BERLEX

TELEFAX
UPS OVERNIGHT

ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

January 18, 2000

ORIG AMENDMENT

BZ

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

Dear Dr. Rarick:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
AMENDMENT TO PENDING APPLICATION:
Final Report of Drug Interaction Study

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

Reference is also made to our submission dated January 6, 2000. In that submission, Berlex provided a timeline as to the status of three studies. At this time, Berlex is submitting the final study report, which consist of two volumes, for the following study:

Drug Interaction Study, **Report B277**: "Open-Label, Crossover Study To Assess The Potential Of Drospirenone (DRSP) To Inhibit CYP2C19 By Evaluating The Metabolic Interaction Between DRSP And Omeprazole As Model Substrate In Healthy Postmenopausal Volunteers Genotyped For Polymorphism Of CYP2C19" (Protocol ME98231). An archival and review copy of the report are provided.

This study was conducted by our parent company, Schering AG, in Berlin, Germany and completed in November 1999. A draft of the protocol for the study was submitted to [redacted] on April 16, 1999 (Serial No. 031) in follow up to our Pre-NDA meeting where the Division suggested that Berlex consider conducting such a study.

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

1 page

As briefly communicated in the teleconference on December 15th, the results indicate that no significant influence from the co-administration of DRSP on the bioavailability (AUC) of the CYP2C19 enzyme substrate (omeprazole) and the CYP2C19 enzyme product (5-hydroxy-omeprazole) was found. Similar results were found for the CYP3A4 enzyme product (omeprazole sulfone). Therefore, the results of this clinical study did not demonstrate an inhibition of the cytochrome P450 enzymes 2C19 and 3A4 by DRSP in humans. Drug-drug interactions between DRSP and drugs whose metabolic pathways are catalyzed by CYP2C19 and CYP3A4 appear highly unlikely.

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

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc007

Desk copy (cover letter): Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: May 4, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Clinical Information Request

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 9, 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

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
5/4/01 02:33:58 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: April 4, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Addendum to April 2, 2001, Memorandum of Telecon, Chemistry Request Clarification, Item # 1

Please refer to your submission dated March 30, 2001, OTHER: Response to Chemistry Request of February 28, 2001

1. [redacted]

Our chemist has reviewed the amendment to [redacted] for Drospirenone for the "Modification to Synthesis C", and has found this modification to be acceptable. Therefore, the amendment to DMF [redacted] for the "Modification to Synthesis C" is effective for this NDA review cycle.

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

/s/

Jeanine Best
4/4/01 01:49:45 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Tran/Rhee

Drafted by: JAB/April 4, 2001
Final: April 4, 2001
Filename:

TELECON

MEMORANDUM OF TELECON

DATE: April 4, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Request for Additional Clinical Information for Review of NDA 21-098

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?
2. In your Safety Update of March 28, 2001 (Item 1.4.5), you state that [redacted] packets 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.
   b) Please provide information on the likely relationship between sales and actual patient use in the countries to which the [redacted]. 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?
3. In the Safety Report for the HRT Study (Protocol 96097), Subject No. 36041 is listed has 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.

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

/s/

Jeanine Best
4/4/01 12:49:28 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Hixon/Monroe

Drafted by: JAB/April 4, 2001
Final: April 4, 2001
Filename:

TELECON

MEMORANDUM OF TELECON

DATE: April 2, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Chemistry Request Clarification

Please refer to your submission dated March 30, 2001, OTHER: Response to Chemistry Request of February 28, 2001

1. The changes to the DMF in the November 6th amendment are acceptable; they are not effective at this time. The DMF changes would be effective at the time of approval of a post approval supplement.
2. The Division acknowledges that the changes in the manufacture of the drospirenone drug substance, as described in the November 6, 2000 CMC amendment (November 6 amendment to Schering AG DMF [redacted], are not being withdrawn, but they would be handled in a post approval supplement.

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Tran/Rhee

Drafted by: JAB/April 2, 2001
Final: April 2, 2001
Filename:

TELECON

APPEARS THIS WAY
ON ORIGINAL

/s/

Jeanine Best
4/2/01 03:04:16 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

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

5 pages

MEMORANDUM OF TELECON

DATE: March 7, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Clinical Information Request

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.

   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.

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.

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.

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.

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Monroe

Drafted by: JAB/March 7, 2001
Final: March 7. 2001
Filename:

TELECON

APPEARS THIS WAY
ON ORIGINAL

/s/

Jeanine Best
3/7/01 11:21:14 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: March 1, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Clinical Information Request

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.

   a) Were serum potassium values for any of these samples provided to Berlex by the [redacted] 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 5 B for the PMS/PMDD Study.

