# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-676**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

# PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

***For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use***

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
*See OMB Statement on Page 3.*

NDA NUMBER
21-676

NAME OF APPLICANT / NDA HOLDER
Berlex Laboratories, Inc.

***The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.***

TRADE NAME (OR PROPOSED TRADE NAME)
YAZ

| ACTIVE INGREDIENT(S) | STRENGTH(S) |
|---|---|
| ethinyl estradiol and drospirenone | 0.020 mg EE ß-cyclodextrin clathrate<br>3 mg DRSP |

DOSAGE FORM
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This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

***FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.***

***For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.***

## 1. GENERAL

| a. United States Patent Number | b. Issue Date of Patent | c. Expiration Date of Patent |
|---|---|---|
| 5,569,652 | October 29, 1996 | October 29, 2013 |

| d. Name of Patent Owner | Address *(of Patent Owner)* | |
|---|---|---|
| Schering AG | Mullerstrasse | |
| | City/State: Berlin, Germany | |
| | ZIP Code: D13342 | FAX Number *(if available)* |
| | Telephone Number: (030) 468-1111 | E-Mail Address *(if available)* |

| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞ | Address *(of agent or representative named in 1.e.)* | |
|---|---|---|
| | Berlex Laboratories, Inc. | |
| | City/State: P.O. Box 1000, 340 Changebridge Road, Montville, NJ | |
| | ZIP Code: 07045-1000 | FAX Number *(if available)* |
| | Telephone Number: (973) 487-2000 | E-Mail Address *(if available)* |

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No


PSC Media Arts (301) 443-1090 EF

***For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.***

**2. Drug Substance (Active Ingredient)** EE + DRSP

| | | |
|---|---|---|
| **2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **2.3** If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☒ No |

**2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

NA

| | | |
|---|---|---|
| **2.5** Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) | ☐ Yes | ☒ No |
| **2.6** Does the patent claim only an intermediate? | ☐ Yes | ☒ No |
| **2.7** If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) NA | ☐ Yes | ☐ No |

**3. Drug Product (Composition/Formulation)** NA

| | | |
|---|---|---|
| **3.1** Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **3.2** Does the patent claim only an intermediate? | ☐ Yes | ☒ No |
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**4. Method of Use**

***Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:***

| | | |
|---|---|---|
| **4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☒ Yes | ☐ No |
| **4.2** Claim Number (*as listed in the patent*)<br>11 through 17<br>19, 20, 22 through 27 — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☒ Yes | ☐ No |

**4.2a** If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

NA

**5. No Relevant Patents** NA

| | |
|---|---|
| For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. | ☐ Yes |

## 6. Declaration Certification

**6.1** ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

***Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.***

| **6.2** Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)* | Date Signed |
|---|---|
| Tatsuya Ikeda | Oct. 7, 2003 |

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

| | |
|---|---|
| ☐ NDA Applicant/Holder | ☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| ☐ Patent Owner | ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |

| | |
|---|---|
| Name<br>Tatsuya Ikeda | |
| Address<br>Berlex Laboratories, Inc. | City/State<br>P.O. Box 1000<br>340 Changebridge Road<br>Montville, NJ |
| ZIP Code<br>07045-1000 | Telephone Number<br>(973) 487-2014 |
| FAX Number *(if available)*<br>(973) 487-2712 | E-Mail Address *(if available)*<br>ted_ikeda@berlex.com |

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## 1. GENERAL

| a. United States Patent Number | b. Issue Date of Patent | c. Expiration Date of Patent |
|---|---|---|
| RE 38,253 E | September 16, 2003 | June 30, 2014 |

| d. Name of Patent Owner | Address *(of Patent Owner)* | FAX Number *(if available)* |
|---|---|---|
| Schering AG | Mullerstrasse<br>City/State: Berlin, Germany<br>ZIP Code: D13342<br>Telephone Number: (030) 468-1111 | E-Mail Address *(if available)* |

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|---|---|---|
| ☞ | Berlex Laboratories, Inc.<br>City/State: P.O. Box 1000, 340 Changebridge Road, Montville, NJ<br>ZIP Code: 07045-1000<br>Telephone Number: (973) 487-2000 | E-Mail Address *(if available)* |

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| | | |
|---|---|---|
| **2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? | ☒ Yes | ☐ No |
| **2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **2.3** If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☒ No |

**2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

NA

| | | |
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**3. Drug Product (Composition/Formulation)** NA

| | | |
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| **3.1** Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
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**4. Method of Use** NA

***Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:***

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| **4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **4.2** Claim Number (*as listed in the patent*) | Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No | |
| **4.2a** If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. | Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* NA | |

**5. No Relevant Patents** NA

| | |
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| ☐ Patent Owner | ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |

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Department of Health and Human Services
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Form Approved: OMB No. 0910-0513
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## 1. GENERAL

| a. United States Patent Number | b. Issue Date of Patent | c. Expiration Date of Patent |
|---|---|---|
| 5,798,338 | August 25, 1998 | July 10, 2015 |

| d. Name of Patent Owner | Address *(of Patent Owner)* | FAX Number *(if available)* |
|---|---|---|
| Schering AG | Mullerstrasse | |
| | City/State: Berlin, Germany | |
| | ZIP Code: D13342 | |
| | Telephone Number: (030) 468-1111 | E-Mail Address *(if available)* |

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

***For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.***

**2. Drug Substance (Active Ingredient)** EE ß-cyclodextrin clathrate

| | | |
|---|---|---|
| **2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? | ☒ Yes | ☐ No |
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NA

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**3. Drug Product (Composition/Formulation)** NA

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**5. No Relevant Patents** NA

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| Schering AG | Mullerstrasse | |
| | City/State: Berlin, Germany | |
| | ZIP Code: D13342 | FAX Number *(if available)* |
| | Telephone Number: (030) 468-1111 | E-Mail Address *(if available)* |

| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) | Address *(of agent or representative named in 1.e.)* | |
|---|---|---|
| | Berlex Laboratories, Inc. | |
| | City/State: P.O. Box 1000, 340 Changebridge Road, Montville, NJ | |
| | ZIP Code: 07045-1000 | FAX Number *(if available)* |
| | Telephone Number: (973) 487-2000 | E-Mail Address *(if available)* |

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No


PSC Media Arts (301) 443-1090 EF

***For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.***

**2. Drug Substance (Active Ingredient)** BE + DRSP

| | | |
|---|---|---|
| **2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? | ☒ Yes | ☐ No |
| **2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **2.3** If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☒ No |

**2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

NA

| | | |
|---|---|---|
| **2.5** Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) | ☐ Yes | ☒ No |
| **2.6** Does the patent claim only an intermediate? | ☐ Yes | ☒ No |
| **2.7** If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) NA | ☐ Yes | ☐ No |

**3. Drug Product (Composition/Formulation)** NA

| | | |
|---|---|---|
| **3.1** Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **3.2** Does the patent claim only an intermediate? | ☐ Yes | ☒ No |
| **3.3** If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☒ No |

**4. Method of Use** NA

***Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:***

| | | |
|---|---|---|
| **4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **4.2** Claim Number (*as listed in the patent*) | Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No | |
| **4.2a** If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. | Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* NA | |

**5. No Relevant Patents** NA

| | |
|---|---|
| For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. | ☐ Yes |

## 6. Declaration Certification

**6.1** ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

***Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.***

| **6.2** Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)* | Date Signed |
|---|---|
| Tatsuya Ikeda | Oct. 7, 2003 |

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

| | |
|---|---|
| ☐ NDA Applicant/Holder | ☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| ☐ Patent Owner | ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |

| | |
|---|---|
| Name<br>Tatsuya Ikeda | |
| Address<br>Berlex Laboratories, Inc. | City/State<br>P.O. Box 1000<br>340 Changebridge Road<br>Montville, NJ |
| ZIP Code<br>07045-1000 | Telephone Number<br>(973) 487-2014 |
| FAX Number *(if available)*<br>(973) 487-2712 | E-Mail Address *(if available)*<br>ted_ikeda@berlex.com |

Department of Health and Human Services
Food and Drug Administration

# PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

***For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use***

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
*See OMB Statement on Page 3.*

NDA NUMBER
21-676

NAME OF APPLICANT / NDA HOLDER
Berlex Laboratories, Inc.

***The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.***

TRADE NAME (OR PROPOSED TRADE NAME)
YAZ

| ACTIVE INGREDIENT(S) | STRENGTH(S) |
|---|---|
| ethinyl estradiol and drospirenone | 0.020 mg EE ß-cyclodextrin clathrate<br>3 mg DRSP |

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

***FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.***

***For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.***

## 1. GENERAL

| a. United States Patent Number | b. Issue Date of Patent | c. Expiration Date of Patent |
|---|---|---|
| RE 37,564 E | February 26, 2002 | June 30, 2014 |

| d. Name of Patent Owner | Address *(of Patent Owner)* | |
|---|---|---|
| Schering AG | Mullerstrasse | |
| | City/State: Berlin, Germany | |
| | ZIP Code: D13342 | FAX Number *(if available)* |
| | Telephone Number: (030) 468-1111 | E-Mail Address *(if available)* |

| e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞ | Address *(of agent or representative named in 1.e.)* | |
|---|---|---|
| | Berlex Laboratories, Inc. | |
| | City/State: P.O. Box 1000, 340 Changebridge Road, Montville, NJ | |
| | ZIP Code: 07045-1000 | FAX Number *(if available)* |
| | Telephone Number: (973) 487-2000 | E-Mail Address *(if available)* |

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

***For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.***

## 2. Drug Substance (Active Ingredient) ES - DRSP

| | | |
|---|---|---|
| **2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? | ☒ Yes | ☐ No |
| **2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **2.3** If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). | ☐ Yes | ☒ No |

**2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.

NA

| | | |
|---|---|---|
| **2.5** Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) | ☐ Yes | ☒ No |
| **2.6** Does the patent claim only an intermediate? | ☐ Yes | ☒ No |
| **2.7** If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) NA | ☐ Yes | ☐ No |

## 3. Drug Product (Composition/Formulation) NA

| | | |
|---|---|---|
| **3.1** Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **3.2** Does the patent claim only an intermediate? | ☐ Yes | ☒ No |
| **3.3** If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) | ☐ Yes | ☒ No |

## 4. Method of Use NA

***Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:***

| | | |
|---|---|---|
| **4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |
| **4.2** Claim Number (*as listed in the patent*) — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? | ☐ Yes | ☒ No |

**4.2a** If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

NA

## 5. No Relevant Patents NA

| | |
|---|---|
| For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. | ☐ Yes |

## 6. Declaration/Certification

**6.1** ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

***Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.***

| 6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)* | Date Signed |
|---|---|
| Tatsuya Ikeda | Oct. 7, 2003 |

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

| | |
|---|---|
| ☐ NDA Applicant/Holder | ☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official |
| ☐ Patent Owner | ☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official |

| | |
|---|---|
| Name<br>Tatsuya Ikeda | |
| Address<br>Berlex Laboratories, Inc. | City/State<br>P.O. Box 1000<br>340 Changebridge Road<br>Montville, NJ |
| ZIP Code<br>07045-1000 | Telephone Number<br>(973) 487-2014 |
| FAX Number *(if available)*<br>(973) 487-2712 | E-Mail Address *(if available)*<br>ted_ikeda@berlex.com |

## 14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to NDA 21-676 for Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets.

BERLEX LABORATORIES, INC.

Tatsuya Ikeda

Tatsuya Ikeda
General Counsel Intellectual Property

Oct. 7, 2003

Date

# EXCLUSIVITY SUMMARY

NDA # 21-676 SUPPL # HFD # 580

Trade Name YAZ Tablets

Generic Name drospirenone 3 mg / ethinyl estradiol 0.020 mg)

Applicant Name Berlex, Inc.

Approval Date, If Known March 16, 2006

## PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-098 Yasmin (drospirenone/ethinyl estradiol)

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES ☐ | NO ☒ |
| Investigation #2 | YES ☐ | NO ☐ |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES ☐ | NO ☒ |
| Investigation #2 | YES ☐ | NO ☐ |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study# 303740

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | | |
|---|---|---|
| Investigation #1 | | ! |
| | | ! |
| IND # 60,738 | YES ☒ | ! NO ☐ |
| | | ! Explain: |
| Investigation #2 | | ! |
| | | ! |
| IND # | YES ☐ | ! NO ☐ |
| | | ! Explain: |

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

---

Name of person completing form: Z Charlene Williamson
Title: Regulatory Health Project Manager
Date: March 20, 2006

Name of Office/Division Director signing form: Daniel Shames, M.D.
Title: Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/
---
Daniel A. Shames
3/20/2006 02:01:23 PM

## Request for Three Years Marketing Exclusivity

Pursuant to 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(4), Berlex Laboratories, Inc. [Berlex] hereby requests a period of three years marketing exclusivity for Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets that is the subject of NDA 21-676.

1. Pursuant to 21 CFR 314.50(j)(4)(i), Berlex Laboratories, Inc. hereby certifies that the clinical investigation included in NDA 21-676, i.e., Study 303740, "Multi-center, open, uncontrolled study to investigate the efficacy and safety of the oral contraceptive SH T 186 DA containing 0.02 mg ethinyl estradiol-β-Cyclodextrin Clathrate and 3 mg Drospirenone in a 24-day regimen for 13 cycles in 1010 healthy female volunteers":
   - meets the definition of a "new clinical investigation" set forth in 21 CFR 314.108(a), and
   - has not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.

   Report A12007 for Study 303740 is located in NDA 21-676 at:

   N21-676\clinstat\oralcontraception\a12007

2. Berlex hereby certifies that we have searched the scientific literature for publicly available reports of relevant clinical investigations [21 CFR 314.50(j)(4)(ii)] and that the list of publications included in NDA 21-676 is complete and accurate. It is our opinion that the published studies and publicly available reports do not provide a sufficient basis for the approval of Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets for oral contraception, without reference to Study 303740. Accordingly, Study 303740 is essential to the approval of NDA 21-676, as the results of this new clinical investigation support a finding of substantial evidence of effectiveness of Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets for oral contraception.

3. Berlex Laboratories, Inc. is the sponsor named in Form FDA 1571 contained in IND 60,738, the Investigational New Drug Application under which Study 303740 had been conducted. Berlex submitted IND 60,738 to the Food and Drug Administration on August 22, 2000 for review by the Division of Reproductive and Urologic Drug Products.

BERLEX LABORATORIES, INC.

Geri A. Besta — October 1, 2003

Geri A. Besta
Manager, Regulatory Intelligence and
Submission Compliance

Date

gab/137

# PEDIATRIC PAGE

## (Complete for all filed original applications and efficacy supplements)

**DA/BLA #:** 21-676 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

**Stamp Date:** October 17, 2003 **Action Date:** March 16, 2006

**HFD** - 580 **Trade and generic names/dosage form:** YAZ (drospirenone 3 mg/ ethinyl estradiol 0.02 mg

**Applicant:** Berlex, Inc. **Therapeutic Class:** 3S

**Indication(s) previously approved:**

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

**Number of indications for this application(s):** 1

**Indication #1:** Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

**Is there a full waiver for this indication (check one)?**

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

## ction A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- X Other: Safety and efficacy of YAZ Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for post pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

| | | | | | |
|---|---|---|---|---|---|
| Min_____ | kg_____ | mo._____ | yr._____ | Tanner Stage_____ |
| Max_____ | kg_____ | mo._____ | yr._____ | Tanner Stage_____ |

**Reason(s) for partial waiver:**

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

❑ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Reason(s) for deferral:**

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*
*Z. Charlene Williamson*
**Regulatory Project Manager**

cc: **NDA 21-676**
**HFD-960/ Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 12-22-03)**

## Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** _____

**Is there a full waiver for this indication (check one)?**

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  **NOTE: More than one may apply**
  **Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

**Min** _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
**Max**_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

**Reason(s) for partial waiver:**

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## ction D: Completed Studies

**Age/weight range of completed studies:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*
*Z. Charlene Williamson*
**Regulatory Project Manager**

**cc:** **NDA 21-676**
**HFD-960/ Grace Carmouze**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

**(revised 10-14-03)**

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

/s/
---
Jennifer L. Mercier
3/16/2006 11:02:05 AM

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

Berlex Laboratories requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of drospirenone 3 mg and ethinyl estradiol 0.020 mg tablets in all relevant pediatric subpopulations in accordance with 21CFR 314.55(a). Additional reference is made to the November, 2000 Draft Guidance, entitled "Guidance for Industry Recommendations for Complying with the Pediatric Rule (21 CFR 314.55(a) and 601.27 (a).

