Teleconference Meeting Minutes

Date: June 19, 2000 **Time:** 9:30-10:00 am **Location:** Parklawn; 17-B45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling Discussion

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex Laboratories, Inc.
Nancy Velez, Manager, Drug Regulatory Affairs
Sharon Brown, Associate Director, Regulatory Affairs
Nancy Konnerth, Manager, Advertising and Labeling
Paul Zhang, Senior Statistician, Biostatistics
Kelly Parsey, M.D., Senior Associate Medical Director
Wolfgang Eder, Director, Project Management
Adel Karara, Ph.D., Associate Director, Clinical Pharmacology
Don Atkinson, Director, Marketing
Jeff Frick, Strategic Business Director
Nancy Bower, Research Toxicologist

Meeting Objective: To discuss June 12 and 15, 2000 label revisions done by sponsor

Background: On May 9, 2000, the sponsor submitted a complete response to the approvable action of March 17, 2000, for their drospirenone/ethinyl estradiol product. Drospirenone (DRSP) is a new progestin and differs from other progestins in that it has antimineralocorticoid activity.

Discussion:

- The following labeling revisions are recommended by DRUDP:
    - **Special Populations** subsection, *Renal Insufficiency* , add the word "mean" to the sentence:

Number of Pages Redacted 1

❖❖❖

Draft Labeling
(not releasable

Decisions:

- Final Labeling is needed by Wednesday, June 21, 2000, in order to circulate Action Package to Director

Action Items:

- Berlex to submit proposed labeling revision by COB today
- Division to submit label revisions as discussed in this T-con by COB today

/S/
Minutes Preparer

/S/
Concurrence, Chair

6/21/00

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.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/ Mann/Monroe
drafted:JAB/June 19, 2000/
concurrence: Monroe,06.19.00/Mann,06.19.00
final:JAB/June 21,2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: June 9, 2000 **Time:** 1:30-2:00 pm **Location:** Parklawn; 17-B45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling Discussion

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Susan Allen, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex Laboratories, Inc.
Nancy Velez, Manager, Drug Regulatory Affairs
Sharon Brown, Associate Director, Regulatory Affairs
Nancy Konnerth, Manager, Advertising and Labeling
Harji Patel, Ph.D., Associate Director, Biostatistics
Paul Zhang, Senior Statistician, Biostatistics
Kelly Parsey, M.D., Senior Associate Medical Director
Adel Karara, Ph.D., Associate Director, Clinical Pharmacology
Don Atkinson, Director, Marketing

Meeting Objective: To discuss June 9, 2000 label revisions done by DRUDP

Background: On May 9, 2000, the sponsor submitted a complete response to the approvable action of March 17, 2000, for their drospirenone/ethinyl estradiol product. Drospirenone (DRSP) is a new progestin and differs from other progestins in that it has antimineralocorticoid activity.

Discussion:
- The following section has been revised by DRUDP to read:

  Effects of Oral Contraceptives on Other Drugs

Interactions of Drospirenone

- Interactions With Drugs That Have The Potential To Increase Serum Potassium

  "There is a potential for hyperkalemia to develop in women taking Yasmin with other drugs that may increase serum potassium levels. Such drugs include ACE Inhibitors, NSAIDS (e.g. indomethacin), potassium sparing diuretics, heparin, and aldosterone antagonists."

  "A drug:drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive post-menopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/mL higher than those noted in the placebo group. No patient in the DRSP/E2 group had an absolute potassium level higher than 5.2 mEq/mL."

- the sponsor prefers the wording "theoretical potential" in the first paragraph; the Division disagrees; "potential" is a more accurate and appropriate word to describe the risk that may exist with Yasmin:drug reactions and hyperkalemia
- the sponsor will be investigating the drug:drug reaction between DRSP and NSAIDS for their HRT indication
- the sponsor prefers the wording of the former second paragraph with the deletion of the words "or statistically":

  "The potential for development of hyperkalemia when drospirenone (DRSP) 3 mg /estradiol (E2) 1 mg or placebo was coadministered with the ACE inhibitor, enalapril maleate, 10 mg twice daily for fourteen days, to twenty-four mildly hypertensive postmenopausal women (age 52-76 years) was evaluated. There were no clinically ——— significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo."

- the Division's description of the actual ACE Inhibitor study is more accurate and useful for physicians in that it provides the most relevant information; the clinical significance is that it provides the slight subtle upward changes that occurred in potassium levels in patients in the treatment group; the Division cannot conclude that there were no clinically significant differences in serum potassium levels from this small study
- the sponsor's proposed revision of the last sentence in the second paragraph:

  "No patient in either treatment or placebo group developed hyperkalemia (5.5meq/mL)," is acceptable

- the sponsor proposed additional language to add to the end of the second paragraph to read:

  "Serum potassium was measured over 24-hours at baseline and at steady state day 14. The DRSP and placebo arms were bioequivalent in terms of serum potassium AUC and Cmax values."

The sponsor requests this additional sentence because their primary endpoint in the Ace Inhibitor study was the AUC for serum potassium; the Division will agree to this statement in the label if the sponsor provides the calculations of bioequivalence for the Biopharm reviewer and the Division concurs with the calculations

Decisions:

- the Division will consider the proposed labeling language and review the results of the bioequivalence data

Action Items:

- Berlex to submit final label for review by June 9, 2000
- Minor editing changes may be conveyed by the Division and negotiated with Berlex by June 15, 2000
- Berlex to submit bioequivalence data on the ACE Inhibitor study by early week of June 11, 2000

/S/
Minutes Preparer

/ / /S/
Concurrence, Chair

6/20/00

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.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Allen/Mann/Monroe
drafted:JAB/June 9, 2000/
concurrence: Mann,06.09.00/Rumble,06.15.00
final:JAB/June 20, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: June 8, 2000 **Time:** 12:30-12-55 pm **Location:** Parklawn; 17-B45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling Information and Guidance

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex Laboratories, Inc.
Nancy Velez, Manager, Drug Regulatory Affairs
Sharon Brown, Associate Director, Regulatory Affairs
Nancy Konnerth, Manager, Advertising and Labeling
Marja Oinonen, Senior Staff Statistician, Biostatistics
Paul Zhang, Senior Statistician, Biostatistics
Kelly Parsey, M.D., Senior Associate Medical Director
Adel Karara, Ph.D., Associate Director, Clinical Pharmacology
Don Atkinson, Director, Marketing
Jeff Frick, Strategic Business Director, Marketing

Meeting Objective: To discuss June 7, 2000 label revisions.

Background: On May 9, 2000, the sponsor submitted a complete response to the approvable action of March 17, 2000, for their drospirenone/ethinyl estradiol product. Drospirenone (DRSP) is a new progestin and differs from other progestins in that it has antimineralocorticoid activity.

