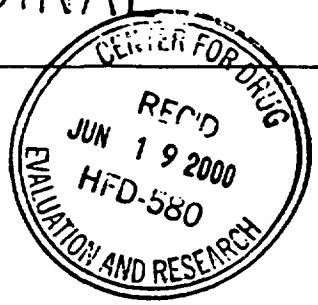
TELEFAX
UPS OVERNIGHT

ORIGINAL



Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

June 15, 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
BC

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 ACE Inhibitor Study

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.

Reference is also made to our submission of April 20, 2000 which provided the FINAL abbreviated report entitled, "Final Statistical Analysis of Serum Potassium Data" for the ACE Inhibitor study entitled, "A Double-Blind, Randomized, Two-Parallel Groups Study To Evaluate The Potential For Developing Hyperkalemia When The Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol Is Coadministered With An ACE Inhibitor In Postmenopausal Women" (Protocol 98106). Additional reference is made to our amendment dated May 8, 2000 which corrected the 90% confidence limits for both Cmax and AUC provided in the April 20th report.

Additional references are made to the teleconferences held on June 7, 8 and 9, 2000 during which the wording in the DRUG INTERACTIONS section of the Physician Package Insert regarding this study was discussed.

On June 9th, Ms. Jeanine Best of the Division asked the undersigned on behalf of the Medical Reviewer, what the normal ranges were for the potassium levels in the ACE Inhibitor Study. The undersigned responded that the lab normal ranges for the potassium concentrations for safety evaluation were 3.5 – 5.3 mEq/L. The Medical Reviewer then asked if these normal ranges were the same for both methods used in the study. The undersigned informed Ms. Best

that the second method was a validated atomic absorption method used for quantitation of AUC and Cmax values and was not a clinical lab. The undersigned referred Ms. Best to page 6 of the Final Statistical Analysis submitted on April 20th. On June 12th, the undersigned read the following additional information on this subject to Ms. Best in a voice mail communication and asked that it be forwarded to the Medical Reviewer as soon as possible. It is provided here as a formal submission to the NDA:

Reference Range ———

Serum potassium concentrations for the primary variable were determined with a validated ——— ———. The newly developed method was validated ———, in accordance with FDA guidance on bioanalytical method validation. Unlike clinical labs, bioanaytical labs measure analytes over a wide range and are not limited to a certain normal range. However, for the purpose of the present study, the lowest and highest values from all subjects obtained at baseline, Pretreatment Day 1 (2.550- 5.465 mEq/L) can be considered as a reference range.

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/drpoc147

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MR MO

CSO INITIALS DATE

TELEFAX
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BERLEX

ORIGINAL

Drug Development & Technology
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June 15, 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
BM

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Revised Physician PI including Racial Breakdown, Age Range and Mean

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.

Reference is also made to our submission of June 12, 2000 which included our most recent version of the Physician Package Insert (PI). This submission did not include the request received that same day from Ms. Jeanine Best of the Division to include in the label a racial breakdown of the clinical trial participants as well as age range and mean. Berlex committed to provide a revised Physician PI with these data as soon as they were available.

Provided in today's submission is a revised electronic Physician PI incorporating this most recent request from Ms. Best. In the **INDICATIONS AND USAGE** section, the sentences underlined in the paragraph below have been added:

> In clinical efficacy studies of **YASMIN** of up to 2 years duration, 2,629 subjects completed 33,160 cycles without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83 % Caucasian, 1 % Hispanic, 1% Black, < 1% Asian, < 1% other, < 1% missing data, 14% not inquired and < 1% unspecified. Fourteen pregnancies were reported. This represents an overall pregnancy rate of 0.55 per 100 woman-years.

For your reference, this information can be found in the Integrated Summary of Efficacy, NDA Vol. 181, page 8 53355. This is the only change that has been made to the labeling submitted on June 12th. However, please note that upon removing all references to YASMIN 21 in the June 12th Physician PI, one sentence regarding the inactive ingredients contained in the active tablets (**DESCRIPTION** section) was inadvertently deleted. This sentence has been added once again in the description of the YASMIN 28 Tablets. In the "marked" version, the sentence appears as being added but is not new information. Incorrect table numbers were also corrected. All changes that appeared as "marked" in the June 12th Physician PI are also "marked" in today's version as comments from the Division have not yet been received.

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. These electronic copies of the Physician PI are provided in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 28 TABLETS, Revised Physician PI" dated June 15, 2000 (see Attachment 1).

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.

As stated in our June 12th submission, we hope to resolve any labeling issues during this week in order to have final labeling available by June 19th. As agreed last week, should any fine tuning issues be unresolved during this week, we will discuss them in a teleconference with Dr. Marianne Mann, Deputy Director, during a teleconference on June 19th. We understand that upon resolution of all issues on June 19th, the final labeling will be forwarded to the Division Director and 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

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

NFV/letter/drpoc143

Desk copy: Ms. Jeanine Best – cover letter

TELEFAX
UPS OVERNIGHT

ORIGINAL

BERLEX

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June 15, 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
5600 Fishers Lane
Rockville, Maryland 20857-1706

(NDA) AMENDMENT

BB

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Response to Biopharmaceutical Reviewer: Formulation Comparison

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.

Reference is also made to a teleconference held with the Division on February 23, 2000. This teleconference was held to discuss expiration dating. During the course of this teleconference, we also discussed the comparison of the manufacturing process at the pilot plant

Reference is also made to a voice mail communication from your representative, Ms. Jeanine Best, to the undersigned on June 13, 2000. In the voicemail, Ms. Best communicated that the Biopharmaceutical Reviewer wanted a comparison between the formulations of Yasmin used in the Renal Impairment Study, the ACE Inhibitor Study and the Yasmin commercial formulation. He wanted the exact composition of the formulations and asked that any manufacturing differences between the formulations be identified. The reviewer requested that Berlex provide the information this week or as soon as possible.

The attached document entitled, "Yasmin®: Comparison Of Tablets Used In The Renal Impairment Study, ACE Inhibitor Study And The Commercial Formulation" responds to the

Biopharmaceutical Reviewer's request. Pages 2 and 3 were previously submitted on February 23, 2000 as a result of the teleconference.

Berlex believes that the attached response provides an adequate response to the reviewer. 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

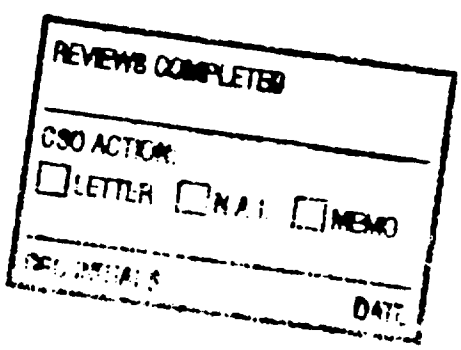
Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc145

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL



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ORIGINAL

Drug Development & Technology
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June 14, 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: Request for Repeated Measurement Analysis

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.

Reference is also made to our Physician Package Insert (PI) submitted to the Division on May 9, 2000. Specific reference is made to the teleconferences between Berlex and Division representatives held on June 7th and 8th, and to the comments received from the Division on June 7th. The Division made the following comment with regard to our ACE Inhibitor study in the **PRECAUTIONS**, DRUG INTERACTIONS section:

> There were no clinically ~~———~~ **{can remain if additional analysis is performed to confirm this}** significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo.

The Division asked that a repeated measurement analysis be done if Berlex wanted to claim that there were no "statistically" significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo. This analysis was telefaxed to the Division on June 8th, subsequent to the teleconference. As requested by Ms. Jeanine Best of the Division on June 13th, a copy of this analysis is provided again immediately following this cover letter as a formal submission for the NDA.

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/drpoc141

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSC ACTION

LETTER N.A.I. M...