**NDA number**: 21-676

**Sponsor:**

Nancy Velez, Manager, Drug Regulatory Affairs
Berlex Laboratories
340 Changebridge Road
P. O. Box 1000
Montville, N. J. 07045-1000

**Indication**

Prevention of pregnancy in women who elect to use an oral contraceptive.

**Age ranges included in pediatric waiver:**

Ages 0 to 11 years

**Reason for waiving pediatric studies:**

Drospirenone (DRSP) 3 mg/Ethinyl Estradiol (EE) 0.020 mg tablets are the subject of this NDA. DRSP 3mg/EE 0.020mg tablets are a reduced-estrogen version of our approved NDA 21-098 for YASMIN® 28 TABLETS (drospirenone 3 mg and ethinyl estradiol 0.030 mg Tablets. The NDA for YASMIN® 28 TABLETS was approved May 11, 2001 for the prevention of pregnancy.

Reference is made to our waiver request for YASMIN® 28 TABLETS dated June 19, 2000. In the May 11, 2001 approval letter, the Division granted the waiver for YASMIN® 28 Tablets with the following statement, "We are waiving the pediatric study requirement for this action on this application".

In accordance with 21 CFR 314.55 (c) (2)(ii), necessary studies are impossible or highly impractical because the number of such patients is so small.

## DEBARMENT CERTIFICATION

### Certification Under Section 306(k)(1) of the FD & C Act

Berlex Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-676 for Drospirenone 3 mg /Ethinyl Estradiol 0.020 mg Tablets.

BERLEX LABORATORIES, INC.

Joan Mutascio

Joan Mutascio
Associate, Regulatory
Submissions & Information

9/29/03

Date

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| | | | |
|---|---|---|---|
| NDA **21-676** | Efficacy Supplement Type SE- | Supplement Number | |
| Drug: **YAZ (drospirenone 3 mg / ethinyl estradiol 0.02 mg) Tablets** | | Applicant: **Berlex, Inc.** | |
| RPM: Charlene Williamson | | HFD-580 | Phone – 301-796-1025 |

| | |
|---|---|
| Application Type: ( **X**) 505(b)(1) ( ) 505(b)(2)<br>(This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)<br><br>**If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.**<br><br>( ) Confirmed and/or corrected | Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (x ) Standard ( ) Priority |
| • Chem class (NDAs only) | 3 |
| • Other (e.g., orphan, OTC) | |
| ❖ User Fee Goal Dates | November17, 2004/ March 16, 2006 |
| ❖ Special programs (indicate all that apply) | (x ) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review<br>( ) CMA Pilot 1<br>( ) CMA Pilot 2 |
| ❖ User Fee Information | |
| • User Fee | (x ) Paid UF ID number 4575 |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other (specify) |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)<br>( ) Other (specify) |

| | |
|---|---|
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes (x ) No |
| • This application is on the AIP | ( ) Yes ( ) No |
| • Exception for review (Center Director's memo) | |
| • OC clearance for approval | |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. | (x ) Verified |
| ❖ Patent | |
| • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | (x ) Verified |
| • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) Verified<br><br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | |
| • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).* | ( ) N/A (no paragraph IV certification)<br>( ) Verified |
| • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.<br><br>Answer the following questions for each paragraph IV certification:<br><br>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).<br><br>*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*<br><br>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?<br><br>*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**No**," continue with question (3).*<br><br>(3) Has the patent owner, its representative, or the exclusive patent licensee | ( ) Yes ( ) No<br><br>( ) Yes ( ) No<br><br>( ) Yes ( ) No |

| | |
|---|---|
| filed a lawsuit for patent infringement against the applicant?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).<br><br>*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* | |
| (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?<br><br>*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "No," continue with question (5).* | ( ) Yes ( ) No |
| (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).<br><br>*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*<br><br>*If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.* | ( ) Yes ( ) No |
| ❖ Exclusivity (approvals only) | |
| • Exclusivity summary<br>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | March 20, 2006 |
| • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ( ) Yes, Application #_____<br>**(X)** No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | 10/16/04 |

| | |
|---|---|
| ❖ Actions | |
| • Proposed action | (X) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | AE – 11/17/2004 |
| • Status of advertising (approvals only) | (x) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | ( ) Yes (x) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | ( ) None<br>( ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | |
| • Most recent applicant-proposed labeling | June 15, 2005 |
| • Original applicant-proposed labeling | October 16, 2003 |
| • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | DDMAC -5/20/05, DSRCS – 4/14/05, DMETS – 1/30/06 |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | N/A |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | N/A |
| • Applicant proposed | |
| • Reviews | CMC – 1/3/2006 |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | 3/16/2006 |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | Action Letter |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | X |
| ❖ Memoranda and Telecons | X |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | N/A |
| • Pre-NDA meeting (indicate date) | 03/18/03 |
| • Pre-Approval Safety Conference (indicate date; approvals only) | N/A |
| • Other | X |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | N/A |
| • 48-hour alert | N/A |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | N/A |

| | |
|---|---|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | MTL – 11/17/2004; 3/16/2006 |
| | |
| ❖ Clinical review(s) *(indicate date for each review)* | 11/17/2004; 3/15/2006 |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | N/A |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | See MO Review – 3/16/06 |
| ❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)* | N/A |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | 3/16/06 |
| ❖ Demographic Worksheet *(NME approvals only)* | N/A |
| ❖ Statistical review(s) *(indicate date for each review)* | 1/18/06 |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | 12/05/05 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | N/A |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | 06/24/04 |
| • Bioequivalence studies | N/A |
| | |
| ❖ CMC review(s) *(indicate date for each review)* | 01/13/06 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | X |
| • Review & FONSI *(indicate date of review)* | N/A |
| • Review & Environmental Impact Statement *(indicate date of each review)* | N/A |
| ❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | N/A |
| ❖ Facilities inspection (provide EER report) | Date completed:<br>**(X)** Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation | ( ) Completed<br>( ) Requested<br>**(X )** Not yet requested |
| | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | 03/15/06 |
| ❖ Nonclinical inspection review summary | N/A |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | N/A |
| ❖ CAC/ECAC report | N/A |

**Appendix A to NDA/Efficacy Supplement Action Package Checklist**

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODEIII**

# FACSIMILE TRANSMITTAL SHEET

**DATE: March 8, 2006**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-796-9897 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-796-1025 |

**Subject:** Subject # 3295 – Adverse Event

**Total no. of pages including cover:** 1

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO



*NDA 21-676*

***Provide additional information for subject 3295 in Study 308021 who had the serious adverse event of unilateral blindness. Provide this information by close of business on March 10, 2006.***

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

/s/
---
Z. Charlene Williamson
3/8/2006 06:54:51 PM
CSO

Scott Monroe
3/8/2006 07:03:08 PM
MEDICAL OFFICER

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODEIII**

# FACSIMILE TRANSMITTAL SHEET

**DATE: March 8, 2006**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-796-9897 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-796-1025 |

**Subject:** Study 308021 -

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO

NDA 21-676

For Study 308021 provide the following information:

For subjects $\leq 35$ years of age and not using back up contraception

- Total 28-day cycles of exposure
- The number of pregnancies during treatment and within 14 days of stopping drug
- The Pearl Index and 2-sided 95% CI based on this information
- Life Table Analysis and 2-sided 95% CI based on this information

Provide the number of pregnancies that occurred between the $15^{th}$ through $28^{th}$ day post stopping study drug.

Provide the preceding information by COB on Friday March 10, 2006

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

/s/
---
Z. Charlene Williamson
3/8/2006 10:59:42 AM
CSO

Gerald Willett
3/8/2006 11:11:11 AM
MEDICAL OFFICER

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODEIII**

# FACSIMILE TRANSMITTAL SHEET

**DATE: March 1, 2006**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-796-9897 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-796-1025 |

**Subject:** Study 308021

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** ☑ YES ☐ NO

Based on our preliminary review of your submission of February 28, 2006, we request the following information for Study 308021.

1. Confirm that the Pearl Index value of 0.5 is based on subjects 35 years of age and younger and only treatment cycles during which no back up contraception was used.

2. A tabular summary of subject disposition to include number subjects randomized, number subjects who started treatment, number subjects who completed treatment, number of subjects who terminated prematurely, and the reasons for premature termination by general category.

3. A summary listing of adverse events leading to premature discontinuation in ≥ 1.0 % of subjects to include the number and percentage of subjects terminating for each adverse event. Format table similar to TT33 page 116 of 3206, Clinical Study Report A12007.

4. A listing by subjects of serious adverse events, to include for each subject, at a minimum, the adverse event, relationship of the event to study drug, and outcome.

Provide the requested information no later than close of business on March 6, 2006.

---

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

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/s/
---
Z. Charlene Williamson
3/1/2006 05:33:51 PM
CSO

Gerald Willett
3/1/2006 05:38:46 PM
MEDICAL OFFICER

**Office of Drug Safety**

# MEMO

**To:** Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Products
HFD-580

**From:** Todd D. Bridges, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

**Through:** Nora Roselle, Pharm.D., Acting Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

**Date:** January 24, 2006

**Re:** ODS Consult 04-0013-5
Yaz (Drospirenone and Ethinyl Estradiol Tablets); 3 mg/0.02 mg
NDA#: 21-676

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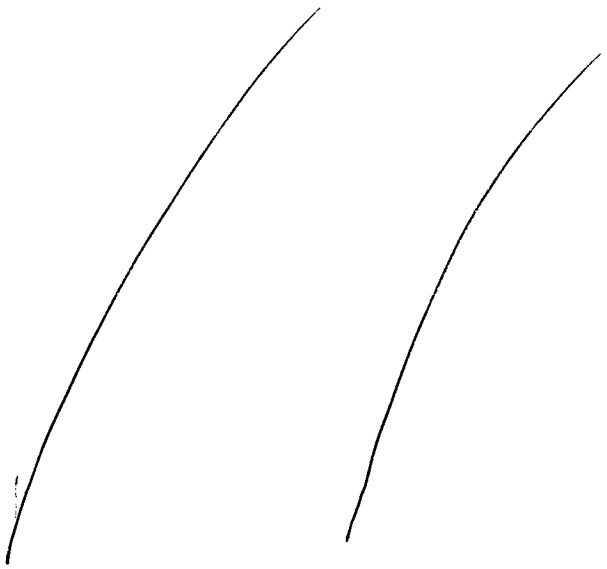
This consult was written in response to a request from the Division of Reproductive and Urologic Products (HFD-580), for reassessment of the proprietary name, YAZ™. In a review dated March 10, 2004 (ODS Consult#: 04-0013, NDA#: 21-676), DMETS recommended against the use of the proposed proprietary name, YAZ™. DMETS was concerned that the proprietary name, YAZ™, could be misinterpreted as an abbreviation for the currently marketed product Yasmin. Misinterpretation of the proposed proprietary name YAZ™ may cause confusion and could result in medication errors. In a correspondence dated May 14, 2004, the sponsor submitted a request for reconsideration of the proposed name. Additionally, the sponsor submitted an independent analysis conducted by the ——— in support of the proposed name YAZ™. In a review dated June 17, 2004 (ODS Consult#: 04-0013-2, NDA#: 21-676), DMETS reviewed and evaluated the — market research study for YAZ™ and concluded that the information provided had failed to provide persuasive evidence for DMETS to reverse its initial decision on the acceptability of the proprietary name, YAZ™. Subsequent to this, the Division of Reproductive and Urologic Products made the decision to allow the use of the tradename, YAZ™. Revised container labels, carton, and patient package insert labeling were submitted for review and comment.

Since the last review dated July 8, 2005 (ODS Consult#: 04-0013-3 and 04-0013-4, NDA#: 21-873), DMETS has not identified any additional proprietary or established names that have the potential for confusion with YAZ™. However, DMETS continues to have concern with the potential for YAZ™ to be misinterpreted as an abbreviation of Yasmin®. Therefore, DMETS still does not recommend the use of the proprietary name, YAZ™.

Upon review of the labels and labeling submitted for this review, we acknowledge that the sponsor revised the labels and labeling in accordance with DMETS' recommendations made in the July 8, 2005 consult (ODS Consults #: 04-0013-3 and 04-0013-4). However, DMETS has identified the following additional areas of possible improvement which might minimize potential user error.

CARTON LABELING (



In summary, DMETS does not recommend the use of the proprietary name, YAZ™, from a safety perspective. Additionally, DDMAC finds the proprietary name, YAZ™, acceptable from a promotional perspective. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward. DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Diane Smith, Project Manager, at 301-796-0538.

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/s/
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Todd Bridges
1/30/2006 01:15:15 PM
DRUG SAFETY OFFICE REVIEWER

Nora L. Roselle
1/30/2006 01:18:13 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/30/2006 02:42:24 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/30/2006 02:53:43 PM
DRUG SAFETY OFFICE REVIEWER

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODEIII**

# FACSIMILE TRANSMITTAL SHEET

**DATE: January 6, 2006**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-796-9897 |
| **Phone number:**973-487-2305 | **Phone number:** 301-796-1025 |

**Subject:** NDA 21-676

**Total no. of pages including cover**: 2

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO

We are requesting the following additional information to assist us in our review of NDA 21-676.

1. Provide an update of all outcomes for pregnancies that have occurred in clinical trials with drospirenone (e.g., YAZ, Yasminelle, and Yasmin). For each case, include the patient identification number, course of the pregnancy, and information regarding all congenital anomalies in infants.

2. Provide a listing by patient of all congenital anomalies identified world-wide through postmarketing safety reports for women taking Yasmin (or the identical product with a different proprietary name).

3. For each of the congenital malformation cases listed in Attachment 8 of the Ingenix Report filed to NDA 21-676 on October 28, 2005, indicate whether the patient was in the Yasmin or other OC initiator group.

Submit the requested information both to the electronic document room and directly to Ms. Williamson by e-mail as soon as possible.

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/s/
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Z. Charlene Williamson
1/6/2006 03:11:24 PM
CSO

Gerald Willett
1/6/2006 03:17:58 PM
MEDICAL OFFICER

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODEIII**

# FACSIMILE TRANSMITTAL SHEET

**DATE: January 4, 2006**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Products |
| **Fax number:** 973-486-2016 | **Fax number:** 301-796-9897 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-796-1025 |

**Subject:** Efficacy Analyses Protocol 304049

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO

We are requesting the following additional analyses/information to assist us in our reviews of NDA 21-676 and NDA 21-873.

**NDA 21-873**

1. Provide the following additional efficacy analyses for Protocol 304049. The requested analysis will be based on the 5 highest daily DRSP-21 scores during each of the 2 baseline cycles and each of the 3 treatment cycles. The 5 highest daily scores during each cycle are to be determined without regard to the phase of the menstrual cycle (i.e., they are not to be restricted only to the 5 days immediately preceding menses). In all other respects, the analyses should be identical to those previously submitted in NDA 21-873. Provide the following new Tables using the format/analyses previously used to generate the following tables in the Appendix (14.1) for Study Report A21566.

    a. Table 15 (pg. 55 of 398)
    b. Table 16 (pg. 56 of 398)
    c. Table 17 (pg. 57 of 398)

**NDA 21-676 (to be filed to NDA 21-873 as well)**

2. Update Appendix 14.5 of the ISS for NDA 21-873 (Narratives of cases of increased serum potassium from spontaneous reporting for Yasmin) to include (a) any new cases reported since the cut off date of the original report and (b) any new information for previously reported cases. Also provide CIOMS or MedWatch reports for each of the cases represented in the updated narrative.

3. Provide a complete and current listing of all postmarketing reports of deaths in Yasmin users (or the identical product under a different proprietary name) in all markets. In the listing, provide, at a minimum, the following: (a) company identifier of the case, (b) age at time of death, (c) duration of use of Yasmin, (d) primary cause of death, (e) secondary or contributing causes of death, (f) reporting country, and (g) risk factors for the event in the respective patient. Provide the listing in both PDF and SAS transport format.

    a. For other requests, Berlex/Schering has often provided narrative for such events. If narratives are available, provide these as well.
    b. Provide CIOMS or MedWatch reports for each of the cases.

Submit the requested information both to the electronic document room and directly to Ms. Williamson either by e-mail or by CD as soon as possible.