Discussion:

- The following section has been revised by the sponsor (with Division input) to read:

  Effects of Oral Contraceptives on Other Drugs

  Interactions of Drospirenone

- *Interactions With Drugs That Have The Potential To Increase Serum Potassium*

  "There is a theoretical potential for the development of hyperkalemia in women using Yasmin concomitantly with other drugs, such as ACE inhibitors, NSAIDS (e.g., indomethocin) potassium-sparing diuretics, heparin and aldosterone antagonists, that may increase serum potassium levels."

- the sponsor would prefer only mentioning indomethacin in the above statement, rather than the general term NSAIDS, but the Division feels that the sponsor has not provided evidence that can refute that the use of NSAIDS (as a class) with drospirenone has no risk
- Yasmin is the first OC that possesses antimineralocorticoid activity, and the potential associated risks; women should be informed of all of these potential risks, even theoretical risks, because there are many other choices on the market, and there are many women that use these products, and the result of hyperkalemia can be death
- The next paragraph in this section has been proposed by the sponsor to read:
  From:

  "The potential for development of hyperkalemia when drospirenone (DRSP) 3 mg /estradiol (E2) 1 mg or placebo was co-administered with the ACE inhibitor, enalapril maleate, 10 mg twice daily for fourteen days, to twenty-four mildly hypertensive postmenopausal women (age 52-76 years) was evaluated. There were no clinically ~~~~ . *<can remain if additional analysis is performed to confirm this>* significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo."

  To:

  "However, no clinically or statistically significant differences in serum potassium concentrations were observed in women given drospirenone (DRSP)/E2 or placebo with an ACE Inhibitor. In this study, DRSP 3 mg/estradiol (E2) 1 mg or placebo was coadministered with the ACE Inhibitor, enalapril maleate, 10 mg twice daily for fourteen days, to twenty-four mildly hypertensive postmenopausal women (age52-76 years)."

- the sponsor wanted to avoid having the above cautionary paragraph in their label; a similar statement appears in the Netherlands label; the Netherlands label was approved prior to completion of the ACE Inhibitor study; the Division does not feel that a single, small study (24 patients), with a single drug allays all concerns for a possible interaction with other potassium sparing drugs, including other ACE inhibitors; physicians should have this precaution available for their reference, as Gynecologists are not used to prescribing OC's that possess antimineralocorticoid activity
- comparison done with the cautions in the Aldactone label, but the Division emphasized that Aldactone is used for a small, specific population and the physicians who prescribe the drug are very aware of its effects, and it is usually prescribed precisely because of its antimineralocorticoid activity.
- the sponsor has completed the requested statistical analysis on the potassium level data in the ACE Inhibitor Study and found that there was no statistical difference found; the words "or statistically" may remain in the above paragraph if the Division's statistician concurs with the sponsor's statistician
- the sponsor also questioned the inclusion of the following paragraph requested by the Division:
  PRECAUTIONS section, 11. **Pregnancy**:

"Sixteen pregnancies that occurred with Yasmin exposure in utero (no more than a single cycle of exposure) have been identified. One baby boy was born with esophageal atresia. This single case does not establish any causal association with Yasmin."

- The Division responded that there is an Agency-wide effort to have labels contain pregnancy and birth outcome data, especially with drugs that can possibly taken by women in early pregnancy without their knowledge of the pregnancy; this information is more useful to women than the current pregnancy classification data; the sponsor can look at other recently approved drugs for use in women to observe such language (such as Antagon)

Decisions:

- the Division will consider the proposed labeling language and review the results of the statistical analysis

Action Items:

- Berlex to fax and e-mail Physician label revisions on pages 14 and 16 by COB today, for review by the Division
- Berlex to return revised labeling on Friday, June 9, 2000, electronically and on a Word diskette, containing marked-up and unmarked copies
- Berlex to submit statistical analysis data on the ACE Inhibitor study on Friday, June 9, 2000

/S/
Minutes Preparer

/S/
Concurrence, Chair
6/19/00

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.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Mann/Monroe
drafted:JAB/June 9, 2000
concurrence: Mann,06.09.00/Rumble,06.13.00
final:JAB/June 16, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: June 7, 2000 **Time:** 3:30-3:50 pm **Location:** Parklawn; 17-B45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling Information and Guidance

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex Laboratories, Inc.
Nancy Velez, Manager, Drug Regulatory Affairs
Sharon Brown, Associate Director, Regulatory Affairs
Nancy Konnerth, Manager, Advertising and Labeling

Meeting Objective: To provide the sponsor with additional labeling edits.

Background: On May 9, 2000, the sponsor submitted a complete response to the approvable action of March 17, 2000, for their drospirenone/ethinyl estradiol product. Drospirenone (DRSP) is a new progestin and differs from other progestins in that it has antimineralocorticoid activity.

Discussion:

- Revise the following section:

  Effects of Oral Contraceptives on Other Drugs

  Interactions of Drospirenone

  - Interactions with drugs that have the potential to increase serum potassium

"There is a potential for the development of hyperkalemia in women using Yasmin concomitantly with other drugs, such as ACE inhibitors, NSAIDS, potassium-sparing diuretics, heparin and aldosterone antagonists, that may increase serum potassium levels."

"The potential for development of hyperkalemia when drospirenone (DRSP) 3 mg /estradiol (E2) 1 mg or placebo was co-administered with the ACE inhibitor, enalapril maleate, 10 mg twice daily for fourteen days, to twenty-four mildly hypertensive postmenopausal women (age 52-76 years) was evaluated. There were no clinically ~~significant~~ *<can remain if additional analysis is performed to confirm this>* significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo."

- the above section was revised to contain language similar to that found in the Netherlands labeling for drospirenone; Division's concern is that Gynecologists are not used to prescribing OC's that have antimineralocorticoid effects; Division is not recommending baseline potassium levels as done in the Netherlands
- the wording '~~significant~~' can remain in the above paragraph if an additional analysis is done and demonstrates a lack of statistical significance; repeated measures analysis by day and treatment effect; this analysis must be performed on the data in presented in Text Table 3 that appeared in the sponsor's April 20, 2000 submission, containing data on potassium levels in the ACE Inhibitor Study
- Insert the following paragraph In **PRECAUTIONS** section, 11. **Pregnancy** to follow the existing paragraph:

"Sixteen pregnancies that occurred with Yasmin exposure in utero (no more than a single cycle of exposure) have been identified. One baby boy was born with esophageal atresia. This single case does not establish any causal association with Yasmin."

