIGINAL

BERLEX

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIGINAL



Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

December 20, 2000

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

NEW CORRESP
NC

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
General Correspondence: Change in Telephone and Telefax Numbers

We wish to inform you that effective Monday, January 1, 2001, the phone number for Berlex Laboratories in Montville, NJ will have a new exchange. The last four digits of the phone number remains unchanged. The new exchange will be 487. The telefax for the Drug Regulatory Affairs Department will be (973) 487-2016. If for any reason, you need to contact Drug Regulatory through the main switchboard, the number will be (973) 487-2000.

Should you have any questions regarding this submission, please contact the undersigned at (973) 276-2305 until December 31, 2000. After that time, I can be reached at (973) 487-2305.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

NFV/letter/drpoc232

TELEFAX
UPS OVERNIGHT

ORIGINAL

BERLEX

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November 14, 2000

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

ORIG AMENDMENT

BM

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Request for Clinical Site Information and Statistical Desk Copy

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter.

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000. Our complete response to this letter was submitted on November 6, 2000.

Additional reference is made to a telephone conversation on November 7th between the undersigned and Ms. Jeanine Best of the Division. Ms. Best acknowledged receipt of the November 6th resubmission which contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under [redacted]) and 96097 (an endometrial protection study conducted under [redacted]). Ms. Best requested the following items:

1. Clinical site information to be provided to the Division of Scientific Investigations;
2. Desk copy of the carton labeling for the Chemist;
3. Desk copy of any statistical information for the Statistician;
4. Desk copy of any pharmacokinetic information for the Pharmacologist.

Clinical site information
Ms. Best asked that clinical site information such as investigator name, address, and phone # be provided for the sites that participated in the two submitted safety studies to be forwarded to the Division of Scientific Investigations for inspection purposes. It was agreed that a table submitted recently to the Division for another Berlex product as a result of a similar request could be used as a template. Attachment 1 contains the clinical site information for Studies 97036 and 96097, alphabetized by investigator within each study.

Desk Copy of Carton Labeling for Chemist
A desk copy of the revised mock-ups of the single unit carton and outer carton that holds 3 units submitted on November 6th is provided in Attachment 2. This copy has been provided for the Chemist.

Desk Copy for Statistician
The following volumes from the November 6th submission of Safety Reports 97036 and 96097 have been copied and are provided for the statistician, following Attachment 2:

Report 97036: Volumes 1 – 4, 10 – 18

Report 96097: Volumes 19 – 34, 57 – 95

This is a total of 68 volumes. Please note that the only section not provided from each report were copies of the Case Report Forms.

Desk Copy for Pharmacologist
The November 6th submission does not contain any pharmacokinetic information.

Please note that Ms. Best also requested on November 7th, financial disclosure information for the clinical sites that participated in Studies 97036 and 96097. This information was provided to the Division on November 9th.

Today's submission completes our response to Ms. Best's requests of November 7th.

Should you require any additional information or have any questions regarding today's submission, please call the undersigned immediately at (973) 276-2305. The fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc224

ORIGINAL

TELEFAX
UPS OVERNIGHT

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November 9, 2000

Susan Allen, M.D, MPH, Director
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Office of Drug Evaluation III
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

NEW CORRESP
#17

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Request for Financial Disclosure Information

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter.

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000. Our complete response to this letter was submitted on November 6, 2000.

Additional reference is made to a telephone conversation on November 7th between the undersigned and Ms. Jeanine Best of the Division. Ms. Best acknowledged receipt of the November 6th resubmission which contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under ——— and 96097 (an endometrial protection study conducted under ———). She stated that whenever new clinical information is amended to an application, financial disclosure information is required for the investigators that participated in the studies. The undersigned told Ms. Best that the information would be obtained and submitted as quickly as possible.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

In response to Ms. Best's request, attached is a Form FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators" for the two studies identified below:

Study No.	No. of Study Sites	Study Title
97036	25	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)
96097	53	A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol, Examining the Effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women

Tables identifying the Principal Investigators and addresses for each study are attached to the form.

Please note that Ms. Best also requested on November 7th the following items as related to the November 6th submission:

1. Clinical site information for the Division of Scientific Investigations;
2. Desk copy of any statistical information for the Statistician;
3. Desk copy of any pharmacokinetic information for the Pharmacologist;
4. Desk copy of the carton labeling for the Chemist.

These additional items will be provided next week.

Should you require any additional information or have any questions regarding today's submission, please call the undersigned immediately at (973) 276-2305. The fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc221

Desk copy: Ms. Jeanine Best

TELEFAX
HAND DELIVERY

ORIGINAL

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
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November 6, 2000

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

ORIG AMENDMENT

BC

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION: Chemistry, Manufacturing and Controls Information

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. Approvable letters were issued for this NDA on March 17, 2000 and July 10, 2000. Reference is also made to our submission of November 6, 2000 which provides a complete response to the July 10, 2000 approvable letter.

We are herein amending this application to provide for chemistry, manufacturing and control (CMC) changes. Reference is made to a telephone conversation of October 23, 2000 between your representative, Ms. Jeanine Best and Ms. Sharon Brown of Berlex wherein Ms. Best advised that this CMC amendment should be provided as a separate submission but mailed with the same package as the November 6, 2000 complete response to the approvable letter. Ms. Best said the CMC amendment would undergo a concurrent 6 month review along with the response to the approvable letter.

This CMC amendment provides for the following changes:

DRUG SUBSTANCE: The NDA-provided manufacturer of DRSP, ——— has proposed changes to the manufacture of DRSP drug substance. Since all drug substance information for this product was provided in Type II Drug Master Files, ——— to provide for the manufacturing changes. A copy of the DMF amendment letter, which also contains a brief outline of the changes, is provided in **Attachment A.** For convenience, a copy of the letter authorizing reference to the DMF is provided in **Attachment B.**

DRUG PRODUCT: Reference is made to a February 11, 2000 teleconference between representatives from the Division and Berlex wherein discussion took place regarding elimination of testing for decomposition products in drug product release testing. Specifically, Dr. Suong Tran, Chemistry Reviewer, suggested that Berlex monitor the first 10 lots of drug product and submit the results in a supplement to be reviewed for the possibility of eliminating the referenced testing.