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/s/
---
Z. Charlene Williamson
1/4/2006 04:46:24 PM
CSO

Scott Monroe
1/4/2006 04:52:51 PM
MEDICAL OFFICER

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your June 15, 2005 complete response to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ™ (drospirenone 3 mg/ethinyl estradiol 0.020 mg) Tablets.

On November 23, 2005, we received your November 22, 2005 major amendment to this application.

We are also in receipt of your emails dated December 2, 2005, that provided tables and selected listings for the final study report for Protocol 308020 and final study reports for the two Phase 3 acne studies.

The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 16, 2006.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-2130.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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/s/

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Jennifer L. Mercier
12/5/2005 01:29:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 21-873
21-767

**ADVICE LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your December 22, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone 3mg/ ethinyl estradiol 0.02 mg) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments. Additional comments may be forwarded to you as we continue the review by other disciplines.

**For Carton/Container Labels:**

Submit revised labeling which incorporates our comments.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-2130.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
---
Jennifer L. Mercier
10/14/2005 01:51:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

**INFORMATION REQUEST LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your June 24, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone and ethinyl estradiol) Tablets.

We have reviewed your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. A data cutoff date of June 2005 for EURAS is acceptable. The Ingenix study should also have a data cutoff of June 2005. The interim reports for both studies should be sent at least three months prior to the December 2005 PDUFA Goal Date.

2. [redacted]

3. Clarify the manner by which assignment to treatment group will be made in the INAS Yaz study. What restrictions, if any, will there be in regard to permitted products in the non-Yaz treatment group? Is the anticipated distribution to be equal numbers of subjects in each treatment group?

4. What is the proposed duration of the INAS Yaz study and anticipated number of treatment years in each treatment group?

5. Provide the final draft protocol for the INAS Yaz study for review by the Division.

6. [redacted]

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
8/4/05 06:05:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex, Inc.
Attention: Nancy Velez, Manager
340 Changebridge Road, P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

We acknowledge receipt on June 16, 2005 of your June 15, 2005 resubmission to your new drug application for YAZ (drospirenone 3 mg/ ethinyl estradiol 0.02 mg) Tablets.

We consider this a complete, class 2 response to our November 17, 2004 approvable action letter. Therefore, the user fee goal date is December 16, 2005.

If you have any question, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Jennifer L. Mercier
6/30/05 02:14:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road, PO Box 1000
Montville, New Jersey 07045-1000

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yaz® (drospirenone/ethinyl estradiol) Tablets.

We also refer to the meeting request dated March 31, 2005 and the Guidance meeting that was scheduled for June 13, 2005. The preliminary responses to your meeting questions were faxed to you on June 9, 2005. Since you agreed to accept the Division's responses, the meeting was canceled. Enclosed are the finalized responses. They will serve as the official minutes of that meeting.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4266.

Sincerely,

*{See appended electronic signature page}*

Scott Monroe, M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

# MEMORANDUM OF MEETING RESPONSES

**Question 1**
Would the Division be able to provide their preliminary assessment of the results of the ovulation inhibition study? This feedback is important because we plan to submit the final report in our Resubmission to NDA 21-676 to demonstrate a clinical benefit of the 24 day regimen over the 21 day regimen that justifies exposing women to 3 additional days of DRSP/EE. Based on your preliminary assessment, does the Division concur with Berlex that the ovulation inhibition study demonstrates a clinical benefit? If not, Berlex will provide any additional analyses which may be useful for the Division immediately after our meeting. We understand that any advice provided is preliminary.

**Division's Answer**

- A preliminary assessment of the results of Study 308382 suggests greater suppression of pre-ovulatory and ovulatory ovarian activity with the 24-day regimen compared to the 21-day regimen using Hoogland scoring. Whether this observation represents a clinical benefit will be determined during the Division's review of the Complete Response. If, during the course of this review, we determine that additional analyses would be useful, we will contact you to discuss further.

- The Division does not anticipate that this observation will be included in labeling

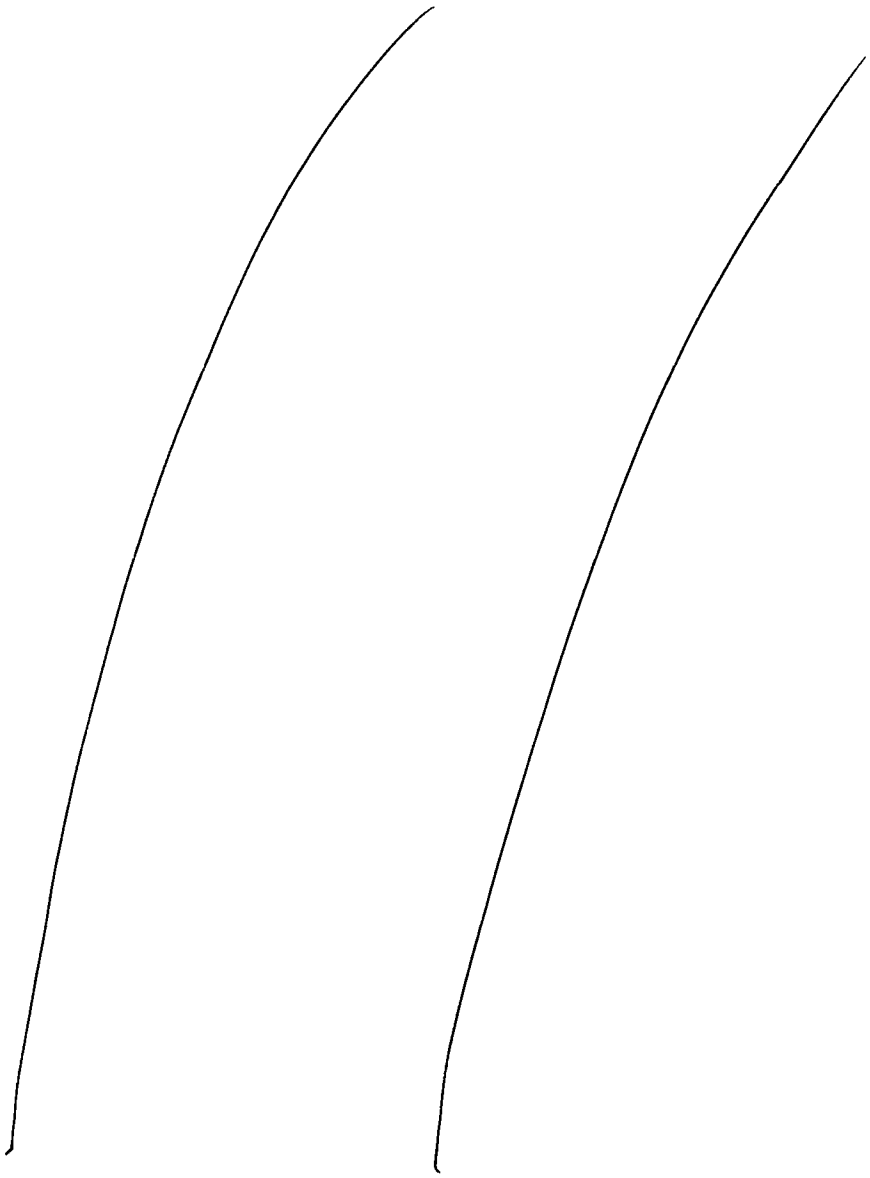
**Question 2**
Based on our analysis, the data from the ongoing postmarketing studies in the US (Ingenix i3 Magnifi Epidemiology) and Europe (EURAS) does not demonstrate a safety signal of different VTE risk for Yasmin as compared to other OCs. We would appreciate knowing whether the Division concurs with our analysis or, if not, what additional analyses may be useful?

**Division's Answer**

- The updated data from the EURAS and Ingenix studies appears to show, within the limitations of the power of the study, a similar combined VTE/ATE risk for Yasmin compared to the other oral contraceptive products.
- The Sponsor's updated interim reports for these studies should have data cut off dates that coincide with submission of the complete response.

**Question 3**
What advice can the Division provide about the proposed YAZ risk management program? Does the Division concur that the risk management program for YAZ, consisting of, for example, a postmarketing active surveillance study YAZ planned in the US, in addition to the risk management program already in place for Yasmin 28, addresses the Division's comments in the approvable letter of November 17, 2004 and supports the approval of YAZ, 24 day?

**Office of Drug Safety Answers, Comments, and follow-up Questions**



APPEARS THIS WAY
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/s/

Scott Monroe
6/23/05 04:56:46 PM

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

---

**DATE:** June 9, 2005

**TO:** Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

**THROUGH:** Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE), HFD-430

Gerald DalPan, M.D., Director
Division of Surveillance, Research, and Communication Support (DSCRS), HFD-410

**FROM:** YAZ RiskMAP Review Team
Division of Drug Risk Evaluation (DDRE), HFD-430
Division of Surveillance, Research and Communication Support (DSRCS), HFD-410

**DRUG:** YAZ™ (Drospirenone 3mg/Ethinyl Estradiol 0.2mg) Tablets, 24 day

**NDA #:** 21-676

**SPONSOR:** Berlex Laboratories, Inc.

**SUBJECT:** Review of Proposed Risk Management Program in Premeeting Package, submitted May 9, 2005

**PID #:** D050322

YAZ ™ is a combination oral contraceptive (COC) regimen consisting of 24 active tablets each containing 3 mg of drospirenone and 0.02 mg of ethinyl estradiol and 4 inert tablets. It provides for a lower estrogen dose of 0.02 mg per day with the same drospirenone dose of 3 mg per day over 24 days instead of the 21 days regimen for Yasmin-28 (drospirenone 3mg/ethinyl estradiol 0.03mg). The rationale for the new 24-day administration is that by shortening the hormone-free interval to four days only, the new regimen would 1) minimize hormonal withdrawal symptoms, and 2) produce a more effective suppression of follicular activity and ovulation inhibition.

The YAZ application received an approvable action on November 17, 2004[1]. The action letter stated that before the application could be approved, it would be necessary for the Sponsor to (1) demonstrate a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/ethinyl estradiol or (2) propose a 21- day regimen for consideration.

Additionally, the action letter stated that the submission should include

. The Sponsor was also urged in the letter to include a proposal to conduct a large, adequately powered post-marketing surveillance study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other COCs that do not contain drospirenone.

The proposed YAZ Risk Management Program includes:

1. U.S. postmarketing surveillance study to be known as the *InterNational Active Surveillance Study of Women Taking YAZ* (INAS YAZ);
2. 

   c) EURAS and Ingenix Study.

Berlex has requested a meeting with DRUDP (which will take place on June 13, 2005) to discuss evidence that the proposed 24-day dosing regimen provides clinical benefit over that provided by the 21-day regimen. The sponsor plans to discuss the results of the ovulation inhibition study that compares the effects of the two regimens on follicular size and the incidence of ovulation in normal cycles and after intentional dosing errors. Berlex proposes to conduct a large, adequately powered post-marketing active surveillance study, similar to EURAS, in the U.S. with YAZ, 24-day to compare the incidence of serious thrombotic and thromboembolic events. The questions for the Agency are included in Appendix 1 of this document.

In preparation for this meeting, DRUDP specifically asked the divisions within the Office of Drug Safety to address the 3rd question which deals with the risk management proposal for YAZ.

**Question 3a. What advice can the Division provide about the proposed YAZ risk management program?**

***Response to Question 3a - with regard to the INAS YAZ Study:***

[1] NDA 21-676, Action letter, November 17, 2005.

A

3 Page(s) Withheld

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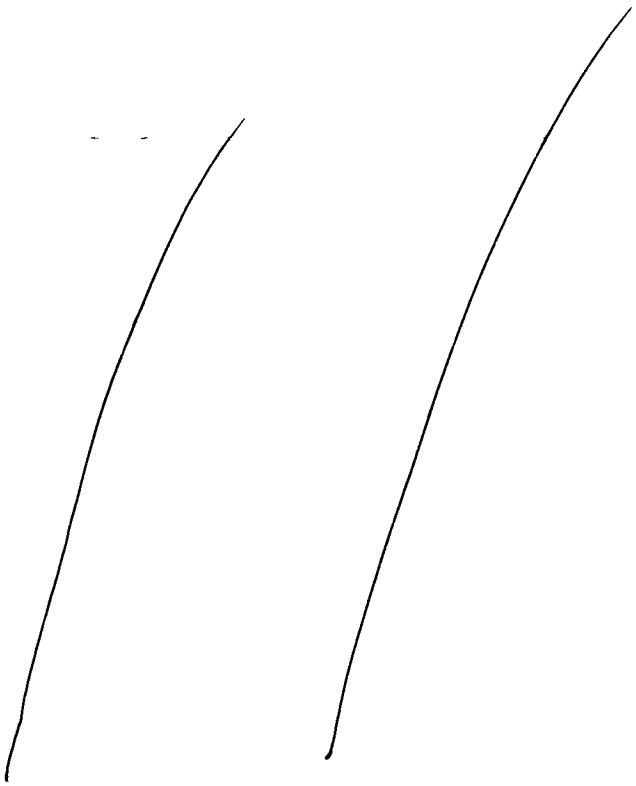
_____ Draft Labeling

_____ Deliberative Process



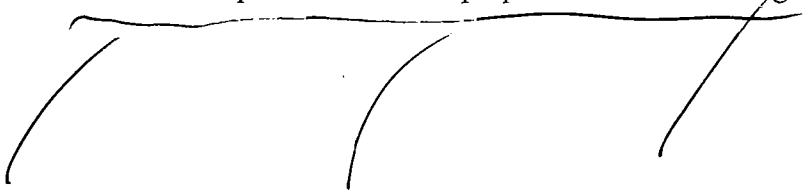
- **WITH REGARD TO COMMENTS ON THE DATA SUBMITTED BY THE SPONSOR**
  - *An attempt was made to confirm the data presented in the briefing package, section 4.2.1.3 Spontaneous VTE reporting rates and section 4.3. Spontaneous reporting of hyperkalemia/increased serum potassium. The report counts appear to be accurate, with a few caveats. Please see table 1 on the next page for comparisons between sponsor counts and AERS counts and the comments/caveats for each data point.*
  - *NDA 21-873 Safety Update Report 2/14/04-2/22/05*
    a. *Text Table 5 (p 18 of 23): Ingenix data table shows an incidence rate (IR) for VTE and ATE combined, but it would be helpful to see the IR broken down separately for VTE and ATE and/or separately for PE, DVT, AMI, CVA.*
    b. *Section 4.2.1.3 Spontaneous VTE reporting Rates (p 18 of 23): it would be helpful for the sponsor to provide summary data on spontaneous reporting rates for ATEs.*

## APPENDIX 1. SPONSOR'S QUESTIONS FOR DRUDP

1. Would the Division be able to provide their preliminary assessment of the results of the ovulation inhibition study? This feedback is important because we plan to submit the final report in our Resubmission to NDA 21-676 to demonstrate a clinical benefit of the 24 day regimen over the 21 day regimen that justifies exposing women to 3 additional days of DRSP/EE. Based on your preliminary assessment, does the Division concur with Berlex that the ovulation inhibition study demonstrates a clinical benefit? If not, Berlex will provide any additional analyses which may be useful for the Division immediately after out meeting. We understand that any advice provided is preliminary.

2. Based on our analysis, the data from the ongoing postmarketing studies in the US (Ingenix Magnifi Epidemiology) and Europe (EURAS) does not demonstrate a safety signal of different VTE risk for Yasmin as compared to other COCs. We would appreciate knowing whether the Division concurs with our analysis or, if not, what additional analyses may be useful?

