CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-873

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
21-873

NAME OF APPLICANT / NDA HOLDER
Berlex, 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)
drospirenone and ethinyl estradiol	Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg

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
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.)*	
☞ Tatsuya Ikeda	340 Changebridge Road P.O. Box 1000	
	City/State: 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)

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**.		
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.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

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*) 11 through 17 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.)*		

5. No Relevant Patents

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	December 15, 2004

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

Department of Health and Human Services
Food and Drug Administration

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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)*

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.)*	FAX Number *(if available)*
Tatsuya Ikeda	340 Changebridge Road P.O. Box 1000	
	City/State: Montville, NJ	
	ZIP Code: 07045-1000	
	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)

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**.		
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.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

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.)*	

5. No Relevant Patents

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Tatsuya Ikeda	December 15, 2004

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

Department of Health and Human Services
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,787,531	September 7, 2004	August 31, 2020

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
Schering AG	Muellerstrasse 178	
	City/State: Berlin, Germany	
	ZIP Code: D13342	
	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.)*	FAX Number *(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

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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
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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.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

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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.)*		

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

Name Tatsuya Ikeda	
Address 340 Changebridge Road P.O. Box 1000	City/State Montville, NJ
ZIP Code 07045-1000	Telephone Number (973) 487-2014
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a. United States Patent Number
RE 37,838 E

b. Issue Date of Patent
September 10, 2002

c. Expiration Date of Patent
June 30, 2014

d. Name of Patent Owner
Schering AG

Address *(of Patent Owner)*
Mullerstrasse

City/State
Berlin, Germany

ZIP Code
D13342

FAX Number *(if available)*

Telephone Number
(030) 468-1111

E-Mail Address *(if available)*

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☞ Tatsuya Ikeda

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P.O. Box 1000

City/State
Montville, NJ

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07045-1000

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3. Drug Product (Composition/Formulation)

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

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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.)*	

5. No Relevant Patents

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	December 15, 2004

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 Tatsuya Ikeda	
Address 340 Changebridge Road P.O. Box 1000	City/State Montville, NJ
ZIP Code 07045-1000	Telephone Number (973) 487-2014
FAX Number *(if available)* (973) 487-2712	E-Mail Address *(if available)* 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
21-873

NAME OF APPLICANT / NDA HOLDER
Berlex, 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)
drospirenone and ethinyl estradiol	Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg

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
RE 37,564 E

b. Issue Date of Patent
February 26, 2002

c. Expiration Date of Patent
June 30, 2014

d. Name of Patent Owner
Schering AG

Address *(of Patent Owner)*
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)

☞ Tatsuya Ikeda

Address *(of agent or representative named in 1.e.)*
340 Changebridge Road
P.O. Box 1000

City/State
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)

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.**		
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.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

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.)*		

5. No Relevant Patents

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	December 15, 2004

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: Tatsuya Ikeda	
Address: 340 Changebridge Road P.O. Box 1000	City/State: Montville, NJ
ZIP Code: 07045-1000	Telephone Number: (973) 487-2014
FAX Number *(if available)*: (973) 487-2712	E-Mail Address *(if available)*: 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
21-873

NAME OF APPLICANT / NDA HOLDER
Berlex, 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)
drospirenone and ethinyl estradiol	Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg

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.

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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 38,253 E	September 16, 2003	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.)*	
☞ Tatsuya Ikeda	340 Changebridge Road P.O. Box 1000	
	City/State: 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)

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**.		
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.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

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

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.)*		

5. No Relevant Patents

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.***

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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	December 15, 2004

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: Tatsuya Ikeda	
Address: 340 Changebridge Road P.O. Box 1000	City/State: Montville, NJ
ZIP Code: 07045-1000	Telephone Number: (973) 487-2014
FAX Number *(if available)*: (973) 487-2712	E-Mail Address *(if available)*: 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 21-873 for Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg Tablets, which was submitted to the Food and Drug Administration pursuant to section 505(b)(1) of the FD&C Act.

EXCLUSIVITY SUMMARY

NDA # 21-873 SUPPL # HFD # 580

Trade Name YAZ Tablets

Generic Name (drospirenone 3 mg / ethinyl estradiol 0.02 mg)

Applicant Name Berlex, Inc.

