1. **Mfg. Report Number 01/00397-GBD, submitted to [redacted] April 30, 2001. This was a 39 year old woman who experienced "heart cramps", angina-like complaints, arrhythmia and furuncle on her face. Was the arrhythmia documented? Is there an EKG?**

   Additional information regarding this case was recently received and is included in the attached follow up MEDWATCH form dated May 4, 2001 that will be submitted to INDs [redacted] On May 3rd, Schering AG spoke with the woman's gynecologist by phone who stated that the woman did not contact a physician when she suffered from her complaints during a weekend, although she told her gynecologist that the complaints were life threatening. Therefore, no EKG, lab data or diagnostic test results are available. The woman has no underlying diseases (no cardiac diseases, no other diseases). The gynecologist reported that the woman suffered from acne on the face and back which showed tendency to develop into furunculosis (data are contradictory to the initial report). However, no treatment was performed. The woman did not suffer from fever.

   No more information is available and the case is now closed.

2. **Mfg. Report Number 01/00394-GBD, submitted to [redacted] on April 30, 2001. This woman experienced an epileptic seizure. Are any hospital records available? We would like to determined if there was anything else going on with the woman that the seizure might be attributed to.**

   Schering AG has been making every effort to obtain additional information regarding this case since the original request on May 2nd. Any information that is obtained will be forwarded to you immediately upon receipt.

3. **Mfg. Report Number 01/00373-GBD, submitted to [redacted] on April 27, 2001. This 33 year old woman experienced visual field defect, speech disturbances, numbness in the right arm, mouth and nasal area, tingling, and severe dizziness. Is there any further medical information available?**

   Schering AG has been diligent in trying to contact the woman on many occasions since May 2nd, but to date has been unable to obtain her agreement to contact her physicians to obtain additional information. As you know, in Germany, if the individual or family refuses to provide this authorization, there is nothing else that can be done to obtain the patient's medical records. If the authorization is received and any additional information is obtained, it will be forwarded to you immediately.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copies: Dr. Scott Monroe
Ms. Jeanine Best

NFV/letter/drpoc172

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BERLEX

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
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May 7, 2001

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

NC
NEW CORRESP

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Clinical Information Request of
May 4, 2001

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000.

Reference is also made to our submission of November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. The November 6th submission contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under ———, and 96097 (an endometrial protection study conducted under ———. The Medical Officer requested information in order to continue his review of the November 6, 2000 submission and NDA 21-098 in six Clinical Information Request Letters. The dates of the requests and the Berlex responses are summarized in the table below:

Date of Clinical Information Request Letter	Date of Berlex Response
December 12, 2000	January 5, 2001
February 2, 2001	February 12, 2001
February 20, 2001	March 9, 2001
March 1, 2001	March 12, 2001
March 7, 2001	March 16, 2001
April 4, 2001	April 9, 2001

Further reference is made to the Clinical Information Request Letter of May 4, 2001 which contained one comment (provided immediately following this cover letter for your reference). This additional information was requested in order to continue review of the NDA. Provided below is our response to this seventh clinical information request. The item requested in the May 4th letter is identified in bold font, followed by our response.

Please provide tables for the distribution of maximum changes in serum potassium levels from baseline for the HRT study:

1. **Population 1 – all subjects – same population as for Table 1 (March 9, 2001 Response)**

2. **Population 2 – on-treatment subjects – same population as for Table 3 (March 0, 2001 Response)**

For each population provide the percentage of subjects with the following serum potassium level changes (similar to Text Table 16 in March 16, 2001 Response):

<-1.5
-1.5 to <-1.0
-1.0 to <-0.5
-0.5 to <-0.1
-0.1 to <0.1
0.1 to <0.5
0.5 to <1.0
1.0 to <1.5
≥1.5

Attached are the following tables:

Table 1: Change from Baseline in Maximum Post Baseline Serum Potassium Values
All Serum Potassium Values

Table 2: Change from Baseline in Maximum Post Baseline Serum Potassium Values
Serum Potassium Values Taken during the Treatment or Within 24 hours

Conclusion:

There is no dose dependent distribution of changes in maximum post baseline serum potassium values. It is noteworthy that all of the subjects receiving the highest dose of DRSP exhibited changes in serum potassium of < 1.5 meq/L. Clearly, there is no DRSP dose dependent trend towards larger shifts in serum potassium levels and there remains no trend towards increased serum potassium levels during treatment with E2/DRSP whether the subject is also taking a NSAID or ACE inhibitor.

This further analysis is consistent with all the data previously submitted to the NDA. The overall conclusion from our Safety Report for HRT Study 96097 submitted on November 6, 2000 remains unchanged, there is no evidence that DRSP causes or contributes to any clinically relevant hyperkalemia.

With this submission, Berlex has responded to all Clinical Information Request letters to date.

In addition, our response to miscellaneous clinical requests communicated by telephone on March 28th by Ms. Jeanine Best of the Division to the undersigned were submitted on April 4th. On March 30th, our response to the Chemistry Request of February 28th was submitted. Clarification of this submission by the Division was received in a telefax dated April 4th. Financial disclosure information for investigators participating in Studies 97036 and 96097 requested by Ms. Kim Colangelo of the Division on April 5th was submitted on April 9th. Ms. Jeanine Best of the Division informed the undersigned on April 12th that the submission was satisfactory and the Financial Disclosure review was finalized.

Please note that on May 2nd, Ms. Best requested by telephone additional information regarding three IND Safety Reports for serious adverse events (AEs) which occurred in women taking Yasmin in Germany and came to our attention as spontaneous, postmarketing reports from our parent company, Schering AG, Berlin, Germany. These AEs were recently submitted to the Yasmin 30 and Yasmin respectively. As communicated to Ms. Best in a telephone conversation today, follow up information on one of the cases, Mfg. Report Number 01/00397-GBD, will be submitted today. Additional information on the remaining two cases, Mfg. Report Numbers 01/00394-GBD and 01/00373-GBD, is being actively pursued with Schering AG and will be submitted immediately upon receipt.

As you know Berlex is expecting approval on May 11, 2001 of this application and will be available immediately to address any issues that may need further clarification.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copies: Dr. Scott Monroe
Ms. Jeanine Best

NFV/letter/drpoc170

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BERLEX

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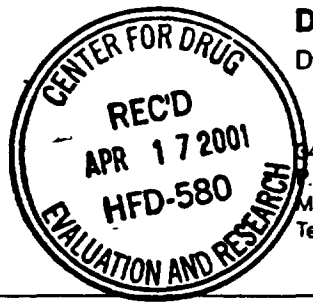
April 16, 2001 ORIGINAL



Susan Allen, M.D, MPH, Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
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BM
ORIG AMENDMENT

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Follow up to April 9, 2001 Submission:
Referenced Publication

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000.

Reference is also made to our submission of November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. The November 6th submission contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under ———) and 96097 (an endometrial protection study conducted under ———). Additional reference is made to the third Safety Update Report for NDA 21-098 dated March 27, 2001.

The Medical Officer requested information in order to continue his review of the NDA in six Clinical Information Request Letters. The dates of the requests and the Berlex responses are summarized in the table on the following page.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Date of Clinical Information Request Letter	Date of Berlex Response
December 12, 2000	January 5, 2001
February 2, 2001	February 12, 2001
February 20, 2001	March 9, 2001
March 1, 2001	March 12, 2001
March 7, 2001	March 16, 2001
April 4, 2001	April 9, 2001

Specific reference is made to our response to the April 4th Clinical Information Request dated April 9th. In Comment 2. a), you asked that we provide the basis for our statement that the number of events is lower than expected based on actual experience with reported numbers of thromboembolic adverse events and deaths during a comparable period following the launch of other combination oral contraceptives. Our response included a reference to an abstract which was included in the April 9 submission. We committed to provide under separate cover the full publication for this abstract entitled, "Oral Contraceptives and Venous Thromboembolic Disease. Analyses of the UK General Practice Research Database and the UK MediPlus Database", Human Reproductive Update 5: 688-706, 1999.

Attached you will find a copy of the publication.

For your information, Berlex has responded to all Clinical Information Requests to date. In addition, our response to miscellaneous clinical requests communicated by telephone on March 28th by Ms. Jeanine Best of the Division to the undersigned following a status meeting on that day were submitted on April 4th. On March 30th, our response to the Chemistry Request of February 28th was submitted. Clarification of this submission by the Division was received in a telefax dated April 4th. Financial disclosure information for investigators participating in Studies 97036 and 96097 requested by Ms. Kim Colangelo of the Division on April 5th was submitted on April 9th. Ms. Jeanine Best of the Division informed the undersigned on April 12th that the submission was satisfactory and the Financial Disclosure review was finalized. In summary, all requests from the Division have been answered.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy: Dr. Scott Monroe
Cover Letter: Ms. Jeanine Best

NFV/letter/drpoc062

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April 9, 2001

Susan Allen, M.D, MPH, Director
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ORIG AMENDMENT

BM

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Clinical Information Request of April 4, 2001

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000.