Decisions:

- the Division will be available on June 19, 2000, between 9:00-10:00 am to fine tune the labeling; i.e., minor editing and wording revisions; if major labeling discussions are requested by the sponsor, then the Division will have to schedule more internal discussions, and include the Office; Division clarified, however, that the bolded warning and contraindications statements were considered pivotal to be included in the labeling

Action Items:

- J. Best to fax and e-mail Physician label revisions by COB
- Berlex to return revised Physician label by Friday, June 9, 2000, electronically and on a Word diskette, containing marked-up and unmarked copies
- Berlex to revise Brief and Detailed Patient labeling to correspond with Physician label and other OC patient labels with the exception of the antimineralocorticoid warnings, and return by Friday, June 9, 2000, electronically, and on a Word diskette, containing marked and unmarked copies

/S/
Minutes Preparer

/S/
Concurrence, Chair 6/19/00.

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/Mann/Monroe
drafted:JAB/June 7, 2000
concurrence: Monroe,06.08.00/Mann,06.08.00/Rumble,06.13.00
final: JAB/June 14, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: June 2, 2000 **Time:** 1:25-1:35 pm **Location:** Parklawn; 17-B45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling Information

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Nancy Velez, Manager, Drug Regulatory Affairs, Berlex Laboratories, Inc.

Meeting Objective: To provide the sponsor with rationale for labeling edits.

Background: On May 9, 2000, the sponsor submitted a complete response to the approvable action received on March 17, 2000, for their drospirenone/ethinyl estradiol product. Drospirenone is a new progestin and differs from other progestins in that it has antimineralocorticoid activity. The sponsor conducted a small study in mild to moderate renally-impaired subjects, controlling diet to low potassium use, and found a small increase in serum potassium levels in some of the subjects who were given the drug product. The sponsor included the following language in the **Special Populations** subsection under Renal Insufficiency: " Therefore, potential exists for hyperkalemia to occur in subjects with mild or moderate renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs."

Discussion:

- labeling discussions occurred amongst the Division and at the Office level, and it was decided that a **WARNING** regarding the use of Yasmin needs to be added to the label, cautioning about use in patients with hepatic dysfunction or renal insufficiency; antimineralocorticoid effects are not expected with other oral contraceptives; it is an unnecessary risk to expose a very small segment of oral contraceptive users (women with renal insufficiency or hepatic dysfuntion) to this potential side effect, when there are many other products on the market that lack this particular side effect

- the following bolded statement needs to be added to the WARNINGS section of the label under the Black Box Warning regarding cigarette use:

  "Yasmin contains the new progestin, drospirenone, which has antimineralocorticoid activity. Potential risks of Yasmin in renally or hepatically impaired patients include hyperkalemia, hyponatremia, and metabolic acidosis. Yasmin is contraindicated in patients with hepatic dysfunction or renal insufficiency."
- The Division will consider minor wording changes but with Office concurrence, DRUDP strongly feels that this warning needs to remain in the label

Action Items:

- J. Best to fax and e-mail Physician label revisions by COB
- Berlex to return revised Physician label within one week on a Word diskette, containing marked-up and unmarked copies
- Berlex to revise Brief and Detailed Patient labeling to correspond with Physician label and return in one week on a Word diskette, containing marked and unmarked copies

/S/
Minutes Preparer

/S/
Concurrence, Chair
6/5/00

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.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Mann

drafted:JAB/June 2, 2000
concurrence: Mann,06.02.00/Rumble,06.05.00
final:JAB/June 5, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: February 23, 2000 **Time:** 10:35-11:05 am **Location:** Parklawn; 17B-43

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Chemistry Teleconference

Meeting Chair: Dr. Moo-Jhong Rhee

External Lead: Ms. Sharon Brown

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (ONDC II) @ DRUDP, (HFD-580)
Suong Tran, Ph.D., Review Chemist, ONDC II @ DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:Berlex Laboratories, Inc:
Sharon Brown, Associate Director, Drug Regulatory Affairs
Geoff Millington, Manager, Drug Regulatory Affairs
Paul Vandenberg, Ph.D., Vice President of Quality Affairs
Nancy Velez, Manager, Drug Regulatory Affairs
Monika Wolff, Ph.D., Head of Analytical Services

Schering AG, Berlin, Germany:
Wolgang Heil, Ph.D., Manager, Oral Dosage Forms
Ralph Lipp, Ph.D., Head of Oral Dosage Forms
Marita Schollmeyer, Ph.D., Section Head, Analytical Development, Female Health Care

Meeting Objective: To discuss and resolve expiration date issue on Yasmin™ Package

Discussion:
- Sponsor is requesting a 36-month expiration date for their drug product but only have 18-month real time data from 3 production batches and 24-month real time data from pilot batches to support the expiration date; normally expiration date can be extrapolated based on six-month accelerated data up to 18-month (per ONDC practice), but real time data are needed for beyond 18 months
- Sponsor reports that they have gone beyond the ICH guidelines (using pilot scale batches of at least 10% size of manufactured batches), and provided 24-month real time data for pilot scale batches; also are doing confirmatory studies with the production scale batches

- If there is a strong linkage between pilot scale and production scale batches, 24-month data from pilot batches can be used to extrapolate the real time data from the production batches up to 24 months
- Sponsor feels they have met the SUPAC/IR requirements for a strong linkage between their pilot scale and full scale batches; will fax one page comparison sheet now for review to justify the strong linkage
- Received manufacturing comparison sheet comparing the pilot plant to the final production site; discussed items; Division requires more information to complete their review; sponsor to fax information by COB today regarding process parameters of the equipment used

Decisions Made:

- Division will review the submitted and to-be-submitted information to see if more than a 18-month expiration date can be granted based on the real time data from the pilot scale batches

Action Items:

- Sponsor to provide fax (followed by Federal Express hard copy) of the process parameters comparing the equipment used in the manufacturing processes of the pilot batches and the production batches
- Sponsor to provide mock-ups of all product containers; fax today, followed by Federal Express delivery of hard copy
- Division agrees to review information in a two day time frame; and notifying sponsor immediately if further information or clarification is needed

/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.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Rhee/Tran
drafted:JAB/February 23, 2000
concurrence:Rhee,02.23.00/Tran,02.23.00
final:JAB/February 23, 2000
MEETING MINUTES

Meeting Minutes

FEB 14 2000

Date: February 11, 2000 **Time:** 9:30-10:00 am **Location:** Parklawn; 17B-45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Chemistry/Biopharmaceutics Teleconference

Meeting Chair: Jeanine Best

External Lead: Geoff Millington

Meeting Recorder: Jeanine Best

FDA Attendees:
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, Division of reproductive and Urologic Drug Products (DRUDP, HFD-580)
Vekateswar Jarugula, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Suong Tran, Ph.D., Review Chemist, DNDC II @ DRUDP (HFD-580)
Monique Wakelkamp-Barnes, Ph.D., Pharmacokinetics Reviewer, OCPB (HFD-870)

External Attendees:
Berlex Laboratories, Inc:
Kishor Dandekar, Ph. D. Associate Director, Clinical Pharmacology
Geoff Millington, Manager, Drug Regulatory Affairs
Monika Wolf, Ph. D., Head of Analytical Services

Schering AG, Berlin, Germany:
Marita Schollmeyer, Ph.D., Section Head, Analytical Development, Female Health Care

Meeting Objective: To discuss and resolve Chemistry and Biopharmaceutic issues.