Approval Date, If Known October 4, 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# 21-676 YAZ (drospirenone/ethinyl estradiol) for Oral Contraception

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

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:

Study 304049
Study 305141

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 # 304049 and 305141

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 # 61,304	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 61,304	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 Heatlth Project Manager
Date: October 4, 2006

Name of Office/Division Director signing form: Scott Monroe, M.D.
Title: Acting 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/

Scott Monroe
10/4/2006 06:23:26 PM

Claim for Three Years Marketing Exclusivity

Pursuant to 21 CFR 314.50(j), and with reference to 21 CFR 314.108(b)(4), Berlex, Inc. [Berlex] hereby requests a period of three years marketing exclusivity for Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets, the subject of NDA 21-873.

1. Pursuant to 21 CFR 314.50(j)(4)(i), Berlex, Inc. hereby certifies that the clinical investigations included in NDA 21-873 for Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets, either directly or by cross-reference to NDA 21-676 for YAZ™ (Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg) Tablets for Oral Contraception, as identified below:

   - meet the definition of a "new clinical investigation" set forth in 21 CFR 314.108(a), and
   - have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.

   PMDD Study contained in NDA 21-873:
   Study 304049, "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 20 g (as Beta-Cyclodextrin Clathrate), in the treatment of Premenstrual Dysphoric Disorder (PMDD)".

   Report A21566 for Study 304049 is located in NDA 21-873 at:

   N21-873\clinstat\pmdd\a21566

   PMDD Study contained NDA 21-873:
   Study 305141, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 g (as Beta-Cyclodextrin Clathrate), in the treatment of Premenstrual Dysphoric Disorder (PMDD)".

   Report A07545 for Study 305141 is located in NDA 21-873 at:

   NDA 21-873 \clinstat\pmdd\a07545

   OC Study Cross-referenced to NDA 21-676:
   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--Cyclodextrin Clathrate and 3 mg Drospirenone in a 24-day regimen for 13 cycles in 1010 healthy female volunteers"

   Report A12007 for Study 303740 is located under Item 8 in NDA 21-676 for YAZ™ (Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg) Tablets, which had been submitted to the Food and Drug Administration on October 16, 2003 for the indication of Oral Contraception.

Claim for Three Years Marketing Exclusivity, Contd.

2. Pursuant to 21 CFR 314.50(j)(4)(ii), Berlex hereby certifies that we have searched the scientific literature for publicly available reports of relevant clinical investigations and that the list of publications included in NDA 21-873 and in NDA 21-676 are 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 the indications of oral contraception and the treatment of Premenstrual Dysphoric Disorder (PMDD) without reference to the aforementioned studies. Accordingly, the studies identified above are essential to the approval of NDA 21-873, as the results of these new clinical investigations support a finding of substantial evidence of effectiveness of Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg Tablets for oral contraception and the treatment of Premenstrual Dysphoric Disorder (PMDD).

3. Berlex, Inc. is the sponsor named in Forms FDA 1571 contained in IND 61,304 and IND 60,738, the Investigational New Drug Applications under which the aforementioned studies had been conducted. Berlex submitted IND 61,304 and IND 60,738 to the Food and Drug Administration on November 20, 2000 and August 22, 2000, respectively, for review by the Division of Reproductive and Urologic Drug Products.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-873 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: December 22, 2004 **Action Date:** October 4, 2006

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

Applicant: Berlex, Inc. **Therapeutic Class:** 2S

Indication(s) previously approved: Oral contraception

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

Number of indications for this application(s): 2

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.

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**

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.

ction 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: NDA21-873
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: For the Treatment of symptoms of Premenstrual Dysphoric Disorder (PMDD) who have no known contraindications to oral contraceptives and who desire 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.

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**
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 copy the fields above and complete pediatric information as

irected. 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 21-873
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/

Z. Charlene Williamson
10/11/2006 05:08:44 PM

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: 21-873

Sponsor:

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

Indications

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

YAZ is indication for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) who have no known contraindications to oral contraceptives and who desire contraception

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.