3. What advice can the Division provide about the proposed YAZ risk management program?



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1 Page(s) Withheld

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**Table 1. Review of Yasmin Reports in AERS through 06 Feb 2005**

| Data Point | Sponsor | AERS Case Counts | Comments |
|---|---|---|---|
| US medically confirmed cases of VTEs | •87 VTE cases | •90 VTE (plus 10 non-medically confirmed)<br>•4 unspecified thrombosis (plus 2 non-medically confirmed)<br>•1 unspecified embolism (non-medically confirmed) | Sponsor does not define VTE or note whether or not all these events are serious (e.g. not sure if this includes menstrual clotting which may be coded as PT thrombosis). The sponsor may be including non-serious cases that may not be in AERS. Duplicates were removed from the AERS listing. |
| Age | •53% (39/74) were 35 years or older<br>•age unknown in 15 cases | •48% (43/90) were 35 years or older<br>•age unknown in 14 cases | |
| Number of PEs | •54% (47/87) of VTE cases<br>•43% (20/47) of PEs occurred in pts 35 years or older<br>•10.6% (5/47) had fatal outcome | •54% (49/90) of VTE cases<br>•43% (21/49) of PEs occurred in pts 35 years or older<br>•10.2% (5/49) had fatal outcome | |
| Number of fatal VTEs | •6 cases, including 5 cases of PE and 1 unspecified thromboembolism | •6 cases, including 5 cases of PE and 1 unspecified thromboembolism<br>•AERS Cases Numbers: 3846003, 3935426, 3946924, 3949697, 3956023, 3956582 | |
| Arterial Thromboembolic Events (ATE) | •Not described in the briefing package | •18 ATEs, including:<br>•13 CVA<br>•3 TIA<br>•1 cerebral infarction<br>•1 cerebral thrombosis | No cases of MI identified in AERS. |
| Elevated serum potassium reports/hyperkalemia | •16 non-serious<br>•no serious reports | •no reports of elevated serum potassium or hyperkalemia identified in AERS. | Unclear if this number includes foreign cases and/or non-medically confirmed cases. Non-serious cases may not be captured in AERS. |

**DDRE/DSRCS YAZ RiskMAP Review Team**

Mary Dempsey, Project Management Officer, ODS IO
Rita Ouellet-Hellstrom, Ph.D., M.P.H., Epidemiologist, ODS/DDRE
Claudia Karwoski, PharmD, Scientific Coordinator of RMP (Detail), ODS IO
Toni Piazza-Hepp, Pharm.D., Deputy Director, ODS/DSRCS
Adrienne Rothstein, Pharm.D., Safety Evaluator, ODS/DDRE
Judy Staffa, Ph.D., R.Ph., Epidemiology Team Leader, ODS/DSRCS
Melissa M. Truffa, R.Ph., Safety Evaluator, Team Leader, DDRE
Mary Willy, Ph.D., Epidemiology Team Leader, ODS/DSRCS

Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE), HFD-430

Gerald DalPan, M.D., Director
Division of Surveillance, Research, and Communication Support (DSCRS), HFD-410

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/s/

Mary Dempsey
6/9/05 11:12:08 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
6/9/05 11:47:08 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
6/9/05 12:18:07 PM
MEDICAL OFFICER

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: June 2, 2005**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** : 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** Information Request

**Total no. of pages including cover**: 1

**Comments:**

**Document to be mailed:** ☑ YES ☐ NO



- Please fax the Division additional information regarding the proportional odds model established for the Hoogland scores in clinical protocol 308382.
- Please submit journal articles where the odds model was utilized.
- Please specify if the model was altered specifically for this study.

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/s/
---
Z. Charlene Williamson
6/2/05 11:57:03 AM
CSO

Gerald Willett
6/2/05 12:19:52 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy Velez, Manager
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ Tablets (drospirenone3 mg / ethinyl estradiol 0.02).

We also refer to your March 31, 2005, correspondence, received April 1, 2005, requesting a meeting to discuss the options being pursued by Berlex in order to gain approval of YAZ.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting will be scheduled at a mutually agreed upon time.

Provide the background information for this meeting (three copies to the NDA and 3 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, we may cancel or reschedule the meeting.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Charlene Williamson
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Z. Charlene Williamson
4/15/05 01:45:48 PM

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy Velez, Manager
340 Changebridge Road
P.O. Box 1000
Montville, NJ 070450-1000

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone/ethinyl estradiol) Tablets.

We also refer to the telephone conference between representatives of your firm and the FDA on November 10, 2004. The purpose of the meeting was to discuss justification for the 3 additional days of exposure to drospirenone.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Scott Monroe, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

# MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** November 10, 2004

**TIME:** 1:00 PM – 2:00 PM

**LOCATION:** PKLN Conference Room 10B45

**APPLICATION:** 21-676

**DRUG NAME:** YAZ Tablets

**TYPE OF MEETING:** Telephone Conference

**MEETING CHAIR:** Scott Monroe, M.D.

**MEETING RECORDER:** Charlene Williamson

**FDA ATTENDEES:**
Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP) HFD-580
Scott Monroe, M.D., Clinical Team Leader, DRUDP; HFD-580
Gerald Willett, M.D., Medical Officer, DRUDP; HFD-580
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP; HFD-580
Charlene Williamson, Project Manager, DRUDP; HFD-580

**EXTERNAL CONSTITUENT ATTENDEES:**

**Schering AG, Berlin, Germany**
Norbert Benda, Ph.D., Senior Project Biometrician
Hartmut Blode, Ph.D., Head of Clinical Pharmacokinetics
Wolfgang Eder, Ph.D., Director, International Project Management, Gynecology and Andrology
Joachim Marr, M.D., Head of Corporate Clinical Development, Female Fertility Control and Hormone Therapy, Global Business Unit Gynecology and Andrology

**Berlex Laboratories, Inc.**
Sharon W. Brown, MS, Director, Global Regulatory Affairs
Marie Foegh, M.D., VP, Medical Affairs
Joseph Sonk, Ph.D., VP, Global Regulatory Affairs
Nancy Velez, Manager, Global Regulatory Affairs

**BACKGROUND:**
YAZ Drospirenone (DSRP) 3 mg/Ethinyl Estradiol (EE) 0.02 mg Tablets, a 24-day regimen of combined oral contraceptive formulation provides a lower estrogen dose of 0.02 mg per day with the same drospirenone dose of 3 mg per day over 24 days instead of the 21 days regimen as in their Yasmin product.

**MEETING OBJECTIVES:**
To discuss with the sponsor their justification for 3 additional days of exposure to drospirenone.

**DISCUSSION POINTS:**
Dr. Monroe led the discussion explaining to the sponsor that there was no substantial clinical evidence to support the increase of exposure from 21-day to 24-day regimen. The 24-day represents more effectiveness than the 21-day, however, because of the heightened awareness at FDA regarding safety there are particular concerns over the 3 additional days of exposure of drospirenone which results in an increase amount of serum potassium. According to the data submitted, the 21-day regimen is as effective as the 24-day, there was no evidence to support that it is less effective and no significant difference between the two regimens. The active dosing days did not provide us with any clear clinical benefits. Berlex commented that the clinical benefits are a decrease in ovulation suppression, a decrease in follicular development and fewer pregnancies, and no difference in adverse events.

**Questions:**
**What are the direct comparisons between the 21 and 24-day to prove benefit?**
*The sponsor indicated that the comparisons between the Pearl Indexes of 0.4 for the 24-day and 0.6 for the 21-day, duration of use for the first month of pill intake, a the 1:1 comparison based on the same geographical area and same duration of use shows that the efficacy on the 24-day should be better in females especially if they miss a pill. The sponsor indicated the in the European Market they are conducting an ovulation inhibition rate comparison study to be ready June 2005. FDA advised Berlex that since the data is subjective and not available for review in the current submission for oral contraception, and might be available for the PMDD submission that it could affect our approval for the 24-day regimen.*

**What are the benefits of the 24-day as an oral contraceptive and as a supplement for the PMDD?**
*The sponsor was told that they can submit a new NDA with an oral contraceptive and PMDD indications, or they can submit an application for oral contraceptives for 24-day regimen supported by well-controlled trials to support the additional three days. The PMDD studies, which are a 24-day regimen, would be reviewed for safety and effectiveness and provide additional information as to why the 24-day is meritorious, and if it would not succeed, the only path forward would be for a 21-day for ovulation inhibition.*

**Can we get a 24-day OC approval?**
*The submission options are PMDD/contraceptive as a secondary claim to support PMDD or to amend the current submission with an ovulation inhibition study, or amend the current application to substitute the 24-day for the 21-day.*

**What is the status of the tradename?**

*The Division has not objected to the name YAZ, but if there is another review cycle for this application, then there will be another review cycle for the tradename.*

**ACTION ITEMS:**
Meeting minutes due to the sponsor within 30 days.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex, Laboratories, Inc.
Attention: Nancy Velez
340 Changebridge Road
P.O. Box 1000
Montville, N.J. 07045-1000

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone 3 mg/ ethinyl estradiol 0.02 mg) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 4, 2004. The purpose of the meeting was to discuss the data reporting from the Ingenix database.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Scott Monroe, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

# MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 4, 2004

**TIME:** 11:00 AM – 12:30 PM

**LOCATION:** Chesapeake Room

**APPLICATION:** NDA 21-676

**DRUG NAME:** YAZ (drospirenone /ethinyl estradiol) Tablets

**TYPE OF MEETING:** Type C

**MEETING CHAIR:** Scott Monroe M.D.

**MEETING RECORDER:** Charlene Williamson

**FDA ATTENDEES**

Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP) HFD-580
Donna Griebel, M.D., Deputy Director, DRUDP; HFD-580
Scott Monroe, M.D., Clinical Team Leader, DRUDP; HFD-580
Gerald Willett, M.D., Medical Officer, DRUDP; HFD-580
Lesley-Ann Furlong, M.D., Medical Officer, DRUDP; HFD-580
Mary Willy, Ph.D., Lead Epidemiologist, Office of Drug Safety (ODS); HFD-430
Rita Ouellet-Hellstrom, Ph.D., Epidemiologist, ODS; HFD-430
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP; HFD-580
Karen Kirchberg, N.P., Project Manager, DRUDP; HFD-580
Patricia Knight, N.P., Project Manager, DRUDP; HFD-580
Charlene Williamson, Project Manager, DRUDP; HFD-580

**EXTERNAL CONSTITUENT ATTENDEES**

Marie Foegh, M.D., V.P., Medical Affairs
Wolfgang Eder, Ph.D., Director, International Project Management, Gynecology and Andrology
Maureen Cronin, M.D., Ph.D., Head, Gynecology and Andrology Coordination
Juergen Dinger, M.D., Ph.D., Head, International Project Management, Gynecology and Andrology
Hari Helajarvi, Director, Medical Assessment, Global Medical Safety Surveillance - USA
Joyce Moscaritola, M.D.
Ilka Schellschmidt, M.D., Core Clinician, Corporate Clinical Development, Gynecology and Andrology
Joseph Sonk, Ph.D., VP, Global Regulatory Affairs
Sharon Brown, M.S., Director, Global Regulatory Affairs
Nancy Velez, Manager, Global Regulatory Affairs

## BACKGROUND AND OBJECTIVES

The Sponsor requested a meeting with the Division to discuss ongoing review issues concerning NDA 21-676. Specifically, the issues focused on

1. The incidence of deaths and thrombotic or thromboembolic adverse events in women using Yasmin for prevention of pregnancy compared to other combination oral contraceptives based on the findings from 2 ongoing postmarketing safety studies (the European Active Surveillance Study and the Ingenix Study)
2. The Sponsor's proposed active surveillance postmarketing safety study for YAZ.

## SPONSOR'S QUESTIONS

1. Does the Division concur that the data presented in EURAS and Ingenix does not show a signal of different VTE risk?

**Division's Response**

*The interim reports, to date, from the EURAS and Ingenix studies do not appear to show a signal of increased risk of VTE for Yasmin compared to other oral contraceptives. However, both studies are ongoing and have not yet reached their projected power for detecting a difference between the treatment groups.*

2. Does the Division concur that the reporting rates calculated for Yasmin® and Ortho Evra® in our submission dated April 23, 2004 are in line with the Agency's calculation?

**Division's Response**

*Yes, the reporting rates are in line with the Agency's calculations.*

3. Does the Division concur with the design of the active surveillance postmarketing study,

**Division's Response**

4. Does the Division concur that the active surveillance postmarketing study is sufficient to support approval of Yaz?

**Division's Response**

*Approval of YAZ for marketing is dependent on a number of review issues in addition to the Sponsor's conducting an acceptable postmarketing safety surveillance study. (See Division's Response to Question No. 3 for comments about the active surveillance postmarketing study).*

## ADDITIONAL COMMENTS AND TOPICS DISCUSSED AT THE MEETING

1.

2. The Division asked the Sponsor if there were any proven advantage(s) of the 24-day active dosing regimen compared to the 21-day active dosing regimen. The Sponsor described some potential, but unproven, benefits and also made reference to the ongoing programs for the prevention of PMDD and treatment of acne. Both of the later programs are using the 24-day active dosing regimen.
3. The Sponsor was informed that the Division of Medication Errors and Technical Support (DMETS) were still recommending against approval of the name YAZ because of potential confusion with YASMIN.

**ACTION ITEMS**

Meeting minutes are due to the Sponsor within 30 days.

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/s/

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Scott Monroe
11/3/04 04:24:57 PM

# NDA REGULATORY FILING REVIEW
**(Including Memo of Filing Meeting)**

NDA # 21-676 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: YAZ Tablets
Generic Name: (drospirenone 3 mg / ethinyl estradiol 0.02 mg)
Strengths:

Applicant: Berlex Laboratories, Inc.

Date of Application: October 16, 2003
Date of Receipt: October 17, 2004
Date clock started after UN:
Date of Filing Meeting: December 10, 2003
Filing Date: Date 16, 2003
Action Goal Date (optional): November 17, 2004 User Fee Goal Date: November 17, 2004

Indication(s) requested: Prevention of Pregnancy in women of child-bearing years (Contraceptive)

Type of Original NDA: (b)(1) ___X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

***NOTE:***

*(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

*(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

____ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S _X_____ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid __10/9/2003_____ Exempt (orphan, government)
_____
Waived (e.g., small business, public health) _____

***NOTE:*** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

*product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES **NO**

  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES **NO**

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? **YES** NO

- Was form 356h included with an authorized signature? **YES** NO
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? **YES** NO

  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A **YES** NO
  **If an electronic NDA, all certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO

- Is it an electronic CTD? N/A YES **NO**
  **If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? **YES** NO

- Exclusivity requested? **YES,** ___3____years NO
***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? **YES** NO
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

***NOTE:*** *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? **YES** NO
**(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers:

- End-of-Phase 2 Meeting(s)? Date(s) _____ **NO**
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) __2/20/2003__ NO
If yes, distribute minutes before filing meeting.

## Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES** NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **YES** NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A **YES** NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

  **N/A** YES NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? **N/A** YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

  YES **NO**

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES** NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? **YES** NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES **NO**

ATTACHMENT

## MEMO OF FILING MEETING

DATE: December 16, 2003

BACKGROUND:
Berlex is developing a low dose combined oral contraceptive product (Drospirenone 3 mg and ethinyl estradiol 0.02 mg) tablet. Each 28-day treatment cycle will consist of 24 active tablets and 4 placebo tablets.

ATTENDEES:
Scott Monroe, M.D., Clinical Team Leader
Jerry Willett, M.D., Medical Officer
Moo-Jhong Rhee, Ph.D., Chemistry Team Lead
Donna Christner, Ph.D., Chemist
Lynnda Reid, Ph.D., Pharmacology Supervisor
Krishan Raheja, Ph.D., D.V.M., Pharmacologist
Shahla Farr, M.S., Statistician
Ameeta Parekh, Ph.D., Pharmacokinetics Team Leader
Myong-Jin Kim, PharmD., Pharmacokinetics Reviewer

ASSIGNED REVIEWERS:

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Jerry Willett, M.D. |
| Secondary Medical: | |
| Statistical: | Shahla Farr, M.S. |
| Pharmacology: | Krishan Raheja, Ph.D. |
| Statistical Pharmacology: | |
| Chemistry: | Donna Christner, Ph.D. |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Myong-Jin Kim, PharmD |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | Roy Blay, Ph.D. |
| Regulatory Project Management: | Charlene Williamson |
| Other Consults: | |

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL FILE __X____ REFUSE TO FILE _____

- Clinical site inspection needed: **YES** NO
- Advisory Committee Meeting needed? YES, date if known _____ **NO**

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

| | | | N/A | YES | NO |
|---|---|---|---|---|---|
| CLINICAL MICROBIOLOGY | **NA** _____ | FILE _____ | | REFUSE TO FILE _____ | |
| STATISTICS | | **FILE __X____** | | REFUSE TO FILE _____ | |
| BIOPHARMACEUTICS | | **FILE ___X___** | | REFUSE TO FILE _____ | |
| • Biopharm. inspection needed: | | | | YES | **NO** |
| PHARMACOLOGY | NA _____ | **FILE ____X___** | | REFUSE TO FILE _____ | |
| • GLP inspection needed: | | | | YES | NO |
| CHEMISTRY | | **FILE ___X___** | | REFUSE TO FILE _____ | |
| • Establishment(s) ready for inspection? | | | | **YES** | NO |
| • Microbiology | | | | YES | **NO** |

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

__x____ Filing issues to be communicated by Day 74. List (optional):

In our filing review, we have identified the following potential review issues:

1. We do not understand fully the reasons for closure of several study sites in Brazil. Provide additional information regarding the reasons for your decision, including the specific sequence of events that led to the closure of each site.