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?

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

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

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

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

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

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

/s/

Jeanine Best
3/1/01 11:01:41 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Monroe

Drafted by: JAB/March 1, 2001
Final: March 1, 2001
Filename

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: February 28, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Chemistry Amendments

1. Please withdraw the chemistry amendments dated November 6, 2000 and January 16, 2001.
2. Please send correspondence confirming your understanding of the February 11, 2000 teleconference, and stating that "impurity specifications will be implemented at release". A request to eliminate this testing can be submitted to the Division in a post-approval supplement. This post-approval supplement must contain data from at least 10 U.S.-marketed lots.

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

/s/

Jeanine Best
2/28/01 01:20:45 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Tran/Rhee

Drafted by: JAB/February 28, 2001
Final: February 28, 2001
Filename:]

TELECON

MEMORANDUM OF TELECON

DATE: February 20, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products,HFD-580

SUBJECT: Clinical and Statistical Information Request

We thank you for your prompt reply to our request of February 2, 2001 for additional information regarding the Safety Report for the PMS/PMDD Study.

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).

1. Please verify that Table 18, pg. 304, Vol. 20 in the Safety report is the correct analysis.
2. Please verify that the potassium values listed for Protocol 96097A in Text Table 5, pg. 24 of the Briefing Document 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.
   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.
   c) Change from baseline potassium where change is based on the maximum post baseline potassium value.
   d) Change from baseline potassium where change is based on the average post treatment potassium value.

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

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

/s/

Jeanine Best
2/20/01 02:29:24 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: February 2, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products,HFD-580

SUBJECT: Clinical Information Request

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)
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.
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.

We have requested this information to facilitate our interpretation of the serum potassium data provided in the PMS/PMDD Study. Specifically, we are interested in knowing (1) if a measurement was obtained while the subject was on active therapy (i.e., one of cycle days 1-21) or on placebo therapy (one of cycle days 22-28) and (2) for how many consecutive days the subject was on active therapy immediately prior to obtaining the blood sample. Similar information is not required for the HRT Study since subjects received the same therapy on each treatment day.

/S/

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Monroe

Drafted by: JAB/February 2, 2001
Final: February 2, 2001
Filename:

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: December 12, 2000

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 276-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division Of Reproductive and Urologic Drug Products,HFD-580

SUBJECT: Clinical Information Request

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.
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).

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)
   b) Listing 16.2.8 (Laboratory Data, Vol 3)
      - Limit data to potassium and sodium values only.
   c) Listing 19 (Laboratory Data Dates, Vol 16)
      - Limit data to column "Lab Type" and entry of "Chemistry," (Paper copy only)
4. Please provide the following new Listings:
   a) Subject potassium values/listings that were basis for potassium values in Table 19 (Vol. 1, page 169) and summary data in Text Table 16 (Vol. 1, page 56); (Paper copy only requested).
   b) Paper and electronic versions of a listing of potassium (K) and sodium (Na) values in the following format:

Subject No.	Treatment	Potassium and Sodium Values		
		Visit A →	Visit B →	Visit Z
		Date, K, & Na	Date, K, & Na	Date, K, & Na
1	DRSP/EE	xx/yy/zz 4.9, 140	xx/yy/zz 4.3, 144	xx/yy/zz 4.5; 141
2	Placebo	xx/yy/zz 4.7, 145	xx/yy/zz 4.6, 143	xx/yy/zz 4.6, 144
Etc				

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

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

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

HRT Study

6. Please provide an electronic version of data contained in Listing 6 (Chemistry, Vol. 30); maintain format of listing with chemistry values in columns by type of chemistry analysis.
7. Please provide the following new listings to include only subjects that received study drug:
   a) A listing of (1) medication start dates, (2) last dose dates, and (3) compliance (%); these are the last 3 columns in Listing 16.2.5 (Vol. 23).
      - Format in columns as shown below:

        "Investigator/Treatment/Subject No./Med start date/Last dose date/% compliance
   b) Paper and electronic versions of a listing of potassium (K) and sodium (Na) values in the format described above under 4 b.
   c) For Text Table 6: Concomitant use of Selected Medications (Vol. 19, Pg 34)
      - Please provide a listing of the subjects by treatment group and concomitant medication who were taking the listed concomitant medications (Paper copy only).
   d) For Table 17 (Vol. 20, Potassium data only, pg. 271, 279, 287, 295, 303)
      - Please provide a listing of the subjects and their K values in each of the respective groups that are represented in the Table for the entry of potassium.