16. DEBARMENT CERTIFICATION

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

Berlex, 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 21-873 for Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg Tablets.

BERLEX, INC.

Joseph S. Sohk, Ph.D.
Vice President, Regulatory Affairs, US

12/16/04
Date

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-873 Supplement # Efficacy Supplement Type SE-

Trade Name: YAZ Tablets

Established Name: drosperinone 3 mg/ ethinyl estradiol 0.02 mg
Strengths:

Applicant: Berlex, Inc.

Agent for Applicant:

Date of Application: December 22, 2004
Date of Receipt: December 23, 2004
Date clock started after UN:
Date of Filing Meeting: February 18, 2005
Filing Date: February 21, 2005
Action Goal Date (optional): User Fee Goal Date: December 2, 2006

Indication(s) requested: Contraception & PMDD

Type of Original NDA: (b)(1) ☒ (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 ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 2
Other (orphan, OTC, etc.)

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

User Fee Status: Paid ☒ 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: NDAs 21-098 & NDA 21-676

- 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 forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  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 included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- 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 and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- 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) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

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

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO ☒

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ 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 ☒

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 18, 2005

BACKGROUND: YAZ Tablets is already approved under NDA 21-676 as an oral contraceptive. This application is for a secondary indication for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) for women who elect to use an oral contraceptive as their method of contraception.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Scott Monroe, M.D.
Gerald Willett, M.D., Lisa Soule, M.D., Leslie Kenna, Ph.D., Julie Bullock, Pharm.D., Donna Christner, Ph.D.,

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Lisa Soule, M.D.
Secondary Medical:	Scott Monroe, M.D.
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 ☒ 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 N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS		FILE	☒	REFUSE TO FILE	☐
• Biopharm. inspection needed?				YES ☐	NO ☒
PHARMACOLOGY	N/A ☐	FILE	☒	REFUSE TO FILE	☐
• GLP inspection needed?				YES ☐	NO ☒
CHEMISTRY		FILE	☒	REFUSE TO FILE	☐
• Establishment(s) ready for inspection?				YES ☒	NO ☐
• Microbiology				YES ☐	NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ 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.

☒ Filing issues to be communicated by Day 74. List (optional): In our filing review, we have identified the following potential review issues:

1. As indicated during the clinical development program, the adequancy of Study 305141 will be a review issue because of the early termination of the study prior to reaching the planned enrollment.

2. Explain the selection of different baseline for different assessment instruments (i.e., why were different times prior to initiation of treatment chosen as baseline?). For example:
Daily Record of Severity of Problems Scale (DRSP), the primary endpoint - baseline was average of the DRSP scores from the 2 run-in cycles, Visits 2 and 3.
The secondary endpoint instruments (CGI, SF-36, Endicott Q-LES-Q and PMTS) - baseline was Visit 4 (first treatment cycle)

3. Confirm that the cross reference to NDA 21-676 includes not only the original submission, but also all the CMC Amendments to that NDA.

4. Color mock-ups of all carton and container labels should be provided, including any graphics planned for the labeling.

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of 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.☐ Convey document filing issues/no filing issues to applicant by Day 74.

Z. 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)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

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

☐ 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)
Patent number(s):

NOTE: *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)
Patent number(s):

☐ 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).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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/

Z. Charlene Williamson
10/12/2006 03:53:33 PM
CSO

Z. Charlene Williamson
10/12/2006 03:57:13 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-873

Berlex, Inc.
Attention: Nancy F. Velez
Associate Director, Global Regulatory Affairs
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/ethinyl estradiol) Tablets.

We also refer to your March 1, 2006 submission which constituted a complete response to our approvable letter dated January 23, 2006.

On August 9, 2006, we received your August 8, 2006 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 December 2, 2006.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
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/

Z. Charlene Williamson
8/25/2006 03:39:16 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: March 16, 2006

From: Corrinne Kulick, DDMAC

To: Charlene Williamson, DRUDP

Re: YAZ (drospirenone and ethinyl estradiol) tablets
NDA 21-873

Attached please find DDMAC's expedited review and comments to the FDA working copy of the YAZ (drospirenone and ethinyl estradiol) tablets for the combined oral contraceptive (NDA 21-676) and Premenstrual Dysphoric Disorder (PMDD) (21-873) indications. DDMAC's comments were provided on the working copy and emailed to the Medical Officer on January 23, 2006. DDMAC's comments provided in this review, do not reiterate comments provided on November 3, 2004 for the oral contraceptive (NDA 21-676) indication as it was assumed that DDMAC's comments provided on November 3, 2004 were considered and either incorporated (or not) into the label provided for the combined indication. Therefore, the January 23, 2006 review focused solely on the PMDD indication.