Reference is also made to our submission of November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. The November 6th submission contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under ———) and 96097 (an endometrial protection study conducted under ——— . The Medical Officer requested information in order to continue his review of the November 6, 2000 submission in five Clinical Information Requests Letters. The dates of the requests and the Berlex responses are summarized in the table below:

Date of Clinical Information Request Letter	Date of Berlex Response
December 12, 2000	January 5, 2001
February 2, 2001	February 12, 2001
February 20, 2001	March 9, 2001
March 1, 2001	March 12, 2001
March 7, 2001	March 16, 2001

Additional reference is made to our third Safety Update Report dated March 27, 2001. The Safety Update contained information on spontaneous reports from marketing experience with Yasmin in Germany from November 2000 – March 1, 2001. Specific reference is made to the one case of death that was included that, at the time, was suspected to be due to pulmonary embolism. This case was originally reported to the Division in a telephone conversation on March 21st between Ms. June Bray of Berlex and Dr. Susan Allen. As required, IND Safety Reports for this case were submitted to the Yasmin 30 [redacted] (Serial No. 038) and Yasmin 20 [redacted] (Serial No. 003) on March 29th which contained some additional information that was obtained after submission of the Safety Update.

Further reference is made to the Clinical Information Request Letter of April 4, 2001 which contained three comments (provided immediately following this cover letter for your reference). This additional information was requested in order to continue the review of NDA 21-098. Provided below is our response to this sixth clinical information request. Each of the items requested in the April 4th letter is identified in bold font, followed by our response.

1. **The Division is concerned about the recently reported death in a woman during her second treatment cycle with Petibelle, in part, because the actual cause of death is not well documented in the information provided to date. Although the death is attributed to a pulmonary embolus, other causes of death such as a cardiac arrhythmia secondary to an electrolyte disorder do not appear to have been excluded. The Division requests that you continue to pursue all options to obtain additional information regarding the cause of death. Is a death certificate available? Are there any records from her emergent medical treatment such as an ECG report or serum electrolytes?**

   As a result of extreme efforts and persistence by our parent company, Schering AG, Berlin, Germany, further information regarding this case was obtained on April 6th. Two contact reports are provided in Attachment 1. The first contact report is written by Juergen Dinger, MD, Head of Development, FC/HT, Schering AG, Berlin. Dr. Dinger pursued contacts to the treating hospital (Regional Hospital, Rastatt, Head Physician, Professor Keller) and the treating physician (Dr. Schmitt-Kloppel). The second contact report by Dr. Felsch, a member of the Drug Safety Department at Jenapharm, a subsidiary of Schering AG, contains information obtained from Dr. J. Bielawski, the woman's gynecologist that prescribed Petibelle.

   The information from the treating hospital suggests that this patient had a chronic disease, which is in contrast to the original information obtained from the prescribing gynecologist. According to the current information, the patient most likely had **chronic** cor pulmonale. The etiology seems to be obesity (body weight >100 kg and small statue) causing alveolar hypoxia leading to pulmonary hypertension and right ventricular hypertrophy (Echocardiography: signs of chronic cor pulmonale and possible right ventricular hypertrophy). The patient may also have been a smoker. The patient became unconscious during the transport to the hospital. The patient was resuscitated in the emergency room and transferred to the Intensive care Unit. The EKGs showed no changes associated with hyperkalemia.

The patient died one or two days later due to cardiovascular failure with hypoxic brain damage. The treating hospital physician thinks that myocardial infarction is a more likely diagnosis than pulmonary emboli, but since the family refused autopsy, the diagnosis will remain unknown. The cause of death as it appears on the death certificate is "myocardial infarct".

2. **In your Safety Update of March 28, 2001 (Item 1.4.5), you stat that approximately [redacted], of Yasmin (Petibelle) have been sold. You also state that "the number of thromboembolic events is lower than expected in the estimated population receiving the drug during the initial marketing period."**

   a) **Please provide the basis for your statement that the number of events is lower than expected based on actual experience with reported numbers of thromboembolic adverse events and deaths during a comparable period following the launch of other combination oral contraceptives.**

   While it is not possible to provide precise comparisons, the reported incidence rates for idiopathic venous thromboembolic events (VTE) were 4.1/10,000 exposed women years and 4.2/10,000 exposed women years in two large European data base studies (see publication and abstract provided in Attachment 2, Am J Obstet Gynecol 179:S78-86, 1998; Human Reproductive Update 5: 688-706, 1999; respectively). Using a VTE rate of 4.1/10,000 we would expect 14.6 VTEs in the projected 214,000 women exposed to Yasmin/Petitbelle for 2 cycles. (A copy of the full publication for the abstract provided in Attachment 2 will be provided under separate cover.)

   b) **Please provide information on the likely relationship between sales and actual patient use in the countries to which the number of [redacted] refers. How many patients are likely to have been treated with Yasmin (Petibelle) for at least two treatment cycles during the period from product launch and 1 March 2001?**

   The number [redacted] Yasmin and Petibelle in Germany from the time of launch (November 2000) through February 2001. In response to your question on actual use, we have gathered data from both the German (launch November 2000) and Belgium (launch January 2001) subsidiaries. In both Germany and Belgium, IMS Health, Division of Dunn and Bradstreet, provides data on actual sales of product to the patient at the pharmacy. The data is captured via bar code. In addition, IMS captures greater than 90% of all dispensed products.

   Germany

   From launch through February 2001, a total of [redacted] cycles were sold to patients. The cycle sales from IMS by month were:

	Nov 2000	Dec 2000	Jan 2001	Feb 2001
Yasmin				
Petibelle				
Total:				

Patients in Germany receive at least one sample cycle on their initial visit. Patients then return back to the physician for a follow-up exam before completing their samples. The physician then writes a script for 1-3 months. Therefore, the minimum number of patients exposed to at least two months of Yasmin usage is 214,000. The 214,000 number is conservative, because it does not include patients given more than one sample in Jan - Feb [redacted] samples have been distributed in Germany since launch) and pharmacies not covered in the IMS numbers.

IMS also reports market share based upon the total number of cycle packs sold to patients. The market share for Yasmin and Petibelle in Feb 2001 were [redacted] respectively. If you take the combined market shares of [redacted] in February and multiply it by the number of eligible German women (approx. 6 million), then you arrive at [redacted]

Belgium

Utilizing the same data and assumptions for Belgium would mean that [redacted] women are using Yasmin of which 8,000 have been on Yasmin for at least two months.

3. **In the Safety Report for the HRT Study (Protocol 96097), Subject No. 36041 is listed as having experienced severe hypokalemia (also listed as a serious adverse event) for which she was hospitalized (per the AE CRF). The subject narrative (pg 87 of Vol. 19 prepared by Berlex), however, states that she was hospitalized for "flu-like symptoms." Please clarify this discrepancy and provide the lowest potassium value obtained for this subject (no abnormal values are provided in the Safety report) as well as the most likely explanation for her severe hypokalemia.**

The patient (Subject 36041) went to the emergency room on January 14, 2000 due to vomiting, diarrhea and chills and was admitted to the hospital for hypokalemia. This serious adverse event (SAE) when reported was described as "flu-like symptoms". At that time, Berlex requested a final report but the report was not received. We have now obtained the final report from the emergency room and the hospital (see Attachment 3).

The report from the emergency room shows that the patient had hypokalemia (serum potassium 2.8 mmol/L), fever (103.6 F) and urinary tract infection. The patient was treated in the emergency room with i.v and oral potassium as well as i.v. antibiotic (Rocephin) and then was admitted to the hospital for hypokalemia and urinary tract infection. The follow-up serum potassium on 1/15/2000 was 4.0 mmol/L. The urine culture confirmed a urinary tract infection with E. Coli. The patient was discharged three days later on 1/17/2000 with serum potassium of 4.7 mmol/L and afebril. The discharge diagnoses were:

1. Urinary tract infection
2. Hypokalemia

The hypokalemia is thought to be due to vomiting, diarrhea and diet.

The narrative should have stated that the patient was hospitalized for hypokalemia.

With this submission, Berlex has responded to all Clinical Information Requests to date. Additional financial disclosure information requested by Ms. Kim Colangelo of the Division on February 22nd for investigators participating in Studies 97036 and 96097 was submitted on March 12th. Ms. Colangelo requested additional information on April 5th that was submitted today under separate cover. On March 30th, our response to the Chemistry Request of February 28th was submitted. As of today, all requests from the Division have been answered.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copies: Dr. Scott Monroe
Ms. Jeanine Best

NFV/letter/drpoc074

APPEARS THIS WAY
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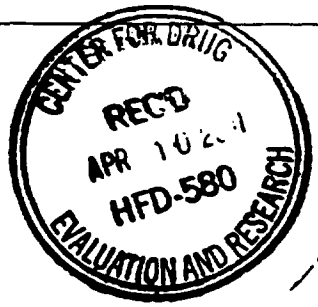

Drug Development & Technology
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April 9, 2001

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

NEW CORRESP
1/C

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to April 5, 2001 Request for Financial Disclosure Information

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

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000. Our complete response to this letter was submitted on November 6, 2000. The November 6th submission contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under) and 96097 (an endometrial protection study conducted under). Financial disclosure information for the Principal Investigators that participated in these studies was provided on November 9th. On February 22, 2001, Ms. Kim Colangelo of the Division requested additional information which was submitted by Berlex on March 12th. The March 12th submission included the following:

1. a revised table (from that provided in the November 9th submission), to be attached to FORM FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators". This listing of Principal Investigator names and addresses was updated to show that all Principal Investigators in Studies 97036 and 96097 had provided financial disclosure information and a third column was added indicating the number of subjects enrolled at each of the sites in these studies.