2. We continue to have concerns about the reports of serious thromboembolic and thrombotic adverse events in women using Yasmin, particularly the number of deaths associated with these adverse events. To assist us in our safety assessment of your combination drug product containing 20 mcg of Ethinyl Estradiol and 3 mg of Drospirenone (YAZ), we request that you provide us with

   a. An updated interim safety report for your ongoing European Active Surveillance

Study (EURAS) for Yasmin no later than 45 days prior to August 17, 2004;

b. Updated safety information for YAZ to include all clinical trial and postmarketing safety information reported to Berlex and/or Schering through July 3, 2004 concerning thromboembolic and thrombotic adverse events and deaths not previously submitted to NDA 21-676. This information should be submitted no later than July 17, 2004.

The request for safety data listed in Items a and b above are in addition to that which we expect to receive as part of your standard 4-Month Safety Update.

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Charlene Williamson
Regulatory Project Manager, HFD-580

## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

## Appendix B to NDA Regulatory Filing Review
## Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

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Z. Charlene Williamson
10/16/04 02:52:25 PM
CSO

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

**DATE:** September 9, 2004

**FROM:** Rita Ouellet-Hellstrom, Ph.D., M.P.H.
Epidemiologist
Division of Drug Risk Evaluation, HFD-430

**THROUGH:** Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

**TO:** Gerald D. Willett, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580

**SUBJECT:** Proposed Phase IV Active Surveillance Study - Yaz

**DRUG:** Yaz (drospirenone 3mg /ethinyl estradiol 0.020 mg) Tablets
**NDA:** 21-676
**PID#:** D040572

**SPONSOR** Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 070450-1000

## 1 EXECUTIVE SUMMARY

On August 31, 200, the Division of Drug Risk Evaluation (DDRE) received a request from the Division of Reproductive and Urologic Drug Products (HFD-580) to review the proposed Phase IV Active Surveillance Study for YAZ Drospirenone (DSRP) 3 mg/Ethinyl Estradiol (EE) 0.02 mg Tablets. The new combined oral contraceptive formulation provides a lower estrogen dose of 0.02 mg per day with the same drospirenone dose of 3 mg per day over 24 days instead of the 21 days regimen for Yasmin-28.

6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/
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Rita Ouellet-Hellstrom
9/9/04 03:09:26 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
9/15/04 01:05:13 PM
DRUG SAFETY OFFICE REVIEWER

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for drospirenone 3 mg/ethinyl estradiol 0.02 Tablets.

We also refer to your August 6, 2004, correspondence, received August 9, 2004, requesting a meeting to discuss the most current information about the reported occurrence and severity of thromboembolic events associated with Yasmin and its relevance to this product.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

| | |
|---|---|
| Date: | October 4, 2004 |
| Time: | 11:00 AM – 12:30 PM |
| Location: | Chesapeake Conference Room |

CDER participants:
Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products, (DRUDP), HFD-580
Donna Griebel, M.D., Deputy Director, DRUDP; HFD-580
Scott Monroe, M.D., Clinical Team Leader, DRUDP; HFD-580
Gerald Willett, M.D., Medical Officer, DRUDP; HFD-580
Rita Ouellet-Hellstrom, Ph.D., Epidemiologist, Office of Drug Safety, HFD-430
Mary Willy, Ph.D., Epidemiologist, Office of Drug Safety, HFD-440
Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP; HFD-580
Charlene Williamson, Regulatory Project Manager, DRUDP; HFD-580

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to williamsonc@cder.fda.gov so that the security staff has time to prepare temporary badges in advance. Upon arrival at FDA,

give the guards either of the following numbers to request an escort to the conference room: Charlene Williamson, 301-827-4266; the division secretary, 301-827-4260.

We have received your information package, if the materials presented in the information package are inadequate to justify holding a meeting, we may cancel or reschedule the meeting.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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Margaret Kober
9/7/04 01:14:31 PM
Chief, Project Management Staff

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE I**

# FACSIMILE TRANSMITTAL SHEET

**DATE: August 17, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez<br>Manager | **From:** Charlene Williamson<br>Regulatory Project Manager |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** Request for datasets

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** • YES ☑ NO



NDA # 21-676

For Study # a15129 YAZ:

Please provide us with one dataset with the exact and complete list of subjects under study, for efficacy; (similar to that of Study A12007 submitted on 6/29/2004) that includes the following variables:

- PID (NUM)
- COUNTRY (CHAR)
- SITE (NUM)
- INV (CHAR)
- TREATMENT ARM (CHAR)
- AGE (NUM)
- RACE (CHAR)
- HEIGHT (NUM)
- WEIGHT (NUM)
- BPD (NUM)
- BPS (NUM)
- DATE OF EACH VISIT (DATE)
- VISIT # (NUM)
- CYCLE (i.e.: screening, baseline, cycle1, …, final examination) (CHAR)
- CYCLE # (i.e.: screening should be equal to 1, baseline should be equal to 2, cycle1=3, …final examination=…) (NUM)
- PREGNANCY (yes/ no, only for under the treatment subjects) (CHAR)
- OTHER METHOD OF CONTRACEPTION (yes/no) (CHAR)
- SEXUALLY ACTIVE (yes/no) (CHAR)
- COMPLIANT (yes/no) (CHAR)
- # OF DAYS UNDER TREATMENT FOR EACH INDIVIDUAL SUBJECT/VISIT SEPARATELY (NUM)
- TOTAL # OF DAYS UNDER TRTMNT FOR EACH SUBJECT (with and without cycles with backup contraception) (NUM)
- TOTAL # OF CYCLES UNDER TRTMNT FOR EACH SUBJECT(with and without cycles with backup contraception) (NUM)
- TOTAL # OF MONTHS UNDER TRTMNT FOR EACH SUBJECT(with and without cycles with backup contraception) (NUM)
- CENSOR (1/0) (NUM)

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/s/
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Z. Charlene Williamson
8/17/04 11:50:59 AM
CSO

Shahla Farr
8/17/04 12:16:56 PM
BIOMETRICS

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE I**

# FACSIMILE TRANSMITTAL SHEET

**DATE: July 30, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez<br>Manager | **From:** Charlene Williamson<br>Regulatory Project Manager |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** Request for datasets

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** • YES ☑ NO



We are reviewing your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide us with **one** dataset with the exact and complete list of subjects under study, for efficacy, (very similar to that of Study A12007 submitted on 6/29/2004) that includes the following variables:

- PID (NUM)
- COUNTRY (CHAR)
- SITE (NUM)
- INV (CHAR)
- TREATMENT ARM (CHAR)
- AGE (NUM)
- RACE (CHAR)
- HEIGHT (NUM)
- WEIGHT (NUM)
- BPD (NUM)
- BPS (NUM)
- DATE OF EACH VISIT (DATE)
- VISIT # (NUM)
- CYCLE (i.e.: screening, baseline, cycle1, …, final examination) (CHAR)
- CYCLE # (i.e.: screening should be equal to 1, baseline should be equal to 2, cycle1=3, …final examination=…) (NUM)
- PREGNANCY (yes/ no, only for under the treatment subjects) (CHAR)
- OTHER METHOD OF CONTRACEPTION (yes/no) (CHAR)
- # OF DAYS UNDER TREATMENT AT EACH VISIT SEPARATELY (NUM)
- TOTAL # OF DAYS UNDER TRTMNT FOR EACH SUBJECT (with and without cycles with backup contraception) (NUM)
- TOTAL # OF CYCLES UNDER TRTMNT FOR EACH SUBJECT(with and without cycles with backup contraception) (NUM)
- TOTAL # OF MONTHS UNDER TRTMNT FOR EACH SUBJECT(with and without cycles with backup contraception) (NUM)
- CENSOR (1/0) (NUM)

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/s/
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Z. Charlene Williamson
7/30/04 03:43:32 PM
CSO

Shahla Farr
7/30/04 03:47:51 PM
BIOMETRICS

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: July 13, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:**

**Total no. of pages including cover:** 5

**Comments:**

**Document to be mailed:** • YES ☑ NO

NDA 21-676

We are requesting the following additional information concerning the post marketing safety of Yasmin to assist us in our review of NDA 21-676 (YAZ). The need for the additional information was conveyed to you during a teleconference on June 28, 2004.

1. On going United Health Care Post marketing Safety Surveillance Study:

   a. Provide specific information on how deaths in the United Health Care database are identified. What is the likelihood that a death in a Yasmin user would be missed?

   b. Provide summary reports, based on chart reviews for all subjects in the United Health Care Database (based on your June 10, 2004 line listing submission) that were identified with the following conditions:
      - Venous thrombosis
      - Pulmonary embolus
      - Stroke (CVA)
      - Myocardial infarction

   c. In the data line listing submission of June 10, 2004 there were women who were only identified as taking anticoagulant medication with no other diagnosis provided. Can you provide additional information as to the reason for anticoagulant use?

   d. In the data line listing submission of June 10, 2004 there were women who were only identified as having imaging studies of the lung or extremities without other diagnoses listed. Can you provide additional information as to the results of this testing?

   e. In the data line listing submission of June 10, 2004 there were numerous tests for fibrin degradation products. Why was this test included in the database search?

   f. Provide the data listings from your submission of June 10, 2004 in SAS transport format so that we can perform our own analysis.

2. EURAS Study Report:

   a. Concerning the April 8, 2004 submission of the EURAS report, page 14, table 7:
      - Explain why the number of "misunderstanding and other diagnoses" were higher for Yasmin compared to the LNG containing oral contraceptives users.

   b. Provide brief summary reports on all patients (similar to those found on pages 65 through 185 in the April 8, 2004 submission) considered "Probable VTE" and if possible for the group where VTE was not confirmed. Provide similar summaries of all patients evaluated for VTE for the planned updated EURAS report discussed during the teleconference of June 28, 2004.

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/s/

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Z. Charlene Williamson
7/13/04 12:20:51 PM
CSO

Gerald Willett
7/13/04 01:39:10 PM
MEDICAL OFFICER

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ™ (drospirenone 3 mg/ethinyl estradiol 0.020 mg) Tablets.

On July 1, 2004, you were faxed an advice letter for the extension of the user fee goal date. Because of the incorrect dates used, this corrected letter is to supersede the previous letter.

On June 11, 2004, we received your June 10, 2004 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 17, 2004.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
7/2/04 01:04:19 PM

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ™ (drospirenone 3 mg/ethinyl estradiol 0.020 mg) Tablets.

On June 25, 2004, we received your June 24, 2004 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 17, 2004.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Jennifer L. Mercier
7/1/04 12:57:43 PM

**CONSULTATION RESPONSE**
**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**(DMETS; HFD-420)**

| **DATE RECEIVED:** | **DESIRED COMPLETION DATE:** June 22, 2004 | **ODS CONSULT #:** |
|---|---|---|
| May 21, 2004 | **PDUFA DATE:** August 17, 2004 | 04-0013-2 |

**TO:** Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

**THROUGH:** Charlene Williamson
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

| **PRODUCT NAME:** | **NDA SPONSOR:** |
|---|---|
| YAZ™<br>(Drospirenone and Ethinyl Estradiol Tablets)<br>3 mg/0.02 mg<br><br>**NDA#:** 21-676 | Berlex Laboratories, Inc. |

**SAFETY EVALUATOR:** Scott Dallas, R.Ph.

**RECOMMENDATIONS:**

1. DMETS has reviewed and evaluated the [redacted] Study for the proposed proprietary name, YAZ™ and continues to be concerned that the proposed name could be misinterpreted as an abbreviation for the medication Yasmin. The proposed name looks like a three letter abbreviation for something rather than a name itself. Therefore healthcare professionals and patients may attempt to associate the name as an abbreviation for another medication. The [redacted] market research study has shown that without prior knowledge of the product information (unaided research) 19 physicians and/or pharmacists (9.5%) associated the name YAZ™ with the proprietary name Yasmin. No information has been presented in the [redacted] Study to alleviate DMETS concern that the introduction of the proprietary name YAZ™ into the marketplace would increase the risk of confusion and medication errors between the medications YAZ and Yasmin. Thus, the information provided has failed to provide persuasive evidence for DMETS to reverse its initial decision on the acceptability of the proprietary name "YAZ™".
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of any label or labeling from the manufacturer.

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**HFD-420; Parklawn Building Room 6-34**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** June 17, 2004

**NDA NUMBER:** 21-676

**NAME OF PRODUCT:** YAZ™
(Drospirenone and Ethinyl Estradiol Tablets)
3 mg/0.02 mg

**NDA SPONSOR:** Berlex Laboratories, Inc.

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products for a reassessment of the proposed proprietary name, YAZ™. In a review dated March 10, 2004 (ODS Consult #04-0013), DMETS recommended against the use of the proposed proprietary name, YAZ™. DMETS was concerned that the proprietary name YAZ™ could be misinterpreted as an abbreviation for the medication Yasmin. Misinterpretation of the proposed proprietary name YAZ™ would cause confusion and could result in medication errors. In a correspondence dated May 14, 2004, the sponsor submitted a request for reconsideration of the proposed name. Additionally, the sponsor submitted an independent analysis conducted by the — in support of the proposed name YAZ™.

The sponsor stated that issues concerning the label and labeling will be addressed in a separate submission. However, the sponsor did submit color mock-ups of the front carton panels for YAZ™ and Yasmin®. DMETS will review and comment on the front carton panel for YAZ™.

PRODUCT INFORMATION
YAZ™ is indicated for the prevention of pregnancy in women who choose to use an oral contraceptive. YAZ™ provides an oral contraceptive regimen consisting of 24 active tablets each containing 3 mg of drospirenone and 0.02 mg of ethinyl estradiol and 4 inert tablets. The patient is to administer one tablet every day without regards to meals. The labeling contains a detailed patient package insert to be provided to the patient.

## II. REASSESSMENT OF YAZ™:

In a correspondence dated May 14, 2004, the sponsor concluded that:

> *"We believe that data provided in this submission supports our conclusion that the tradename YAZ™ is similar, yet distinct, from YASMIN®, will not be misinterpreted with the existing product YASMIN® and will not add to the confusion in the marketplace".*

In developing the name, the sponsor states the following two goals were considered:

1. [redacted]

2. *Develop a name that is distinct enough to avoid prescribing and dispensing errors. In this respect, Berlex's interests are in agreement with those of the Agency."*

In response to the first goal, DMETS recognizes [redacted]

In support of the second goal, the sponsor submitted an independent analysis of the proposed name. The [redacted] conducted this independent analysis, which will be evaluated below.

A. [redacted] STUDY AND ANALYSIS

**Market Research for Proposed Name YAZ™ dated May 13, 2004**

The [redacted] conducted a study to evaluate if "YAZ™ is confusingly similar in sound or appearance to proprietary or nonproprietary names of drugs in the United States and whether YAZ™ makes claims that are false, misleading, or fanciful". The report stated that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were Obstetricians/Gynecologists (50), Primary Care Physicians (50), Community Pharmacists (50), and Institution-based Pharmacists (50). These medical professionals participated in various aspects of Sections A and B of the market research study. [redacted] professionals conducted and evaluated Section C of the market research study. An independent panel of five actively practicing pharmacists participated and evaluated the results of the study in Section D. The four sections of the study as well as study findings are discussed below.

1. Section A – Practitioner Nomenclature Review: Physicians

[redacted] asked 100 physicians to view the test name, YAZ™, and identify any proprietary or nonproprietary names that they considered similar to the test name based on sound and/or appearance. They were also asked to identify whether YAZ™ had sound-alike or look-alike properties to any medical terms, including acronyms and abbreviations. These two assessments were conducted without providing the respondents any information about the product (e.g., unaided research). Then the respondents were provided with the proposed product profile and were asked to specify any misleading connotations, exaggerations, or other hyperbole.