51 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Corrinne Kulick
3/16/2006 12:07:35 PM
DDMAC REVIEWER

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 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 21-873

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

We note that the sensitivity analysis you provided to us on January 15 included imputed data for the placebo arms as well as the DRSP/EE arms. The analysis we had in mind would impute only for the DRSP/EE subjects who met the Full Analysis definition but were not included in the modified ITT analysis. Would you please provide us with a redone analysis by COB 1/20?

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/s/

Z. Charlene Williamson
1/19/2006 12:00:22 PM
CSO

Lisa Soule
1/19/2006 12:25:25 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 12, 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 21-873

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

1. Per our telephone discussion today, please complete the following table:

Study 305141: Detailed Reason for Withdrawal from Treatment

	Study 305141			
Patient Disposition	DRSP/EE→Placebo N=34		Placebo→DRSP/EE N=30	
	N	%	N	%
Completed Treatment	14	41.2	11	36.7
Withdrew from Treatment	20	58.8	19	63.3
Treatment Period 1	8	23.5	8	26.7
Wash-out Phase	7	20.6	2	6.7
Treatment Period 2	5	14.7	9	30.0
Reason for Withdrawal				
Protocol violation	1	2.9	1	3.3
Adverse event	4	11.8	2	6.7
Lack of efficacy	0	0	1	3.3
Consent withdrawn	7	20.6	5	16.7
Lost to follow-up	3	8.8	8	26.7
Pregnancy	2	5.9	1	3.3
Other	3	8.8	1	3.3
Reason for Withdrawal in TP1	DRSP/EE→Placebo N=34		Placebo→DRSP/EE N=30	
Total withdrawn	8	23.5	8	26.7
Protocol violation				
Adverse event				
Lack of efficacy				
Consent withdrawn				
Lost to follow-up				
Pregnancy				
Other				
Reason for Withdrawal in Wash-out	DRSP/EE→Placebo N=34		Placebo→DRSP/EE N=30	
Total withdrawn	7	20.6	2	6.7
Protocol violation				
Adverse event				
Lack of efficacy				
Consent withdrawn				
Lost to follow-up				
Pregnancy				
Other				
Reason for Withdrawal in TP2	DRSP/EE→Placebo N=34		Placebo→DRSP/EE N=30	
Total withdrawn	5	14.7	9	30.0

Protocol violation				
Adverse event				
Lack of efficacy				
Consent withdrawn				
Lost to follow-up				
Pregnancy				
Other				

2. Please provide any further clarification available regarding reason for withdrawal of consent for all subjects withdrawing on this basis for either study.

APPEARS THIS WAY ON ORIGINAL

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 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 21-873

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

In order to address concerns relating to the study misconduct discovered at the [redacted] please recalculate the primary efficacy endpoint in both studies, using the Full Analysis population with this site excluded. Specifically, please provide the data displayed in Tables -17 for Study 304049 and in Tables 13-15 for Study 305141.

In addition, please provide the number of subjects in Study 305141 with and without any imputed efficacy scores, as listed in Table 13 for Study 304049.

We appreciate your prompt response.

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/s/

Z. Charlene Williamson
1/10/2006 02:46:59 PM
CSO

Lisa Soule
1/10/2006 03:10:02 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 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 21-873

Total no. of pages including cover: 1

Comments:

Document to be mailed: ☐ YES ☑ NO

We are requesting the following additional information to assist us in our review of NDA 21-873.