/S/

Jeanine Best, M.S.N., R.N., Regulatory Project Manager

cc:
Archival NDA 21-098
HFD-580/Division Files
HFD-580/Monroe

Drafted by: JAB/December 12, 2000
Final: December 12, 2000
Filename:

TELECON

APPEARS THIS WAY
ON ORIGINAL

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

2 pages

BC51

Meeting Minutes

1) 2000

Date: September 25, 2000 **Time:** 9:00-10:30 AM **Location:** Parklawn; Conference Room "C"

NDA 21-098 **Drug:** Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Type "A" Industry Meeting

Meeting Chair: Dr. Susan Allen

External Lead: Ms. June Bray

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Victor Raczkowski, M.D., M.S., Deputy Director, Office of Drug Evaluation III, (ODE III; HFD-103)
Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Jerry Willett, M.D., Acting Team Leader, DRUDP (HFD-580)
Dena Hixon, M.D., Medical Officer, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Doug Throckmorton, M.D., Deputy Director, Division of Cardio-Renal Drug Products, (DCRDP; HFD-110)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D., Team Leader, Division of Biometrics II (DB II) @ DRUDP (HFD-580)
Terri Rumble, B.S.N, Chief, Project Management Staff, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex/SAG
Don Atkinson, Director, Marketing, Female Healthcare
June Bray, Vice President, Drug Regulatory Affairs
Sharon Brown, Associate Director, Drug Regulatory Affairs
Wolfgang Eder, Ph.D., Director, Project Management, Female Healthcare
Marie Foegh, M.D., Director, Female Healthcare
Adel Karara, Ph.D., Associate Director, Clinical Pharmacology
Pran Marrott, M.D., Vice President, Cardiovascular Development
Louise Palma, Manager, Clinical Data Management
Harji Patel, Ph.D., Associate Director, Biostatistics
Rolf Schuermann, M.D., Head, Clinical Research, Female Healthcare

Nancy Velez, Manager, Drug Regulatory Affairs

Consultants:

Meeting Objective: To discuss the sponsor's response to the issues presented in the July 10, 2000 Approvable Action letter for Yasmin.

Background:
Yasmin is a combination oral contraceptive that contains a new molecular entity, drospirenone (DRSP), a progestin that has anti-mineralocorticoid activity similar to that of spironolactone. Berlex received an Approvable Action for Yasmin on March 17, 2000 because results from a study in renally impaired patients were not available. The results from the study in renally impaired patients, potassium data from an ACE Inhibitor interaction study, and revised labeling were submitted on May 8 and 9, 2000. Berlex received a second Approvable Action for Yasmin on July 10, 2000 because the Agency felt that further clinical studies were needed to assess the theoretical risk of hyperkalemia in women using the product.

Discussion:
- See attached slides for presentation content

Questions:
1. Based on the additional data, does the Division concur that no additional studies are needed prior to approval?

- the summary reports for the PMDD/PMS study (Protocol 97036) and the HRT study (Protocol 96097) presented in today's meeting package appear to provide the additional study data to further assess the risk of hyperkalemia in women using Yasmin as outlined in the July 10, 2000 Approvable letter; the sponsor should submit these studies for review, along with the other items outlined in the July 10, 2000 Approvable letter, as a complete response to the July 10, 2000 Approvable letter; final study reports for these studies are not required as long as the essential safety data are provided in detail; the submission will be reviewed on a standard six-month review clock for a resubmission, once a complete response has been received

- the sponsor should submit electrocardiographic data from clinical studies, if any, which are pertinent to the assessment of the risk of hyperkalemia

- the sponsor should include data from studies using high does of drospirenone, and in special populations in its assessment of the risk of hyperkalemia
- the sponsor could examine and assess other potential benefits such as blood pressure reduction from the studies already conducted

2. Does the Phase 4 program, including the education aspect as outlined, address the Division's request?

- without final labeling, it is premature to give definitive comments on the proposed Phase 4 program; initial comments/recommendations include:
  - define the duration of the proposed components of the Phase IV program
  - include an assessment of prescribing behavior changes during conduct of the educational program
  - for the surveillance program to assess monitoring of inappropriate prescribing of Yasmin, a cut-off level of inappropriate prescribing should be determined prior to initiation of this program; a plan should be developed to manage inappropriate prescribing if the level of such prescribing exceeds the predetermined cut-off; chart reviews should be included in assessing inappropriate prescribing behaviors
  - the outline for the surveillance program for Adverse Events is good, but the Division will need more detail on the proposed program in the future
  - the Division has requested OPDRA's input on the proposed pregnancy monitoring program
- the sponsor reported that administrative reviews followed by chart reviews are not feasible; the sponsor must provide an argument for not performing chart reviews
- the sponsor's material should focus on the potential risk of hyperkalemia and not on the potential theoretical benefits of the antimineralocorticoid action
- the sponsor is aware that they cannot promote theoretical benefits without clinical studies to support the claims
- the sponsor will propose additional labeling changes in the resubmission; the renal impairment language and use in patients on NSAIDS will be revised