INITIALS DATE

TELEFAX
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BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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June 12, 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
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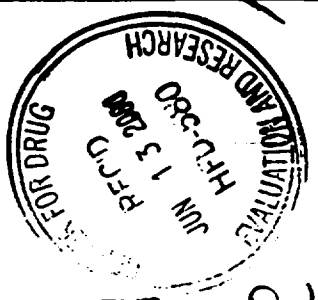

ORIG AMENDMENT BL

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 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.

Reference is also made to our most recent labeling submission dated May 9, 2000. The Division provided comments on the May 9th Physician Package Insert (PI) on June 2, 6, 7, and 9. Teleconferences to discuss these comments were held on June 7, 8 and 9. The Division asked that our Brief and Detailed Patient Labels be revised to correspond with the Physician PI edits.

Provided in today's submission are a revised electronic Physician PI as well as 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 12, 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 electronic copies of the Division's comments provided via the Internet by Ms. Best to the undersigned on June 7 were used to generate the strike out version. Miscellaneous hard copy comments received by telefax after June 7th were also incorporated.

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.

Please note the following when reviewing this version of the labeling:

- On June 7, the Division provided an additional paragraph to be inserted in the **PRECAUTIONS** section under PREGNANCY. The first sentence provided by the Division read, "Sixteen pregnancies that occurred with Yasmin exposure in utero (no more than a single cycle of exposure) have been identified." Please note that all documentation provided in NDA 21-098 indicates that there were 14 pregnancies that occurred with Yasmin. In order to be consistent with our statement regarding these pregnancies in the INDICATIONS AND USAGE section, we have changed the Division's statement to reflect 14 pregnancies rather than 16.

- During our June 9th teleconference, we discussed appropriate wording for the **PRECAUTIONS**, DRUG INTERACTIONS section, specifically, "Interactions With Drugs That Have The Potential To Increase Serum Potassium". In support of a statement that was discussed and now appears in this section on page 15 (marked version) regarding bioequivalence of the DRSP/E2 and placebo groups in terms of serum potassium AUC and Cmax, the Division requested the SAS output for the AUC and Cmax analyses. These data are provided in Attachment 4.

  For your information, during the June 9th teleconference, the Division was referred to Table 6 of the final statistical analysis of serum potassium data from the abbreviated ACE Inhibitor Report for the AUC and Cmax 90 % Confidence Intervals. On May 8th, we submitted an amendment to the NDA which changed the Confidence Intervals for AUC and Cmax but did not affect the final results of the study. The title page of the report reflecting the amendment date to the report of May 5, 2000 and the corrected page 19 were submitted. For your convenience in review, these pages reflecting the correct Confidence Intervals are provided again in Attachment 5.

- Immediately following the June 9th teleconference, additional minor fine tuning in the wording of the DRUG INTERACTIONS section, "Interactions With Drugs That Have The Potential To Increase Serum Potassium", was done.

- Berlex has decided not to market the Yasmin 21 blister at this time. All references to Yasmin 21 tablets have been removed from the labeling.

- Today the undersigned received a request from Ms. Jeanine Best of the Division to provide in the label a racial breakdown of the clinical trial participants. She also asked that the age range and mean age be provided. This request has not been incorporated into today's revised Physician PI as additional time is needed to gather these data. We will provide these data in a revised Physician PI as soon as they are available.

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

As discussed during our teleconferences last week, we hope to resolve any issues regarding this version of the labeling during this week in order to have final labeling available by June 19th.

As agreed, should any fine tuning issues be unresolved during this week, we will discuss them in a teleconference with Dr. Marianne Mann, Deputy Director, during a teleconference on June 19th. We understand that upon resolution of all issues on June 19th, the final labeling will be forwarded to the Division Director and Office Director for final approval.

As you know, Berlex intends to launch YASMIN® 28 Tablets in early July, therefore, we appreciate all of your efforts to finalize the labeling as soon as possible in order for us to proceed with preparation of our launch supplies.

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/drpoc135

Desk copy: Ms. Jeanine Best – cover letter

APPEARS THIS WAY
ON ORIGINAL

TELEFAX
UPS OVERNIGHT

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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Telephone: (973) 276-2000

May 24, 2000

ORIGINAL

Susan Allen, M.D., MPH, Acting 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

ORIGINAL

BP

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Response to FDA Request for Information
(Pharmacology/Toxicology Reviewer)

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.

Additional reference is made to our submission dated May 9, 2000 which included a revised Physician Package Insert (PI) incorporating all comments received from the Division to date as well as the results of the renal impairment and ACE inhibitor studies.

Reference is also made to the voice mail communication the undersigned received today from Ms. Jeanine Best of the Division. Ms. Best stated that the Pharmacology/Toxicology reviewer would like some additional data submitted. She referred to our May 9th submission, in the **PRECAUTIONS** section of the PI under PREGNANCY, where we dispute the following statement, asking that it be removed:

Berlex stated that this effect was within the historical control range for Han:Wistar rats at Schering AG and we offered to submit the historical range data upon request. Ms. Best stated that the Pharmacology/Toxicology Reviewer would like to see these data as soon as possible.

In response to Ms. Best's request, attached please find four pages containing the historical control data for visceral anomalies in rat fetuses for the period from 1979 to 1998.

We trust that the information provided in this submission satisfies your request. As discussed with Ms. Best on May 22nd, we look forward to receiving your first round of labeling comments by the close of business day on June 2nd.

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/drpoc116

Desk copy: Ms. Jeanine Best
Dr. Alexander Jordan

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

As noted in our April 20, 2000 submission, the *Renal Impairment Study* will be submitted in May. This submission provides for the final DRAFT report of the study entitled, "Open-label study to assess the effect of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repated oral administration over 14 days". The final report for this study will be submitted next week and should not deviate much from the DRAFT report.

The study was an open-labeled, non-randomized study with one treatment. Because subjects with varying degrees of renal function were included, each individual was classified to a renal function group by her creatinine clearance. The study has four phases: screening took place up to four weeks before treatment, pretreatment took place two days prior to treatment, treatment occurred for 14 days and post-treatment occurred 14 days after treatment.

The study was conducted to evaluate DRSP's effects on serum potassium to assess the risk of hyperkalemia in female subjects with mild or moderate renal insufficiency and to evaluate the effect of renal function on the pharmacokinetics of DRSP.

The conclusion of the study revealed that the mean potassium serum concentration did not show a clinically significantly change during steady-state treatment with DRSP in all renal function groups. A difference in the pharmacodynamic effects of DRSP on the serum potassium concentration in subjects with mild or moderate renal insufficiency compared to subjects with normal renal function was not found. Also, all steady-state treatment potassium concentration values measured were 5.5 mmol/l or under for all study participants in all three renal groups.

Based on a statistical model, the concomitant intake of potassium sparing drugs (ACE inhibitors and beta receptor inhibitors) could elevate the potassium concentration in the renally impaired during DRSP intake if their pretreatment potassium concentrations are at least in the upper normal range. The pharmacokinetic data indicate that the DRSP concentrations in serum increased moderately with decreasing creatinine clearance. This change is not expected to be of clinical relevance due to the excellent tolerability of DRSP.

As noted in a telephone conversation between Ms. Best and the undersigned on April 12, 2000, it is understood that the review clock will begin upon receipt of the final report of the renally impaired study. Since it is anticipated that this study will be submitted in early May, Berlex will call soon after to begin the steps to arrange a teleconference. It is hoped that we can address any outstanding issues, discuss and finalize the labeling.

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/drpoc100

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

BERLEX

UPS OVERNIGHT

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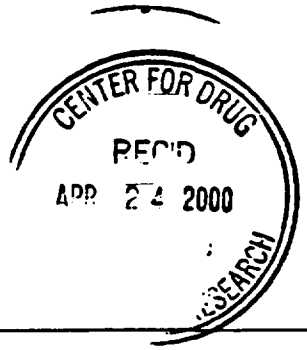
April 20, 2000



Susan Allen, M.D., MPH, Acting 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

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
Final Statistical Analysis of Serum Potassium Data from ACE Inhibitor Study

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.