Provide a listing of the DRSP-21 values that will be used to generate Item 1-a in our earlier Information Request of January 4, 2006. Provide the listing in the following format:

Subject ID	Treatment	Baseline 1		Baseline 2		Treatment Cycle 1		Treatment Cycle 2		Treatment Cycle 3	
		5 days with highest scores*	Mean DRSP-21 Score	5 days with highest scores	Mean DRSP-21 Score	5 days with highest scores	Mean DRSP-21 Score	5 days with highest scores	Mean DRSP-21 Score	5 days with highest scores	Mean DRSP-21 Score

* 5 days with highest scores: In this column, list the 5 cycle days with the highest DRSP-21 values which serve as the basis for the respective mean DRSP-21 score.

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/s/

Z. Charlene Williamson
1/5/2006 06:29:16 PM
CSO

Scott Monroe
1/5/2006 06:35:01 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

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 27, 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: Serum Progesterone

Total no. of pages including cover: 1

Comments:

Document to be mailed: YES • NO

Serum progesterone concentrations of 1.56 ng/mL may be associated with a corpus luteum (indicative of prior ovulation) or a luteinized follicle. A serum progesterone of 5 ng/mL or greater is rarely a result of a luteinized follicle and is a better indicator of prior ovulation. We acknowledge that the Hoogland grading system considers a serum progesterone concentration of 5 nmol/l as compatible with ovulation. The Division is not opposed to your using a value of 4 ng/mL (instead of 5 ng/mL) as a cut off for the requested recalculation if you prefer.

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/s/

Z. Charlene Williamson
10/27/2005 02:05:07 PM
CSO

Scott Monroe
10/27/2005 02:16:36 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676/21-873

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, and December 22, 2004, new drug applications (NDAs) 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 submission dated June 15, 2005 which constituted a complete response to our approvable letter of November 17, 2004.

We are reviewing your submission and have the following information requests. We request a written response by close of business November 4, 2005 in order to continue our evaluation of your NDA.

1. Provide the outcome of the EURAS Advisory Council assessment from September 27, 2005.

2. Provide a cumulative up-to-date listing of deaths, thrombotic and thromboembolic events that occurred in all clinical trials with drospirenone 3mg/ethinyl estradiol 0.02mg (both 21 and 24 day dosing regimens). Provide the requested information in both PDF and SAS transport file format and in table format utilizing the following tabular headings:

Table column headings

Protocol number
Regimen (24 day, 21 day, other)
Subject number (PID)
Site number
Country
Subject age
Subject weight (kg, BMI)
Death (yes or no)
Date of death
Cause of death
Thrombotic and Thromboembolic adverse events (specify DVT, PE, AMI, stroke etc.)
Calendar date of onset

Time on study drug
Outcome
Additional thromboembolic risk factors

3. Submit any additional clinical summaries for Ingenix similar to the October 7, 2004 submission (Attachment 1) that have been produced since the October 7, 2004 submission.

4. Submit any additional clinical summaries for EURAS similar to the April 8, 2004 and August 11, 2004 submissions that have been produced since the August 11, 2004, submission.

5. Submit the full Ingenix semi-annual analytic report that was submitted to IND 51,693 on July 19, 2005 to both NDAs 21-676 and 21-873.

6. Clarify the status of data collected on the last two cohorts in the Ingenix study (Q403 and Q104). As these cohorts have been under follow-up for approximately 18-21 months, explain the delay in providing data on these cohorts.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at 301-796-1025.

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/

Margaret Kober
10/17/2005 01:49:19 PM
Chief, Project Management Staff

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 21-873

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/ethinyl estradiol) Tablets.

On August 29, 2005, we received your August 26, 2005 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 January 20, 2006.

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 Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
9/13/2005 05:47:59 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-873

Berlex, Inc.
Attention: Nancy Velez, Manager Regulatory Affairs
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 (drospirenone 3 mg/ ethinyl estradiol 0.02 mg) Tablets.

We also refer to your August 30, 2005, correspondence, received September 2, 2005, requesting a meeting to discuss the Agency's decision to extend this application's User Fee Date for an additional 3 months. We have considered your request and concluded that the meeting is now unnecessary based on the series of telephone calls between Joseph Sonk and Margaret Kober that has occurred in the interim.