DMETS Response:

DMETS has referenced Appendix IV from the [redacted] study below, to show that without prior knowledge of the product information physicians responded that the proposed name YAZ™ had a similar sound or appearance to Yasmin.

Physician's Responses for YAZ:

| Existing Drug Names | Similar Sound | Similar Appearance |
|---|---|---|
| FORTAZ | 1 | 1 |
| YASMIN | 6 | 7 |

In the next component, ~ included physicians and pharmacists. Appendix II from the ~ study shows that without prior knowledge of the product information 19 physicians and/or pharmacists (9.5%) associated the name YAZ™ with the proprietary name Yasmin.

| Number | Responses for YAZ | Percentage |
|---|---|---|
| 177 | No Associations | 88.5% |
| 19 | Yasmin | 9.5% |
| 2 | Regular strength | 1% |
| 1 | Extended release | 0.5% |
| 1 | Herbal remedy | 0.5% |
| 200 | Total | 100% |

The results from both unaided studies indicate that physicians and pharmacists view the proposed proprietary name, YAZ™, as having the potential to sound and or look similar, and even elicit an association with the marketed name Yasmin. These unaided studies do not negate, but actually confirm DMETS concern for potential confusion and errors between YAZ™ and Yasmin.

DMETS acknowledges that the results from Section A did not indicate that the physicians had any other issues with medical term similarities or exaggerative/inappropriate name identification.

2. Section B – Handwritten and Verbal Analysis: Pharmacists

~provided fifty actively practicing pharmacists with a verbal prescription for YAZ™, and another group of fifty pharmacists with a written prescription for YAZ™. The objective of this phase is to determine if any of the sample YAZ™ prescriptions would be interpreted as a currently marketed brand or established name product. The results from this section of the study indicated that the pharmacists interpreted the verbal and handwritten prescription correctly.

DMETS Response:

~reports that no respondents in either the written or verbal phase misinterpreted the name. Negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Therefore, these findings are not considered significant.

DMETS also notes that pharmacists who participated in the written phase are instructed to respond with an exact interpretation of what has been scripted on the prescription. Therefore, it may be difficult to detect in this study if

pharmacists in the real world would interpret the name, YAZ™ as an abbreviation for the proprietary name, Yasmin. DMETS also notes that the names YAZ™ and YAS are phonetically very similar. Therefore, DMETS it is very interesting that no participants phonetically interpreted the verbal prescription for YAZ incorrectly as YAS.

Additionally, Appendix IV from the —study below, demonstrates that without prior knowledge of the product information pharmacists responded that the proposed name YAZ™ had a similar sound or appearance to Yasmin.

Pharmacists' Responses for YAZ:

| Existing Drug Names | Similar Sound | Similar Appearance |
|---|---|---|
| PASER | | 1 |
| YASMIN | 5 | 4 |

The results from this unaided study indicate that pharmacists view the proposed proprietary name, YAZ™, as having the potential to sound and or look-alike, with the marketed name Yasmin.

DMETS acknowledges that the results from Section B did not indicate that the pharmacists had any other issues with medical term similarities or exaggerative/inappropriate name identification.

3. Section C – Computer-Assisted Analysis

— professionals conducted and evaluated this section of the research. — concluded that computerized analyses of Phonologic/Orthographic similarity between existing drug names in the research found limited name similarity overall with YAZ™. A specific comparison between YAZ™ and Yasmin indicated that there were no measurement thresholds exceeded for sound and look-alike similarity. —searched medical references for similar medical terms to YAZ™ and also any medical terms, acronyms, abbreviations similar to the prefix and suffix for YAZ™. — concluded there were no issues related to YAZ™ or the prefix/suffix for YAZ™.

Based on the results from this section and Section B, — stated that the "absence of identifiable name similarity between Yasmin and the proposed name candidate suggest that these agents will be correctly distinguished from one another in the real world practice."

DMETS Response:

DMETS has concerns with both the methodology and results in Section B, and therefore DMETS can not rely on this data as an indicator for confusion. Also, the —professionals did not specifically evaluate DMETS concern as to whether YAZ™ could be confused as an abbreviation for the medication Yasmin. Despite the results of Section C, DMETS notes that practitioners in Sections A and B indicated that YAZ either sound or look similar to Yasmin and they also associated YAZ with Yasmin.

4. Section D – PROFESSIONAL REVIEW COMMITTEE

The committee stated:

> *"Upon review of the performance of YAZ across all safety measurements in Sections A, B, and C of the research, the name candidate showed a very low risk of confusion." ... "With regard to product similarities for names identified in the research, the one product that shared all profile characteristics with the test product was the antecedent brand Yasmin. Look-alike similarity between Yasmin and the test name is limited to the first two letters (Ya). The remaining portions of each name (-min vs. –z) are easily distinguished from one another when written. Additionally, upon pronunciation, the extra syllable in Yasmin provides a strong cue for differentiation between the two names. ... Thus, despite the product commonalties, the differences between the names should provide a safeguard against confusion. In the event of confusion between these two agents, the risk of patient harm is likely to be negligible."*

DMETS Response:

The committee concluded that Yasmin shared all profile characteristics with YAZ™, but did not address if YAZ™ could be misinterpreted as an abbreviation for the medication Yasmin. DMETS continues to believe that the introduction of YAZ™ into the marketplace would increase the risk of confusion and errors between the products YAZ™ and Yasmin.

Based on DMETS understanding of the therapeutic differences between the products, DMETS acknowledges that the risk of patient harm may be low. However, DMETS questions the rationale of increasing confusion and possibly medication errors with the introduction of the proprietary name YAZ™ into the marketplace.

B. THREE CAPITAL LETTER ABBREVIATIONS

Abbreviations to identify a medication can commonly be presented as three capital letters. Healthcare professionals have used three letter abbreviations to identify medications for many years. Organizations such as the Institute of Safe Medication Practices are attempting to educate healthcare professionals that abbreviations should not be used to identify a medication. Even the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has recognized the dangers of using abbreviations. One of JCAHO's 2004 National Patient Safety Goals is to prohibit the use of "dangerous" abbreviations, acronyms, and symbols. However, the organization also recognizes that healthcare professionals have used abbreviations, acronyms, and symbols for so long that compliance with this goal will take time. Thus, it is also reasonable to assume that healthcare professionals will continue to use abbreviations to identify medications for some time to come.

If YAZ™ is approved, then DMETS is concerned that healthcare professionals and patients may interpret YAZ™ as an abbreviation and not as a proprietary name. — research results indicate that without any exposure to any product information (unaided research) 19 physician and or pharmacists associated the name YAZ™ with the name Yasmin. This unaided association confirms DMETS concern that YAZ™ could be interpreted as an

abbreviation for the medication Yasmin. As reported earlier one participant in DMETS prescription study interpreted the verbal prescription order for YAZ™ as the medication Yasmin.

Table 1 has been included below to present some examples of three letter abbreviations for an intended medication(s), and the corresponding misinterpreted medication(s).

Table 1. Three Letter Abbreviations for Intended Medications and the corresponding Misinterpreted Medication

| Abbreviation | Intended Medication | Misinterpreted Medication |
|---|---|---|
| **AZT** | Zidovudine (Retrovir) | Azathioprine |
| **CPZ** | Compazine (Prochlorperazine) | Chlorpromazine |
| **DPT** | Demerol-Phenergan-Thorazine | Diphteria-pertussis-tetanus |
| **HCT** | Hydrocortisone | Hydrochlorothiazide |
| **MTX** | Methotrexate | Mitoxantrone |
| **TAC** | Triamcinolone | Tetracaine, Adrenalin, Cocaine and Tazorac |

Even old abbreviations can be misinterpreted for newer medications. FDA has received two MedWatch reports in which Tazorac cream 0.1% has been inadvertently dispensed to two pediatric patients from the same family with eczema instead of the intended medication, triamcinolone cream 0.1%. The reports indicate that the name of the medication was abbreviated as "TAC", to refer to the medication triamcinolone. Both pediatric patients experienced adverse effects from being administered the wrong medication, along with experiencing secondary infections. The mother did not discover the wrong medication was dispensed until after the children received 10 days of therapy.

A dispensing error where Yasmin is dispensed for YAZ™ may go undetected for months. Physicians can prescribe 6 months or even 12 months worth of oral contraceptive medication for a patient by indicating a number of refills on either a written prescription or on a verbal order over a telephone. If a pharmacist enters the medication incorrectly, then the dispensing error may not be detected until the patient returns to the physician's office or until all the refills are depleted from the prescription, or until an adverse event is reported.

## III. COMMENTS TO THE SPONSOR:

DMETS has reviewed, evaluated and commented on the market research study conducted by the ——→ and has also included additional comments concerning abbreviations composed of three capital letters.

### A. — STUDY AND ANALYSIS

**Market Research for Proposed Name YAZ™ dated May 13, 2004**

——— conducted a study to evaluate if "YAZ™ is confusingly similar in sound or appearance to proprietary or nonproprietary names of drugs in the United States and whether YAZ™ makes claims that are false, misleading, or fanciful". The — report stated that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were Obstetricians/Gynecologists (50), Primary Care Physicians (50), Community

Pharmacists (50), and Institution-based Pharmacists (50). These medical professionals participated in various aspects of Sections A and B of the market research study. [redacted] professionals conducted and evaluated Section C of the market research study. An independent panel of five actively practicing pharmacists participated and evaluated the results of the study in Section D. The four sections of the study as well as study findings are discussed below.

1. Section A – Practitioner Nomenclature Review: Physicians

[redacted] asked 100 physicians to view the test name, YAZ™, and identify any proprietary or nonproprietary names that they considered similar to the test name based on sound and/or appearance. They were also asked to identify whether YAZ™ had sound-alike or look-alike properties to any medical terms, including acronyms and abbreviations. These two assessments were conducted without providing the respondents any information about the product (e.g., unaided research). Then the respondents were provided with the proposed product profile and were asked to specify any misleading connotations, exaggerations, or other hyperbole.

DMETS Response:

DMETS has referenced Appendix IV from the [redacted] study below, to show that without prior knowledge of the product information physicians responded that the proposed name YAZ™ had a similar sound or appearance to Yasmin.

Physician's Responses for YAZ:

| Existing Drug Names | Similar Sound | Similar Appearance |
|---|---|---|
| FORTAZ | 1 | 1 |
| YASMIN | 6 | 7 |

In the next component, [redacted] included physicians and pharmacists. Appendix II from the [redacted] study shows that without prior knowledge of the product information 19 physicians and/or pharmacists (9.5%) associated the name YAZ™ with the proprietary name Yasmin.

| Number | Responses for YAZ | Percentage |
|---|---|---|
| 177 | No Associations | 88.5% |
| 19 | Yasmin | 9.5% |
| 2 | Regular strength | 1% |
| 1 | Extended release | 0.5% |
| 1 | Herbal remedy | 0.5% |
| 200 | Total | 100% |

The results from both unaided studies indicate that physicians and pharmacists view the proposed proprietary name, YAZ™, as having the potential to sound and or look similar, and even elicit an association with the marketed name

Yasmin. These unaided studies do not negate, but actually confirm DMETS concern for potential confusion and errors between YAZ™ and Yasmin.

DMETS acknowledges that the results from Section A did not indicate that the physicians had any other issues with medical term similarities or exaggerative/inappropriate name identification.

2. Section B – Handwritten and Verbal Analysis: Pharmacists

—provided fifty actively practicing pharmacists with a verbal prescription for YAZ™, and another group of fifty pharmacists with a written prescription for YAZ™. The objective of this phase is to determine if any of the sample YAZ™ prescriptions would be interpreted as a currently marketed brand or established name product. The results from this section of the study indicated that the pharmacists interpreted the verbal and handwritten prescription correctly.

DMETS Response:

— reports that no respondents in either the written or verbal phase misinterpreted the name. Negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Therefore, these findings are not considered significant.

DMETS also notes that pharmacists who participated in the written phase are instructed to respond with an exact interpretation of what has been scripted on the prescription. Therefore, it may be difficult to detect in this study if pharmacists in the real world would interpret the name, YAZ™ as an abbreviation for the proprietary name, Yasmin. DMETS also notes that the names YAZ™ and YAS are phonetically very similar. Therefore, DMETS it is very interesting that no participants phonetically interpreted the verbal prescription for YAZ incorrectly as YAS.

Additionally, Appendix IV from the —study below, demonstrates that without prior knowledge of the product information pharmacists responded that the proposed name YAZ™ had a similar sound or appearance to Yasmin.

Pharmacists' Responses for YAZ:

| Existing Drug Names | Similar Sound | Similar Appearance |
|---|---|---|
| PASER | | 1 |
| YASMIN | 5 | 4 |

The results from this unaided study indicate that pharmacists view the proposed proprietary name, YAZ™, as having the potential to sound and or look-alike, with the marketed name Yasmin.

DMETS acknowledges that the results from Section B did not indicate that the pharmacists had any other issues with medical term similarities or exaggerative/inappropriate name identification.

3. Section C – Computer-Assisted Analysis

— professionals conducted and evaluated this section of the research. — concluded that computerized analyses of Phonologic/Orthographic similarity between existing drug names in the research found limited name similarity overall with YAZ™. A specific comparison between YAZ™ and Yasmin indicated that there were no measurement thresholds exceeded for sound and look-alike similarity. —searched medical references for similar medical terms to YAZ™ and also any medical terms, acronyms, abbreviations similar to the prefix and suffix for YAZ™. — concluded there were no issues related to YAZ™ or the prefix/suffix for YAZ™.

Based on the results from this section and Section B — stated that the "absence of identifiable name similarity between Yasmin and the proposed name candidate suggest that these agents will be correctly distinguished from one another in the real world practice."

DMETS Response:

DMETS has concerns with both the methodology and results in Section B, and therefore DMETS can not rely on this data as an indicator for confusion. Also, the —professionals did not specifically evaluate DMETS concern as to whether YAZ™ could be confused as an abbreviation for the medication Yasmin. Despite the results of Section C, DMETS notes that practitioners in Sections A and B indicated that YAZ either sound or look similar to Yasmin and they also associated YAZ with Yasmin.

4. Section D – PROFESSIONAL REVIEW COMMITTEE

The committee stated:

> *"Upon review of the performance of YAZ across all safety measurements in Sections A, B, and C of the research, the name candidate showed a very low risk of confusion." ... "With regard to product similarities for names identified in the research, the one product that shared all profile characteristics with the test product was the antecedent brand Yasmin. Look-alike similarity between Yasmin and the test name is limited to the first two letters (Ya). The remaining portions of each name (-min vs. –z) are easily distinguished from one another when written. Additionally, upon pronunciation, the extra syllable in Yasmin provides a strong cue for differentiation between the two names. ... Thus, despite the product commonalties, the differences between the names should provide a safeguard against confusion. In the event of confusion between these two agents, the risk of patient harm is likely to be negligible."*

DMETS Response:

The committee concluded that Yasmin shared all profile characteristics with YAZ™, but did not address if YAZ™ could be misinterpreted as an abbreviation for the medication Yasmin. DMETS continues to believe that the introduction of YAZ™ into the marketplace would increase the risk of confusion and errors between the products YAZ™ and Yasmin.

Based on DMETS understanding of the therapeutic differences between the products, DMETS acknowledges that the risk of patient harm may be low. However, DMETS questions the rationale of increasing confusion and possibly medication errors with the introduction of the proprietary name YAZ™ into the marketplace.

B. THREE CAPITAL LETTER ABBREVIATIONS

Abbreviations to identify a medication can commonly be presented as three capital letters. Healthcare professionals have used three letter abbreviations to identify medications for many years. Organizations such as the Institute of Safe Medication Practices are attempting to educate healthcare professionals that abbreviations should not be used to identify a medication. Even the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has recognized the dangers of using abbreviations. One of JCAHO's 2004 National Patient Safety Goals is to prohibit the use of "dangerous" abbreviations, acronyms, and symbols. However, the organization also recognizes that healthcare professionals have used abbreviations, acronyms, and symbols for so long that compliance with this goal will take time. Thus, it is also reasonable to assume that healthcare professionals will continue to use abbreviations to identify medications for some time to come.

If YAZ™ is approved, then DMETS is concerned that healthcare professionals and patients may interpret YAZ™ as an abbreviation and not as a proprietary name. — research results indicate that without any exposure to any product information (unaided research) 19 physician and or pharmacists associated the name YAZ™ with the name Yasmin. This unaided association confirms DMETS concern that YAZ™ could be interpreted as an abbreviation for the medication Yasmin. As reported earlier one participant in DMETS prescription study interpreted the verbal prescription order for YAZ™ as the medication Yasmin.