Discussion:
Chemistry:

- Division still has issues with January 31, 2000 response to Chemistry IR letter:
  - Question # 19; Blister label should contain lot and expiration date
  - Question # 20; In Attachment 10 of the amendment, there is a typing error in the unit carton label for the 21 day dose; submitted carton states "28 days"
  - Question # 9; Sponsor wants to omit release testing for decomposition products; sponsor saw no degradation products for drospirenone during development and accelerated stability testing and believes that the product is very stable

- FDA finds ethinyl estradiol to be not as stable as drospirenone; in addition, Yasmin is treated as a new NME as a whole; therefore, release testing for impurities and decomposition products must be implemented; without this data, it would be difficult to assess any future change in the manufacturing process
- A request to omit this release testing may be reviewed in a post approval supplement, when test results are available for a significant number of product lots that show the lack of impurities and decomposition products at release; results from the first ten lots as proposed by the sponsor would be acceptable for review in such a supplement

Biopharmaceutics:

Major Metabolite Information:

- Received fax regarding information on the two major metabolites of drospirenone; DRUDP will review this data
- The enzyme responsible for the formation of these two metabolites should be characterized; if not formed in *in vitro* studies, then not p450 dependent process; Division cannot find control to support sponsor's statement; sponsor to provide more in-depth report early next week

Dissolution Information:

- Biopharm and Chemistry reviewers have ongoing discussion with regard to dissolution specification; this discussion will continue into next week and Division will inform sponsor of decision
- Division recommendation is [redacted] @ 20 minutes; sponsor understands SUPAC guidelines to be Q[redacted], @ 30 minutes; Division interpretation is that timepoint dissolution specifications are based on data submitted for the drug product
- Dissolution profile of drospirenone @ 20 minutes= [redacted] release; therefore, data at 20 minutes would be more discriminating from an *in vitro* point of view; *in vivo* determination would be up to the sponsor

Action Items:

- Sponsor to amend Blister Label to include lot and expiration date information
- Sponsor to correct typing error on product carton for the 21 day dose packet
- Sponsor to implement stability testing for at least 10 lots at release
- Sponsor to submit additional in-depth information on the two main metabolites of drospirenone during week of 2/13/00
- Division to respond to sponsor with regard to dissolution profile conclusions by 2/18/00

/S/

Chair/Minutes Preparer

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/PM/Best
HFD-580/Tran/Jarugula/Rumble
HFD-870/Wakelkamp
drafted:JAB/February 11, 2000
concurrence:Wakelkamp,02.11.00/Tran,02.11.00/Rumble,02.14.00
final:JAB/February 14,2000
MEETING MINUTES

Teleconference Memo

Date: January 27, 2000 **Time:** 10 am **Location:** Parklawn; 17B-45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

FDA Attendees:
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Berlex Laboratories, Inc. Attendees:
Sharon Brown, Associate Director, Drug Regulatory Affairs

Meeting Objective: To receive Berlex Laboratories, Inc.'s decision on whether they are still seeking an approval action, with restrictive labeling, or an approvable action for this review cycle.

Decisions Made:

- Berlex Laboratories, Inc. have decided to accept an approvable action for this review cycle, since their renal impairment study is still underway; they do not want to accept the restrictive labeling that would come with an approval action during this review cycle
- Berlex Laboratories, Inc. understands that for the Division will only grant the previously agreed upon two month review clock for the next review cycle, if the only information to be reviewed at that time is the renal impairment study and labeling; any other outstanding issues at the end of the current review cycle will lead to the standard review clock.

/S/

Memo Preparer

cc:
Original NDA 21-088
HFD-580/DivFile
final:JAB/February 28, 2000
Meeting Minutes Memo

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: January 4, 2000 **Time:** 2:45-2:55 pm **Location:** Parklawn; 17-B45

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Teleconference/Guidance

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Nancy Velez, Manager, Drug Regulatory Affairs, Berlex Laboratories, Inc.

Meeting Objective: To inform sponsor of anticipated action for NDA and timeline expectations information requests, study information requests, and revised labeling.

Background: PDUFA goal date is March 17, 2000; Division goal date is January 21, 2000, and since drug product contains an NME, it will require Office sign-off. The sponsor has two outstanding drug metabolism studies, a renal impairment study that is still in progress, outstanding chemistry and DMF holder information requests, outstanding 4-month Safety Update information, and outstanding labeling revision edits.

Discussion:

- Notified sponsor that an approval of their drug product at this time would require a label that mimics the spironalactone label, since data is not available on use in renally impaired patients; this is clearly not the desired approach for this product by either the sponsor or by the FDA, as the labeling could be quite restrictive and is based on incomplete data
- The preferred approach is to proceed with the NDA review and await the renal study results for final labeling; this may involve the need for an "approvable" action (pending final Division/Office concurrence), with the later submission of the renal study results an labeling that is appropriate for Yasmin

- Should the only outstanding issues at the time of an approvable action be the renal study results and finalized labeling, FDA would review this information in a 2-month time frame once submitted; completing the current NDA review in all other regards is therefore necessary, however, and there are several outstanding issues.
- Notified sponsor to respond to following requests within two weeks:
    1. Chemistry Information request
    2. Coordinate DMF holder (drospirenone) information response
    3. Submit the two outstanding drug metabolism studies
    4. Submit 4-month Safety Update information
    5. Submit updated label
    6. Submit protocol for renal impairment study; require a multiple-dose study with at least one cycle of use in renally impaired patients; cannot be a single-dose PK study, and, if this is the case, consider revising protocol in order to obtain a Yasmin label rather then a spironalactone label

Decisions made:

- Approvable letter will be issued at PDUFA goal date of March 17, 2000 if the above requests are responded to in a timely manner and the reviews progress as anticipated without problems
- Will continue to revise and edit all sections of the label with the exception of section on renally impaired patients
- Will commit to a 2-month review clock for review of the renal impairment study and final labeling, if that is the only data to be reviewed at the time; if other data needs to be reviewed then the standard review time will apply

Action Items:

- Berlex Laboratories will respond to above requests within two weeks

/S/
Minutes Preparer

/S/ 1/19/00
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/Mann/Rumble

drafted:JAB/January 6, 2000/
concurrence:Mann,01.06.00/Rumble,01.07.00
final:JAB/January 10,2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

DEC 16 1999

Date: December 15, 1999 **Time:** 10:20-11:00 am **Location:** Parklawn; 17B-43

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

Indication: Oral Contraception

Sponsor: Berlex Laboratories

Type of Meeting: Guidance

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Dena Hixon, M.D., Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Vekateswar Jarugula, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Suong Tran, Ph.D., Review Chemist, DNDC II @ DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)

External Attendees:
Dr. Harmut Blode, Scientist, Department of Pharmacokinetics, Schering AG
Ms. Nancy Bower, Research Toxicologist
Dr. Marie Foegh, Director, Female Health Care
Dr. Kelly Parsey, Associate Director, Female Health Care
Dr. Armen Melikian, Associate Director, Clinical Pharmacology
Ms. Nancy Velez, Manager, Drug Regulatory Affairs
Mr. Geoff Millington, Manager, Drug Regulatory Affairs

Meeting Objective:
To discuss Clinical, Chemistry, and Clinical Pharmacology issues that will impact approval and labeling of drug product.

Background:
Drug product is a combination oral contraceptive and contains a new molecular entity, drospirenone, a progestin that has properties similar to spironolactone.

Discussion:

Chemistry Issues:

- First review is complete; Information Request letter will be forthcoming in a few days
- Additional stability data has not been submitted, therefore, product would have very limited expiration (12 months)date unless data is submitted in a timely manner
- DMF deficiencies for drospirenone component; deficiency letter has been sent to the DMF holder; suggest sponsor coordinate with the DMF holder for a timely response

Clinical and Clinical Pharmacology Issues:

- Drug product (drospirenone) is extensively metabolized and is a new molecular entity; therefore, studies are required in renally and hepatically impaired patients.
- Require study results from renally impaired patients; this is critical to labeling of the drug product, or restrictive labeling (mimicking the spironolactone label) will be required
- Require drug/drug interaction study with omeprazole (2C-19 substrate) because of metabolism of drug product and possible interactions with other 2C-19 substrate products
- A drug/drug interaction study with ACE Inhibitors would also be helpful, particularly with post menapausal patients taking this drug as HRT, (a separate indication)
- OC Class Labeling does not exclude hepatically impaired patients; since NME, a small study with mild to moderately impaired patients (10-20 patients) would provide critical information; could do as a Phase 4 commitment

Decisions made:

Berlex Laboratories:

- Will submit chemistry stability information within 2 weeks
- Will hold ongoing conversations with deficient DMF holder to correct deficiencies in a timely manner
- Renal Impairment Study (a multiple dose study looking at creatinine clearance and hyperkalemia) is underway in Europe; to be completed in 1st quarter, 2000; results will be available in April, 2000; will submit a draft report when available
- Drug/drug interaction study with omeprazole (2C-19 and 3A-4 substrates) is complete; no interactions shown; will submit draft report at the beginning of January 2000; final report to be submitted at the end of January, 2000
- ACE Inhibitor drug/drug interaction study is underway with the HRT combination of drospirenone (3 mg) and estradiol in postmenapausal women; clinical part of study to finish in January 2000, with some results available by end of March 2000; will submit as data becomes available
- Have not done any study with hepatically impaired patients; would consider a Phase 4 commitment to do such a study
- No other clinical studies with the drug product are underway
- Will submit revised label around January 1, 2000; understand initial Division revisions are only preliminary and more will be forthcoming

FDA:

- PDUFA goal date (10-month) is March 17, 2000; Division is attempting to accelerate that date; however data on renally impaired subjects is considered very important; recommend submitting such data, even if it results in a 3-month review clock extension

- Will coordinate a revised goal date with sponsor; dependent on information submitted and timing of submission; major amendments would extend the review clock for 90 days; may extend 10-month clock to 13-months or 12-month clock to 15-months.
- Division will make every effort to address labeling and continue reviews so that the data o renally impaired subjects could be reviewed expeditiously
- The spironalactone label contains many warnings and precautions; these may also apply to drospirenone without support from data in renally impaired subjects

Unresolved decisions:

Action Items:

- Berlex Laboratories to develop plan and timeline for submitting data and information; will respond to Division in two weeks
- 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.

APPEARS THIS WAY
ON ORIGINAL

Date: January 28, 1999 **Time:** 10:00 AM - 11:30 AM **Location:** Parklawn C/R 'O'

Drug Name: drospirenone and ethinyl estradiol Tablets

External Participant: Berlex Laboratories, Inc.

Type of Meeting: Pre-NDA

Meeting Chair: Lisa Rarick, M.D.

External Participant Lead: Nancy Velez

Meeting Recorder: Christina Kish

FDA Attendees:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
Shelley Slaughter, M.D., Ph.D. - Medical Officer Team Leader, DRUDP (HFD-580)
Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)
Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D.- Chemist, DNDCII @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M. - Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics; Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Vanketeswar Jarugula, Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:
[redacted]
Herman Ellman, M.D. - Medical Director, Endocrinology and Fertility Control
Peter Boerrigter, M.D. - Senior Associate Medical director, Endocrinology and Fertility Control
Peter Cascella, Ph.D. - Associate Director, Clinical Pharmacology
Michael Dolker, Ph.D. - Head Statistician, Endocrinology and Fertility Control
Nancy Bower, M.S. - Research Toxicologist, Preclinical Development
June Bray - Director, Drug Regulatory Affairs
Sharon Brown - Associate Director, Drug Regulatory Affairs
Geoff Millington - Manager, Drug Regulatory Affairs
Nancy Velez - Manager, Drug Regulatory Affairs

[redacted]
Dr. rer. nat. Hartmut Blode - Scientist, Dept. Of Pharmacokinetics
Dr. rer. nat. Beate Seibert - Head of Project and Study Planning, Biological Development, Experimental Toxicology

January 28, 1999

Meeting Objectives:
To gain agreement on the proposed content and format of the upcoming NDA submission.