Reference is made to a telephone conversation on April 12, 2000 between Ms. Jeanine Best of the Division and the undersigned. Ms. Best informed the undersigned that the Division had received our recent submissions to the NDA but that upon issuance of the approvable letter of March 17, 2000, the review clock had stopped. She stated that the reviewers are not obligated to review any additional information until a complete response to the approvable letter is received, that is, until the final report of the renal impairment study is submitted. Berlex acknowledges this fact and understands that the review of today's submission may not occur until after submission of the final report of the renal impairment study. However, we would like the Division to have today's submission immediately available and hope if time permits that a review can be done.

References are also made to our teleconference on December 15, 1999 and the submission dated January 6, 2000. In the January 6th submission, Berlex provided a timeline as to the status of three studies outstanding at the time. The final report for the *Omeprazole Drug Interaction Study* was submitted on January 18, 2000. A "Summary of Serum Potassium

Results"[1] from the *ACE Inhibitor Study* was submitted on February 28, 2000. The DRAFT statistical analysis of serum potassium data from the ACE inhibitor study was submitted on March 16, 2000. The final report for the *Renal Impairment Study* will be submitted in May.

Berlex committed in the January 6th letter to submit a FINAL "abbreviated" report of the ACE Inhibitor study at the end of March. As stated in our submissions of February 28th and March 16th, Berlex consulted the Guideline for Industry entitled, "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" and recognized that it was using the term "abbreviated" somewhat differently to describe the reports that would be submitted to the Division from the definition used in the guideline. The ACE Inhibitor study was originally conducted for the purposes of our HRT indication. As stated during the teleconference on December 15th, this study was conducted under [redacted] During this teleconference, the Division requested data from this study. Therefore, for the purposes of submission of this study, Berlex defines "abbreviated" as a report that is less than a full report and the emphasis is placed on the serum potassium data.

This submission amends NDA 21-098 to provide for a FINAL abbreviated report entitled, "Final Statistical Analysis of Serum Potassium Data" for the ACE Inhibitor study entitled, "A Double-Blind, Randomized, Two-Parallel Groups Study To Evaluate The Potential For Developing Hyperkalemia When The Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol Is Coadministered With An ACE Inhibitor In Postmenopausal Women" (Protocol 98106).

As described in the submissions of February 28th and March 16th, in this study, drospirenone (DRSP) 3 mg/estradiol (E2) 1 mg or placebo tablet was orally administered daily for fourteen days to mild hypertensive postmenopausal females maintained on 10 mg bid enalapril maleate therapy. Twenty-four (24) volunteers entered and completed this double-blind, randomized, two parallel groups study. Serum potassium concentrations were determined over a 24-hour period on pretreatment Day 1 (prior to the first DRSP/E2 dose) and on treatment Day 14 (after last treatment dose). In addition, a pre-morning dose single serum potassium determination was performed on pretreatment day 2 and treatment days 2, 4, 6, 8, 10, and 12 to continuously monitor serum potassium concentrations.

This study began in December of 1999 and the last subject completed on February 23, 2000. In our DRAFT statistical analysis submitted on March 16th, the study had been unblinded to the statistician only for the purposes of providing the statistical analysis prior to database lock. In addition, because the database was not yet locked, the data listings were not presented by treatment group. The FINAL statistical analysis that is attached contains the unblinded data, including the data listings presented by treatment group.

The FINAL statistical analysis confirms and expands on the results provided in the DRAFT statistical analysis. Results of the statistical analysis of serum potassium log-transformed Cmax and AUC show that there were no statistically significant differences between placebo and DRSP/E2 treatment groups in terms of both serum potassium Cmax and AUC. The

[1] This document contained the serum potassium concentrations obtained from all of the subjects but the treatment group had not yet been defined. It did not include a description of statistical methods used in the study nor a statistical analysis.
[2] The protocol was submitted to the Division on November 16, 1999 (Serial No. 032).

obtained narrow 90% confidence intervals on both Cmax and AUC further demonstrate the precision of the observed parameter ratio measurements. The data supports the conclusion that there are no clinically or statistically significant differences in serum potassium concentrations in mildly hypertensive postmenopausal women maintained on enalapril therapy who are administered DRSP/E2 or placebo for 14 days.

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

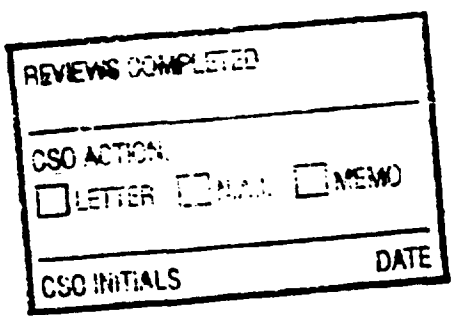
Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc096

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL



BERLEX

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April 4, 2000

ORIGINAL

Susan Allen, M.D, MPH, Acting 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

BP

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
Potassium Data from Renal Impairment Study

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.

Reference is also made to our teleconference on December 15, 1999 to discuss Clinical, Clinical Pharmacology and Chemistry issues that would impact the approval and labeling of YASMIN and to the follow-up submission dated January 6, 2000. Additional reference is made to the approvable letter dated March 17, 2000 and our response to that letter dated March 29th.

In the January 6th submission, Berlex provided a timeline as to the status of three studies outstanding at the time. The final report for the omeprazole drug interaction study was submitted on January 18, 2000. The DRAFT report of the ACE inhibitor study was submitted on March 16th, with the final report to follow in mid April. The third study, the renal impairment study, is the subject of today's submission.

In the submission of January 6th, Berlex stated that some results from the renal impairment study would be submitted at the end of March 2000. Berlex is submitting herewith a "Summary of Potassium Results" from the renal impairment study, Study No. 303063, entitled, "Open-Label Study To Assess The Effects Of 3 mg Drospirenone (DRSP) On Serum Potassium And To Evaluate The Pharmacokinetics Of DRSP In Female Volunteers With Impaired Or Normal Renal Function After Repeated Oral Administration Over 14 Days".

For your information, this summary of the serum potassium concentration results is based on data which were available before the final data release. The complete set of data, including the pharmacokinetic results, will be analyzed and provided in the next few weeks in a full study report that includes a detailed discussion of all of the results.

The approvable letter of March 17th states that final results from this renal impairment study, as well as revised DRAFT labeling that includes appropriate information from the study, will have to be addressed before our application may be approved. As stated in our submission of March 29th, we plan to submit the DRAFT report of this study by the end of April 2000, together with the revised labeling and a request for a teleconference. Following the teleconference, final labeling will be prepared and submitted with the final report of the renal impairment study in mid May.

Renal Impairment Study 303063, Summary of Potassium Results

This study investigated both pharmacodynamics (effect on serum potassium) and pharmacokinetics of DRSP under multiple dose, steady-state conditions (14 days of daily DRSP dosing) in three groups of female subjects with three levels of renal impairment (as determined by creatinine clearance, CC).

Serum potassium levels and serum DRSP levels were investigated in three groups (Group 1: CC >80 mL/min, n=11; Group 2: CC, 50-80 mL/min, n=10; and Group 3: CC, 30-50 mL/min, n=7) of female volunteers (age 30-65). The test drug, 3 mg DRSP, was administered once a day for 14 days. The pretreatment serum potassium levels were determined on three consecutive days, just prior to 14-days of DRSP regimen. The serum potassium levels at DRSP steady state condition were determined on the last three days of the DRSP regimen. The primary target variable was defined as the mean of each of these 3 measurements. In addition, repeated potassium determinations were performed for safety reasons. Blood samples for pharmacokinetics determinations were obtained just before (baseline) and on the last day of DRSP regimen and for 7-days thereafter.