Attachment C contains Certificates of Analysis for 13 lots of Yasmin drug product. Decomposition testing results for all lots fall well within the specifications for decomposition products of both EE and DRSP. The proposed revised specification, K280E2A0, which reflects the elimination of decomposition products on release, is provided in **Attachment D**.

Should you require any additional information or have any questions regarding this submission, please call the undersigned at (973) 276-2354.

Sincerely,

BERLEX LABORATORIES

Geoffrey Millington
Manager
Drug Regulatory Affairs

GPM/120

Desk copy: Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

TELEFAX
HAND DELIVERY

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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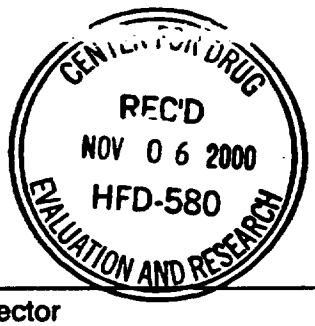
November 6, 2000



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

ORIG AMENDMENT
AZ B2

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION: Complete Response to July 10, 2000 Approvable Letter

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter.

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000 (attached immediately following this cover letter for your reference). Berlex learned of this unexpected action on our application during the teleconference on July 10th with representatives from the Division and ODE III. The letter stated that:

A. additional studies were needed to assess the risk of hyperkalemia in women using Yasmin® 28 Tablets;
B. Berlex previously agreed in the July 7, 2000 submission to the Phase IV commitments proposed by the Division on July 5th (the commitments are listed in the July 10th letter);
C. draft labeling revised to reflect new data collected in additional studies performed would have to be submitted;
D. revised carton labeling was needed;
E. another Safety Update Report was needed.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

On September 11, 2000, Berlex submitted a briefing package to the Division which contained additional data to address items A and B above. A Type A Meeting was held between Division and Berlex representatives on September 25, 2000 to discuss these data. (Division minutes of the meeting are attached to this cover letter for your reference).

A. Risk of Hyperkalemia

During the September 25th meeting, Berlex presented new serum potassium data in 1373 subjects from our PMS/PMDD study 97036 (younger women, an OC population) conducted under [redacted], and our endometrial protection study 96097 (older women, a postmenopausal population) conducted under [redacted] which were recently completed and were not included in the Yasmin NDA. An analysis was conducted and presented of the risk of developing hyperkalemia using these data, using data from six studies previously submitted in the NDA, as well as data from one study included in our approved Levlite® NDA. Also presented was an evaluation of cardiovascular adverse events that could potentially be related to hyperkalemia from subjects who received DRSP in the clinical studies included in the briefing package. Berlex concluded:

1. Yasmin did not present a risk for hyperkalemia in the OC population including use in patients on NSAIDs, ACE inhibitors or with mild – moderate renal disease;
2. Yasmin did not present a risk for the occurrence of cardiovascular adverse events potentially related to hyperkalemia.

The Division felt that the summary results from the two new studies appeared to provide the additional data needed to further assess the risk of hyperkalemia in women using Yasmin. The Division asked that Berlex submit these studies for review, stating that the reports should contain details on study design, include patient data and that essential safety data should be provided in detail. The Division asked that these safety reports, along with the other items identified in the July 10th approvable letter, be submitted as a complete response to the approvable letter. The submission would be reviewed on a standard 6 month review clock for a resubmission. Berlex committed to provide this response in 8 weeks or less. Berlex also informed the Division that, based on the new data, the draft labeling would be revised; for example, with regard to renal impairment patients and in patients using NSAIDs. The revised labeling would be included in the response to the approvable letter.

B. Phase IV Commitments

Also during the September 25th meeting, Berlex presented its proposed Phase IV program as outlined in the July 7, 2000 submission. Berlex anticipated frequent dialogue with Division representatives to finalize the full program/protocol within 120 days of approval. In response to the Berlex presentation, the Division stated that without final labeling, it would be premature to give definitive comments on the proposed program; however, comments/recommendations were provided (see attached minutes of the September 25th meeting).

Today's submission constitutes a complete response to the July 10, 2000 approvable letter. Each of the items requested in the July 10th letter are identified in bold font, followed by our response.

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

As agreed during the September 25th meeting with the Division, safety reports containing the new serum potassium data not previously submitted to the Yasmin NDA are herewith provided.

The Safety Report for PMS/PMDD Study 97036D – Amendment 1 consisting of 18 volumes (Volumes 1 – 18 of this submission) and entitled, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)", is provided in Attachment 1. This study was conducted under ——— which is being reviewed by the Division of Neuropharmacological Drug Products.

The Safety Report for HRT Study 96097A consisting of 77 volumes (Volumes 19 – 95 of this submission) and entitled, "A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol, Examining the Effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women", is provided in Attachment 2. This study was conducted under ———

B. Phase IV Commitments

Berlex has addressed the comments/recommendations provided by the Division at the September 25th meeting and outlined in the minutes regarding the proposed Phase IV program. The revised Phase IV program is provided in Attachment 3 (Volume 96) and consists of:

1. an educational outreach program
2. an active surveillance program to determine:
    a. the inappropriate prescribing of Yasmin (i.e. women prescribed Yasmin with hepatic or renal impairment);
    b. occurrence of clinical events potentially related to hyperkalemia with use of Yasmin;
    c. and the monitoring of breakthrough pregnancies that occur with Yasmin for the occurrence of fetal/child malformations.

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

A revised electronic Physician Package Insert (PI) reflecting the substantial new data presented and discussed at the September 25th meeting is provided in Attachment 4 (Volume 96) in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 21/28 TABLETS Labeling" dated November 6, 2000.

For your information, the only changes made to the last DRAFT Physician PI submission of July 7, 2000 are as follows:

CONTRAINDICATIONS

"Severe" has been added to precede "Renal insufficiency"

WARNINGS

In the first sentence of the bolded warning for YASMIN 28 Tablets, "Severe" has been added to precede "renal insufficiency" as a contraindication.