2. a listing of Subinvestigators who participated in Studies 97036 and 96097 but did not provide financial disclosure information. The reason why the information was not obtained, as well as the efforts that were made by Berlex to obtain the information were provided.

3. a listing of Subinvestigators who participated in Studies 97036 and 96097 but for whom financial disclosure information was not requested because they had been erroneously included in box #6 of the Form FDA 1572. It was determined that these Subinvestigators were not directly involved in the treatment or evaluation of the subjects.

On April 5, 2001, in a telephone conversation with the undersigned, Ms. Colangelo requested additional information. She noted that a new signed and dated FORM FDA 3454 was not included in the March 12th submission to accompany the revised table of Principal Investigators. She also stated that an overall listing of Subinvestigators at each site was needed – those that *did* comply by providing the required financial disclosure information and those that *did not* so that she could properly assess the compliance rate at each site. The undersigned agreed to provide the requested information as soon as possible.

Attached immediately following this cover letter is a new FORM FDA 3454 that is signed by our Medical Director and is dated April 6, 2001. A revised attachment to accompany this new FORM FDA 3454, also dated April 6th, follows the form. The attachment identifies all of the Principal and Subinvestigators in Studies 97036 (Attachment 1) and 96097 (Attachment 2). The address of the Principal Investigators are provided, the number of subjects enrolled at each site, as well as a comprehensive listing of the Subinvestigators that *did* provide financial disclosure information and those that *did not*. Please note, in response to Ms. Colangelo's question, that all Principal Investigators in Studies 97036 and 96097, with the exception of three that did not enroll any subjects, provided financial disclosure information certifying that they had no disclosable financial arrangements/interests.

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

Sincerely,

BERLEX LABORATORIES

Nancy E. Velez
Manager
Drug Regulatory Affairs

Desk copies: Ms. Kim Colangelo
Ms. Jeanine Best

NFV/letter/drpoc076

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ORIGINAL

April 4, 2001

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

ORIG AMENDMENT

15L

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Follow up to Safety Update of March 27, 2001 –
Labeling for Switzerland

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000. Our November 6, 2000 clinical amendment provided a complete response to the July 10, 2000 approvable letter.

Further reference is made to the Safety Update submitted on March 27th. It was reported that the following countries had obtained National marketing authorizations:

Country	Date of Marketing Authorization
Colombia	December 28, 2000
Czech Republic	December 20, 2000
Estonia	February 9, 2001
Switzerland	December 21, 2000

The approved labeling in Colombia, the Czech Republic and Estonia are translations into the respective national languages from the same labeling approved for Latvia and Hungary. An English translation of the labeling approved in Latvia and Hungary was submitted to the Division in the Safety Update Report (Attachment 6) included in the November 6, 2000 amendment (the response to the July 10, 2000 approvable letter).

Berlex stated in the March 27th Safety Update that the approved labeling for Switzerland was being translated into English and would be provided within one week. Attached is a copy of the approved labeling for Switzerland, which has been translated into English. A copy of the labeling in the original language is also attached.

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

Sincerely,

BERLEX LABORATORIES

Nancy R. Velez
Manager
Drug Regulatory Affairs

Desk copy: Dr. Scott Monroe
Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc070

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ FINAL ☐ MEMO

CSO INITIALS DATE

ORIGINAL

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

April 4, 2001

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

NEW CORRESP

1/C

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Telephone Requests of March 28, 2001

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000. Our November 6, 2000 clinical amendment provided a complete response to the July 10, 2000 approvable letter.

Reference is also made to a telephone conversation on March 28, 2001 between Ms. Jeanine Best of the Division and the undersigned. Ms. Best informed the undersigned that the Division held a status meeting that day for YASMIN and had a few questions. The questions are provided below in bold, followed by our responses.

1. **If possible, please provide more information on the death case, for example, EKG or lab data. The Division would like to see if the woman had any other problems.**

Ms. Best acknowledged that the Division had reviewed the information provided in the Safety Update Report submitted on March 27th of the case of the woman who died of suspected pulmonary embolism while taking Yasmin in Germany but would like more information, if possible. The undersigned informed Ms. Best on March 28th that Berlex was still trying to obtain any additional information but, as stated in the Safety Update, no autopsy was performed and the woman's husband has refused to authorize the release of medical information. In Germany, if the family refuses to provide this

authorization, there is nothing else that can be done to obtain the patient's medical records. The undersigned told Ms. Best that, as required, an IND Safety Report of the death would be submitted that day or the next, to the appropriate INDs in the Division and would incorporate any additional information that was obtained. The undersigned agreed to convey the Division's request to management and follow up with Ms. Best.

On March 29th, an IND Safety Report was submitted to the Yasmin 30 OC [redacted] and Yasmin 20 OC [redacted] A MedWatch form containing all of the information to date was included. Some of this information was obtained after submission of the Safety Update Report. Our parent company, Schering AG, Berlin, Germany, has been diligent in approaching the woman's husband several times until very recently but he will not authorize the release of his wife's medical records. The German hospital (name unknown) will not release any information without a letter of authorization from the husband.

2. **In the Safety Update Report, various countries are identified as marketing Yasmin or pending approval, etc. Canada is missing. What are the marketing plans for Canada?**

The undersigned informed Ms. Best on March 28th that she believed the Canadian regulatory authorities had questions regarding the Canadian submission and responses were being prepared at this time. The undersigned agreed to confirm this.

Berlex Canada received a Notice of Non-Compliance from Health Canada on January 30, 2001. They expect to submit their response within the required 90 days, by the end of April. Berlex Canada expects approval of Yasmin by the end of 2001 or early in 2002.

3. **What are the standard laboratory values (reference values) for serum potassium in the Yasmin 20 trials?**

The Division was reviewing the serum potassium data submitted in the Safety Update Report of March 27th, as requested in their Clinical Information Request letter of March 1st. On March 28th, the undersigned agreed to obtain the reference values and submit them to the Division.

The serum potassium data were obtained from subjects participating in the non-comparative, multi-center, open study being conducted in Europe, South America and the United States, Protocol No. ME303740 entitled, "Multi-center,open, uncontrolled study to investigate the efficacy and safety of the oral contraceptive SH T 186 DA containing 0.02 mg ethinylestradiol-β-Cyclodextrin Clathrate and 3 mg drospirenone in a 24-day regimen for 13 cycles in 1010 healthy female volunteers". This Phase 3 protocol and the US site were submitted in our initial IND submission on August 22, 2000 for Yasmin 20 for the indication of oral contraception, [redacted] This study began in Europe and in the US in October 2000.

A central supervisory laboratory is being used for the laboratory samples in Protocol ME303740. The reference range for serum potassium is 3.6 – 5.0 mmol/L.

4. **Page 12 and 13 of the Briefing Document[1] reference data that suggest that 1.4 out of 10,000 women receiving an oral contraceptive is likely to be renally impaired. The Division would like additional data to support that statement.**

We used the [redacted] to determine the risk posed to the population at large, were Yasmin to be prescribed to women with renal impairment[2]. With respect to renal impairment prevalence, we calculated that approximately 1.22/1000 women had renal impairment based on the [redacted] data [redacted] looking at women ages 15-44 years in year 1998 (443 women with renal impairment /362615 women age 15-44 years). Of these 362615 women, 52 (1.43/10000) had renal impairment and took an oral contraceptive.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copies: Dr. Scott Monroe
Ms. Jeanine Best

NFV/letter/drpoc071

REVIEWS COMPLETED

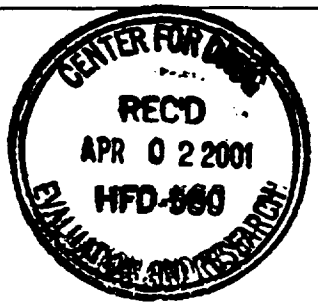
SUBMISSION
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

[1] Submitted to the Division on September 11, 2000 in preparation for our September 25, 2000 meeting to discuss the risk of hyperkalemia in women using Yasmin
[2] ICD9 Codes 580.XX – 589.XX

ORIGINAL

TELEFAX
UPS OVERNIGHT



Drug Development & Technology
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March 30, 2001

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

ORIG AMENDMENT

12C

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Chemistry Request of February 28, 2001

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000. Our November 6, 2000 clinical amendment provided a complete response to the July 10, 2000 approvable letter.

Reference is also made our Chemistry, Manufacturing and Controls (CMC) amendment dated November 6, 2000 and to our January 16, 2001 response to the CMC Discipline Review Letter of December 12, 2000. Additional reference is made to the February 28, 2001 telefax from the Division asking that the November 6th and January 16th submissions be withdrawn and that Berlex confirm its understanding of a teleconference held on February 11, 2000 regarding impurity specifications. (A copy of the February 28th telefax is provided immediately following this cover letter for your reference.) Further reference is made to a telephone conversation on March 1, 2001 between Ms. Jeanine Best of the Division and the undersigned regarding the February 28th telefax.