Discussion Points:

- Background
  - the sponsor has developed a new oral contraceptive
  - this will be a standard 12 month review
  - because this is a new molecular entity it will be signed off at the Office level
  - the sponsor anticipates filing the NDA early second quarter 1999
- Labeling
  - the sponsor's proposal to include pre-menstrual syndrome and acne indications are not acceptable
  - the proposed format for the label is acceptable
  - a section for drug-drug interactions should be included especially given the drugs potential for spironolactone-like activity
  - a clinical studies section discussing study data should be included
  - the how supplied section should include the final packaging form
  - the carcinogenicity section title should be revised to "CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY"
- Chemistry Manufacturing and Controls
  - the final packaging will be blister packages of 21 or 28 days
  - there are no differences between the clinical and commercial formulations
  - although two formulations were used in the phases of study, a bioequivalence study has been performed to link the two
  - all synthetic pathways and impurities have been identified; a full characterization will be submitted in the NDA application
  - the sponsor is encouraged to check the draft stability guidelines for storage conditions
  - the sponsors proposed tradename Yasmin has been submitted to the labeling and nomenclature committee for consideration
- Toxicology
  - a teleconference was held on January 19, 1999, during which it was determined that should an additional pre-clinical carcinogenicity study be required, it will be requested as a Phase 4 commitment
  - the studies completed for the pre-clinical portion of the application are sufficient for filing
- Clinical Pharmacology
  - the biopharmaceutic studies to be submitted in support of the new application will be sufficient for filing

- special population studies for renally and hepatically impaired patients should be considered by the sponsor if existing clinical data do not address safety and efficacy in these populations
- if the special studies have not been completed at the time an action is taken on the application, the lack of data will become labeling issues
- the sponsor is requested to consider confirming the *in-vitro* findings of CYP2C19 inhibition by conducting *in-vivo* studies (possible substrates: omeprazole, mephenytoin)
- the NDA should include details of the clinical formulation and the to-be-marketed formulation

- Clinical

  - the sponsors proposal to include in labeling post hoc secondary analysis of weight loss and quality of life claims with their product as compared to the comparator product will not likely be acceptable
  - if the sponsor is interested in pursuing such claims, another clinical study in which these outcomes are the primary endpoints should be performed, the sponsor is encouraged to submit draft protocols for review before initiating such studies
  - the sponsor did not treat uterine bleeding disturbances during the pivotal trials
  - all subjects in the endometrial biopsy study received an exit biopsy at cycle 13, these data will be provided in the NDA application
  - mineralocorticoid effects of this drug will be a safety issue, the sponsor is requested to submit various subset analysis to examine this issue
  - several of the warnings and contraindications currently in the spironolactone label may become part of this oral contraceptive label if the issues are not addressed. The sponsor is encouraged to submit justifications regarding why specific labeling restrictions are not germane to this drug product in their NDA submission
  - the sponsor should provide a separate listing of study subjects who enrolled in this study after having used other contraceptive products (oral, injectables or implants) as well as the time between discontinuation of the previous product before initiation of study drug (see attachment 1)

- Statistics

  - the sponsors proposed format and content is acceptable
  - the methods for summarizing the overall results are acceptable
  - the content and format of the SAS tables appear acceptable, a list of specific subset analysis will be provided (see attachment 2), and should be included in the NDA submission

- Miscellaneous

  - the proposed NDA index is acceptable
  - the case report form and case report tabulations are acceptable, the sponsor is reminded that they may submit these electronically and may request a copy of the guidance document regarding this if interested
  - the sponsor is encouraged to submit review summaries on disk in a word processing format, these should include both clinical and biopharmaceutic study summaries

drospirenone and ethinyl estradiol tablets
January 28, 1999

Decisions Reached:

- the overall proposal for the NDA application appears acceptable
- additional biopharmaceutic special population and drug interaction studies should be considered by the sponsor
- should additional toxicology studies be required they will be requested as Phase 4 commitments

Unresolved Issues: none

Action Items: see decisions reached

/S/

Minutes Preparer 2/19/99

/S/

Concurrence, Chair

ATTACHMENTS
Additional Items Requested from Berlex during 1.18.99 meeting
Data Request List for Contraceptive Studies

APPEARS THIS WAY
ON ORIGINAL

Additional Items Requested from Berlex during 1/18/99 Meeting:

1) Provide a listing of subjects who were enrolled and who had used OCs within 2 months of enrollment

2) Provide a listing of all subjects enrolled who were former injectable contraceptive users (E,P or A) and the date of last injection prior to enrollment

3) Provide a list of all subjects enrolled who were former contraceptive implant users and the date of implant removal prior to enrollment.

4) Analyze efficacy rates (perfect and typical use without an additional BCM) for the following groups:

- All subjects who did not use another BCM and who did not fall into one of these categories:

    a) Prior OC use within 2 months of enrollment
    b) Prior injectable hormonal product (E, P or A) within 10 months of enrollment

APPEARS THIS WAY
ON ORIGINAL

Data Request List for Contraceptive Studies

Efficacy Data: (1 Record per subject)

- Study Number
- Subject ID
- Center ID
- Treatment group (include code list)
- All demographic or physical characteristics used for entry criteria
- Age
- Race (include code list)
- Date on which first tablet was taken
- Did the subject become pregnant? (1=yes; 0=no)
  - If a pregnancy occurred, provide:
    - The cycle in which conception occurred
    - Date the pregnancy was diagnosed
    - Date of lab test confirming pregnancy
    - The outcome of the pregnancy (include code list)
    - The number of days from the first tablet taken to the cycle of conception
- Did the subject complete the study? (1=yes; 0=no)
  - If subject did complete the study, provide:
    - Cycle during which subject completed
    - Total number of cycles completed
    - Date on which last tablet was taken
    - Cycle during which last tablet was taken
    - The number of days from the first tablet taken to the last tablet taken
  - If subject did NOT complete the study, provide:
    - Date of discontinuation
    - Reason for discontinuation (include code list)
    - Cycle during which subject discontinued
    - Number of cycles completed prior to discontinuation
    - Date on which last tablet was taken
    - Cycle during which last tablet was taken
    - The number of days from the first tablet taken to discontinuation

Meeting Minutes

Date: February 12, 1997 **Time**: 9:30 - 11:00 AM **Location**: 13B-45 Parklawn

Drug Name: Drospirenone and ethinyl estradiol

External Participant: Berlex and Schering AG

Type of Meeting: Phase III

Meeting Chair: Lisa Rarick, M.D.