The conclusion of the attached summary of serum potassium results is that, based on pre-database release figures, DRSP intake does not appear to show a clinically significant effect on the serum potassium concentration even in subjects with mild or moderate renal function impairment.

This study was conducted by our parent company, Schering AG, in Berlin, Germany. It began in October 1999 and ended very recently in March of this year.

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

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc085

Desk copy: Ms. Jeanine Best (cover letter)

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSP ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

ORIGINAL

BERLEX

TELEFAX
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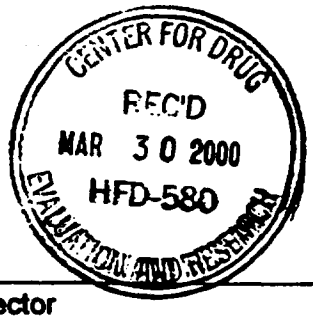
NEW CORRESP



Drug Development & Technology
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March 29, 2000

Susan Allen, M.D, MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
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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

NC

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to 3/17/00 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.

Reference is also made to our approvable letter dated March 17, 2000 (attached immediately following this cover letter for your reference). 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 deficiencies cited in the letter and described below.

The approvable letter states that the following will have to be addressed before the application may be approved:

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

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

As stated in our submission of January 6, 2000, Berlex plans to submit a DRAFT report of the study in renally-impaired patients entitled, "Open-Label Study To Assess The Effects Of 3 mg Drospirenone (DRSP) On Serum Potassium And To Evaluate The Pharmacokinetics Of DRSP In Female Volunteers With Impaired Or Normal Renal Function After Repeated Oral Administration Over 14 Days" (Protocol 303063), to the Division by the end of April 2000. Revised DRAFT labeling that includes the appropriate information from this study will be included in this submission, along with a request for a teleconference. The objective of the teleconference will be to discuss and resolve any issues with regard to the labeling previously submitted and the addition of the renal impairment data.

Following the teleconference, final DRAFT labeling will be prepared and submitted with the final report of the renal impairment study in mid May. The Division's minutes dated January 11, 2000 of the teleconference on January 4th to inform the sponsor of the anticipated action for the NDA and timeline expectations for information requests, study information requests and revised labeling, state that the final renal study results and finalized labeling will be reviewed in a 2-month time frame once submitted. We hope to accelerate this time frame through submission of the DRAFT study report and labeling at the end of April for your review. The final report will confirm the results submitted in the DRAFT report and we believe should not be substantially different from the DRAFT report.

The approvable letter also states that if additional information relating to the safety and effectiveness of the drug becomes available, that revision of the labeling may be required. Information on pregnancy outcome, ACE inhibitor interaction and NSAID interaction are noted. Berlex agrees to evaluate the information and revise the labeling should any of this information have an impact on the labeling.

In accordance with 21 CFR § 314.50 (d) (5) (vi) (b), a Safety Update Report is requested in the approvable letter by submitting all of the information we now have regarding YASMIN®. Ms. Jeanine Best of the Division confirmed for the undersigned in voice mail communications on March 22nd and 23rd, 2000, that Berlex could update the NDA with any new information that was obtained since the last period that was submitted in the previous Safety Update Report. The undersigned stated that Berlex would use the same format as was used in the previous report. **Berlex intends to submit this second Safety Update Report in April 2000.** The reporting period will be January 16 – March 17, 2000. 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.

In addition, Berlex acknowledges the following additional items noted in the approvable letter and provides these comments:

1. **Our submissions of February 28 and 29, 2000 were not reviewed in the current review cycle.**

   The February 28th submission provided a summary of serum potassium results from our ACE Inhibitor Study entitled, "A Double-Blind, Randomized, Two-Parallel Groups Study To Evaluate The Potential For Developing Hyperkalemia When The Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol Is Coadministered With An ACE Inhibitor In Postmenopausal Women" (Protocol 98106). Ms. Jeanine Best of the Division informed the undersigned on January 31st that this information is required for the hormone

replacement indication but not for the OC but, if available, the Division would like to see it. Therefore, it is understood that review of this submission should not affect the time frame for the approval of YASMIN.

The February 29th submission included revised electronic labeling [Physician Package Insert (PI), Brief Summary Patient PI and Detailed Patient PI] and container mock-ups (blister, day label, pouch and carton). Berlex incorporated into this DRAFT labeling of February 29th, comments received from the Division on February 18th, 23rd, and 28th in a timely manner with the understanding that, other than sections affected by results from the ACE inhibitor and renal impairment studies, this labeling would be reviewed during the current review cycle and included in the action package forwarded to the Office Director. Berlex was surprised to learn in the approvable letter that the labeling was not reviewed. It is important that Berlex receive comments on the sections of the labeling which are not affected by the ACE inhibitor and renal impairment study results as soon as possible. As stated previously, Berlex will request a teleconference to discuss the labeling.

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

Berlex will call to confirm receipt of this letter and to obtain tentative dates for a teleconference. However, in the meantime, should you require any additional information or have any questions, please feel free to call the undersigned 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/drpoc078

Desk copy: Ms. Jeanine Best (cover letter)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

UPS OVERNIGHT

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March 16, 2000

ORIGINAL

Susan Allen, M.D., MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
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U.S. Food and Drug Administration
5600 Fishers Lane
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ORIGINAL AMENDMENT

BS

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
DRAFT Statistical Analysis of Serum Potassium Data from ACE Inhibitor Study

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.

References are made to our teleconference on December 15, 1999 and the submission dated January 6, 2000. In the January 6th submission, Berlex provided a timeline as to the status of three studies outstanding at the time. The final report for the omeprazole drug interaction study was submitted on January 18, 2000. There are two remaining reports that need to be submitted, the ACE inhibitor study and the renal impairment study.

As committed in the January 6th letter, Berlex submitted on February 28th, a "Summary of Serum Potassium Results"[1] from the ACE Inhibitor Study. Berlex also committed in the January 6th letter to submit a DRAFT "abbreviated" report of the ACE Inhibitor study in mid March with the final "abbreviated" report coming at the end of March. As stated in the February 28th submission, Berlex consulted the Guideline for Industry entitled, "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" and recognized that it was using

[1] This document contained the serum potassium concentrations obtained from all of the subjects but the treatment group had not yet been defined. It did not include a description of statistical methods used in the study nor a statistical analysis.

the term "abbreviated" somewhat differently to describe the reports that would be submitted to the Division from the definition used in the guideline. The ACE Inhibitor study was originally conducted for the purposes of our HRT indication. As stated during the teleconference on December 15th, this study was conducted under [redacted] During this teleconference, the Division requested data from this study. Therefore, for the purposes of submission of this study, Berlex defines "abbreviated" as a report that is less than a full report and the emphasis is placed on the serum potassium data.

This submission amends NDA 21-098 to provide for a DRAFT abbreviated "Statistical Analysis of Serum Potassium Data" for the ACE Inhibitor study entitled, "A Double-Blind, Randomized, Two-Parallel Groups Study To Evaluate The Potential For Developing Hyperkalemia When The Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol Is Coadministered With An ACE Inhibitor In Postmenopausal Women" (Protocol 98106).

As described in the submission of February 28th, in this study, drospirenone (DRSP) 3 mg/estradiol (E2) 1 mg or placebo tablet was orally administered daily for fourteen days to mild hypertensive postmenopausal females maintained on 10 mg bid enalapril maleate therapy. Twenty-four (24) volunteers entered and completed this double-blind, randomized, two parallel groups study. Serum potassium concentrations were determined over a 24-hour period on pretreatment Day 1 (prior to the first DRSP/E2 dose) and on treatment Day 14 (after last treatment dose). In addition, a pre-morning dose single serum potassium determination was performed on pretreatment day 2 and treatment days 2, 4, 6, 8, 10, and 12 to continuously monitor serum potassium concentrations.