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BACKGROUND

November 6, 2000 CMC Amendment

The November 6th amendment provided for changes in the manufacture of the DRSP drug substance by the manufacturer, our parent company, Schering AG, Berlin, Germany. The Type II Drug Master File containing the information on the drug substance, ——— , was amended to provide for the changes. A copy of the DMF amendment letter was included in the amendment. A brief summary of the changes is provided below:

- ———

  ———

- Quality specification tightened for particle size and diisoproply ether
- Batch analysis comparison of 3 batches of synthesis C and modified synthesis C
- Impurity comparison of 3 batches of synthesis C vs modified synthesis C

In addition, with regard to the drug product, Berlex referred to the discussion during the February 11, 2000 teleconference with Dr. Suong Tran, Chemistry Reviewer, regarding elimination of testing for decomposition products in drug product release testing. Dr. Tran had suggested that Berlex monitor the first 10 lots of drug product and submit the results in a supplement to be reviewed for the possibility of eliminating the referenced testing. Berlex submitted in the November 6th amendment Certificates of Analysis for 13 European lots of Yasmin drug product. The decomposition testing results for all of the lots fell well within the specifications for decomposition products of both EE and DRSP. It was proposed in the amendment that testing for decomposition products on release be eliminated.

January 16, 2001 Response to CMC Discipline Review Letter of December 12, 2000

On December 12, 2000, the Division issued a Discipline Review Letter in response to the November 6th amendment providing reasons why the proposal to eliminate release testing for impurities was unacceptable. In Berlex's January 16th response to this letter, additional arguments were provided to eliminate the testing.

February 28, 2001 Telefax, Chemistry Request

The Division asked that the November 6th and January 16th submissions be withdrawn and that Berlex confirm its understanding of the February 11th teleconference, stating that impurity specifications will be implemented at release. The Division stated that a request to eliminate the testing could be submitted in a post approval supplement that must contain data from at least 10 US marketed lots.

In the telephone conversation on March 1st, the undersigned stated that it appeared that the Division wanted to withdraw the November 6th and January 16th submissions because of our arguments to eliminate the impurity testing. It did not appear that the changes to the DMF in the November 6th amendment were in question and we did not want to withdraw them. The undersigned asked Ms. Best to confirm with the chemist that the DMF changes were acceptable.

Ms. Best confirmed with Dr. Moo-Jhong Rhee, Chemistry Team Leader, that the changes to the DMF in the November 6th amendment are acceptable. He recommended that in order to keep those changes, Berlex should submit correspondence referring to the DMF changes as effective but withdrawing everything else that would be handled in a post approval supplement. Ms. Best suggested that after the approval of Yasmin, Berlex submit a supplement with data from US marketed lots, not European marketed lots, and at that time, propose elimination of the impurity testing.

CONCLUSION

1. Berlex and the Division agree that the changes in the manufacture of the drospirenone drug substance, as described in the November 6, 2000 CMC amendment (November 6 amendment to [redacted]), are effective and are not being withdrawn.

2. Berlex agrees to withdraw the proposal to eliminate the test for impurities at release of the Yasmin drug product as described in the November 6, 2000 amendment and January 16, 2001 chemistry response letter. Impurity specifications will be implemented at release. Should Berlex wish to eliminate this testing after approval, a request will be submitted in a post approval supplement containing data from at least 10 US marketed lots.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy: Ms. Jeanine Best
Dr. Moo-Jhong Rhee

NFV/letter/drpoc065

TELEFAX
UPS OVERNIGHT

ORIGINAL

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March 27, 2001

ORIG AMENDMENT

Susan Allen, M.D, MPH, Director
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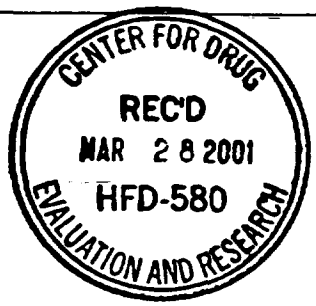


Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Additional Response to Clinical Information Request of March 1, 2001 – Safety Update, Potassium Levels

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000.

Reference is also made to our submission of November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. The November 6th submission contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under [redacted] and 96097 (an endometrial protection study conducted under [redacted]. The Medical Officer requested information in order to continue his review of the November 6, 2000 submission in five Clinical Information Requests Letters. The dates of the requests and the Berlex responses are summarized in the table below:

Date of Clinical Information Request Letter	Date of Berlex Response
December 12, 2000	January 5, 2001
February 2, 2001	February 12, 2001
February 20, 2001	March 9, 2001
March 1, 2001	March 12, 2001
March 7, 2001	March 16, 2001

Specific reference is made to the Clinical Information Request Letter of March 1, 2001 which contained six comments. In the interest of time, our response to four of the comments was submitted on March 12th. Berlex committed in the letter to respond on March 23rd to the remaining two comments: 1) a request for an additional Safety Update for Yasmin, including postmarketing experience and 2) a request for baseline and one-month potassium levels from our Yasmin 20 trials. On March 23rd and 26th, the undersigned informed Ms. Jeanine Best of the Division that Berlex was pursuing additional follow up information for the Safety Update and the submission would be delayed until March 27th.

Following is our response to the remaining two comments in the March 1st letter. Each of the comments is identified in bold font, followed by our response. A copy of the March 1st letter is provided for your convenience immediately following this cover letter.

3. Please provide the 4-Month Safety Update for Yasmin, including any post marketing experience with Yasmin.

This is the third Safety Update Report being submitted for Yasmin. The first Safety Update Report was requested in the March 17, 2000 approvable letter and was submitted on May 4, 2000. The second Safety Update Report was requested in the July 10, 2000 approvable letter and was submitted on November 6, 2000.

Per the procedure followed for the two previous Safety Update Reports, Berlex is updating the NDA with any new information that was obtained since July 10, 2000 (the cut-off date for inclusion of data into the last Safety Update Report of November 6, 2000) through March 1, 2001 (the date of the Clinical Information Request Letter) The same format used in the previous reports is used in this latest Safety Update Report which is found in Attachment 1.

6. Please provide baseline and one-month serum potassium levels (as soon as the data is available) for patients in the Yasmin 20 trials.

Baseline and one-month serum potassium levels are available for 241 subjects participating in the non-comparative, multi-center, open study being conducted in Europe, South America and the United States, Protocol No. ME303740 entitled, "Multi-center,open, uncontrolled study to investigate the efficacy and safety of the oral contraceptive SH T 186 DA containing 0.02 mg ethinylestradiol-β-Cyclodextrin Clathrate and 3 mg drospirenone in a 24-day regimen for 13 cycles in 1010 healthy female volunteers". This Phase 3 protocol and the US site were submitted in our initial IND submission on August 22, 2000 for Yasmin 20 for the indication of oral contraception, ~~~~~ This study began in Europe and in the US in October 2000. The potassium levels for the 241 subjects in this study are provided in Attachment 2.

Please note that in our previous response of March 12th to the March 1st requests, it was stated that potassium data on approximately 400 subjects would be submitted today. That number included both subjects with baseline values only and subjects with baseline and one-month potassium levels. The original data listing received at Berlex was regenerated to include only those subjects with both baseline and one-month potassium levels, 241 subjects.

As you know, special precautions are being utilized in this protocol regarding handling of the samples for the analysis of potassium in order to ensure reliable results.

Berlex has now provided a complete response to the Clinical Information Request Letter of March 1st. Berlex has responded to all Clinical Information Requests. Additional financial disclosure information requested by Ms. Kim Colangelo of the Division for investigators participating in Studies 97036 and 96097 was submitted on March 12th.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy: Dr. Scott Monroe
Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc054

APPEARS THIS WAY
ON ORIGINAL

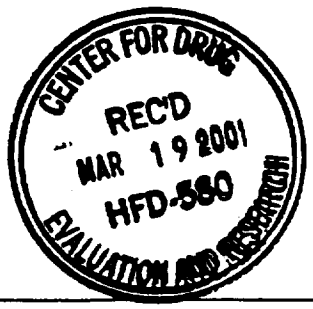
REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

TELEFAX
UPS OVERNIGHT



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March 16, 2001

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

ORIG AMENDMENT

BM

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Clinical Information Request of March 7, 2001

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 November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. Additional reference is made to the Clinical Information Request Letter dated December 12, 2000. The Medical Officer requested this information in order to continue his review of the November 6, 2000 submission. On January 5, 2001, we submitted our response to this request.

On February 2, 2001, a second Clinical Information Request letter was received requesting information to continue the review. Our response to that letter was submitted on February 12, 2001.

On February 20, 2001, a third Clinical Information Request Letter was received requesting information to continue the review. Our response to that letter was submitted on March 9, 2001.

On March 1, 2001, a fourth Clinical Information Request Letter was received requesting information to continue the review. Our response to that letter was submitted on March 12, 2001.

Further reference is made to a fifth Clinical Information Request Letter received on March 7, 2001 (provided immediately following this cover letter for your reference). This additional information was also requested by the Medical Officer in order to continue his review of the November 6, 2000 submission. Provided on the following pages is our response to this fifth request. Each of the items requested in the March 7th letter is identified in bold font, followed by our response.