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

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
9/13/2005 07:32:29 PM

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: August 5, 2005

TO: Charlene Williamson, Regulatory Project Manager
Lisa Soule, Medical Officer
Gerald Willett, Medical Officer
Division of Reproductive and Urologic Products, HFD-540

THROUGH: Ni A. Khin, 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 21-873

PROTOCOL(s): Protocol #304049 entitled: "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg Ethinyl Estradiol 20 µg (as Beta-Cycldextrin Clathrate), in the Treatment of Premenstrual Dysphoric Disorder (PMDD)", and

Protocol #305141 entitled: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 µg (as Beta-Cyclodextrin Clathrate), in the Treatment of Premenstrual Dysphoric Disorder (PMDD)"

SPONSOR: Berlex, Inc.

DRUG: YAZ

INDICATION: Treatment of premenstrual dysphoric disorder (PMDD)

CHEMICAL CLASSIFICATION: 2

THERAPEUTIC CLASSIFICATION: S

INSPECTION SUMMARY GOAL DATE: August 12, 2005

ACTION GOAL DATE: October 23, 2005

I. BACKGROUND:

In this NDA application, the sponsor included results of Protocols 304049 and 305141 for the use of YAZ® (drospirenone 3 mg/ethinyl estradiol 20 μg) in the treatment of PMDD. The objective of the study was to determine the efficacy of YAZ® in women experiencing PMDD.

This inspection of the sites of Drs. Moreines and Drosman was requested by the reviewing division because these sites were among the higher enrolling sites.

The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site):

NAME	CITY	STATE/ COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
Robert Moreines, M.D.	Kenilworth	New Jersey	29 Mar 05	17 Jun 05	NAI/011540
Steven Drosman, M.D.	San Diego	California	29 Mar 05	22 Jul 05	VAI/011577

Site # 27
Robert Moreines, M.D. Protocol #304049, 15 subjects
1700 Galloping Hill Road
ClinSearch, Inc.
Kenilworth, New Jersey 07033
See **Overall Assessment and Recommendations**, below

a. 15 subjects were randomized to the study with 4 subjects dropping out and 11 completing the study. Source documents for five of the subjects were reviewed in depth, including, but not limited to consent forms, test article accountability, safety assessments, adverse event reporting, and concomitant medications.

b. There were no limitations to the inspection.

c. A Form FDA 483 was not issued. No significant deviations from regulations were noted.

Site # 8
Steven Drosman, M.D.
3651 Fourth Avenue, Suite 200
Genesis Center for Clinical Research
San Diego, California 92103
See **Overall Assessment and Recommendations**, below

Protocol # 304049, 40 subjects
Protocol # 305141, 14 subjects

a. 40 subjects completed study protocol 304049 and 14 subjects completed study protocol 305141. Records for sixteen subjects were reviewed in depth for protocol 304049 and records for six subjects were reviewed in depth for protocol 305141.

b. There were no limitations to the inspection.

c. A Form FDA 483 was issued noting that the following adverse events were assessed by the study coordinator, not the investigator as required by protocol:

Patient	Adverse Event	Date
840049	melancholy	8/21/03
840049	dry mouth	8/21/03
840049	URI	9/17/03
840049	breast tenderness	9/17/03
840049	eye irritation/dryness	10/21/03
840071	breast tenderness	10/7/03
840071	increased anxiousness	10/7/03
840071	nausea	10/31/03
840071	chest cold	11/24/03

The Form 483 noted that the following subjects had pregnancy tests performed at various visits with expired test kits:

Patient Identification	Date of Test	Recorded Expiration Date of Kit
840009	6/30/03	2/1/03
840071	7/14/03	2/1/03
840069	6/17/03	2/1/03
080009	6/21/02	1/11/02

Subject 840069 was not excluded despite a daily regimen of tetracycline.

Three subjects received physical/gynecologic al examinations by a nurse practitioner not identified on the Form 1572.

Of note was subject 840056 who complained of bilateral leg numbness. The protocol specifically addresses this adverse event as possibly signaling thrombotic events that may require the subject's exclusion from the study at the investigator's discretion. This event was apparently not assessed by the investigator until approximately four months after resolution of the complaint. The subject completed the study.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this application by Dr. Moreines appear adequate in support of the relevant submission.