Decisions:
- the sponsor will submit their complete response to the July 10, 2000 letter in four to eight weeks; this submission will be placed on a six-month review clock

Action items:
- Meeting Minutes to sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Allen/Willett/Hixon/Monroe/Fulong/Parekh/Kammerman/Rumble
HFD-103/Raczkowski
HFD-110/Throckmorton
drafted:JAB/September 25, 2000
concurrence:Kammerman,09.25.00/Furlong,09.25.00/Raczkowski,09.25.00/Rumble,09.26.00/
Monroe,09.26.00/Hixon,09.29.00/Allen,10.17.00
final:JAB/October 17, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

FDA Meeting -Yasmin®

September 25, 2000

FDA approvable letter dated July 10, 2000

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

Agenda

Discussion Point	Discussion Leader	Time
Introduction	June Bray	2 min.
Hyperkalemia & Clinical Studies	Marie Foegh, M.D.	7 min.
Cardiovascular Safety & Clinical Studies	Marie Foegh, M.D.	5 min.
Overview of Spironolactone/ Potential Benefits of Yasmin		8 min.
Conclusion & Sumary	Marie Foegh, M.D.	1 min.
Phase IVCommitments / Educational Program	Don Atkinson	5 min.
Concluding Remarks	June Bray	2 min.

Evaluation Parameters

- Serum potassium levels
- Cardiovascular adverse events related to hyperkalemia
- New initiatives to better understand the risks in the target population

DRSP Patient Population

- OC NDA
  - US patients = 326
- New data
  - Young women - 129 (Placebo Control)
  - Age 45+ (HRT) - 891 (E2 Control)

Total new US patients: 1020

Populations Evaluated for Risk of Hyperkalemia

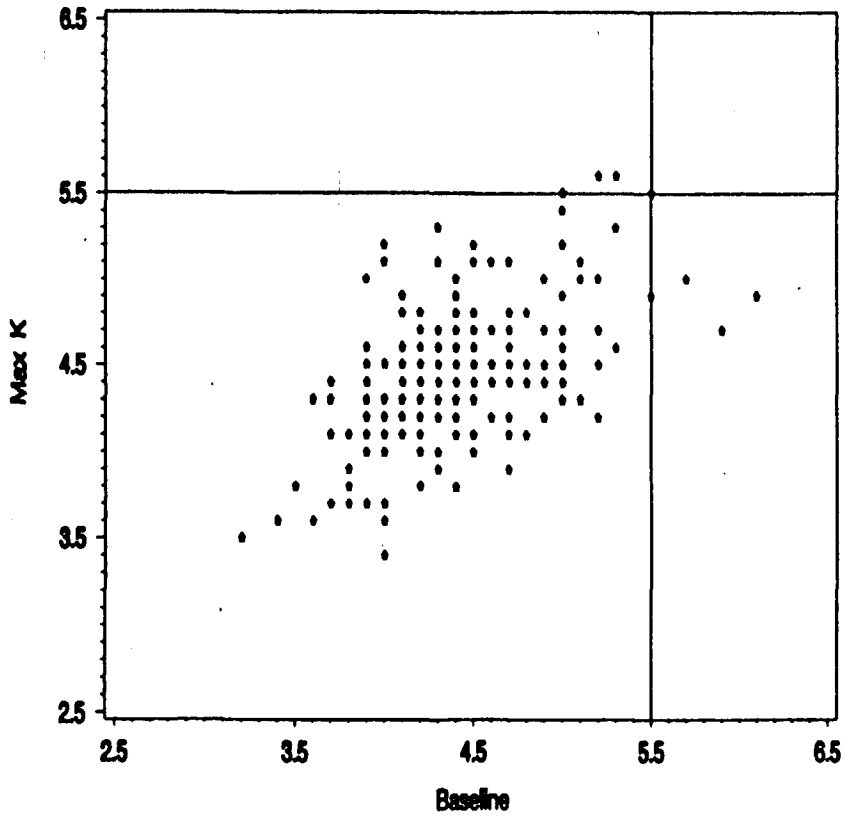
Population	NDA	NEW	Total
Younger Women 96049, 92052, 93044, ***97036***	3282	**259**	3541
Older Women ***96097***		**1114**	1114
Special Population			
ACE inhibitors (98106)	24		24
Renally impaired (303063)	28		28
Higher Dose			
High dose of DRSP (89092)	12		12
Very high single dose of DRSP (89015)	30		30
Total	**3376**	**1373**	**4749**
Total DRSP	**3250**	**1020**	**4270**