PRECAUTIONS
8. DRUG INTERACTIONS
Effects of Drospirenone on Other Drugs
- **Interactions with Drugs that have the Potential to Increase Serum Potassium)**

The first paragraph in this section has been revised as follows:

> There is a potential for an increase in serum potassium that could result in hyperkalemia in women taking **YASMIN 28** Tablets with other drugs that may increase serum potassium levels. Such drugs include ACE inhibitors, potassium-sparing diuretics, heparin, and aldosterone antagonists.

This last change is substantiated by the additional data presented at the meeting in the HRT and PMS/PMDD populations which showed no indication that NSAIDS increased serum potassium levels.

In accordance with previous procedure, a clean copy as well as a strike out version of the Physician PI are provided, identified as "unmarked" and "marked", respectively. A hard copy of the unmarked and marked versions are also provided following the diskette in Attachment 4.

Berlex Laboratories certifies that the diskette provided herewith was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created September 27, 2000.

D. 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.**

Revised mock-ups of the single unit carton and outer carton that holds 3 units are provided in Attachment 5 (Volume 96).

E. Under 21 CFR § 314.50 (d) (5) (vi) (b), we request that you update your NDA by submitting all safety you now have regarding your new drug.

This same request was made in the March 17th approvable letter with the same criteria of information to be included (see criteria outlined in attached July 10th letter). The Safety Update Report in response to the March 17th request was submitted on May 4, 2000. Per previous procedure, for this July 10th request, Berlex is updating the NDA with any new information that was obtained since March 17, 2000 (the cut-off date for inclusion of data into the May 4th Safety Update Report) through July 10, 2000 (the date of the approvable letter) The same format used in the previous report is used in this latest Safety Update Report which is found in Attachment 6 (Volume 96).

In addition, Berlex acknowledges the following additional item noted in the approvable letter:

YASMIN may not be legally marketed until we have been notified in writing that the application has been approved.

In summary, this 96 volume submission constitutes our complete response to the July 10, 2000 approvable letter. As stated in the Division's minutes of the September 25th meeting, this submission will be reviewed on a standard 6 month review clock for a resubmission. Berlex is immediately available to respond to any questions regarding this submission and appreciates any efforts that can be made to expedite its review. As you know, we had planned to launch YASMIN in July of this year. Plans are now underway for a first half 2001 launch.

CMC AMENDMENT

Please note that another amendment providing for Chemistry, Manufacturing and Control (CMC) changes is also being submitted under separate cover today. On October 23, 2000, Ms. Sharon Brown of Berlex informed Ms. Jeanine Best of the Division about this upcoming amendment and discussed the logistics of its submission. Ms. Best advised that this CMC amendment should be provided as a separate submission but mailed in the same package as today's complete response to the approvable letter. Ms. Best said the CMC amendment would undergo a concurrent 6 month review along with this response to the approvable letter.

Should you require any additional information or have any questions regarding today's submission, please call the undersigned immediately at (973) 276-2305. The fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc214

Desk copy: Ms. Jeanine Best

Vice President
Drug Regulatory Affairs

TELEFAX
UPS OVERNIGHT

September 19, 2000

Drug Development & Technology
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Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

MK

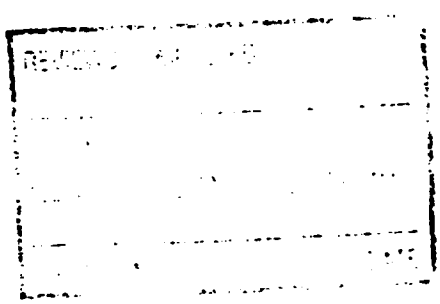
Re: NDA 21-098 - Yasmin® 28 Tablets
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)

Dear Dr. Allen:

Reference is made to NDA 21-098 for Yasmin 28 Tablets, and our meeting scheduled for Monday September 28, 2000 at 9:00 AM. Further reference is made to my telephone conversation with Ms. Jeanine Best, MSN, RN, on September 18.

Enclosed is a one page synopsis provided by [redacted] regarding his review of our pre-meeting package dated September 8. While [redacted] is not listed as a meeting attendee, we had hoped that Dr. [redacted] would be able to attend the September 25 meeting. Unfortunately due to a schedule conflict, this will not be possible.

[redacted] and concluded that "I see no evidence that Yasmin causes increases in serum potassium concentration or that it causes arrhythmias". He also states "In summary, though there is a theoretical basis by which Yasmin might cause increases in serum potassium, in the database provided to me I saw no evidence that such occurred".



evaluation of the data further supports our analysis in that Yasmin has not been associated with an increase in serum potassium levels.

We are looking forward to a productive meeting so we may move forward with obtaining approval of this NDA.

Sincerely,

BERLEX LABORATORIES

June K. Bray
Vice President
Drug Regulatory Affairs

cc: Ms. Jeanine Best, MSN, RN

Enclosure

JKB/letter/yasmin032

APPEARS THIS WAY
ON ORIGINAL

September 14, 2000

Marie Foegh, M.D.
Director, Female Health Care Clinical R&D
Berlex Laboratories
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Dr. Foegh:

This letter is my assessment of a review of the briefing package for NDA 21-098 Yasmin 28 tablets (drospirenone 3 mg and ethinyl estradiol 0.03 mg). This briefing package included a number of analyses. Substantial data examined whether Yasmin affects serum potassium concentrations. Other analyses assessed whether or not Yasmin had adverse cardiovascular effects, namely arrythmogenesis. I see no evidence that Yasmin causes increases in serum potassium concentration or that it causes arrythmias. Particularly instructive are the studies in patients with renal insufficiency, where again no effect is discernible. Studies in these patients do not include patients with severe renal insufficiency, but it is important to realize that patients with this level of renal dysfunction also have fertility problems and therefore would be unlikely to receive an oral contraceptive. In addition, such patients will be actively monitored by their physicians so that if they did receive such a drug, it is highly likely that serum potassium concentrations will be monitored on a sufficiently regular basis to detect any effect that might have occurred.

In summary, though there is a theoretical basis by which Yasmin might cause increases in serum potassium, in the database provided to me I saw no evidence that such occurred.

Sincerely,

BERLEX

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

September 15, 2000

BL
ORIG AMENDMENT

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

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Labeling for European Union, Iceland and Norway

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS, an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. (Please note that on June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.)

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000. A Type A meeting has been scheduled for September 25th to discuss our reply to this letter.