External Participant Lead: Sharon Brown, Associate Director, Regulatory Affairs, Berlex

Meeting Recorder: Christina Kish, CSO

FDA Attendees:
Lisa Rarick, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP (HFD-580)
Philip Corfman, M.D., Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Office of New Drug Chemistry II ONDCII) @ DRUDP (HFD-580)
Amit Mitra, Ph.D., Chemist, ONDCII @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., Pharmacologist, DRUDP (HFD-580)
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader, Division of Pharmaceutical Evaluation (DPEII) @ DRUDP (HFD-580)
Venkateswar Jarugulav, Ph.D., Biopharmaceutics Reviewer, DRUDP (HFD-580)
Kate Meaker, Ph.D., Statistician, Division of Biometrics II @ DRUDP (HFD-580)
Christine Mauck, M.D., Medical Officer, DRUDP (HFD-580)

External Constituents:
[redacted] Laboratories, Inc.:
Sharon Brown, Associate Director, Drug Regualtory Affairs, Biomedical
Nancy Bower, Project Leader, Toxicology
Michael Dolker, Ph.D., Head Statistician, Endocrinology and Fertility Control
Herman Ellman, M.D., Director, Endocrinology and Fertility Control
Brenda Marczi, Associate Director, Drug Regulatory Affairs, Biopharmaceuticals
Armen Melikian, Ph.D., Associate Director, Clinical Phamacology

Schering AG:
Hartmut Biode, Ph.D., Scientist, Department of Pharmacokinetics
Norman Nashed, Ph.D., International Project Manager
Beate Seibert, Ph.D., Toxicologist, Scientific Assistance

drospirenone/ethinyl estradiol
Berlex

Meeting Objectives:
To obtain the Division's concurrence that the drug development program may be sufficient to support an NDA for the indication of prevention of pregnancy. In addition the Sponsor requested initial feedback regarding potential use of this product for Hormone Replacement Therapy (HRT) and Pre-menstrual Syndrome.

Discussion Points:

- dosage will be 3 mg drospirenone and 0.03 mg ethinyl estradiol
- drospirenone is a new synthetic steroid
  - it is a 17α - spironolactone
  - possesses progestational, antimineralocorticoid and antiandrogenic properties
  - profile of action is similar to progesterone
- Chemistry Manufacturing and Control
  - three synthetic routes used, A, B, and C
    - route A produced pre-clinical drug product
    - route B produced all drug used in the to-be-submitted clinical trials
    - route C is the to-be-marketed synthesis route
    - difference between B and C are change of starting material, change of oxidizing agent, and change of purification of drospirenone crude
    - what, if any, further testing needs to be carried out between routes B and C?
  - drug manufacture will be carried out in a new plant in Weimar Germany
  - 12 month stability data at room temperature and 6 month stability data at 40°C will be available at the time of filing, is this sufficient?
- Pre-Clinical Studies
  - a wide range of pre-clinical studies was carried out (see attachments); is this sufficient to support the filing of an NDA?
  - carcinogenicity studies have been carried out on the rat (2 years); The mouse carcinogenicity studies are ongoing
  - can the sponsor sacrifice at 18 months rather than 24 months?
  - are the carcinogenicity trials suitable?
- Biopharmaceutic Studies
  - Phase I studies have been completed and most results reported in the IND, some are still under analysis and will be reported shortly
  - Food study show a decrease in C_{max} and AUC of estradiol and C_{max} of drospiranone were similar

- two subjects gave unexpected plasma values, sponsor believes this to be due to subjects' reaction to food not due to the drug
- clinical trial subjects were not given instructions regarding food fed or fasted during the trial
- are the completed studies sufficient to support the filing of an NDA?
- drospirenone has a tendency towards isomerization at low pH (pH 1-2), assays have included IRA specific to drospirenone, and kinetic studies at various pH's; is this sufficient for characterization of the isomer?

- Clinical Studies
  - Pivotal trial completed and carried out in Germany using Desogen (European tradename "Marvelon"), as a comparator
  - second trial is to be carried out in the U.S. protocol under the IND
  - ethnic make up of the Phase III trials study population was approximately 96% Caucasian
  - U.S. study will recruit a more varied ethnic mix to better reflect the U.S. population
  - both Pearl Indices and life tables will be presented in the NDA
  - drospirenone has been found to block p450 but to a lesser extent than gestodene; more data will be provided
  - a single thromboembolic event has occurred in this study to a subject who had just had surgery; it is not apparent whether the event was due to the study drug, or was a post-operative complication
  - initial pregnancy rates reported but subjects who used an alternative method of contraception were not included; they will be included in the intent-to-treat analysis
  - is the Phase 3 clinical program adequate to support the filing of an NDA?
  - is the safety database sufficient to support the filing of an NDA?

-
  -

- Hormone Replacement Therapy
  - if the estradiol component is found to be equivalent to Estrace, can the sponsor obtain those indications?

- what needs to be assessed to show bioequivalence to Estrace?

Decisions Reached:

- more information regarding synthesis route C, including proof of structure is required
- a reference standard synthesized from route C must be used
- a description of the fungus used in step 1 of the synthetic process must be provided as well as any information regarding kill steps
- chromatograms of the drug substance made by route C must be included in the NDA
- proof of structure including the reference standard should be prepared using route C and characterized
- provided the equipment and process are essentially the same between the two plants that will be used to manufacture the drug, the sponsor may follow SUPAC guidelines
- the stability program proposed and underway is acceptable, however while 6 months stability data are acceptable for filing of an NDA, the NDA will need to be supplemented with six months more stability data during the review process
- accelerated data can be submitted during the review process; the sponsor will need to calculate shelf-life at room temperature
- the pre-clinical studies are sufficient to support the filing of an NDA, however if further impurities are found from using synthesis route C, toxicity of those impurities will have to be characterized
- the rat carcinogenicity study is acceptable, however, a decision regarding the acceptability of the mouse carcinogenicity study is still pending
- the sponsor should submit blood plasma levels from the mouse study to aid in the decision
- the pharmacokinetic studies are adequate, however the Division requires that the sponsor also include assay validation data, *in vitro* drug metabolism information, drug-drug interaction studies and methodology and data; a dissolution dissolution specification of
- the isomerization issue should be addressed by including *in vitro* studies and kinetic information at various pH levels, in the biopharmaceutic section of the NDA
- the sponsor reported "efficacy rate" should be reported as a "failure rates."

- the Phase 3 clinical program appears adequate in terms of reported cycles to support the filing of an NDA, however the Division would like to review the protocol used in the pivotal European study and the analysis plan
- the safety database appears to be adequate in terms of size to support the filing of an NDA
- a PMS indication would require two pivotal studies to for filing; there is currently no drug approved for this indication that can be used as an active control, however the sponsor is encouraged to address potential blinding issues in any placebo controlled study they design
- clinically relevant improvement of PMS symptoms should be defined prior to initiating any study for PMS
- a draft protocol should be submitted for review
- a PMS indication might not be granted if the drug to be tested does not show improvement in the mood component of the syndrome
- if bioequivalence can be shown for the estrogen component of the sponsor's combination drug, the sponsor may obtain the same indications as the innovator drug (Estrace)
- bioequivalence will need to be shown by usual Office of Generic Drug criteria: for example, estradiol, estrone and estrone sulfate will all have to be evaluated
- if the sponsor decides that more than two doses may be candidates for marketing for hormone replacement therapy the sponsor should show equivalence for the highest and lowest doses. For the middle doses the sponsor may be granted a waiver if they can show dose proportionality

Unresolved Issues: Mouse carcinogenicity study (see action items)

Action Items:

Item	Responsible Person	Due Date
Information regarding Synthesis Route C	Sharon Brown	TBA
Information regarding mouse blood plasma levels	Sharon Brown	ASAP
Teleconference with the sponsor re: mouse study	C. Kish	2 weeks
Submission of European clinical protocol	Sharon Brown	TBA
Submission of data on the P 450 system	Sharon Brown	TBA

/S/
Minutes Preparer

/S/
Concurrence, Chair

ATTACHMENTS

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

There was no advisory Committee Meeting held for this drug product.