Questions regarding information provided in Submissions of November 6, 2000 and January 5, 2001.

1. **The procedures that were followed in Studies 97036D and 96097A to exclude the reporting of elevated serum potassium values that may have been a result of hemolysis or "extended cellular contact" also may exclude elevated potassium values that are a result of clinical hyperkalemia. Listed below is the description of the procedures as described in the Safety Reports.**

   "The presence of hemolysis was determined visually by the laboratory assistant or technologist as the serum samples were being organized into loads. Slightly hemolyzed specimens were analyzed, and the results were reviewed by the technologist. Changes of greater than approximately 20% from the previous results were indicative of hemolysis interference. If no previous result was available, rejection due to hemolysis was at the discretion of the reviewing technologist. Severely hemolyzed specimens were not analyzed.

   In addition, potassium values between 6.0 and 7.3 mEq/L were suspicious for extended cellular contact, except when these values correlated with previous results. Microscopic demonstration of greater than 10 red blood cells per high-power field (RBCs/HPF) was indicative of prolonged cellular contact. In this case, the values for potassium, LDH, glucose, and phosphorous were rejected."

   a) **Please explain how you were able to ensure that instances of true clinical hyperkalemia were not overlooked because of these procedures.**

   Berlex understands this point and it is well taken. [redacted] was used as the Central Laboratory. In accordance with their SOP, [redacted] does not release results from hemolyzed or prolonged cell contact. Therefore, Berlex has provided serum potassium values for all samples provided by [redacted] nas cancellation codes for samples that are hemolyzed and for specimens proved to have prolonged cell contact.

   The procedures described in the Safety Reports are according to their SOP which reads, "the presence of hemolysis was determined visually by the laboratory assistant or technologist as the serum samples were being organized into loads. Slightly hemolyzed specimens were analyzed, and

the results were reviewed by the technologist. Changes of greater than approximately 20% from the previous results were indicative of hemolysis interference. If no previous result was available, rejection due to hemolysis was at the discretion of the reviewing technologist. Severely hemolyzed specimens were not analyzed.

In addition, potassium values between 6.0 and 7.3 mEq/L were suspicious for extended cellular contact, except when these values correlated with previous results. Microscopic demonstration of greater than 10 red blood cells per high-power field (RBCs/HPF) was indicative of prolonged cellular contact. In this case, the values for potassium, LDH, glucose, and phosphorous were rejected."

Berlex can assure you that every sample value received from ——— for serum potassium was included in the safety report. The patients in Studies 97036A and 96097A were followed continuously for adverse events for the period of drug exposure namely, 3 and 12 months, respectively.

In preparation for the Briefing Package submitted on September 8, 2000, Berlex consulted with cardiology experts, ——— and developed a list of AEs that may be associated with hyperkalemia. The following is a list those cardiovascular events that may be related to hyperkalemia: arrhythmia; bradycardia; tachycardia; dizziness; palpitations and syncope.

None of the patients (except one) with samples discarded due to hemolysis or prolonged cell contact reported any of the above listed cardiovascular events that might have been related to hyperkalemia. This patient (#24028) experienced a cardiovascular event (syncope). This event occurred in the lowest DRSP dose group (0.5 mg DRSP) in study (96097A) [see submission dated 11/6/00, volume 86, page 1314].

b) **Please provide us with a listing of all blood samples for which serum potassium values were not included the Safety Reports for Studies 97036D and 96097A because of the procedures described above. Please provide us with the serum potassium values for these samples if they are available. We realize that Question Number 5b in the request of December 12, 2000 and Question Numbers 1 and 1a in the request of March 1, 2001 also addressed this issue.**

——— Laboratories was used as the Central Laboratory. In accordance with their SOP, ——— does not release these values to the sponsor. Berlex has provided serum potassium values for all samples provided by ——— (as noted in response to Question 1a above).

Attachments 1 and 2 provide the listing of all blood samples for which serum potassium values were not included in the Safety Reports for Studies 97036D and 97097A. These listings were previously submitted in

response to the December 12, 2000 and March 2, 2001 Clinical Information Requests and are provided again for ease of review.

2) **In your response of January 5, 2001, you stated that there was an error in the number of subjects identified as using NSAIDs in Text Table 12 (pg. 54) of the Safety Report for the PMS/PMDD study. You stated that the correct values should be 60 and 57 subjects in the Placebo and DRSP/EE groups, respectively. Presumably, this correction also applies to Text Table 13 (pg. 54) in the Safety Report. Please confirm.**

Upon receipt of this clinical information request, Berlex reviewed both Text Table 12 and Text Table 13. In conducting this review, Berlex realized that the numbers had been reversed inadvertently. The correction has been made. Berlex has corrected both Text Table 12 and 13 and have reproduced them below.

Text Table 12: Number of Subjects Included in the Analysis of Serum Potassium Concentrations (Subjects With Postbaseline Data)

Treatment Group	Number of Subjects	Number of Subjects Using NSAIDs
Placebo	115	57
DRSP 3 mg/EE 30μg	115	60

DRSP = drospirenone; EE = ethinyl estradiol; NSAIDs = nonsteroidal anti-inflammatory drugs.

Text Table 13: Number (%) of Subjects With Postbaseline Serum Potassium Values ≥ 5.5 mEq/L (Subjects With Postbaseline Data)

Treatment Group	All Subjects		Subjects Using NSAIDs	
	N	N (%) ≥ 5.5 mEq/L	N	N (%) ≥ 5.5 mEq/L
Placebo	115	1 (0.9)	57	1 (1.8)
DRSP 3 mg/EE 30 μg	115	1 (0.9)	60	1 (1.7)

DRSP = drospirenone; EE = ethinyl estradiol; N = total number of subjects; n = number of subjects; NSAIDS = nonsteroidal anti-inflammatory drugs.

3) **Do the numbers of 60 and 57 for NSAID users in the Placebo and DRSP/EE groups referred to in Question 2 above also include some subjects who were taking only "Aspirin and products containing ASA"? The information provided in Table 10 (pg. 103) of the PMS/PMDD Safety Report indicates that only 58 subjects in the Placebo group were using NSAIDs, excluding ASA products.**

As noted above the numbers in the treatment groups are reversed. There were 57 subjects in the Placebo group and 60 in the DRSP/EE group. Yes, 60 and 57 are the number of subjects who had both baseline and post-baseline serum potassium values AND used either NSAIDs and/or Aspirin (including products containing ASA).

In Table 10, 58 is the number of subjects who were randomized to the Placebo group and used NSAIDs excluding ASA products. The number of subjects who were randomized to the Placebo group and used either NSAIDs and/or Aspirin containing products is 62.

4) **The analysis presented in Text Table 16 (pg. 56) of the Safety Report for the PMS/PMDD Study is likely to be incorrect since the Table indicates that 70 and 64 subjects in the DRSP/EE and Placebo groups, respectively, used NSAIDs. If Text Table 16 is not correct, please provide a corrected version as this is the only analysis in the Safety Report that compares serum potassium values in subjects who did, and did not, use NSAIDs during the Clinical Trial. If the analysis is correct, please explain the apparent discrepancies in numbers of NSAID users in the different Tables.**

Your observation is correct; Text Table 16 has been corrected (see Attachment 3); however the analysis is correct. The discrepancy occurred as a result of two factors: (1) inconsistency in the definition of NSAIDs (sometimes this definition included OTC); and (2) sometimes the information was captured prior to randomization.

Berlex apologizes for any inconveniences or confusion that we may have caused. It is our goal to respond to all requests as quickly as possible. All corrections that have been made during the process of responding to the Clinical Information Requests letters will be made in the Final Clinical Study reports. Changes to the Safety Report submitted on November 6, 2000 cannot be made in a timely fashion. However, the changes will be made when these reports are written as Final Clinical Study Reports (which would include efficacy).

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc053

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

TELEFAX
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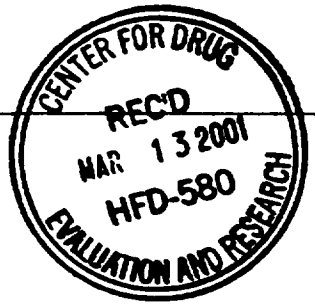

Drug Development & Technology
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March 12, 2001

NEW CORRESP
N-L

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

Dear Dr. Allen:

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

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

Reference is also made to a second approvable letter issued by the Office of Drug Evaluation III on July 10, 2000. Our complete response to this letter was submitted on November 6, 2000. The November 6th submission contained new clinical data: Safety Reports for Studies 97036 (a PMS/PMDD study conducted under [redacted]) and 96097 (an endometrial protection study conducted under [redacted]). Financial disclosure information for the Principal Investigators that participated in these studies was provided on November 9th.