On September 7th, Ms. Jeanine Best of the Division left a voice mail message for the undersigned requesting for the Medical Officer a copy of the labeling for Yasmin® (drospirenone 3 mg and ethinyl estradiol 0.030 mg tablets) that was recently approved by the European Union. Attached please find the Yasmin® labeling that was approved through the Mutual Recognition Process at the beginning of August 2000 for the European Union, as well as Norway and Iceland. National marketing authorizations will now be issued for these countries based on this labeling.

Please also note that Berlex reported in the Safety Update Report dated May 4, 2000 that Yasmin® was approved in the Netherlands in March of 2000. A copy of the approved Dutch labeling was included in that submission.

For your information, Berlex recently learned that Yasmin® was approved for marketing in Latvia in May of 2000 and in Hungary in June of 2000.

To date, Yasmin® has not been marketed in any country.

Should you require any additional information or have any questions regarding this submission, please feel free to call the undersigned at (973) 276-2305. The fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy E. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc204

Desk copy: Ms. Jeanine Best

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

June K. Bray
Vice President
Drug Regulatory Affairs

BERLEX

HAND DELIVERED

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2161
Fax: (973) 276-2016

September 8, 2000

Susan Allen, M.D., MPH, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

MIR

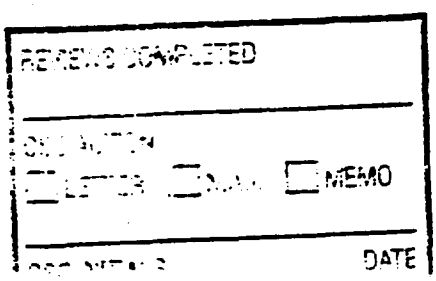
Dear Dr. Allen:

Re: NDA 21-098 - Yasmin® 28 Tablets
Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
Meeting Confirmation and Briefing Package

Reference is made to NDA 21-098 for Yasmin® 28 Tablets, which was submitted on May 14, 1999. Further references are made to my telephone conversations with Ms. Jeanine Best, Regulatory Project Manager, and Mr. Randy Olmstead, Technical Information Specialist, on August 18 and 22, 2000 respectively, regarding our request for a Type A meeting. Berlex wishes to thank the Division for accommodating our request for this meeting to take place in September. This letter confirms our meeting on Monday, September 25, 2000 at 9AM in the Parklawn Building, Conference Room C. A copy of the proposed agenda, list of questions, and list of attendees can be found in Attachment A. The purpose of this meeting is to discuss our reply to the Yasmin approvable letter dated July 10, 2000.

Berlex received an approvable letter for this NDA on March 17, 2000. We responded to this letter on March 29, 2000 and had anticipated receiving an approval letter on July 10.

However, the Division requested a teleconference on July 10, 2000 during which Berlex was informed of your concern regarding the potential risk for developing hyperkalemia. (Berlex received a second approvable letter after this teleconference took place). For reference, a copy of the approvable letter, the Division's minutes of the July 10 teleconference, and our reply to the approvable letter are located in Attachment B.



Berlex is providing a one-volume briefing package which includes new serum potassium data in 1373 subjects from our PMS/PMDD study conducted under [redacted] and our endometrial protection study conducted under [redacted] These studies were just recently completed and therefore were not included in the Yasmin NDA.

In addition, we have conducted an analysis of the risk of developing hyperkalemia using serum potassium data from these two new studies plus six studies previously submitted in the Yasmin NDA. We also analyzed serum potassium data from one study previously submitted from our approved Levlite (levonorgestrel/ethinyl estradiol) NDA 20-860. The total number of subjects included in the total analysis is 2548. Please refer to text table 2 located on pages 17-19 of the briefing package for the details of these studies.

The briefing package also includes an evaluation of cardiovascular adverse events that could potentially be related to hyperkalemia, from all clinical studies that included subjects who received drospirenone. Berlex as well as our consultants have evaluated these data and find no correlation between hyperkalemia and the specified cardiovascular events.

As a result of the analyses and evaluation of this new data by Berlex and our consultants, we maintain that any additional study or studies would not provide any meaningful information prior to approval. We also believe that the proposed phase IV program in addition to any post marketing spontaneous safety reports we will receive from our parent company, Schering AG, when the product is launched in Europe, will satisfy any safety concerns the Division may have.

Please contact the undersigned at (973) 276-2161 if you have any questions regarding this submission.

Sincerely,

BERLEX LABORATORIES

June K. Bray
Vice President
Drug Regulatory Affairs

cc: Ms. Jeanine Best, MSN, RN

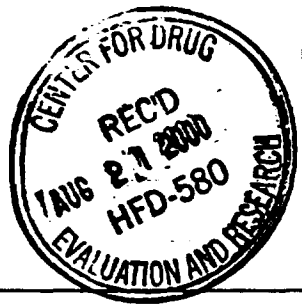
JKB/letter/yasmin029

June K. Bray
Vice President
Drug Regulatory Affairs

ORIGINAL

TELEFAX
UPS OVERNIGHT

August 18, 2000



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2161
Fax: (973) 276-2016

Susan Allen, M.D., MPH, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA [illegible] RHESP
N/C

Dear Dr. Allen:

Re: NDA 21-098 - Yasmin 28 Tablets
Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
Type A Meeting Request

Reference is made to NDA 21-098 for Yasmin 28 Tablets, to the teleconference held on July 10, 2000 between representatives of the Division and Berlex, and to the approvable letter dated July 10, 2000. Further reference is made to my telephone conversation earlier today with Ms. Jeanine Best, Regulatory Project Manager, regarding our intent to request a Type A meeting to discuss our reply to the Yasmin approvable letter.

Berlex is requesting that this meeting be scheduled on September 25 or 26, if possible. These meeting dates are being requested due to the availability of our consultants. However, if the Division is unable to accommodate a meeting on these dates, Berlex will make every effort to meet with the Division at your earliest convenience. We request that this meeting take place in September, so we can move forward with obtaining approval of the Yasmin NDA.

Berlex will provide a pre-meeting package a minimum of two weeks prior to the scheduled meeting date.

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS 8/22/00 DATE

Your consideration of having the meeting on September 25 or 26 is greatly appreciated. Please contact the undersigned at (973) 276-2161 if you have any questions regarding this meeting request.