Serum Potassium Evaluations

- Serum Potassium (serum - K^+ $\geq$5.5 mEq/L)
  - Incidence of hyperkalemia
  - Mean change in serum K^+
  - Shifts from baseline of serum K^+
  - Scatter plot of baseline vs highest serum K^+
  - Impact of NSAID or ACE inhibitor on serum K^+
  - Impact of mild or moderate renal insufficiency on serum K^+
  - Impact of high dose

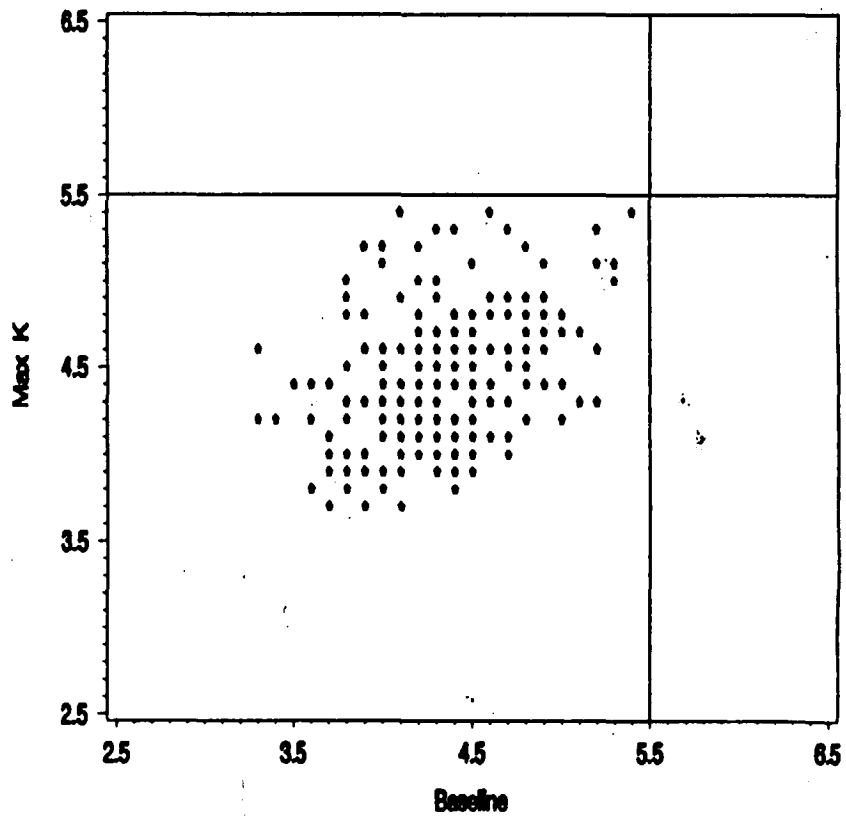
Maximum Serum Potassium vs. Baseline Potassium

Study 96097 - E2 1mg



Maximum Serum Potassium vs. Baseline Potassium

Study 96097 - E2 1mg/DRSP3mg



Yasmin
NDA 21-098

Special Studies

Studies show no clinically significant effects on serum potassium in hypertensive subjects receiving concomitant ACE inhibitors or subjects with mild to moderate renal insufficiency

Quantification of Potential Risk

- Incidence of hyperkalemia in the 16 to 44 year age group is 0.004% ①
- Number of women taking oral contraceptives with renal dysfunction is 1.4/10,000②
- Subjects with moderate to severe renal impairment are symptomatic and will be under medical care

①National Health & Nutrition Examination Survey (NHANES III)

Interpretation of Potassium Evaluations

1. Elevated serum potassium levels were equally distributed among controls and DRSP/combination groups
2. No apparent effect of NSAID or ACE Inhibitor use
3. No patients had serum potassium >6.0 mEq/L
4. No dose-response relationship

Conclusion

Yasmin did not present a risk for hyperkalemia in the OC population including use in patients:

- –On NSAIDs
- –On ACE inhibitors
- –With mild-moderate renal disease