Additional reference is made to a telephone conversation on February 22, 2001 between Ms. Kim Colangelo of the Division and the undersigned. Ms. Colangelo was reviewing the financial disclosure information of November 9th and asked that the number of subjects/site for Studies 97036 and 96097 be provided. In addition, in Study 97036, she acknowledged and found acceptable that three Principal Investigators did not have financial disclosure information because there was no enrollment at their sites. However, for Study 96097, where three Principal Investigators had not responded to requests for the information, she asked that explicit information be provided explaining what due diligence efforts were made to try to obtain it. In addition, because it was unclear in the November 9th submission if Subinvestigators had provided financial disclosure information in addition to the Principal Investigators, Ms. Colangelo

asked the undersigned to provide a list of any Subinvestigators in the two studies that did not provide the information. Due diligence efforts to obtain the information from each Subinvestigator that did not comply was also requested. Ms. Colangelo stated that the financial disclosure rule applies to anyone listed on the Form FDA 1572. In response to Ms. Colangelo's question regarding the status of Studies 97036 and 96097 at the time the financial disclosure regulations went into effect in February of 1999, the undersigned stated that they were well underway or completed but would provide the exact dates.

The information that follows is provided in response to all of Ms. Colangelo's requests.

1. Attachment 1 contains a revised table from that provided in the November 9th submission, which was attached to Form FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators". The same listing of Principal Investigator names and addresses is provided, however, a third column has been added to show the number of subjects enrolled at each of the sites in Studies 97036 and 96097. (Note: Footnotes in the previous table indicating financial disclosure information had not been obtained for Drs. Stuccio-White, Targum and Thorneycroft have been removed as this information was obtained on March 12, 2001, see #2 below).

2. The following three Principal Investigators that participated in Study 96097 had not previously responded to requests for financial disclosure information: Nina Stuccio-White, DO, Steven Targum, MD and Ian Thorneycroft, MD. All three of these Principal Investigators provided this information to Berlex on March 12, 2001.

3. Attachment 2A contains a listing of Subinvestigators who participated in Studies 97036 and 96097 but did not provide financial disclosure information. The reason why the information was not obtained, as well as the efforts that were made by Berlex to obtain the information are provided. Please note that it was determined in January 2000 when the process of obtaining financial disclosure information began at Berlex, that many Subinvestigators had been erroneously included in box #6 of the Form FDA 1572 that were not directly involved in the treatment or evaluation of the subjects. Financial disclosure information was never requested from these individuals for that reason. These individuals are identified in Attachment 2B.

4. *Study 97036*, a PMS/PMDD study conducted under ———— , entitled, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)", was conducted from December 1997 – July 1999.

   Study 96097, an endometrial protection study conducted under ———— entitled, "A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol, Examining the Effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women", was conducted from January 1998 – April 2000.

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

Sincerely,

BERLEX LABORATORIES

Nancy P. Velez
Manager
Drug Regulatory Affairs

Desk copy: Ms. Kim Colangelo

Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc047

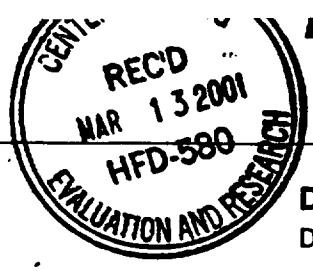
APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

TELEFAX
UPS OVERNIGHT



ORIGINAL

BM

Drug Development & Technology
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March 12, 2001

ORIG AMENDMENT

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

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Clinical Information Request of March 1, 2001

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 November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. Additional reference is made to the Clinical Information Request Letter dated December 12, 2000. The Medical Officer requested this information in order to continue his review of the November 6, 2000 submission. On January 5, 2001, we submitted our response to this request.

On February 2, 2001, a second Clinical Information Request letter was received requesting information to continue the review. Our response to that letter was submitted on February 12, 2001.

On February 20, 2001, a third Clinical Information Request Letter was received requesting information to continue the review. Our response to that letter was submitted on March 9, 2001.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Reference is made to a fourth Clinical Information Request Letter received on March 1, 2001 (provided immediately following this cover letter for your reference). This additional information was also requested by the Medical Officer in order to continue his review of the November 6, 2000 submission. Provided on the following pages is our response to this fourth request. Each of the items requested in the March 1st letter is identified in bold font, followed by our response.

Request for additional information for Clinical Studies 97036D (PMS/PMDD Study) and 96097A (HRT Study)

1. **Please provide a listing of all serum chemistry samples that were collected in the HRT Study for which no serum potassium values were included in the Safety Report. The format of the listing should be similar to that of Attachment 5B in your prior communication of January 5, 2001.**

   The attached table provides a listing of all serum chemistry samples that were collected in the HRT study and is similar to the one provided in the January 5, 2001 submission.

   a) **Were serum potassium values for any of these samples provided to Berlex by the Central Laboratory but not included in the Safety Report? If so, please provide us with the values for these samples. This request for potassium values not included in the Safety Report also applies to those samples listed as "hemolyzed, or received beyond stability," etc. that were identified in attachment 5B for the PMS/PMDD Study.**

   was the Central Laboratory. It is the policy of e not to release to the sponsor values from samples that are hemolyzed or received beyond stability. Berlex has provided serum potassium values for all samples provided by

2. **We have noted that the mean post baseline maximum potassium values for the four DRSP treatment groups in Text Table 6 (September 11, 2000, pg. 26) are numerically higher than the mean value for the estrogen alone group. This small difference is not surprising in view of the anti-aldosterone effect of DRSP. The effect of DRSP, however, does not appear to be dose-related. Can you explain why the effect does not appear to be dose-related?**

   The kidney has a high capacity for handling potassium and in order to see a dose effect; the doses of DRSP needed to be much higher to show an effect on serum potassium in postmenopausal women.

3. **Please provide the 4-Month Safety Update for Yasmin, including any post marketing experience with Yasmin.**

   Berlex is currently working on the 4-month Safety Update and it will be submitted on March 23rd.

4. **The following patients were terminated prematurely because of a cardiovascular adverse event. No serum potassium concentrations during the respective cardiovascular adverse events were provided in the Safety Reports. Please provide, if available, any additional pertinent serum potassium data that you may have (e.g., specimens collected outside of the Study Protocol) for the following patients:**

a) PMS/PMDD Study: Pts. 2018, 12070, and 19014

Patient Number	Summary of Findings	Potassium Values in Database
02018	Regular lab in database at Visit 3. No unscheduled labs in database or CRF.	Visit 3: 3.8
12070	Regular labs in database at Visit 3 and Last Visit (Visit 12). No unscheduled labs in database or CRF.	Visit 3: 4.2 Visit 12: 3.8
19014	Regular lab at Visit 3 and Unscheduled lab (Visit 6.01) in database.	Visit 3: 3.5 Visit 6.01: 3.5

b) HRT Study: Pts. Nos. 24027, 8035, 31014, 17018, 26005

'atient Number	Summary of Findings	Potassium Values in Database
24027	Regular labs in database at visits 1, 5, 7. No unscheduled labs in database or CRF. No SAE report on file with additional information.	Visit 1: 4.4 Visit 5: 4.2 Visit 7: 4.3
08035	Regular labs in database at visits 1, 5. Patient was hospitalized for tachycardia. Had labs drawn during hospitalization. Serum potassium reported as 4.1.	Visit 1: 4.2 Visit 5: 4.8
31014	Regular labs in database at visits 1, 5. No unscheduled labs in database or CRF. No SAE report on file with additional information.	Visit 1: 4.4 Visit 5: 4.3
17018	Regular labs in database at visits 1, 5, 7. No unscheduled labs in database or CRF. No SAE report on file with additional information.	Visit 1 : 4.5 Visit 5 : 4.3 Visit 7 : 4.1
26005	Regular labs in database at visit 1. Per AE pages and end of treatment page, patient discontinued due to vaginal bleeding, nausea, dizziness, and loss of appetite.	Visit 1: 4.6

5. **Pt. 26006 is listed as having and abnormal ECG with an onset date of January 8, 1999. What was the abnormality?**

Patient 26006 is a 53-year-old woman who was hospitalized for cough, fever, chills and shortness of breath. The ECG revealed non-specific ST and T abnormalities.

6. **Please provide baseline and one-month serum potassium levels (as soon as the data is available) for patients in the Yasmin 20 trials.**

Data on approximately 400 Yasmin 20 subjects will be submitted on March 23.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc040

APPEARS THIS WAY
ON ORIGINAL

UPS OVERNIGHT

March 9, 2001

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

ORIG AMENDMENT

13 M

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Clinical Information Request of February 20, 2001

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 November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. Additional reference is made to the Clinical Information Request Letter dated December 12, 2000. The Medical Officer requested this information in order to continue his review of the November 6, 2000 submission. On January 5, 2001, we submitted our response to this request. On February 2, 2001, a second Clinical Information Request letter was received requesting information to continue the review. Our response to that letter was submitted on February 12, 2001.

Further reference is made to the third Clinical Information Request Letter dated February 20, 2001 (provided immediately following this cover letter for your reference). This additional information was also requested by the Medical Officer in order to continue his review of the November 6, 2000 submission. Provided on the following pages is our response to this third request. Each of the items requested in the February 20th letter is identified in bold font, followed by our response.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

To facilitate our completion of the review of the Safety Report for HRT Protocol 96097A, please reply to the following questions and provide the additional analyses described below. We realize that several of these requested analyses were included in the September 11, 2000 Briefing Document, but they were not included in the Safety Report, per se. In addition, the information contained in the Briefing Document did not include, for the most part, the original statistical outputs, but rather transcribed summary tables and listings. Finally, we have noted some differences in the information provided in the Briefing Document and the Safety Report. For example, the number of patients listed as using NSAIDS or ACE inhibitors in Text Table 4 (pg 23) of the briefing document (e.g., 69 patients in the E2 group) does not agree with Table 18 (pg 304) of the Safety Report (e.g., 45 patients in the E2 group). Similarly, the number of patients in the E2 group with elevated potassium values using NSAIDS in the Briefing Document (2 in Table 4) differs from that in the Safety Report (0 in Table 18).