This study began in December of 1999 and the last subject completed on February 23, 2000. The study has been unblinded to the statistician only for the purposes of providing this statistical analysis of the serum potassium concentrations prior to database lock. Please note that the data listings have not been presented by treatment group in this DRAFT abbreviated report because the database is not yet locked. This information will be presented in the final abbreviated report planned for the end of this month.

Results of the statistical analysis of serum potassium log-transformed Cmax and AUC show that the 90% confidence intervals fell within the regulatory bioequivalence requirement of 80%-125%. The data supports the conclusion that there are no significant differences in serum potassium concentrations on day fourteen of administration of DRSP/E2 or placebo in mildly hypertensive postmenopausal women maintained on an ACE inhibitor.

---

[2] The protocol was submitted to the Division on November 16, 1999 (Serial No. 032)

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 E. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc074

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

BERLEX

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ORIGINAL

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March 15, 2000

Susan Allen, M.D, MPH, Acting Director
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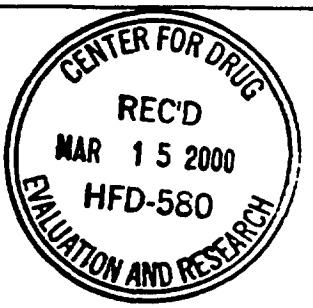

ORIG AMENDMENT
BS

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Request for Additional Creatinine and Potassium Data

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.

Reference is also made to our submission of March 9, 2000, which provided individual data and statistical tables for both creatinine and potassium from our pivotal European study, Report AI51, in response to the Division's request of March 6th for frequency distribution tables. Data were provided for subjects that 1) started the study with normal baseline values and ended the study with above normal values and 2) started the study with above normal values and ended the study with normal values. All of these data were provided for the study drug arm only, DRSP 3 mg/EE 0.030 mg tablets. Also in response to the Division's request, Berlex reported that of the subjects that started the study with normal baseline creatinine values and ended the study with above normal values, none doubled (or more) their creatinine values from baseline.

On March 13th, Ms. Jeanine Best of the Division informed the undersigned that the Office Director would like the same information that was provided in the March 9th submission provided in the same way for 1) the active control arm of the European study (Study 92052, Report AI51) and 2) the study drug arm for the uncontrolled US study (Study 96049, Report 98180). The Office Director also wanted to know if the active control in the European study has any antimineralocorticoid activity.

EUROPEAN STUDY

In response to Ms. Best's request, Attachment 1 contains the SAS output that has been compiled by our parent company, Schering AG, Berlin, Germany, for the European study (Study 92052, Report AI51). For both creatinine and potassium for the active control arm of the study (30 µg EE/150 µg desogestrel tablets, European trade name "Marvelon"), individual subject data as well as statistical tables are provided for subjects that 1) started the study with normal baseline values and ended the study with above normal values and 2) started the study with above normal values and ended the study with normal values. As with the March 9th submission, please note that with regard to the statistical tables, in cases where more than one measurement was done for a given visit, the maximum of the measurements of a subject at this visit was included in the calculations.

In summary, the attached tables indicate the following:

Creatinine

- 18 subjects started the study with normal values at baseline that rose to above normal at the end of the study. Of these 18 subjects, none doubled (or more) their creatinine values from baseline.
- 2 subjects started the study with above normal values that went to normal at the end of the study

Potassium

- 78 subjects started the study with normal values at baseline that rose to above normal at the end of the study
- 42 subjects started the study with above normal values that went to normal at the end of the study

In response to Ms. Best's question regarding antimineralocorticoid activity of Marvelon, to the best of our knowledge, Marvelon, marketed in the US by Organon under the trade name "Desogen", nor its active metabolite, 3-keto-desogestrel, have any antimineralocorticoid activity.

US STUDY

Attachment 2 contains the SAS output generated by Berlex Laboratories for the uncontrolled US study (Study 96049, Report 98180). The database was searched for both creatinine and potassium for DRSP 3 mg/EE 0.030 mg tablets for subjects fufilling the same criteria stated above and revealed the following:

Creatinine

- 0 subjects started the study with normal values at baseline that rose to above normal at the end of the study
- 0 subjects started the study with above normal values that went to normal at the end of the study

Potassium

- 1 subject started the study with a normal value at baseline that rose to above normal at the end of the study
- 0 subjects started the study with above normal values that went to normal at the end of the study

Transition tables confirming these subject numbers are provided as well as individual data for the one subject who started the study with a normal potassium value at baseline that rose to above normal at the end of the study is provided.

We trust that the information provided in this submission satisfies your request. Should you require any additional information or have any questions, 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/drpoc073

Desk copy: Ms. Jeanine Best (cover letter only)
Dr. Florence Houn

APPEARS THIS WAY
ON ORIGINAL

BERLEX

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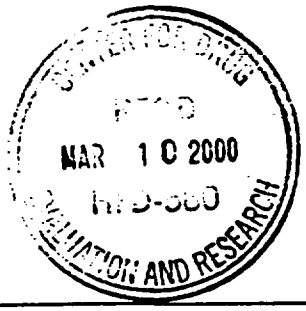
ORIGINAL



Drug Development & Technology
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March 9, 2000

Susan Allen, M.D, MPH, Acting 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
B2

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Response to Request for Frequency Distribution Tables

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.

Reference is also made to telephone conversations on March 6 and 7, 2000 between Ms. Jeanine Best of the Division and the undersigned. Ms. Best stated that the Office Director requested from our European study, Report AI51, frequency distribution tables for both creatinine and potassium for subjects that 1) started the study with normal baseline values and ended the study with above normal values (41 subjects for creatinine, 79 subjects for potassium) and 2) started the study with above normal values and ended the study with normal values (6 subjects for creatinine, 35 for potassium). Ms. Best asked that we provide the means at baseline and at the end of the study (last lab obtained), the subject counts for the above criteria and the number of creatinine subjects that doubled or more their values from baseline. She also asked that the tables be provided in SAS format.

In response to Ms. Best's request, the attached SAS output has been provided by our parent company, Schering AG, Berlin, Germany, who conducted the European study. Individual subject data has been included to review in conjunction with the statistical tables. Please note with regard to the statistical tables that in cases where more than one measurement was done for a given visit, the maximum of the measurements of a subject at this visit was included in the calculations.

The attached tables confirm the following subject counts quoted by Ms. Best on March 6th:

Creatinine

- 41 subjects started the study with normal values at baseline that rose to above normal at the end of the study
- 6 subjects started the study with above normal values that went to normal at the end of the study

Potassium

- 79 subjects started the study with normal values at baseline that rose to above normal at the end of the study
- 35 subjects started the study with above normal values that went to normal at the end of the study

In response to Ms. Best's question, there were no subjects that doubled (or more) their creatinine values from baseline.

We trust that the information provided in this submission satisfies your request. Should you require any additional information or have any questions, 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/drpoc068

Desk copy: Ms. Jeanine Best (cover letter only)
Dr. Florence Houn

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

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ORIGINAL

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March 3, 2000

Susan Allen, M.D, MPH, Acting 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
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Rockville, Maryland 20857-1706

NEW CORRESP

NC

Dear Dr. Allen:

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

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.

Reference is also made to a telephone conversation between Ms. Lana Pauls of the Division and the undersigned on February 23, 2000. During this conversation, Ms. Pauls informed the undersigned that financial disclosure information is needed for the foreign investigators. Ms. Pauls acknowledged the financial certification for the US study that appears in Item 19 of NDA 21-098. Ms. Pauls noted our statement that Berlex is working with our parent company, Schering AG, trying to obtain financial information for over 100 European investigators. In addition to these studies, Ms. Pauls requested that we update the financial disclosure form to include investigators for the renal impairment study. Ms. Pauls stated that the Division had elevated this study to pivotal status.