The data submitted in support of this application by Dr. Drosman appear adequate in support of the relevant submission despite a lack of timely assessment and reporting of adverse events. The review division medical officer should determine whether the data from subject 840069 who was on a daily antibiotic regimen should be excluded from study analysis.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

cc:
HFD-580/Doc. Rm. NDA 21-873
HFD-45/Program Management Staff (electronic copy)
HFD-46/RF
HFD-46/c/r/s
HFD-46/Blay

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/s/

Roy Blay
8/8/05 04:15:31 PM
CSO

Ni Aye Khin
8/8/05 05:32:42 PM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: May 20, 2005

To: Charlene Williamson, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products (DRUDP)
HFD-580

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
HFD-042

Subject: NDA 21-873
DDMAC carton labeling comments for YAZ Tablets

DDMAC has reviewed the proposed carton labeling submitted in a consult request by DRUDP on April 7, 2005, for YAZ Tablets and we have no comments at this time.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Michelle Safarik
5/20/05 09:47:23 AM
DDMAC REVIEWER

MEMORANDUM

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

DATE: April 14, 2005

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

VIA: Charlene Williamson, Consumer Safety Officer
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for YAZ (drospirenone an ethinyl estradiol) Tablets, NDA 21-873

Background:
The sponsor submitted a Brief Summary Patient Package Insert and a Detailed Patient Package Insert for YAZ (drospirenone an ethinyl estradiol) Tablets, NDA 21-873, on December 22, 2004, as an oral contraceptive and for the treatment of premenstrual dysphoric disorder in women who desire oral contraception.

Comments and recommendations:
We have the following comments and recommendations:

1. Revise the patient labeling for Yaz following the March 2004, Draft Guidance; *Guidance for Industry: Labeling for Combined Oral Contraceptives.*

2. Avoid the use of UPPER CASE lettering to emphasize important information. Upper case lettering is difficult to read. Bold or underline for word or statement emphasis. The tradename is the exception to this recommendation and may be in upper case letters.

Please call us if you have any questions.

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/s/

Jeanine Best
4/14/05 09:55:30 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/14/05 02:45:17 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-873

Berlex Laboratories, Inc.
Attention: Nancy Velez, Manager
P.O. 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 have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 18, 2005 in accordance with 21 CFR 314.101(a).

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

1. As indicated during the clinical development program, the adequacy of Study 305141 will be a review issue because of the early termination of the study prior to reaching the planned enrollment.

2. Explain the selection of different baselines for different assessment instruments (i.e., why were different times prior to initiation of treatment chosen as baseline?). For example:
   - Daily Record of Severity of Problems Scale (DRSP), the primary endpoint – baseline was average of the DRSP scores from the 2 run-in cycles, Visits 2 and 3.
   - The secondary endpoint instruments (CGI, SF-36, Endicott Q-LES-Q and PMTS) – baseline was Visit 4 (first treatment cycle)

3. Confirm that the cross reference to NDA 21-676 includes not only the original submission, but also all the CMC Amendments to that NDA.

4. Color mock-ups of all carton and container labels should be provided, including any graphics planned for the labeling.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing 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 modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response 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, 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/

Margaret Kober
3/7/05 03:09:22 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-873

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

Dear Ms. Velez:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	YAZ™ (drospirenone 3 mg / ethinyl estradiol 0.02 mg) Tablets
Priority Classification:	Standard (S)
Date of Application:	December 22, 2004
Date of Receipt:	December 23, 2004
Our Reference Number:	NDA 21-873

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 21, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
Attention: Division Document Room,
5600 Fishers Lane
Rockville, Maryland 20857

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/

Margaret Kober
1/27/05 10:47:30 AM
Chief, Project Management Staff

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

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, Inc.
340 Changebridge Road (P.O. Box 1000)
Montville, NJ 07045-1000

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 487 - 2157

3. PRODUCT NAME

YAZ™ [Drospirenone 3 mg/Ethinyl Estradiol 0.020 mg] Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-873

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

4892

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
Gerri A Berta	Manager, Drug Regulatory Affairs	12/13/2004

FORM FDA 3397 (12/03)