Upon receipt of your letter, Berlex reexamined the data relating to NSAID and ACE inhibitor use. We agree with your observation that there is a discrepancy in the number of patients listed as using NSAID or ACE inhibitors between the September 11, 2000 Briefing Package and the November 6, 2000 HRT Safety Report. The discrepancy between the two documents occurred as a result of three factors: (1) inconsistency in definition of NSAIDs (sometimes this definition included OTC); (2) aspirin sometimes fell into a separate category and not captured as an NSAID; and (3) sometimes the information was captured prior to randomization. Upon receiving this clinical information request, Berlex has developed a strict all-inconclusive list of NSAIDs (including aspirin and Ibuprofen [OTC and prescription]. As a result of this strict all-inconclusive list, the number of postmenopausal women on NSAIDs or ACE inhibitors almost doubled. The distribution of the NSAIDs or ACE inhibitors using the strict all inconclusive classification is distributed evenly among the five treatment groups. Updated tables based on this reclassification are attached as Tables 1-6.

1. **Please verify that Table 18, pg. 304, Vol. 20 in the Safety report is the correct analysis.**

   The analysis is correct but due to the revised classification of NSAIDs and ACE Inhibitors; this table has been updated and is identified as Table 5.

2. **Please verify that the potassium values listed for Protocol 96097A in Text Table 5, pg. 24 of the Briefing Document are correct.**

   Berlex has reviewed the potassium values listed for this table and verified that the values are correct.

3. **Please provide the 4 analyses listed below (items a-d) concerning the changes in post baseline potassium values relative to baseline values for each of the 5 treatment groups. The requested analyses are presumably similar to those that were employed in Text Table 6, pg. 26, of the Briefing Document. The tables summarizing the analyses, however, should provide more information than was presented in Text Table 6 and should provide similar descriptive information as that included in Table 20, pg 320, Vol. 20 concerning changes in serum lipids. Each of the analyses should include the change from baseline potassium for (1) all subjects, (2) subjects who**

have not used either NSAIDS or ACE inhibitors, and (3) subjects who used neither NSAIDS nor ACE inhibitors. Each of the requested analyses should be performed separately based on the following 4 conditions:

a) **Change from baseline potassium for all subjects with baseline and post baseline potassium data.**

The attached identified as Tables 1 and 2 provide the descriptive information requested based on the new classification of NSAID or ACE inhibitors.

b) **Change from baseline potassium only for those subjects with baseline data and post baseline potassium data obtained while the subject was receiving study drug or was within 24 hours after the final dose of study drug.**

The attached identified as Tables 3 and 4 provide the descriptive information requested based on the new classification of NSAID or ACE inhibitors.

c) **Change from baseline potassium where change is based on the maximum post baseline potassium value.**

The attached identified as Tables 1 and 3 provide the descriptive information requested based on the new classification of NSAID or ACE inhibitors.

d) **Change from baseline potassium where change is based on the average post treatment potassium value.**

The attached identified as Tables 2 and 4 provide the descriptive information requested based on the new classification of NSAID or ACE inhibitors.

4. **Provide 2 reanalysis of the maximum potassium changes from baseline similar to that in Table 4 (pg. 107) of the Briefing Document. One analysis is to be based on all subjects and the other analysis is to be based only on subjects who had a post baseline potassium value while receiving study drug or within 24 hours of the final dose as requested in Item 3b above.**

The attached Tables 5 and 6 provide the results of two analyses requested. Table 5 is for all subjects and Table 6 is for the subjects whose serum K were taken during treatment.

5. **Please provide an analysis by visit for serum potassium in a format similar to that used to generate Table 20, pg. 320, Vol. 20.**

Table 7 provides serum potassium by treatment and visit for all subjects and Table 8 is for the subjects who used NSAIDs or ACE inhibitors during treatment.

6. **Please verify that Text Figures 4-8 (pg. 32-35) in the Briefing Document are correct. If not, please provide updated Figures.**

Berlex has reviewed these figures and confirm they are correct since they are generated based on all serum potassium values and are independent of the classification of NSAID or ACE inhibitors.

CONCLUSION

Based on the revised classification of NSAIDs or ACE inhibitors, we found that there was an increase in the number of postmenopausal women on these medications. The percentage of women with serum potassium in the 5.5 to <6 mEq range increased in the E2/DRSP 2mg group. The percentage in the E2/DRSP .5 and E2/DRSP 1mg decreased. In the E2/DRSP 3mg group there were no subjects with a serum potassium above 5.5 mEq (see Table 5).

The overall conclusion provided in the safety report remains unchanged. The use of DRSP + E2 either alone or concomitantly with NSAIDs or ACE inhibitors is not associated with the risk of hyperkalemia.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc039

APPEARS THIS WAY
ON ORIGINAL

BERLEX

TELEFAX
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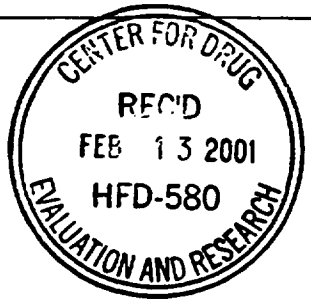

Drug Development & Technology
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February 12, 2001

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

ORIG AMENDMENT
BM

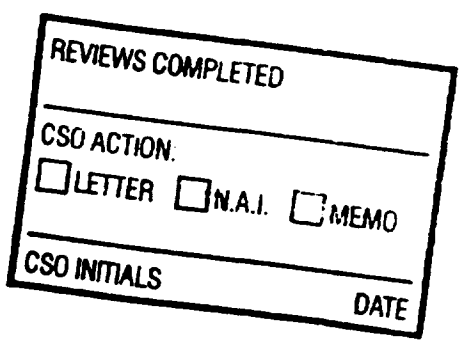
Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Clinical Information Request of February 2, 2001

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 November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. Additional reference is made to the Clinical Information Request Letter dated December 12, 2000. The Medical Officer requested this information in order to continue his review of the November 6, 2000 submission. On January 5, 2001, we submitted our response to this request.

Further reference is made to the second Clinical Information Request Letter dated February 2, 2001 (provided immediately following this cover letter for your reference). This additional information was also requested by the Medical Officer in order to continue his review of the November 6, 2000 submission. Provided on the following pages is our response to this second request. Each of the items requested in the February 2nd letter is identified in bold font, followed by our response.



Please provide the following information for serum potassium samples from subjects in the Yasmin 28 Tablets Treatment Group in the PMS/PMDD Study:

1. **For each serum potassium measurement obtained while a subject was on treatment (Visit 9 for subjects treated beyond 3 months) please provide the following information in the format of a listing by subject:**

   a) **Treatment cycle during which the sample was obtained (i.e., Cycle 1, 2, 3, 4, 5, or 6)**

   b) **Date on which the specific treatment cycle started (not the date on which Study Drug was first started)**

   c) **Day of the specific treatment cycle (response must be one of days 1 to 28)**

The requested data listings for the active treatment group are provided in Attachment 1 in **Listing 1A** and **Listing 1B**. We have also included the data listings for the placebo group in these same listings.

Listing 1A contains a listing of all subjects with blood drawings for serum potassium on cycle days 1 – 21.

Listing 1B contains a listing of all subjects with blood drawings for serum potassium on cycle days 22 – 28.

Listings 1A and 1B both contain the following information:

The subject number (column 1), the study drug start and stop date (columns 2 and 3), the treatment cycle and the first date of each treatment cycle (columns 4 and 5), the date of the blood sampling for serum K+, the serum K+ value (meq/L) and the day within the treatment cycle of the blood sampling (columns 6, 7 and 8). The last column (column 9) shows the number of days the subject remained on treatment after the serum K+ was collected (SMEnd = Study Medication End).

2. **For each end-of-treatment serum potassium measurement obtained within 7 days of the end of dosing (if not included in No. 1 above) please provide the following information:**

   a) **Date on which the last treatment cycle started**

   b) **Last day of the final treatment cycle on which Yasmin was taken (response must be one of days 1 to 28)**

   c) **If it is easier to provide the requested information for all end-of-treatment measurements (instead of only those obtained within 7 days of final dosing), this is acceptable.**

The requested data listings for the active, as well as placebo treatment groups, are provided in Attachment 2 in **Listing 2**. Listing 2 contains a listing of all subjects with blood drawings for

serum potassium after end of treatment. The following information is included:

The subject number (column 1), the study drug start and stop date (columns 2 and 3), the last treatment cycle and the first date of the last treatment cycle (columns 4 and 5), the last dose day (column 6), the date of the blood sampling for serum K+, the serum K+ value (meq/L) and the day within the treatment cycle of the blood sampling (columns 7, 8 and 9). The last column (column 10) shows the number of days between study drug stop date and collection of serum K+ (SMEnd = Study Medication End).