In response to Ms. Pauls' request, attached are two Forms FDA 3454. One form covers the two studies below:

Study Number	Report Number	Study Title
92052	A151	A multicenter, open-labeled, randomized study on cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 26 cycles under long term- contraceptive use
93044	AJ06	Study of cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 2100 healthy women over 13 cycles of contraceptive use

The second form covers the renal impairment study identified below. Since financial disclosure was already completed for the above studies prior to this request, another financial disclosure form was completed for the renal impairment study.

Study Number	Report Number	Study Title
303063	Not available	Open-label study to assess the effects of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days

All of these studies were conducted by our parent company, Schering AG, in Berlin, Germany

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/drpoc062

Desk copy (cover letter): Ms. Lana Pauls
Ms. Jeanine Best

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

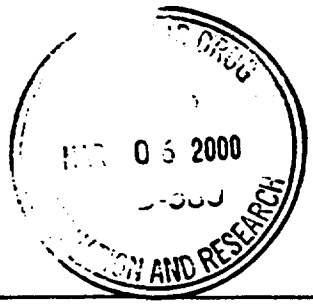
BERLEX

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

March 2, 2000



ORIGINAL

Susan Allen, M.D, MPH, Acting 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
BM

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Miscellaneous Clinical Review Questions

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.

Reference is also made to a telephone conversation between Ms. Jeanine Best of the Division and S. Brown on February 29th, 2000. During this conversation Ms. Best communicated questions regarding congenital anomalies from two pregnancies from Study 93044, Report number AJ06, entitled, "Study of cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 2100 healthy women over 13 cycles of contraceptive use". The medical officer was seeking additional information regarding subject 1721 who delivered a baby with coarctatio aortae and subject 198 who delivered a child with esophageal artresia. Our parent, Schering AG provided the following responses.

Subject 1721

4/24/ 95 day of stop study medication (according to "documentation of drug failure ")
4/25/ 95 projected time of conception
5/12/ 95 day of diagnosis pregnancy by urine analysis
5/18/ 95 confirmed pregnancy by transvaginal ultrasound
12/28/95 delivery

According to the documentation, pregnancy occurred one day after last tablet intake . There is a typing error in the research report (tablet-taking interval April 4 - April 26 instead of April 24 as stated in the documentation). As requested, a copy of the case report form for this subject is attached.

Subject 198:

4/4/95 day of diagnosis pregnancy by β-HCG Test

We are attempting to obtain additional follow up information regarding these cases; we will submit any additional information, if obtained.

We trust that the information provided in this submission addresses your 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,

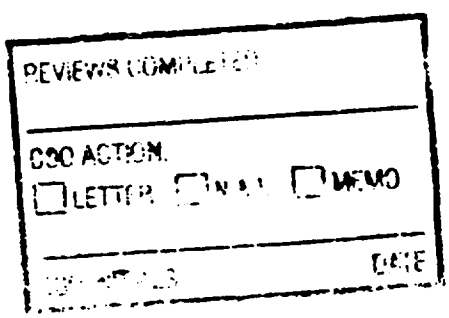
BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc064

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL



BERLEX

TELEFAX
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ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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Telephone: (973) 276-2000

February 29, 2000

Lisa Rarick, M.D., Director
DIVISION OF REPRODUCTIVE AND UROLOGIC ORIG AMENDMENT
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

BL

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Revised Labeling and Container Mock-ups

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.

On January 14, 2000, Berlex Laboratories submitted to the Division a revised electronic copy of the YASMIN Physician Package Insert (PI) in Word format, incorporating the Division's first round of comments received up to that date. On February 18th, Ms. Jeanine Best of the Division forwarded via telefax to the undersigned a second round of comments on the revised PI. These comments included the Pharmacology reviewer's comments on our separate Pharmacology/Toxicology section of the PI submitted to the Division on February 4th (this separate section was requested by the reviewer on January 18th). Additional Biopharmaceutical comments were telefaxed on February 23rd. On February 28th, Ms. Best telefaxed a corrected copy of the Pharmacology/Toxicology section of the PI which replaced the copy telefaxed on February 18th. This corrected copy allowed for the elimination of the separate Pharmacology/Toxicology section and transferred the Pharmacology/Toxicology information provided in that section (including comments from the Division) to the CARCINOGENESIS and PREGNANCY sections of the PI under **PRECAUTIONS**. On February 24th, Ms. Best informed the undersigned that a revised PI should be submitted to the Division early as possible during the week of February 28th as it would be included in the action package being sent to the Office early during that week.

During a teleconference on February 23rd between the Division and Berlex representatives to discuss the expiration dating period for YASMIN, Dr. Suong Tran, Reviewing Chemist, requested mock-ups of all YASMIN product containers. On February 24th, the undersigned

informed Ms. Best that this was an unexpected request and the mock-ups would most likely be submitted on February 28th, if they were completed. Ms. Best told the undersigned that the mock-ups were also needed for the action package for the Office.

Electronic Labeling

This submission amends NDA 21-098 to provide for a revised electronic Physician PI reflecting all of the Division's comments to date. Also revised and included in electronic format are the Brief Summary Patient PI and Detailed Patient PI. For your information, editorial changes have been made to the Brief Summary Patient PI and Detailed Patient PI since their initial submission on December 3rd, 1999. These electronic copies of the labeling are provided in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 21/28 TABLETS Labeling" dated February 29, 2000 (see Attachment 1).

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. Please note that electronic copies of the Division's comments provided via the Internet by Ms. Best to the undersigned on February 23rd and 28th were used to generate the strike out version.

Berlex Laboratories certifies that the diskette provided herewith was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created January 26, 2000.

Please note the following when reviewing the strike out version of the labeling:

GENERAL

Berlex changes appear in italic font

PRECAUTIONS: CARCINOGENESIS and PREGNANCY

In addition to the editorial changes Berlex has proposed, Berlex is providing justification for changes with a scientific basis:

- **9. Carcinogenesis:**

Berlex disputes the following statement and proposes that it be removed:

The increased incidence of pituitary adenomas observed in mice given all doses of the combination of drospirenone and ethinyl estradiol is attributed to the ethinyl estradiol component of the combination. In general, the incidence of pituitary adenomas observed in mice given the combination of drospirenone and ethinyl estradiol is less than that observed in the groups of mice given ethinyl estradiol alone (See table which follows). This, coupled with a very low incidence of pituitary adenomas in animals given drospirenone alone indicates that this is an estrogenic effect. This is also consistent with information in the literature (Heywood R, Wadsworth PF. The experimental toxicology of

estrogens. In: Chaudhury RR (ed). *Pharmacology of Estrogens*. New York, New York:Pergamon Press, 1981;63-80.)

Incidence of Pituitary adenoma									
Control	Combination			E2 alone			DRSP alone		
4/110	11/55	13/54	23/55	7/55	27/55	41/55	1/54	0/55	0/55

Berlex disputes the following statement and proposes that it be removed:

"...

The incidence of hepatocellular adenoma in groups of animals given drospirenone alone was low and not significantly different than controls [0/55 (0%), 0/55 (0%) and 1/55 (2%) in the animals given the low-, mid- and high-doses, respectively, versus 1/110 (1%) in the controls].

10. Pregnancy

Berlex disputes the following statement and proposes that it be removed:

The historical normal range for this finding in Han:Wistar rats at Schering AG is 0.7% to 34.1% of fetuses/group. Although the incidence for this finding in this study was significantly greater than controls, the incidence (6.1%) is within the historical range at the testing laboratory and therefore not noteworthy. Historical range data is available upon request.

ADVERSE REACTIONS

With regard to the following statement in this section, "The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related", the Division states that the adverse reactions that follow the statement are not listed in order of frequency. In response, Berlex has not changed this section as this information is class labeling, is not available to Berlex, and appears in this order in all other marketed OCs. Berlex agrees to revise this section if the Division provides the pertinent information.

Please note that in accordance with previous procedure, and in the interest of time, the revised version of the Physician PI was also sent to Ms. Best via the Internet today.