Table 1 has been included below to present some examples of three letter abbreviations for an intended medication(s), and the corresponding misinterpreted medication(s).

Table 1. Three Letter Abbreviations for Intended Medications and the corresponding Misinterpreted Medication

| Abbreviation | Intended Medication | Misinterpreted Medication |
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| **CPZ** | Compazine (Prochlorperazine) | Chlorpromazine |
| **DPT** | Demerol-Phenergan-Thorazine | Diphteria-pertussis-tetanus |
| **HCT** | Hydrocortisone | Hydrochlorothiazide |
| **MTX** | Methotrexate | Mitoxantrone |
| **TAC** | Triamcinolone | Tetracaine, Adrenalin, Cocaine and Tazorac |

Even old abbreviations can be misinterpreted for newer medications. FDA has received two MedWatch reports in which Tazorac cream 0.1% has been inadvertently dispensed to two pediatric patients from the same family with eczema instead of the intended medication, triamcinolone cream 0.1%. The reports indicate that the name of the medication was abbreviated as "TAC", to refer to the medication triamcinolone. Both pediatric patients experienced adverse effects from being administered the wrong medication, along with experiencing secondary infections. The mother did not discover the wrong medication was dispensed until after the children received 10 days of therapy.

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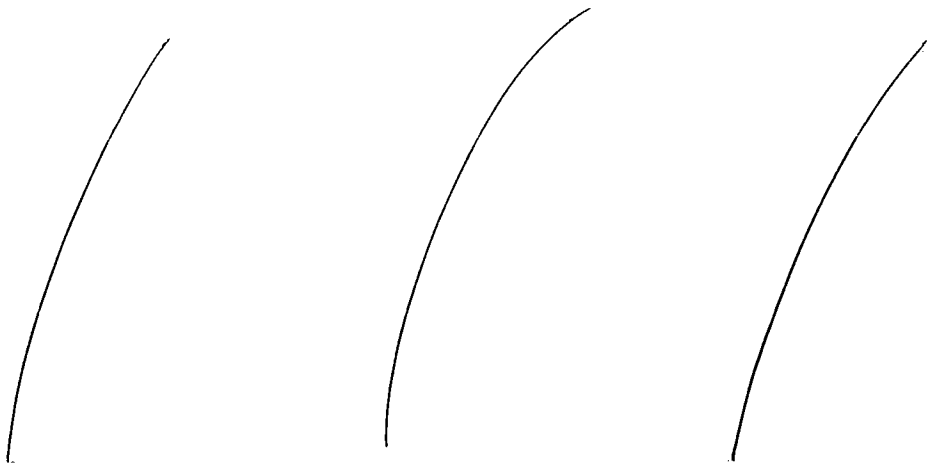
C. LABELING, AND SAFETY RELATED ISSUES

In the review of the carton labeling of YAZ™, DMETS has attempted to focus on safety issues relating to possible medication errors.



## IV. RECOMMENDATIONS:

A. DMETS has reviewed and evaluated the [redacted] Study for the proposed proprietary name, YAZ™ and continues to be concerned that the proposed name could be misinterpreted as an abbreviation for the medication Yasmin. The proposed name looks like a three letter abbreviation for something rather than a name itself. Therefore healthcare professionals and patients may attempt to associate the name as an abbreviation for another medication. The [redacted] study has shown that without prior knowledge of the product information (unaided research) 19 physicians and/or pharmacists (9.5%) associated the name YAZ™ with the proprietary name Yasmin. No information has been presented in the [redacted] Study to alleviate DMETS concern that the introduction of the proprietary name YAZ™ into the marketplace would increase the risk of confusion and medication errors between the medications YAZ and Yasmin. Thus, the information provided has failed to provide persuasive evidence for DMETS to reverse its initial decision on the acceptability of the proprietary name "YAZ™".

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of any label or labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

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Scott Dallas
7/1/04 02:57:58 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/1/04 03:19:09 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/1/04 03:33:58 PM
DRUG SAFETY OFFICE REVIEWER

**DEPARTMENT OF HEALTH & HUMAN SERVICES** **Public Health Service**

**Division of Scientific Investigations**
**Office of Medical Policy**
**Center for Drug Evaluation and Research**
**Food and Drug Administration**
**Rockville MD 20857**

## CLINICAL INSPECTION SUMMARY

DATE: June 21, 2004

TO: Charlene Williamson, Regulatory Project Manager
Gerald Willett, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-676

PROTOCOL: **Protocol # 303740** entitled: "Multi-center, Open, Uncontrolled Study to Investigate the Efficacy and Safety of the Oral Contraceptive SHT 186 Containing 0.02 mg ethinylestradiol-β-Cyclodextrin Clathrate and 3 mg Drospirenone in a 24 Day Regimen for 13 Cycles in 1010 Healthy Female Volunteers"

SPONSOR: Pharmacia & Upjohn

DRUG: SHT 186

INDICATION: Contraception

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: S (Standard Review, Substantially Equivalent)

INSPECTION SUMMARY GOAL DATE: July 17, 2004

ACTION GOAL DATE: August 17, 2004

I. BACKGROUND:

A single inspection assignment was issued on March 8, 2004, for Dr. Gloria Bachmann for protocol # 303740 for the purpose of validating data in support of pending NDA 21-676 for contraception.

Study Objective: To confirm the safety and efficacy of SHT 186 utilizing efficacy parameters such as the number of unintended pregnancies and cycle control parameters, and safety parameters such as adverse events, physical examinations, vital signs, and laboratory findings.

Methodology: A multi-center, open, uncontrolled study.

Inclusion Criteria: Female subjects 18-35 year old, in general good health desiring contraception.

1° Efficacy Endpoint: Number of unintended pregnancies (Pearl Index)

Dosage: 0.02 mg ethinylestradiol-β-Cyclodextrin Clathrate and 3 mg Drospirenone in a 24 Day Regimen for 13 Cycles

II. RESULTS (by site):

| NAME | CITY | STATE | ASSIGNED DATE | RECEIVED DATE | CLASSIFICATION/FILE NUMBER |
|---|---|---|---|---|---|
| | | | | | |
| G. Bachmann, M.D. | New Brunswick | NJ | 08 Mar 04 | 1 Jun 04 | 05055/VAI |

Site #1
Gloria Bachmann, M.D.
Women's Health Institute
125 Paterson Street
New Brunswick, New Jersey 08901-1977
See **Assessment and Recommendations**, below

a. 87 subjects were screened for the study. 10 subjects were screen failures and 24 dropped out. All consent forms were reviewed. Subject 1274's pregnancy was reported in the efficacy data listings but subject 1224's pregnancy was not. Both subjects were reported as prematurely discontinuing the study.

b. There were no limitations to the inspection except as note immediately below.

c. A Form 483 was issued noting the single observation that study records for subjects 1243 and 1270 were inadvertently shredded but were reconstructed from other existing documentation. Original consent forms and the nurse's notes for study visits for these two subjects could not be replaced.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted by Dr. Bachmann appear satisfactory in support of the relevant submission.

Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U. M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
HFD-580 Doc. Rm. NDA 21-676
HFD-45/Program Management Staff (electronic copy)
HFD-46/RF
HFD-46/c/r/s
HFD-46/Blay

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/s/
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Michele Lackner
6/23/04 02:10:35 PM
TECHNICAL

please sign

Khin U
6/24/04 02:45:23 PM
MEDICAL OFFICER

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

**INFORMATION REQUEST LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone 3 mg/ethinyl estradiol 0.02) Tablets.

We also refer to your submission dated June 11, 2004.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

From the stability data submitted on June 11, 2004, it was seen that the levels of [redacted] dropped an average of [redacted] from [redacted] to [redacted] for all three lots at 25°C and 30°C. All other degradants stayed approximately the same. A footnote to the stability specification table in that submission states the "Testing standards [redacted] became valid on July 01, 2003 after the [redacted] data had been collected. Only the most recent time station [redacted] was performed according to testing standard [redacted], before the respective development version was applied." Decomposition Products indicates that method [redacted] was used for the [redacted] station and method [redacted] was used for all time stations after [redacted]

In light of this information, please outline the exact differences in the methods used to evaluate [redacted] at all time stations. Is the drop in [redacted] between the [redacted] test stations due to experimental error, a revised correction factor, or any other reasons?

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
6/23/04 04:49:40 PM

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE:** June 17, 2004

| | |
|---|---|
| **To:** Nancy Velez | **From:** Charlene Williamson<br>Regulatory Project Manager |
| Berlex Laboratories, Inc. | Division of Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** (301) 827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** (301) 827-4260 |

**Subject:** NDA – 21-676

**Total no. of pages including cover:** 2

**Comments:** **Information Request**

**Document to be mailed:** NO

Please provide us with **one** dataset with the exact and complete list of subjects under study (for efficacy) that includes the following variables:

PID, SITE, INV, COUNTRY, AGE, SEX, RACE, HEIGHT, WEIGHT, PULSE, BPD, BPS, DATE OF EACH VISIT, VISIT # (1, 2, 3 ...), PREGNANCY (Yes/No) (under treatment only – please do not remove the pregnancies in Brazil), OTHER METHOD OF CONTRACEPTION (Yes/No), # OF DAYS UNDER TREATMENT, CENSOR (1/0)

No other variables are needed at this time.

Please provide this data only as "CHAR" (character) values when possible. No need to submit both "NUM" and "CHAR" values for each variable.

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/s/
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Z. Charlene Williamson
6/17/04 10:43:32 AM
CSO

Shahla Farr
6/21/04 02:25:38 PM
BIOMETRICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

**INFORMATION REQUEST LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone 3 mg/ ethinyl estradiol 0.02 mg) Tablets.

We also refer to your original NDA 21-098 submission dated May 14, 1999, and your Clinical Protocol 92032, titled "Open-labeled, randomized study of the influence of the oral contraceptives SH T 470 FA and SH T 470 IA on hemostasis in comparison with Marvelon." We believe that the findings from this study were described in final report AE91.

To facilitate our ongoing review of NDA 21-676, in particular, the thrombotic and thromboembolic risk that may be associated with the use of YAZ for prevention of pregnancy, we request that you submit to NDA 21-676 final study report AE91 ("Open-labeled, randomized study of the influence of the oral contraceptives SH T 470 FA and SH T 470 IA on hemostasis in comparison with Marvelon") as soon as possible.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Jennifer L. Mercier
6/17/04 05:46:23 PM

**MEMORANDUM**

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

---

DATE: June 7, 2004

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Office of Drug Safety

Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Gerald DalPan, M.D., Director
Division of Surveillance, Research, and Communication Support, HFD-410

SUBJECT: Risk Management Plan Review (RMP)
YAZ [Drospirenone (DSRP) 3 mg/Ethinyl Estradiol (EE) 0.020 mg tablets, 24-day administration
Submitted October 17, 2003
NDA 21-676
PID #:040027

SPONSOR Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, NJ 070450-1000

***** CONTAINS IMS HEALTH DATA *****
***** NOT TO BE USED OUTSIDE FDA WITHOUT PRIOR CLEARANCE BY IMS HEALTH *****

## 1 EXECUTIVE SUMMARY

The Office of Drug Safety (ODS) received a request from the Division of Reproductive and Urologic Drug Products (HFD-580) on January 14, 2004 to review the proposed Risk Management Plan (RMP) for YAZ Drospirenone (DSRP) 3 mg/Ethinyl Estradiol (EE) 0.02 mg Tablets (proposed tradename YAZ), 24-day administration submitted by Berlex, Inc. The proposed new combined oral contraceptive formulation provides a lower estrogen dose of 0.02 mg per day with the same drospirenone dose of 3 mg per day over 24 days instead of the 21 days regimen for Yasmin-28.

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# 23 Page(s) Withheld

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/s/

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Rita Ouellet-Hellstrom
6/7/04 03:33:06 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
6/8/04 02:29:28 PM
MEDICAL OFFICER

Mark Avigan
6/9/04 04:54:19 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

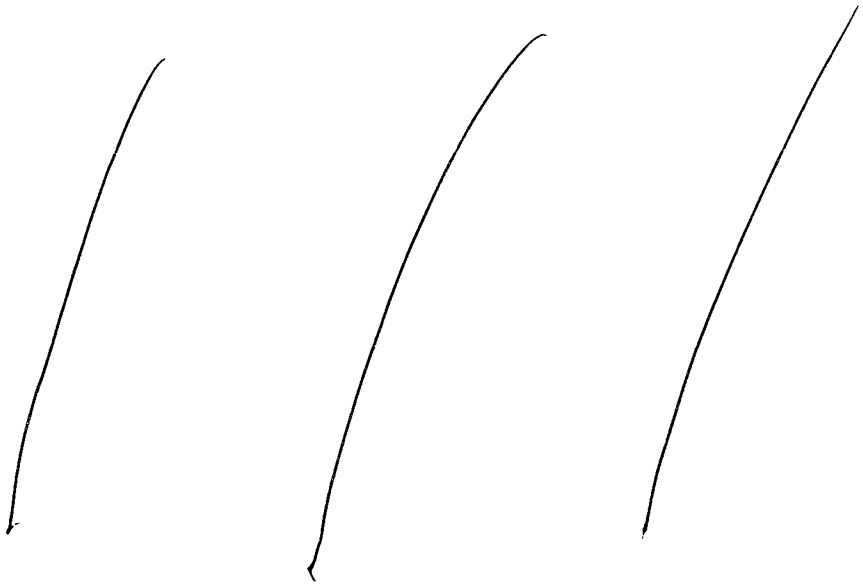
**INFORMATION REQUEST LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
Manager, Drug Regulatory Affairs
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.



If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
6/7/04 04:05:10 PM

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: May 21, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** Information Request

**Total no. of pages including cover:** 2

**Comments: See Attached**

**Document to be mailed:** • YES ☑ NO

To facilitate our review of NDA 21-676 please provide the following information.

1. Provide a listing of all subjects from protocols 14523 and 303740 who had potassium levels equal to or greater than 5.5 mmol/L. Incorporate the following information in the listing:

   - Patient Identification number (PID)
   - Study site
   - Potassium level
   - Date of test
   - All adverse events (provide both the preferred and verbatim terms) for the respective patient and the date of each AE
   - Explanation for the elevated potassium value

   Provide by June 4, 2004.

2. Provide line listings from the post-marketing United Health Care monitoring analysis of thromboembolic events for Yasmin submitted to NDA 21-355 on April 19, 2004. Provide the following information in the line listing:

   - Patient identification number
   - Age
   - ICD coding number (and definition of that code, e.g., DVT)
   - Date of the event
   - Name of the oral contraceptive used

   Provide by June 4, 2004.

3. Revise the United Health Care database ICD-9 coding search to also include code 415.1 in addition to 415.11 (Pulmonary embolism + Pulmonary embolism, iatrogenic).

4. Revise the United Health Care database ICD-9 coding to search for all ICD codes related to stroke (ICD 436 etc.).

5. Provide by June 11, 2004, a revised analysis and line listing of thrombotic and thromboembolic adverse events based on the United Health Care database used for the submission of April 19, 2004 that includes patient information identified by the additional codes listed in Items 3 and 4 above.

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/s/
---
Z. Charlene Williamson
5/21/04 05:39:08 PM
CSO

Scott Monroe
5/21/04 05:42:25 PM
MEDICAL OFFICER

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: May 20, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** Biopharm Request

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** • YES ☑ NO

The following question pertains to the review of Study B862; an "Open-label, randomized, crossover study to evaluate the relative bioavailability of ethinylestradiol (EE) and drospirenone (DRSP) from two tablet formulations each containing 20 µg EE + 3 mg DRSP (SH T00186D and SH T00186A) in comparison with a [redacted] suspension of 40 µg EE + 6 mg DRSP after single oral administration in healthy postmenopausal volunteers".
Please provide bioequivalence calculations with 90% confidence intervals as recommended in the guidance "Statistical Approaches to Establishing Bioequivalence" (January 2001). This guidance can be found at http://www.fda.gov/cder/guidance/3616fnl.pdf.