ADDITIONAL DATA

We have also provided in Attachment 3, summary tables of serum potassium by collection day relative to treatment cycle date for serum potassium collected during the treatment period and collected during post treatment.

Table 1 is a summary of serum K+ values [mean, standard deviation (SD) and the serum K+ range] during each cycle for the cycle period days 1-21 and days 22-28. (For your information, subjects who finished their Cycle 6 study drug prior to scheduling their follow up visit continued taking study drug in an additional "Cycle 7" until they were scheduled for the follow up visit.)

Table 1 shows that in the DRSP/EE population, 36 of the 47 samples drawn during cycle days 1-21 were obtained per protocol in cycle 4. Similarly in the placebo population, 42 of 51 samples drawn during cycle days 1-21 were obtained in cycle 4. The blood samples drawn during cycle days 22-28 were mainly obtained in cycle 3 (11 of 13 and 19 of 26 for the DRSP/EE and placebo groups, respectively).

In the DRSP/EE population, the mean serum K+ values are similar in samples drawn during cycle days 1-21 and days 22-28. The same is the case for the placebo group.

Table 2 is a summary of serum K+ values [mean, standard deviation (SD) and the serum K+ range] in the immediate post treatment period (days 1-7 post treatment) and the post treatment period beyond day 7 (≥ day 8).

Table 2 shows that in the DRSP/EE population, 51 of the 98 samples were drawn during days 1-7 post treatment. Similarly in the placebo population, 49 of 99 samples were drawn during days 1-7 post treatment. The remainder of the blood samples were drawn at the post treatment period beyond day 7 (≥ day 8).

In the DRSP/EE population, the mean serum K+ values are similar in samples drawn at days 1-7 post treatment compared to samples drawn during cycle days 1-21 and days 22-28. The same is the case for the placebo group.

CONCLUSION

Although this study 97036 contains fewer serum potassium values compared to the much larger endometrial safety study (Study 96097) it confirms that there is no difference between the mean serum potassium values during exposure to DRSP/EE compared to periods of placebo exposure or post-treatment.

3. The information for this request can presumably be obtained from the CRF entitled "Calendar of Premenstrual Symptoms" that has data fields for all of the requested information.

The majority of the information for this request was obtained from the "Calendar of Premenstrual Symptoms". In the cases below, the following calculations were performed to obtain the data:

Day of serum K relative to treatment (Trt) cycle used in treatment period listings (Listings 1A and 1B) and summary Table 1 is computed as:

Labdate – First_date_of_specific_Cycle + 1

Day of serum K relative to end of study medication used in post treatment listing (Listing 2) and summary Table 2 is the number of days between study drug stop date and collection of serum K which was computed as:

Labdate – SMEnd

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

Sincerely,

BERLEX LABORATORIES

Nancy R. Velez
Manager
Drug Regulatory Affairs

Desk copy (cover letter): Ms. Jeanine Best

NFV/letter/drpoc024

APPEARS THIS WAY
ON ORIGINAL

TELEFAX
UPS OVERNIGHT

ORIGINAL

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January 16, 2001

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

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to CMC Discipline Review Letter of December 12, 2000

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

Approvable letters were issued for NDA 21-098 on March 17, 2000 and July 10, 2000. Our May 8 and 9th, 2000 submissions provided a complete response to the March 17th letter and our clinical amendment of November 6, 2000 provided a complete response to the July 10, 2000 approvable letter.

Reference is also made to our November 6, 2000 amendment which provided for chemistry, manufacturing and controls changes. Finally, reference is made to your Discipline Review Letter (Chemistry Deficiency Letter) of December 12, 2000 which provided comments on the November 6th amendment.

This submission provides responses to the comments in your letter of December 12th. (A copy of the December 12th letter immediately follows this cover letter for your reference.) The Division's comments are provided first in bold, followed by our responses.

1. **The [redacted] for drospirenone has been found to be deficient. The DMF holder has been notified that approval of your application is contingent upon adequate information being provided in the DMF.**

2. **Your proposal to eliminate release testing for impurities is not acceptable for the following reasons:**

   - **Because only one out of 25 product lots per year will be placed on stability study, no information on impurities would be available for the majority of market product lots. The testing for impurities is necessary in order to avoid the release of a drug product lot that has exceedingly high levels of these components and / or that might exceed the shelf-life specifications during the expiration dating period.**

   - **Without impurity data at release, it would be difficult to be alerted to any unexpected problem in the manufacturing process or to validate any post-approval change in the manufacturing process.**

   At minimum, testing for Total Impurities should be performed prior to the release of every product lot. The release specifications should be ≤ 5.0% Total Impurities for ethinyl estradiol and ≤ 0.5% Total Impurities for drospirenone.

According to ICH Q6A:

1. Process impurities from the new drug substance synthesis included in the drug product are normally controlled during drug substance testing, and are therefore not included in the total impurities.
2. When it has been demonstrated that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application, degradation product testing may be eliminated upon approval by the regulatory authorities.

For the following reason the applicant is of the opinion that the release testing for impurities is not necessary:

1. The applicant well controls the process impurities for the new active substance drospirenone. Detailed information can be found in [redacted] 3. Furthermore, impurities of the active substance ethinyl estradiol are well monitored and presented in [redacted]
2. The applicant provides data to demonstrate that the drug substance does not degrade in the specific formulation during manufacture and storage. The results of the performed tests are presented in the attached report "Results of investigation on impurities during manufacturing and storage of SH T 470FA".
3. The starting levels of degradation products in 13 currently released batches of Yasmin as well as in the 6 batches monitored in the stability studies (3 pilot and 3 production plant) are well below the specified limits and thus well controlled. The maximum measured value for the sum was 1.1% for ethinyl estradiol and < 0.1% for drospirenone (for details see the attached report "Results of investigation on impurities during manufacturing and storage of SH T 470FA").
4. To ensure a tighter monitoring and in view of the results mentioned above, the applicant has tightened the limits for impurities of ethinyl estradiol as presented below. The limits for

drospirenone impurities are already very tight and were therefore not revised. The revised quality specification No. K280E2A0 was submitted in the November 6, 2000 amendment.

K280E2A0	K280EG20

total

Should you require any additional information or have any questions regarding this submission, please call the undersigned at (973) 487-2354.

Sincerely,

BERLEX LABORATORIES

Geoffrey Millington
Manager
Drug Regulatory Affairs

GPM/010

Desk copy: Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

January 5, 2001

ORIG AMENDMENT

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

BM

Dear Dr. Allen:

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

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.

Additional reference is made to the submission dated November 6, 2000 which provided a complete response to the July 10, 2000 approvable letter. Reference is also being made to the clinical information request letter dated December 12, 2000. For ease of review, a copy of this letter is being provided in Attachment 1. The request is reproduced below in bold followed by our response.

1. **Please provide several modified and new data listings to facilitate the review. The listing should be structured as described below:**

   a) **All listings to include only subjects treated with one or more doses of study drug.**

   b) **Order of entries on listing to be consistent and to follow usual order of earlier submission (i.e., center, treatment, and subject).**

   c) **Paper copies and electronic files of all listings should be provided except where otherwise noted. Electronic listings to be in ASCII format, Excel (Office 97 version) or SAS transport format (preferred).**

   d) **Listings need to be clear and readily interpretable.**

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ F.A.L. ☐ MEMO

CSO INITIALS DATE

As requested, the new and modified data listings are attached and include subjects treated with one or more doses of study drug and are ordered by center, treatment and subject. Paper and SAS transport format files are provided except where otherwise noted. This response consists of three volumes and is organized according to the clinical information request letter. For example, Attachment 3A contains the information requested in 3a of the letter. Attachment 2 contains the narratives of the PMS/PMDD and HRT studies in Word 97 format. Attachment 3 contains the SAS transport files.

2. **Please provide narrative portions of Final Reports (pg. 1-62, PMS/PMDD Study) and (pg. 1-50, HRT Study) and Text Tables (if possible) in electronic format (Word 97 is preferred).**

The narrative and text tables of the final report (pgs. 1-62, PMS/PMDD) are provided in Word 97 on a compact disc and are located in Attachment 2. For the purposes of the November 6, 2000 submission, cross-referencing for this report was done electronically. However, for this submission, there is no electronic link. Therefore, the cross-reference now reflects the term "Error-no bookmark".

The narrative and text tables of the final report (pgs. 1-50, HRT) are provided in Word 97 on a compact disc and are located in Attachment 2. Internal cross-referencing for this report was done manually. Therefore, all cross-referencing notations remain in place.

PMS/PMDD Study

3. **Please modify the following previously supplied listings as requested above in No. 1:**

a) Listing 16.1.7 (Subject Disposition, Vol. 1)

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

b) Listing 16.2.8 (Laboratory Data, Vol. 3)

- **Limit data to potassium and sodium values only.**

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

c) Listing 19 (Laboratory Data Dates, Vol. 16)

- **Limit data to column "Lab Type" and entry of "Chemistry," (Paper copy only)**

The paper copy of this information is located in Attachment 3C.

4. **Please provide the following new Listings:**

a) Subject potassium values/listings that were basis for potassium values in Table 19 (Vol. 1, pate 169) and summary data in Text Table 16 (Vol. 1, page 56); (Paper copy only requested).