Container Mock-ups

Per Dr. Tran's request on February 23rd, this submission also amends NDA 21-098 to provide for mock-ups (e.g. artwork and colors, per Ms. Best) of all YASMIN containers. The following are provided in Attachment 2:

1. Blister
2. Day Label
3. Pouch
   - Sample pouch
   - Trade pouch
4. Carton
   - Single unit carton
   - Outer carton (holds 3 units)

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.

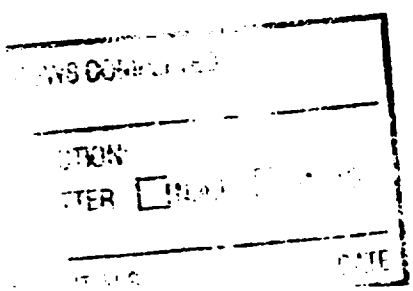
Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc058

Desk copy: Ms. Jeanine Best



ORIGINAL

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BERLEX

ORIG AMENDMENT

BB

Drug Development & Technology
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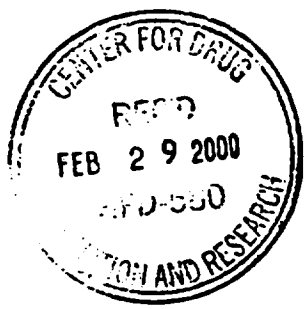
February 28, 2000

Susan Allen, M.D., MPH, Acting 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



Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
Data from ACE Inhibitor Study

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.

References are made to our teleconference on December 15, 1999 and the submission dated January 6, 2000. In that submission, Berlex provided a timeline as to the status of three studies. The final report for the omeprazole drug interaction study was submitted on January 18, 2000. There are two remaining reports that need to be submitted.

As agreed in the January 6 letter, Berlex is submitting the potassium data from the ACE Inhibitor Study. The draft abbreviated report of this study is scheduled for submission in mid March with the final abbreviated report coming at the end of March. Berlex has consulted the Guideline for Industry entitled, "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications". It is recognized that Berlex is using the term "abbreviated" somewhat differently from the definition in the guideline. The ACE Inhibitor study was originally conducted for the purposes of our HRT indication. As stated during the teleconference on December 15th, this study was conducted under ——— . For your reference, the protocol was submitted on November 16, 1999 (Serial No. 032). During this teleconference, the Division requested data from this study. Therefore, for the purposes of submission of this study, Berlex defines

"abbreviated" as a report that is less than a full report and the emphasis is placed on the serum potassium data.

ACE Inhibitor Study: "A Double-Blind, Randomized, Two-Parallel Groups Study To Evaluate The Potential For Developing Hyperkalemia When The Hormone Replacement Therapy Combination Drug Product Drospirenone/Estradiol Is Coadministered With An ACE Inhibitor In Postmenopausal Women" (Protocol 98106)

In this study, drospirenone (DRSP) 3 mg/ estradiol (E2) 1 mg or placebo tablet was orally administered daily for fourteen days to mild hypertensive postmenopausal females maintained on 10 mg bid enalapril maleate therapy. Twenty-four (24) volunteers entered and completed this double-blind, randomized, two parallel groups study. Serum potassium concentrations were determined over a 24-hour period on pretreatment Day 1 (prior to the first DRSP/E2 dose) and on treatment Day 14 (after last treatment dose). In addition, a pre-morning dose single serum potassium determination was performed on pretreatment day 2 and treatment days 2, 4, 6, 8, 10, and 12 to continuously monitor serum potassium concentrations.

The clinical portion of the study was recently concluded, thus the study has not yet been unblinded. The attached document is intended to serve as a summary report of the serum potassium concentrations obtained from all subjects. There were no serious adverse events reported; no subject was discontinued from the study and there were no deaths. Although data have not been grouped by treatment, examination of individual serum potassium data from all volunteers does not reveal any evidence of hyperkalemia for the duration of the study. The results clearly support the conclusion that when DRSP is administered in the presence of a potassium sparing drug such as an ACE inhibitor, there is no risk of developing hyperkalemia.

The results of the serum potassium data from the ACE inhibitor interaction study support the claim that the antialdosterone activity of DRSP in the investigated dosage is not similar to that of spironolactone. Although DRSP effect on serum potassium was evaluated in postmenopausal women, the same results would be applicable to a younger population. This is because YASMIN contains the same dose of 3 mg DRSP as the DRSP/E2 HRT product and the fact that the older postmenopausal population is even more susceptible to alterations in fluid/electrolyte balance.

Further evidence that differentiates DRSP from spironolactone will be forthcoming from the ongoing study in renally impaired patients (Protocol 303063) which is evaluating the risk of hyperkalemia in a patient population with limited excretory capacity for potassium. However, we believe that the ACE inhibitor study is a more relevant test for the antialdosterone activity of DRSP compared to the renal study. This is because the former evaluates DRSP effect on serum potassium when given concomitantly with an ACE inhibitor which has been associated with severe hyperkalemia when given with potassium-sparing diuretics whereas the renal study evaluates the excretory reserve capacity of the kidneys with regard to potassium in patients with mild / moderate renal insufficiency.

The study began in December of 1999 and the last patient completed on February 23, 2000. An archival and review copy of this summary are being provided in one volume.

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/drpoc055

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ MEMO

CSO [illegible] DATE

ORIGINAL

BERLEX

TELEFAX
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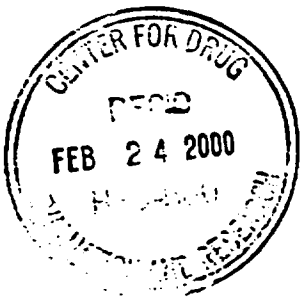

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

February 23, 2000

ORIG AMENDMENT

CC

Susan Allen, M.D, MPH, Acting 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

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Follow up Information from Today's Teleconference Regarding Expiration Dating

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.

Reference is also made to the teleconferences between Division and Berlex representatives on February 22nd, 2000 and today to discuss the expiration dating for YASMIN tablets.

As requested by Dr. Moo-Jhong Rhee of the Division and as agreed during today's teleconference, attached please find a comparison of the manufacturing process at the pilot plant (SAG Berlin, Germany) and the final production site (Schering GmbH und Co. Produktions KG, Weimar, Germany). An earlier version of this comparison was telefaxed to the Division during the teleconference and was discussed. Dr. Rhee requested additional information regarding the process parameters for Step 2 ——— , and Step 8 ——— in the table. This information has been incorporated into the attached table which now replaces the version discussed during the teleconference.

We believe that this comparison provides the strong link between the pilot and production scale batches which Dr. Rhee required in order for the pilot scale data to support the proposed expiration ———

We trust that the information provided in this submission addresses all of your concerns. Please call me immediately at (973) 276-2305 if you require any additional information or have any questions regarding this submission. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc050

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

DSD ACTION

☐ LETTER ☐ N.A.I. ☐ MEMO

BERLEX

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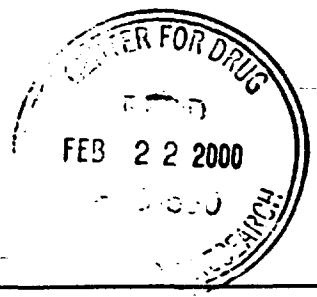

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
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February 18, 2000

Susan Allen, M.D, MPH, Acting 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

ORIGINAL

BZ

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Documentation of Dissolution Specification Agreement;
Response to Miscellaneous Biopharmaceutical and Chemistry Review Questions

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.

Reference is also made to our submission of January 28, 2000 which contained our responses to the Division's comments and information requests that resulted during the review of the Chemistry section of our NDA. These comments were communicated in the Division's letter of December 16, 1999.

Additional reference is also made to the teleconference of February 11, 2000 between Division and Berlex representatives to discuss Chemistry and Biopharmaceutics issues, which included discussion of the January 28th submission. Division minutes of this teleconference were telefaxed to Berlex on February 14th. (The minutes are provided immediately following this cover letter for your reference.) This submission addresses all outstanding issues from the February 11th teleconference and Division minutes of February 14th.