/S/

4.18.01

APPEARS THIS WAY
ON ORIGINAL

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

There were no Federal Register Notices for this drug product.

/S/

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 11, 2001

FROM: Florence Houn MD

SUBJECT: Office Director's Note

TO: NDA 21-098 YASMIN 28 Tablets (ethinyl estradiol and drospirenone) Berlex Labs Inc.

This memo documents my decision to approve YASMIN 28 Tablets in this third application cycle because the overall effects on serum potassium are small, making risk for hyperkalemia slight. Furthermore, a solid risk management program to minimize risks will accompany the product marketing.

Berlex Laboratories is seeking a pregnancy prevention indication for this combined oral contraceptive. Berlex submitted clinical trials data to address safety concerns of the potassium-sparing diuretic effect of 3.0mgs of drospirenone, a new progestational agent with antimineralocorticoid activity comparable to 25mg of spironelactone. This drug can affect serum potassium. Berlex presented labeling and a risk communication and risk management plan to monitor contraindicated use in order to implement corrective action to minimize risks of hyperkalemia. Approval is granted after revisions of labeling, including the addition of serum potassium testing during the first cycle of YASMIN 28 Tablets in patients who are chronically taking other drugs that may contribute to hyperkalemia (NSAIDs, potassium-sparing diuretics, potassium supplements, ACE inhibitors, angiotensin II receptor inhibitors), and agreement on the risk management plan that includes an evaluation component on contraindicated usage and measurement of compliance with blood testing.

This drug presented a real dilemma because it offers no additional benefits over other approved oral contraceptives, which already subject young women to risks of venous thromboembolic disorders, but has properties that increase serum potassium. During the pre-NDA phase, the risk of hyperkalemia was not discussed. During the first cycle, FDA stated there was need for a renal study to investigate risk of hyperkalemia. During the second cycle, the division reviewed the renal study of 28 patients on low potassium diets. Serum potassium was increased by 37% in the drug group with moderate renal disease compared to the normal renal function group. The study also showed 5 of 7 patients with renal impairment and taking potassium-sparing diuretics had increases of up to 0.33mEq/L. Furthermore, a study of 24 mildly hypertensive, postmenopausal women on enalapril (ACE inhibitor) showed a mean increase of serum potassium of 0.22 mEq/L. These increases in potassium led FDA to seek additional information on the risk of hyperkalemia and a risk management program for the drug.

During this current cycle, the company presented data in several studies, of significance was an estrogen-only controlled study in 4 dose groups of drospirenone/ ethinyl estradiol in post-menopausal women. Mean potassium changes between no drug to on drug for 190 women are higher for drospirenone/estradiol (D/E) subjects than estradiol alone subjects in a dose-response fashion: estradiol only mean change -0.01mEq/L, D 0.5mg/E +0.06mEq/L, D1.0mg/E +0.07mEq/L, D2.0mg/E +0.10mEq/L, D3.0mg/E +0.09mEq/L. The maximum changes in values of potassium in the 190 patients were: estradiol only max change +1.20mEq/L, D 0.5mg/E +1.4mEq/L, D1.0mg/E +1.5mEq/L, D2.0mg/E +1.7mEq/L, D3.0mg/E +1.3mEq/L. Finally, the percentage of subjects who had changes in potassium from baseline to on drug of greater than or equal to 0.5mEq/L were: estradiol only 11%, D 0.5mg/E 14%, D1.0mg/E 16%, D2.0mg/E 16%, D3.0mg/E 17%. This clearly refutes the pharmaceutical company's statement that YASMIN has no effect on potassium. However, it does show

the effect is small. Moreover, there were no patients with clinical signs of hyperkalemia. FDA also disagrees that the five-arm study, allowing subjects to enroll while on NSAID and ACE inhibitors, shows no affect of these other drugs with YASMIN on serum potassium. The subjects who reported use of ACE inhibitors or NSAIDs were not monitored to ensure appropriate timing of blood sampling and even exposure to both drugs. Thus, drug interactions on serum potassium cannot be ruled out and labeling states chronic users of daily NSAIDs, etc. should have a potassium level during the first month of YASMIN therapy. Thus, the population with normal kidney function will likely handle these types of effects without a problem. The high-risk population (renal patients, drug interaction patients, etc.) will be addressed in the labeling and the risk management program.

Marketing in Germany began November 2000. The adverse events were reviewed but provided limited information because of the short postmarketing experience and lack of follow up on some adverse events.

The risk management program was reviewed by OPDRA. Measurement of contraindicated usage and compliance with blood testing are important measurable evaluation criteria for success of risk communication. The plan was well-thought out and showed commitment to tracking safe and appropriate use. FDA asked for interim reports on the monitoring and prespecified, agreed upon levels of success and intervention.

In my last memo I stated what was needed was more trial data pushing the dose or in vulnerable populations (or both) or a well-monitored post marketing experience to convince me of safety. The data provided to us include clinical trial data from postmenopausal women, certainly a more at risk population for concomitant use of medications and comorbid conditions. Although clinical trials populations are generally healthier than their age-matched non-trial subjects, the data were useful in assessing risk.

My decision to allow marketing in part rests with the need to allow implementation of risk management programs so these tools can be successfully developed and implemented to help assure safety. Without advancing these programs, the only tools left are labeling and non-approval decisions. Labeling has problems with dissemination, awareness, and understanding while non-approval decisions are very blunt tools not responsive to graded situations of risk benefit. The company was notified on May 11, 2001 that approval for this product would be granted, but the company needed to carefully market this drug and communicate risks such that contraindicated populations do not incur risk and adverse events. Should such events occur (in the high-risk, contraindicated population or in those without risks for hyperkalemia), FDA's support of the product, given that it offers comparable contraceptive efficacy as other approved products, would be considerably diminished. There is a low threshold for taking further regulatory action if hyperkalemic adverse events occur in marketing. The company's marketing representative understood these statements and stated they were committed to appropriate marketing.

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/s/

Florence Houn
5/15/01 07:37:03 AM
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