Sincerely,

BERLEX LABORATORIES

June K. Bray
Vice President
Drug Regulatory Affairs

cc: Ms. Jeanine Best, MSN, RN

JKG/letter/Yasmin/026

APPEARS THIS WAY
ON ORIGINAL

TELEFAX
UPS OVERNIGHT

ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

ORIG AMENDMENT

July 21, 2000

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

CENTER FOR DRUG REC'D JUL 25 2000 HFD-580 EVALUATION AND RESEARCH

CENTER FOR DRUG REC'D JUL 24 2000 HFD-580 EVALUATION AND RESEARCH

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to 7/10/00 Approvable Letter

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. (Please note that on June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.)

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000 (attached immediately following this cover letter for your reference). Berlex learned of this unexpected action on our application during the teleconference on July 10th with representatives from the Division and ODE III. The letter states that before our application may be approved, items identified in the letter must be addressed.

In accordance with 21 CFR § 314.110 (a) (1), we are notifying you of our intention to file additional data to the NDA to address the items identified in the July 10th approvable letter. The items are identified below in bold font, followed by the Berlex response.

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

As suggested by representatives from the Division and ODE III during the July 10, 2000 teleconference, Berlex will further assess the risk of hyperkalemia in women using

drospirenone. Upon finalization of our response to this issue, Berlex will submit all available supportive information in a request for a Type A meeting.

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/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.**

[Please note that, although the content is essentially the same, the four Phase 4 commitments above (from the attached July 10th approvable letter) have been re-worded slightly from those forwarded to Berlex via the Internet by Ms. Jeanine Best of the Division on July 5, 2000, subsequent to the teleconference that day. The Phase 4 commitments received in the July 5th email were incorporated into our submission of July 7, 2000.]

As stated in the submission of July 7th and reiterated here, Berlex agreed to the Phase 4 commitments as follows:

Berlex acknowledges the Division's concerns with YASMIN as communicated during the teleconference on July 5, 2000. We agree to provide a full program/protocol to address the four Phase 4 commitments as described above within 120 days of approval.

We have reviewed the article cited by Dr. Marianne Mann of the Division during the teleconference which was published in the June 15, 2000 New England Journal of Medicine

entitled, "Thrombotic Thrombocytopenic Purpura and Clopidogrel – A Need for New Approaches to Drug Safety". We agree to fufill the Phase 4 commitments through an active surveillance program in a meaningful sample of YASMIN users over an appropriate time period based on the principles described in this article.

We anticipate frequent dialogue with Divison representatives in order to finalize the details of the Phase 4 program/protocols.

On July 6th, we telefaxed this wording of our commitment to the Division and asked that it be reviewed. Ms. Best informed the undersigned on July 7th that the wording would not be reviewed in time for the July 7th submission. She stated that the July 6th wording should be incorporated into the submission. To date, we have not received a response on this commitment; therefore, we assume it is acceptable.

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.

Berlex agrees with these statements.

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.**

Berlex agrees to revise the carton labeling as recommended above.

Under 21 CFR § 314.50 (d) (5) (vi) (b), we request that you update your NDA by submitting all safety you now have regarding your new drug. This same request was made in the March 17th approvable letter with the same criteria of information to be included (see criteria outlined in attached July 10th letter). The Safety Update Report in response to the March 17th request was submitted on May 4, 2000. Per previous procedure, for this July 10th request, Berlex will update the NDA with any new information that was obtained since March 17, 2000 (the cut-off date for inclusion of data into the May 4th Safety Update Report) through an end date to be determined. The same format used in the previous report will be used in this latest Safety Update Report.

In addition, Berlex acknowledges the following additional item noted in the approvable letter:

YASMIN may not be legally marketed until we have been notified in writing that the application has been approved.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Should you require any additional information or have any questions regarding this submission, please feel free to call the undersigned at (973) 276-2305. The fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc190

Desk copy: Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Rockville MD 20857

JUL 10 2000

RECEIVED

JUL 13 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

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Berlex Laboratories, Inc.	July 21, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(973) 276 – 2305	(973) 276 –2016

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
340 Changebridge Road
P.O. Box 1000
Montville, New Jersey 07045 –1000

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Drospirenone 3 mg/Ethinyl Estradiol 0.030 mg	YASMIN®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
DRSP = 6β, 7β; 15β, 16β-Dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone
EE = (1) 19-Norgrena-1,3,5(10)-trien-20-yne-3,17-diol,(17α)
(2) 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

CODE NAME (*If any*)
ZK 30595
ZK 4944

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	3 mg Drospirenone and 0.030 mg Ethinyl Estradiol	Oral

(PROPOSED) INDICATION(S) FOR USE:
Oral Contraception

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Response to July 10, 2000 Approvable Letter

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached page

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 3331 (3/97)

	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50 (c))
	4.	Chemistry section
		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8.	Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12.	Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306 (k)(1))
	17.	Field copy certification (21 CFR 314.5 (k) (3))
	18.	User Fee Cover Sheet (Form FDA 3397)
	19.	OTHER (Specify) Financial Certification

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Nancy F. Velez	Nancy F. Velez Manager	July 21, 2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
340 Changebridge Road P.O. Box 1000 Montville, New Jersey 07045 – 1000	(973) 276 -2305

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Washington, DC 20201

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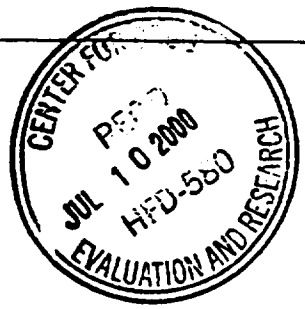

Drug Development & Technology
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July 7, 2000

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

ORIG AMENDMENT

BL

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Revised Labeling, Phase 4 Commitments

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. On June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.