Reference is also made to a voice mail message from Dr. Suong Tran, Chemistry Reviewer, to the undersigned, received this afternoon, regarding the expiration date for YASMIN. The response to Dr. Tran's question is also provided in this submission.

Dissolution Specification

In the January 28th submission, which included 18 month stability data on three production scale lots, Berlex proposed a dissolution specification of —— % at 30 minutes for DRSP and EE. During the February 11th teleconference, Dr. Venkat Jarugula, Biopharmaceutics Reviewer, questioned this specification, stating that at 20 minutes the dissolution profile of DRSP indicates an —— release. Following the teleconference, the Biopharmaceutics and Chemistry reviewers conferred and proposed the following specifications, communicated by Ms. Jeanine Best of the Division to the undersigned on February 14th:

DRSP: Q = —— % at 30 minutes, **EE:** Q = —— % at 30 minutes

On February 17th, the undersigned communicated to Ms. Best in a voice mail message that Berlex agreed to the specification for DRSP but was very concerned about the EE specification because of the variability in dissolution results for individual tablets that has been seen after 18 months time. Berlex proposed a specification of Q = —— % at 30 minutes for EE. That same afternoon, Ms. Best left a voice mail message for the undersigned stating that the Division accepted Berlex's counter proposal for the dissolution specifications as follows:

DRSP: Q = —— % at 30 minutes, **EE:** —— % at 30 minutes

Per Ms. Best's request, agreement on these specifications between Berlex and the Division is documented here and has also been telefaxed to the Division today. Also per Ms. Best's request, all outstanding issues from the February 11th teleconference are being addressed in this submission.

Release Testing for Impurities and Decomposition Products

In the Division's letter of December 16th, release specifications including testing for impurities and degradation products were requested (Comment 9). Berlex stated in the January 28, 2000 response that it was shown during the development of YASMIN Tablets that the pharmaceutical manufacturing process does not lead to any decomposition of both drug substances. Schering AG, therefore, intended to omit testing for decomposition products in the drug product release specification.

During the teleconference on February 11th, Dr. Tran, stated that although DRSP appears to be stable, EE is not and because YASMIN is a new molecular entity, release testing for impurities and decomposition products must be implemented to assess any future change in the manufacturing process. Berlex stated that nothing had been seen from DRSP on accelerated and stress testing which shows any case of degradation products increasing. Although comfortable with the current specifications, Berlex agreed with Dr. Tran's suggestion to monitor the first 10 lots and submit the results in a supplement. The results would be reviewed at that time to possibly omit this release testing in the future.

Berlex will revise Quality Specification No. K280E280 to include release testing for impurities and decomposition products.

Labeling

During the teleconference on February 11th, Berlex agreed to accommodate Dr. Tran's requests with regard to labeling, as noted in the minutes of February 14th and stated below:

- Blister label should contain lot and expiration date (Question #19 from submission of January 28th)

  Immediately following this cover letter is a revised blister label for YASMIN 21 and 28 TABLETS which includes an imprinting area for the lot number and expiration date.

- In Attachment 10 of the amendment, there is a typing error in the unit carton label for the 21 day dose; submitted carton states "28 days" (Question #20 from submission of January 28th)

  Following the revised blister label described in the bullet above is a revised single unit carton label for YASMIN 21 TABLETS which corrects the typographical error. This label is provided as both a marked and unmarked version.

Expiration Date

This afternoon Dr. Tran left a voice mail message for the undersigned asking that it be confirmed that the expiration date for YASMIN starts from the date of manufacture and not from the date of packaging. Berlex confirms that the expiration dating period for YASMIN tablets begins with the date of manufacture.

We trust that the information provided in this submission addresses all of your 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
Manager
Drug Regulatory Affairs

NFV/letter/drpoc047

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BERLEX

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Division of Berlex Laboratories, Inc.

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February 17, 2000

ORIG AMENDMENT

05

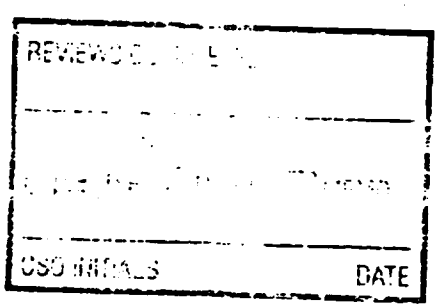
Susan Allen, M.D, MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Miscellaneous Biopharmaceutics Review Questions

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.

Reference is also made to the teleconference of February 11, 2000 between Division and Berlex representatives to discuss Chemistry and Biopharmaceutics issues. Division minutes of this teleconference were telefaxed to Berlex on February 14th. (The minutes are provided immediately following this cover letter for your reference.) Additional reference is made to telephone conversations between Ms. Jeanine Best of the Division and the undersigned on February 14th and 15th during which Ms. Best communicated additional miscellaneous questions from the Biopharmaceutics Reviewer on our NDA. This submission provides responses to all outstanding Biopharmaceutics review questions provided to Berlex in these communications.



QUESTION 1

As discussed during the February 11th teleconference, the Division asks for the following information regarding the two major metabolites of DRSP[1], as stated in their minutes of February 14th:

- **The enzyme responsible for the formation of these two metabolites should be characterized; if not formed in *in vitro* studies, then not P450 dependent process; Division cannot find control to support sponsor's statement; sponsor to provide more in-depth report early next week**

Our response is provided below.

In-Depth Evaluation of Involvement of CYP450 Enzymes in the Biotransformation of DRSP: the formation of two metabolites: ZK 151414 (acid form after opening of lactone ring), and ZK 202313 (sulfate conjugate)

Subsequent to the in vitro study included in the NDA (Report AY74, NDA Vol. 51, page 6 04521), our parent company, Schering AG, Berlin, Germany, conducted an additional study to further characterize the role of specific liver cytochrome P450 isoenzymes (CYP) in the biotransformation of DRSP (see Report B186[2], provided in Attachment 1). Genetically engineered V79 cells expressing single CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 were used in this in vitro study. Non-transfected V79 cells served as a control.

Radiolabelled DRSP, acid derivative ^{14}C-ZK 152973 (sodium salt of ZK 151414) and isomer ^{14}C-ZK 35096 of DRSP were each incubated with the live V79 cells expressing individual CYP isoenzymes and with non-transfected V79 cells. Formation of metabolites was investigated using [redacted]. The elution pattern of the 4-5 metabolites formed in various cell preparations indicated that DRSP did not exhibit substrate specificity towards human CYP1A2, 2A6, 2C9, 2C19, 2D6 and 2E1. All these cells lines exhibited a similar elution profile as compared to the non-transfected V79MZ cell line. The cell line expressing CYP3A4 exhibited a different metabolic pattern compared to the V79MZ and other cell lines. Two more polar metabolites, M4 (3%) and M5 (6-12%), were observed. (Note: these metabolites, however, were not observed in the human plasma). The metabolite M2 was observed in all test systems, including CYP3A4 and V79MZ cell lines, suggesting that its formation is not a CYP450 dependent process. The metabolite M2, which showed similar chromatographic retention behavior as the acid form of DRSP, ZK 151414 (opening of lactone ring), is one of the two main metabolites found in the human plasma.

Overall Summary: Pathways and Enzymes in DRSP Biotransformation

The biotransformation scheme of DRSP is shown in Figure 1 (see Attachment 2). The metabolic pathways and enzymes involved are derived from the structures of the observed metabolites

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[1] Please note that Report B283 was submitted to the NDA on February 10, 2000, confirming for the Biopharmaceutical Reviewer that these two metabolites are not pharmacologically active. As stated in the Division's minutes of February 14th, this information is currently under review.

[2] This study was conducted by Schering AG, Berlin, Germany, was received after submission of our NDA, and was therefore not included.