Additionally, you submitted a draft protocol (# ME98231) on Aprill 16,1999 entitled "Open-Label, Crossover Study to Assess the Potential of Drospirenone (DRSP) to Inhibit CYP 2C19 by Evaluating the Metabolic Interaction Between DRSP and Omeprazole as a Model Substrate in Healthy Postmenopausal Volunteers Genotyped for Polymorphism of CYP 2C19". It was noted that the study was scheduled to start in June 1999. Please submit the results of that study with this NDA.

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/s/

Z. Charlene Williamson
5/20/04 02:56:28 PM
CSO

Ameeta Parekh
5/21/04 11:41:26 AM
BIOPHARMACEUTICS
I concur

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

**INFORMATION REQUEST LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
340 Changebridge Road,
PO Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone and ethinyl estradiol) Tablets 3mg/0.02mg.

We have reviewed your tradename submission and are providing the following comments and recommendations.

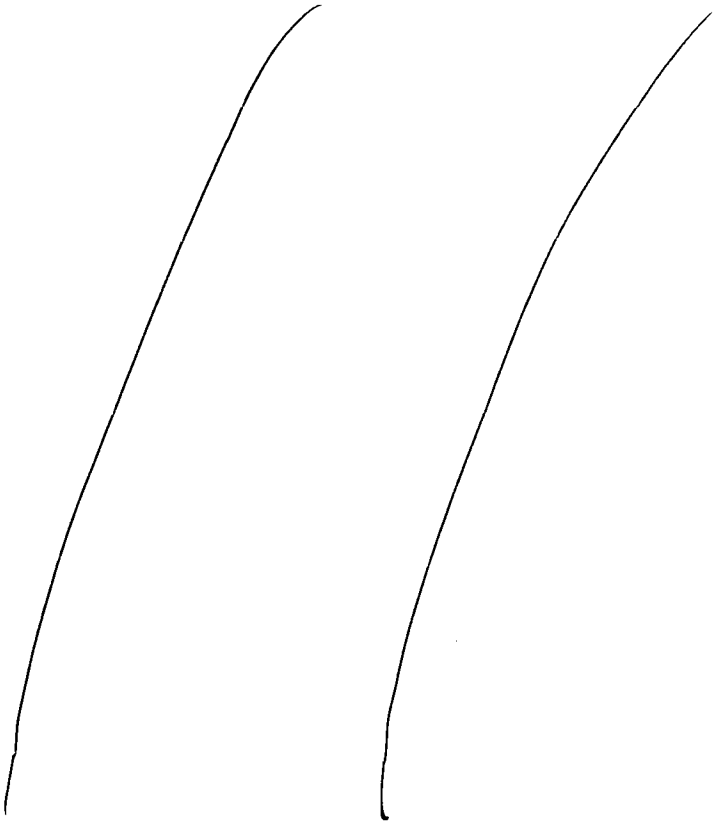
## GENERAL COMMENTS

We do not recommend the use of the proprietary name "YAZ." The primary concerns relate to the look-alike and sound-alike confusion with Yasmin. Although, the proposed name only consists of 3 letters and 1 syllable, it could be misinterpreted as an abbreviation for Yasmin. Because both products are oral contraceptives, the medications would be prescribed in the same patient population by the same physicians (specialist – OB/GYN physicians or general practitioners). We are concerned that the introduction of the product name YAZ could be interpreted as an abbreviation for the currently marketed product Yasmin. In addition, the lack of differentiating product characteristics could increase the risk of confusion and medication errors.

New contraceptive products are identified by either a new proprietary name or by the addition of a modifier to an existing proprietary name. A review of the approved and currently marketed proprietary names or oral contraceptive products does not indicate that any proprietary name could be considered a contraction or an abbreviation of another proprietary name. Therefore, we are concerned that the introduction of a name that could be misinterpreted as an abbreviation of an existing product will further add to the confusion in the marketplace.

## LABELING COMMENTS

We have reviewed the draft container label, carton, and package insert labeling of YAZ, focusing on safety issues relating to possible medication errors. We have identified the following areas of possible improvements, which might minimize potential user error.



If you have any questions, please call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Margaret Kober
5/3/04 06:07:23 PM
Chief, Project Management Staff

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: April 30, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** CMC

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** • YES ☑ NO

From analysis of the dissolution data from the primary stability batches, we feel that dissolution acceptance criteria for both drug substances should be set at **Q = — at 30 minutes,** which better reflects your manufacturing capability.

In the drug product stability section, you state that a better analytical method was developed at — for the degradation product — This changed showed a large increase in this compound from approximately — to — still well under the acceptance criteria of — What are the differences between the old and new methods? Do you have a side-by-side analysis of the two methods? Is the increase is due to the change in the method or to an actual increase in degradation products?

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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/s/

Z. Charlene Williamson
4/30/04 03:22:56 PM
CSO

Donna Christner
4/30/04 03:31:25 PM
CHEMIST
I concur

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: February 18, 2004**

| | |
|---|---|
| **To:** Nancy F. Velez | **From:** Charlene Williamson |
| **Company:** Berlex Laboratories, Inc. | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 973-487-2016 | **Fax number:** 301-827-4267 |
| **Phone number:** : 973-487-2305 | **Phone number:** 301-827-4260 |

**Subject:** Information Request

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** ☑ YES • NO

- What is your plan for risk management in regard to YAZ, is it separate from the measures already taken for Yasmin?

- The agency has continued concerns regarding the thrombotic and thromboembolic risks associated with drospirenone/ethinyl estradiol oral contraceptive combination. How do you propose to assess the risks of serious thrombotic and thromboembolic adverse events in users of YAZ compared to other contraceptives?



APPEARS THIS WAY
ON ORIGINAL

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/s/
---
Z. Charlene Williamson
2/20/04 11:13:18 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

**INFORMATION REQUEST LETTER**

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your October 17, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg) Tablets.

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The sponsor states that the chosen dissolution medium water provided equivalent or slightly better discrimination when compared to 0.2 N HCI and a pH 4.5 buffer solution. Submit the dissolution data using different dissolution media other than water.

2. Address the fate of cyclodextrin once the complex of cyclodextrin and Ethinyl estradiol dissociates following oral administration. This can be based on animal and/or human data or literature information.

3. Specify the amount of cyclodextrin used in the formulation.

4. It is stated in the NDA submission that an additional clinical study is planned to evaluate the effect of Drospirenone on CYP3A4 using midazolam as a substrate. Clarify the status of this study and the proposed submission date.

5. Provide a Letter of Authorization to review DMF [redacted]

If you have any questions, please call Charlene Williamson, Regulatory Project Manager, at 301-827-4260.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Margaret Kober
1/20/04 09:39:06 AM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**FILING REVIEW LETTER**

NDA 21-676

Berlex Laboratories, Inc.
Attention: Nancy Velez, Manager
340 Changebridge Road
P.O. Box 1000
Montville, NJ 070450-1000

Dear Ms. Velez:

Please refer to your October 16, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ™ (Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on December 16, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. We do not understand fully the reasons for closure of several study sites in Brazil. Provide additional information regarding the reasons for your decision, including the specific sequence of events that led to the closure of each site.

2. We continue to have concerns about the reports of serious thromboembolic and thrombotic adverse events in women using Yasmin, particularly the number of deaths associated with these adverse events. To assist us in our safety assessment of your combination drug product containing 20 mcg of Ethinyl Estradiol and 3 mg of Drospirenone (YAZ), we request that you provide us with

   a. An updated interim safety report for your ongoing European Active Surveillance Study (EURAS) for Yasmin no later than 45 days prior to August 17, 2004;

   b. Updated safety information for YAZ to include all clinical trial and postmarketing safety information reported to Berlex and/or Schering through July 3, 2004 concerning thromboembolic and thrombotic adverse events and deaths not previously submitted to NDA 21-676. This information should be submitted no later than July 17, 2004.

The request for safety data listed in Items a and b above are in addition to that which we expect to receive as part of your standard 4-Month Safety Update.

We are providing the above comments to give you preliminary notice of potential review issues. Our review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modifies as we review the application.

While we anticipate that any response to the above requests for additional information submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Charlene Williamson, Regulatory Project Manager, at (301) 827-4266.

Sincerely,

*{See appended electronic signature page}*

Daniel Shames, M.D.
Division Director,
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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/s/
---
Margaret Kober
12/24/03 03:27:49 PM
signed for Dr. Shames

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

# PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

***See Instructions on Reverse Side Before Completing This Form***

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Berlex Laboratories, Inc.
P.O. Box 1000
Montville, NJ 07045-1000

2. TELEPHONE NUMBER *(Include Area Code)*
( 973 ) 487 - 2157

3. PRODUCT NAME
Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 21-676

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4575

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
*(See Item 8, reverse side if answered YES)*

**Public reporting burden for this collection of information** is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| Jean A. Bertin | Manager, Regulatory Intelligence and Submission Compliance | 10/1/2003 |

FORM FDA 3397 (1/03)

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation III**

# FACSIMILE TRANSMITTAL SHEET

**DATE:** 3/19/03

| | |
|---|---|
| **To:** Nancy Velez | **From:** Karen Anderson |
| **Company:** Berlex | Division of Reproductive and Urologic Drug Products |
| **Fax number:** (973) 487-2016 | **Fax number:** (301) 827-4267 |
| **Phone number:** | **Phone number:** (301) 827-4260 |

**Subject:** Pre-NDA Meeting Minutes 2/20/03

**Total no. of pages including cover:** 6

**Document to be mailed:** YES NO

**Meeting Minutes**

**Date:** February 20, 2003 **Time:** 10:30 AM –12:00 PM

**Location:** PKLN; Conference Rm "Chesapeake"

**IND:** 60,738 **Indication:** Oral Contraceptive

**Drug Name:** (Drospirenone 3 mg / Ethinyl Estradiol-B-Cyclodextrin Clathrate 0.020 mg) Tablets

**Sponsor:** Berlex

**Meeting Type:** Pre-NDA

**Meeting Chair:** Scott Monroe, M.D.- Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**Meeting Recorder:** Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

**FDA Attendees:**
Donna Griebel, M.D. - Deputy Director, DRUDP (HFD-580)
Scott Monroe, M.D. - Medical Team Leader, DRUDP (HFD-580)
Lesley Furlong, M.D. - Medical Officer, DRUDP (HFD-580)
Jean Salemme, Ph.D. - Chemist Reviewer, Division of New Drug Chemistry II @ DRUDP (HFD-580)
Krishan Raheja, Ph.D. - Pharmacologist, DRUDP (HFD-580)
Venkat Jarugula, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Moh-Jee Ng, M.S. - Biostatistics Reviewer, Division of Biometrics II (DBII @ DRUDP (HFD 580)
Nenita Crisostomo, R.N. - Regulatory Project Manager, DRUDP (HFD-580)
Karen Anderson, N.P. - Regulatory Project Manager, DRUDP (HFD-580)

**External Attendees:**
Shawn Hoskin - Senior Project Specialist, Analytical Services, Berlex
Harmut Blode, Ph.D. - Head of Clinical Pharmacokinetics, Schering AG
Carole Sampson-Landers, M.D. - Medical Director, Clinical Development
Norbert Benda, Ph.D. - Project Biometry G&A 1, Strategic Business Unit Gynecology and Andrology, Schering AG
Sharon Brown, M.S. - Director, Drug Regulatory Affairs, Female Health Care, Berlex
Ann-Mari Bresky, M.Sc. - Project Manager, Berlex
Nancy Bower, M.S. - DABT Manager, Toxicology, Berlex
Joachim Marr, M.D. - Head of Corporate Clinical Development, Female Fertility Control and Hormone Therapy, Strategic Business Unit Gynecology and Andrology, Schering AG
Minoo Niknian, Ph.D. - Director, Statistics, Female Health Care, Berlex
Nancy Velez – Manager, Drug Regulatory Affairs, Female Health Care, Berlex

**Background:** Berlex is developing a low dose combined oral contraceptive product (Drospirenone 3 mg and Ethinyl Estradiol-B-Cyclodextrin Clathrate 0.020 mg tablets). Each 28-day treatment cycle will consist of 24 active tablets and 4 placebo tablets.

**Purpose of the Meeting:** Guidance for NDA submission.

**Discussion Points:**
**Chemistry**

1. Does the Division agree with the proposal to provide drug substance information via Type II Drug Master Files?

Answer: Yes.

Additional Comments: We note that you reference DMFs for the manufacture of the drug substances, ethinyl estradiol/beta-cyclodextrin complex and drospirenone, and you reference the DMF for the manufacture of beta-cyclodextrin. Please determine if the beta-cyclodextrin used in the pre-clinical and clinical batches is the same as that manufactured in the DMF. If the manufacturers are different, provide an impurity profile for each batch of beta-cyclodextrin batch used. Our thinking is that beta-cyclodextrin is a novel excipient, similar to a drug substance. As such, we recommend you follow ICH Q3A, impurities in drug substances, to characterize the impurities present in the beta-cyclodextrin.

2. Does the Division concur that the described stability data submission plan is adequate to support a — expiration date?

Answer: We agree to review additional stability data during the NDA review period if the data are received by three months before the PDUFA date. A — expiry based on — real-time data and — accelerated data could be possible if the data are determined to be acceptable.

**Pharmacology and Toxicology**

1. Does the Division concur that the type, duration and design of the nonclinical studies conducted with the active ingredients are sufficient to support marketing approval of — — Drospirenone / Ethinyl Estradiol-B-Cyclodextrin Clathrate 0.020 mg tablets)?

Answer: Yes

2. Does the Division concur that the nonclinical literature summary for B-Cyclodextrin provides sufficient documentation of the safety of this excipient?

Answer: Yes

3. Does the Division concur that Berlex Laboratories, Inc. can cross-reference this information and submit and summarize in this NDA only those nonclinical reports that were finalized after May 14, 1999.

Answer: Yes

**Biopharmacology**

1. Does the Division concur that the clinical pharmacology studies conducted for —— and the clinical pharmacology studies conducted for approved NDA 21-098, Yasmin, are sufficient to support the filing of the NDA for —— (Drospirenone / Ethinyl Estradiol-B-Cyclodextrin Clathrate 0.020 mg tablets)?

Answer: Yes for filing.

Additional comment:
- Provide an explanation of the food effect on the new formulation in the NDA.
- Provide a full profile of the dissolution data.

2. Does the Division concur that Berlex Laboratories, Inc. can cross-reference this information and submit and summarize in this NDA only those clinical pharmacology reports that were performed for development of —— ?

Answer: Yes.

**Clinical**

1) Our single pivotal Phase 3 study, which was conducted to assess the efficacy and safety of —— , will satisfy the requirements of the "Guidelines for Preclinical and Clinical Testing of Steroidal Contraceptives" by providing data from at least 200 women completing 13 cycles of treatment on Yasmin 20 and approximately 11,000 cycles. Does the Division concur that this is adequate to support the filing of the NDA?

Answer: Yes, with the expectation that there are $\geq$ 10,000 cycles to support the data.

2) Does the Division concur that Berlex Laboratories, Inc. can cross-reference the information provided in Yasmin 30 IND 51,693 and approved Yasmin 30 NDA 21-098 to support the —— NDA?

Answer: Yes.

Additional Comments to Sponsor

Please provide the following in the NDA submission:

- CRFs for all pregnancies.
- Outcome information for the pregnancies for the NDA.
- Data sets for the ISS, as well as data sets for the individual studies.
- Further follow-up on the two deaths in the pivotal clinical trial.

- Pregnancy rates for other phase III trials with — e.g. Acne trial with Ortho Tri-Cyclen comparator, and bleeding trial with Mercilon comparator).

The sponsor also confirmed that data from the four Brazilian centers, which were closed prematurely due to inadequate site resources, will be included and analyzed for the NDA.

The sponsor will also provide an interim analysis from the EURAS study as soon as possible during the NDA review cycle.

**Statistics**

1. Does the Division concur that the statistical methods utilized for the pivotal studies are acceptable?

Answer: Yes, with the following requests:
- Please calculate all Pearl Indices consistently – using either number of cycles of exposure or number of women years of exposure.
- Please provide the reference for the confidence interval for the Poisson rate parameter used for Pearl Index.

**Action Items:**
- Sponsor will submit the NDA Quarter 3, 2003 (electronic format).
- Minutes to sponsor within 30 days.

Minutes prepared: Karen Anderson, N.P. - Project Manager
Chair concurrence: Scott Monroe, M.D. - Medical Team Leader

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/s/

Scott Monroe
3/18/03 04:34:13 PM