Reference is also made to a teleconference held on July 5th between representatives of Berlex and the Division, the ODE III and the Office of Postmarketing Drug Risk Assessment (OPDRA). At that time, Berlex was informed of ODE III concerns regarding the approval of YASMIN, additional comments on our most recent labeling submissions[1] were provided and Phase 4 studies desired by the Division were described. The Division asked that the following be provided in a submission by 12 noon on July 7th:

1. All changes to date to the Brief and Detailed Patient Labels and Physician Package Insert (PI) be incorporated into revised labeling;

2. Berlex confirm the change made by the Division to the bolded warning in the Physician PI as follows,"YASMIN 28 Tablets contains 3 mg of the progestin drospirenone, which has antimineralocorticoid activity comparable to a 25 mg dose of spironolactone";

[1] The June 20th submission contained the most recent versions of the Brief and Detailed Patient Labels, the June 22nd submission contained the most recent version of the Physician PI

3. Berlex provide a written commitment to provide a full program/protocol to address the Phase 4 commitments desired by the Division within 120 days of approval.

Please note that Ms. Jeanine Best of the Division forwarded to the undersigned via the Internet on July 5th the Division comments on the labeling and the list of Phase 4 studies desired by the Division. In addition, Ms. Best also sent via the Internet on July 5th a spelling correction in the bolded warning and verbally communicated to the undersigned on July 6th additional changes in the CLINICAL PHARMACOLOGY and CONTRAINDICATIONS sections.

In accordance with the Division's requests, today's submission contains the following:

1. Revised Labeling

A revised electronic Physician PI with revised Brief and Detailed Patient Labels appended to it (as requested by the Division), reflecting all of the Division's comments to date is provided. Also as requested by the Division, separate Brief and Detailed Patient Labels are provided. These electronic copies of the labeling are provided in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 28 TABLETS Revised Labeling" dated July 7, 2000 (see Attachment 1).

In accordance with previous procedure, a clean copy as well as a strike out version of the labeling are provided, identified as "unmarked" and "marked", respectively. Please note that for ease of review, the marked versions contain only the latest revisions, i.e., those comments received on and after July 5th. In addition, typographical errors and minor inconsistencies that Berlex has recently identified have also been marked.

Berlex Laboratories certifies that the diskette provided herewith was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created June 14, 2000.

A hard copy of the unmarked labeling is provided in Attachment 2 and marked labeling in Attachment 3.

In accordance with previous procedure, this revised version of the labeling was also sent to Ms. Best via the Internet today, password protected.

2. Confirmation of Data for the Division

As provided in a voice mail communication to Ms. Jeanine Best on July 6th, Berlex confirms that 3 mg of drospirenone has antimineralocorticoid activity comparable to a 25 mg dose of spironolactone. This statement is supported by in vivo data provided in the NDA, specifically, Report 5995/II entitled, "Progestogens With Antimineralocorticoid Activity" (NDA Vol. 7, page 5 00756).

3. Phase 4 Commitments

The Division stated that Berlex should commit to providing a full program/protocol to address the Phase 4 commitments desired by the Division within 120 days of approval. The Division required a commitment in writing prior to approval. In order to reach agreement in a timely fashion, Berlex telefaxed to the Division on July 6th proposed wording of this commitment to be incorporated into today's official submission to the NDA. Ms. Best informed the undersigned today that this wording would not be reviewed in time for today's submission but should be included as it was telefaxed to the Division yesterday.

Below is the list of the desired Phase 4 studies (received from Ms. Best on July 5th), followed by the Berlex commitment in italic font:

Phase 4 studies desired by the Division; sponsor should commit to providing a full program/protocol to address these phase 4 commitments within 120 days of approval. Commitment in writing is required prior to approval.

- The first phase 4 commitment was for the sponsor to provide an educational outreach program for health care providers and patients, focusing on Yasmin's contraindications in patients with renal/hepatic impairment or patients predisposed to hyperkalemia due to its potential antimineralocorticoid activity
- The second phase 4 commitment was a surveillance or evaluation 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; full case report summaries of all such inappropriate prescriptions, including patient outcome, would then be required.
- The third phase 4 commitment would be to use the same database to again evaluate all patients prescribed Yasmin for the subsequent outcome 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.
- The fourth phase 4 commitment would be to 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

Berlex acknowledges the Division's concerns with YASMIN as communicated during the teleconference on July 5, 2000. We agree to provide a full program/protocol to address the four Phase 4 commitments as described above within 120 days of approval.

We have reviewed the article cited by Dr. Marianne Mann of the Division during the teleconference which was published in the June 15, 2000 New England Journal of Medicine entitled, "Thrombotic Thrombocytopenic Purpura and Clopidogrel – A Need for New Approaches to Drug Safety". We agree to fufill the Phase 4 commitments through an active surveillance program in a meaningful sample of YASMIN users over an appropriate time period based on the principles described in this article.

We anticipate frequent dialogue with Divison representatives in order to finalize the details of the Phase 4 program/protocols.

It should be noted that Berlex was surprised to learn four days before the expected action date on our application of these commitments. We are committed, however, to achieving approval by the action date of July 10th.

With this submission, Berlex believes it has addressed all outstanding issues communicated during the July 5th teleconference. We acknowledge the Office concerns with YASMIN and understand that there are ongoing discussions at the Center level regarding the action on this product. As discussed, please keep us informed on the status of these discussions. As you know, Berlex is immediately available and welcomes the opportunity to meet or respond to any concerns.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc180

Desk copy: Ms. Jeanine Best – cover letter

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

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Drug Development & Technology
Division of Berlex Laboratories, Inc.

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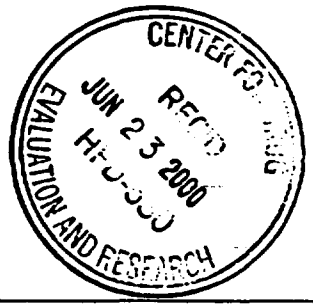
June 22, 2000



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

ORIG AMENDMENT

BL

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Revised Physician Package Insert

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. On June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.

Reference is also made to our most recent labeling submission dated June 20. Additional reference is made to the teleconference on June 21st between Dr. Marianne Mann and Ms. Jeanine Best of the Division and the undersigned. In the DRUG INTERACTIONS section of the Physician Package Insert (PI), specifically, "Interactions With Drugs That Have The Potential To Increase Serum Potassium", the Division objected to the term "bioequivalence" used to describe serum potassium levels. Today, the Division telefaxed suggested re-wording for this section in their minutes of the teleconference.

Berlex telefaxed a slightly re-worded version of this section back to the Division today. The Medical Officer reviewed Berlex's version and telefaxed a re-written version this afternoon. The undersigned communicated to Ms. Best via voice mail today that the Division's re-wording is acceptable (see attached telefax from the Division with the most recent version of the section) and it will be incorporated into a revised Physician PI. This revised PI would be sent via the Internet to Ms. Best and would be formally submitted to the NDA.

Provided in today's submission is a hard copy of the revised Physician PI incorporating the new wording for the DRUG INTERACTIONS section. In accordance with previous procedure, a

clean copy as well as a strike out version of the Physician PI are provided. Please note that for ease of review, the marked version contains only the latest revisions, i.e., those communicated on June 21st and 22nd.

In accordance with previous procedure, this revised version of the Physician PI was also sent to Ms. Best via the Internet today, password protected.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

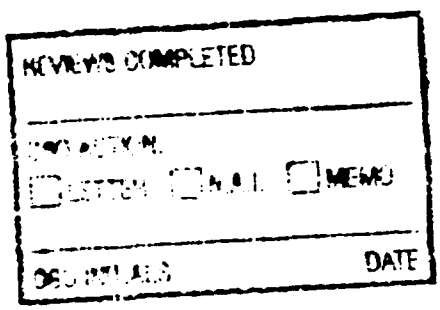
BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc167

Desk copy: Ms. Jeanine Best – cover letter



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June 21, 2000

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Susan Allen, M.D., MPH, Director
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5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIGINAL

ORIG AMENDMENT

BC

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Carton Mock-Ups Including Lot Number and Expiration Date

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. On June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.

Reference is also made to our submission of February 29, 2000 which included mock-ups of our single unit and outer cartons (holds 3 units). On June 16th, Ms. Jeanine Best of the Division informed the undersigned that the Chemistry Reviewer was reviewing the carton mock-ups and wanted to know where the lot number and expiration date were going to be placed. Carton mock-ups containing this information were telefaxed to Ms. Best that same day and again on June 19th when the undersigned was told that the response to this request had not been received.

Provided today is a formal submission of the same mock-ups for the single unit carton and outer carton which were provided in the telefaxes of June 16th and 19th, indicating where the lot number and expiration date will be imprinted.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc163

Desk copy: Ms. Jeanine Best – cover letter

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CSO INITIALS	DATE

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June 20, 2000

ORIGINAL

Susan Allen, M.D., MPH, Director
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Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT
BL

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Revised Labeling

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. On June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.

Reference is also made to our most recent labeling submissions dated June 12 and June 15, 2000. The versions of the Brief and Detailed Patient Labels included in the June 12th submission and Physician Package Insert (PI) included in the June 15th submission were discussed in a teleconference held on June 19th between representatives of the Division and Berlex. The Division's comments were communicated during the teleconference and were also forwarded by Ms. Jeanine Best of the Division via the Internet to the undersigned that same day. Wording for the *Drug Interactions* section of the Physician PI, specifically, "Interactions With Drugs That Have The Potential To Increase Serum Potassium" was telefaxed to the Division following the teleconference and was found acceptable.

Provided in today's submission are a revised electronic Physician PI as well as revised Brief and Detailed Patient Labels reflecting all of the Division's comments to date. These electronic copies of the labeling are provided in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 28 TABLETS Labeling" dated June 20, 2000 (see Attachment 1).

In accordance with previous procedure, a clean copy as well as a strike out version of the labeling are provided, identified as "unmarked" and "marked", respectively. Please note that for

ease of review, the marked versions contain only the latest revisions, i.e., those comments received and agreed upon on June 19th.

Berlex Laboratories certifies that the diskette provided herewith was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created June 7, 2000.

A hard copy of the unmarked labeling is provided in Attachment 2 and marked labeling in Attachment 3.

In accordance with previous procedure, this revised version of the Physician PI was also sent to Ms. Best via the Internet today, password protected.

The labeling provided in this submission incorporates all of the Division comments and reflects all of the agreements reached between the Division and Berlex through June 19th. No additional changes have been made. As discussed during the June 19th teleconference, we understand that this version of the labeling will be included in the action package that will be forwarded to the Division Director tomorrow, June 21st. Berlex will be immediately available to respond to any outstanding issues. Upon resolution of any these issues, the package will then be forwarded to the Office Director for final approval.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc158

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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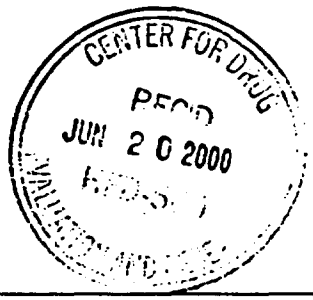
June 19, 2000



Susan Allen, M.D., MPH, Director
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Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

NEW CORRESP
NC

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Waiver for Pediatric Studies

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. On June 12, 2000, the Division was informed that the YASMIN 21 blister would not be marketed at this time. All references to YASMIN 21 tablets were removed from the labeling.

Further reference is made to a voice mail communication from your representative, Ms. Jeanine Best to the undersigned on June 16, 2000. Ms. Best requested that Berlex submit a waiver request for pediatric studies. In response, on June 16th, Berlex submitted details of telephone conversations between the undersigned and Ms. Jennifer Mercier of the Division on May 27, 28, June 1 and 7, 1999 (see attached). In these conversations, Berlex was informed that no further action was needed on our part with regard to the waiver for Pediatric Studies. This information was also telefaxed to the Division on June 16th. Ms. Best called upon receipt of the telefax and stated that regardless of the agreement between Ms. Mercier and the undersigned, Berlex still needed to request a waiver.

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

Berlex Laboratories requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of the drug product in all relevant pediatric subpopulations in accordance with 21 CFR 314.55(c)(2)(ii), i.e., necessary studies are impossible or highly

impractical because the number of such patients is so small. Yasmin® is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

Berlex hopes that the above satisfies the Division's request for the waiver for pediatric studies and that no further action is required on the part of Berlex.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc161

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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ORIGINAL

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June 16, 2000

Susan Allen, M.D., MPH, Director
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DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
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Rockville, Maryland 20857-1706

NEW CORRESP

GC

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Waiver for Pediatric Studies

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000.

Further reference is made to the telephone conversation between your representative, Ms. Jeanine Best and the undersigned today. In this conversation, Ms. Best requested that Berlex submit a waiver request for pediatric studies. Berlex believes that we have agreed with the Division that a written request for pediatric studies was not required. This fact is documented during telephone conversations between the undersigned and Ms. Jennifer Mercier of the Division on May 27, 28, June 1 and 7, 1999.

May 27
I asked about the letter from the Division dated May 19, 1999 acknowledging receipt of the NDA and the reference to the pediatric study requirement. I told Ms. Mercier that I had reviewed the final rule and would like to discuss it with her. I explained that because the subject of the NDA is an OC, we planned to request a full waiver for the pediatric studies described under 314.55. I said I wanted to discuss how extensive the request for the waiver needed to be.

May 28
In a voicemail, Ms. Mercier told me that the NDA acknowledgment letter that referred to the pediatric information is a letter that is automatically generated by a computer. She said we would not need to request a waiver because she believes OCs are considered an automatic waiver - they are not considered for pediatric use.

When I returned Ms. Mercier's call, I asked again about the waiver for the pediatric studies and whether there was a specific way it should be handled. I referred to Ms. Mercier's statement that OCs were probably considered an automatic waiver. I told her that the only thing I could find in the final rule was a list of diseases that qualified for an automatic waiver. There was no section on indications, for example, oral contraception. I asked if, in our response to the May 19th acknowledgment letter, we should basically just re-state what was provided in the section for a full waiver in 314.55.

June 1

Ms. Mercier left a message in the afternoon saying that she was trying to locate information about the pediatric waiver for OCs. She said that the Division is under the understanding that the automatic waiver includes OCs. She said she sent an email to someone who deals with the pediatric section only of the labeling but has not heard from her. She said she will try to contact her again and provide me with the response as soon as she hears.

When I returned Ms. Mercier's call, I told her that I had received her message regarding the pediatric waiver the previous day and was looking forward to hearing the result of her inquiry.

June 7

Regarding the pediatric information requested in the acknowledgment letter for the YASMIN NDA, Ms. Mercier said she is under the understanding that Berlex can disregard that information – it does not apply to our application. She stated that it applies only to "new NDAs or new types of supplements other than labeling." She said that if we were submitting a new NDA, the pediatric studies would be a requirement and we would have to request a waiver in the NDA package.

Berlex hopes that the above satisfies the Division's request for the waiver for pediatric studies and that no further action is required on the part of Berlex.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc153

Desk copy: Ms. Jeanine Best – cover letter

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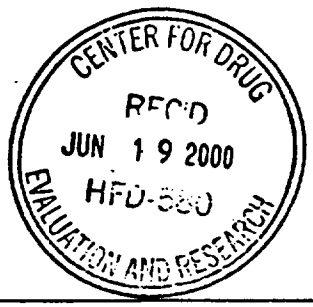
Telephone: (973) 276-2000

June 16, 2000



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

DRUG AMENDMENT
BM

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Response to Clinical Questions Regarding Safety Update of May 4, 2000

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000.

A Safety Update Report was requested in the approvable letter and was submitted on May 4, 2000. The Report covered the period from January 16 – March 17, 2000[1].

On June 8, 2000, Ms. Jeanine Best of the Division forwarded via the Internet comments from the Medical Reviewer on the Safety Update Report. This submission provides responses to those comments. The Medical Reviewer's comments are provided first in bold, followed by our responses:

1. **The Sponsor states that 27 subjects terminated prematurely from Study (Protocol) 97036 because of adverse events. Twenty (20) of the 27 were assigned to active drug and only 7 were assigned to placebo. Does the Sponsor have an explanation for this imbalance of almost 3:1?**

[1] These dates correspond to the cut-off date for inclusion of data into the previous Safety Update Report (submitted on February 3, 2000) and the date of the approvable letter.

Certain side effects that commonly occur with oral contraceptive use are expected in clinical studies. Breast tenderness, irregular bleeding, and headaches were more common on the active drug than the placebo and is not unusual.

2. **Attachment 1 is labeled "List of Subjects who Dropped Out with any Adverse Experience." Does the listing include all premature terminations who experienced an AE at any time during their participation in the study as the listing title implies or only those subjects who discontinued because of the listed AE(s)? The remainder of the questions assumes, in some instances, that the listed AE(s) was the cause of the subject's termination.**

   Attachment 1 includes only those subjects who dropped out because of the adverse event that is listed.

3. **Three subjects receiving active study drug were reported to have experienced serious adverse events. Subject Nos. 07038 and 24014 are not included in the listing of terminations in Attachment 1. Did both of these subjects continue treatment until a normal protocol termination?**

   Subject 24014 is actually subject 24004. This was an error in our Safety Update. This subject had a serious event: basal cell carcinoma, however, the subject completed the study. Subject 07038 also completed the study after the occurrence of the serious adverse event: recurrence of Bell's Palsy.

4. **Additional information regarding 3 subjects included in the listing in Attachment 1 is requested. The Subject Nos. and the adverse events of interest are: (1) No. 12013 (palpitations); No. 19003 (chest pain and dyspnea); and No. 19017 (vertigo). The additional information should include (1) start and stop dates, (2) start date also expressed as treatment day or day on study drug, (3) severity of AE, (4) outcome of AE, (5) treatment administered for management of the AE, and (6) any investigator comments about each of the AEs.**

Random number	AE start	AE stop	Day on drug	Severity	Outcome	Additional treatment
12013	07/09/98	07/10/98	21	moderate	Drug discontinued	none
19003	10/18/98	10/25/98	31	mild	Drug discontinued	none
19017	12/10/98	12/14/98	1	mild	Drug discontinued	none

There were no other investigator comments for any of these events.

5. **Is further information about the cause of the chest pain and dyspnea in Subject No. 19003 available? If the Investigator did not believe there was an association between the study drug and the AEs, do you know why treatment was stopped and the subject terminated from the Study?**

   No further information is available regarding the chest pain and dyspnea for subject 19003. The subject was seen on November 19, 1998 after the resolution of the symptoms on October 25, 1998. Study medication was then discontinued. The subject discontinued the

study due to the adverse events, but the investigator thought it was unlikely that the events were related to use of the study drug.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc151

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

REVIEW COMPLETED

CBO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CBO INITIALS DATE