CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

CHEMISTRY REVIEW(S)

NDA 21-355

Angeliq Tablets
(drospirenone/estradiol)
0.5 mg/1 mg

Berlex Laboratories, Inc.

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-355

2. REVIEW #: 5

3. REVIEW DATE: 5-AUG-2005

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS:

   Chemistry Reviews # 1, 2, 3, and 4

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document/DFS Date
Amendment	31-MAR-2005
Amendment	6-MAY-2005
Amendment	15-JUL-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Berlex Laboratories, Inc.
Address:	340 Changebridge Road PO Box 1000 Montville NJ 07045
Representative:	Not Applicable
Telephone:	973-487-2184

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Angeliq Tablets 0.5 mg/1 mg
   b) Non-Proprietary Name (USAN): drospirenone and estradiol
   c) Code Name/# (OGD only): Not Applicable
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 4

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Hormone Replacement Therapy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY:
    0.5 mg drospirenone and 1 mg estradiol per tablet

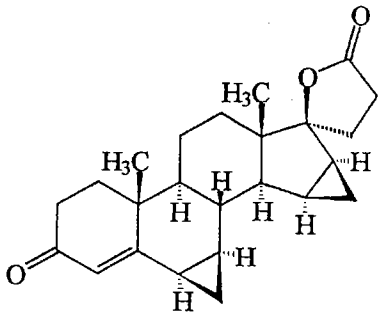
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    __x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

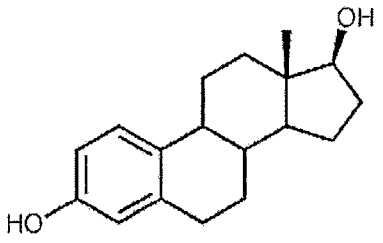


Drospirenone

Drospirenone (USAN name):

1. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5*H*)-furan]-3,5′(2*H*)-dione

2. 17-hydroxy-6β,7β,15 β,16 β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone
CAS-67392-87-4
Molecular formula: $C_{24}H_{30}O_3$
Molecular weight: 366.50



Estradiol

Estradiol (USAN name)
1. Estra-1,3,5(10)-triene-3,17-diol, (17β)
2. Estra-1,3,5(10)-triene-3,17 β -diol
CAS-50-28-2
Molecular formula: $C_{18}H_{24}O_2$
Molecular weight: 272.38

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
12138	II	Schering AG	Drospirenone	1	Adequate	11-MAY-2004	Reviewed by S. Tran
4684	II	Schering AG	Estradiol	3	Adequate	23-SEP-2004	Reviewed by B. Cai
[redacted]	III	[redacted]	[redacted]	3	Adequate	28-MAY-2004	Reviewed by D. Christner
[redacted]	III	[redacted]	[redacted]	3	Adequate	2-JUN-2004	Reviewed by D. Christner
[redacted]	III	[redacted]	[redacted]	4	N/A		21 CFR [redacted]
[redacted]	III	[redacted]	[redacted]	4	N/A		21 CFR [redacted]

[illegible]	III	[illegible]		4	N/A		21 CFR 175.105, 175.300, 176.170, 176.180, 177.1210

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-098	Yasmin (3 mg drospirenone and 0.030 mg ethinyl estradiol) Tablets
IND	53,842	drospirenone and estradiol tablets
IND	[illegible]	[illegible]
IND	[illegible]	[illegible]

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	ACCEPTABLE	11-APR-2005	S. Adams
Pharm/Tox	*Not Applicable*		
Biopharm	ACCEPTABLE	12-JUL-2005	J. Bullock
Methods Validation	*Not Applicable*		
EA	*Not Applicable*		
Microbiology	*Not Applicable*		

19. ORDER OF REVIEW (OGD Only) Not Applicable

The Chemistry Review for NDA 21-355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is APPROVAL.

Refer to the Basis for Approvability in Section C below for details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

History of the NDA:

- Review cycle 1: The NDA was first submitted on 14-DEC-2001 for the dosage strengths [redacted]. On 17-OCT-2002, a Non-Approval (NA) letter was issued for clinical deficiencies. At the time of the action, all chemistry were satisfactorily resolved (see Chem. Review #3). Labeling was not yet reviewed by the Division, but packaging labels were finalized by this reviewer and DMETS (10-SEP-2002 and 30-SEP-2002 amendments).
- Review cycle 2: On 18-MAR-2004, an amendment was submitted in response to the 17-OCT-2002 NA letter. The amendment was accepted by FDA to be a Complete Response (NDA resubmission), with a review clock of 6 months. The Complete Response included the [redacted] strength 3 mg drospirenone/1 mg estradiol. Also in the Complete Response, the applicant submitted a change in the primary (product-contact) container/closure system of the drug product [redacted] blister packs. This change was made in compliance with the Poison Prevention Packaging Requirements (1-NOV-2002 Federal Register) for hormone therapy products packaged on or after 1-NOV-2002. Stability data and a new expiration dating period accompanied the change in packaging. In addition, a new packaging site was added for the blister packaging. The chemistry recommendation of APPROVAL was filed on 17-AUG-2004, with acceptable labeling (see Chem. Review #4 and Addendum). On 9-SEP-2004, a teleconference was held between the clinical division and the applicant. As a result of this teleconference, the 10-SEP-2004 amendment was submitted for the addition of the dosage strength 0.5 mg drospirenone/1 mg estradiol [redacted] strength 1 mg drospirenone/1 mg estradiol.. On 13-SEP-2004, the chemistry recommendation was changed to APPROVABLE (see Chem. Rev. #4 Addendum #2) because there was no chemistry

information in the NDA for the 0.5 mg drospirenone/1 mg estradiol dosage strength, which was only added to the NDA eight calendar days before the action goal date. On 14-SEP-2004, an APPROVABLE (AE) letter was issued for chemistry deficiencies (lack of CMC information on the dosage strength 0.5 mg drospirenone/1 mg estradiol).

- Review cycle 3: On 31-MAR-2005, an amendment was submitted in response to the 14-SEP-2004 AE letter. The amendment was accepted by FDA to be a Complete Response (NDA resubmission), with a review clock of 6 months.

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug product –
  Refer to Chem. Reviews #1, 2, 3, and 4 for detailed information.

  Name: Angeliq Tablets (drospirenone/estradiol)
  Strengths: 0.5 mg drospirenone/1.0 mg estradiol
  Dosage form: immediate release tablet for oral administration; non-sterile
  Indication: Hormone Replacement Therapy
  Packaging: 28 tablets in a foil-backed ———) blister pack.
  Formulation - All inactive ingredients are compendial excipients. Inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.
  The differences between the clinical/pilot batch (product code SHT00641AA) and the drug product intended for marketing (product code SHT00641A) are the manufacturing site and scale, color of the film coats, and embossing of the commercial tablets. Comparative dissolution data are provided for the pilot-scale and commercial products.
  The 0.5 mg drospirenone/1 mg estradiol tablet is round, biconvex, pink film-coated with an embossment of "—— marked inside a hexagon ———

- Drug substances – USANs: drospirenone and estradiol;
  Reference is made to Drug Master Files 4684 and 12138 for all chemistry reviews of these drug substances. Refer to Chem. Reviews #1, 2, 3, and 4 for detailed information. Both DMFs are currently in the adequate status (23-SEP-2004 review for DMF 4684 and 11-MAY-2004 review for DMF 12138).

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: oral
- Dosing schedule: one tablet per day
- Dosage strength: 0.5 mg drospirenone/1 mg estradiol per tablet
- Expiry: 24 months when stored at room temperature. As agreed by FDA at the 21-OCT-2004 meeting, an expiry of 24 months can be based on ——— stability data at 25 °C/60% RH and ——— accelerated stability data at 40 °C/75% RH for three full-scale commercial tablet batches in the packaging intended for marketing, with

the supportive data of [redacted], at 25 °C/60% RH for one pilot-scale clinical batch. In addition, the 60-month data for the dosage strength 1 mg drospirenone/ 1 mg estradiol are acceptable as supportive because this product and the commercial product are manufactured by the same processes, have the same primary packaging, and only differ by the relative amounts of drug substances, lactose, and color ingredients.

C. Basis for Approvability or Not-Approval Recommendation

- All chemistry issues were previously resolved satisfactorily for the higher dosage strengths (Chem. Reviews #1-4), and there is no chemistry issue in this current review of the to-be-marketed dosage strength.
- A recommendation from the Office of Compliance is "Acceptable" (11-APR-2005 by S. Adams).
- On 31-MAR-2005, new packaging labels (mock-ups) were submitted. The new labels (including the proprietary name) are acceptable per chemistry perspective because the chemistry information is essentially the same as that of the previous labels found acceptable in the Chem. Review #4 and Addendum, with the only change being the dosage strength to reflect the to-be-marketed dosage strength.

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

17 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Suong Tran
8/5/05 10:45:30 AM
CHEMIST

paper sign-off 8/5/05

Moo-Jhong Rhee
8/5/05 02:23:00 PM
CHEMIST
I concur

NDA 21-355

Angeliq Tablets
(drospirenone/estradiol)
1 mg/1 mg

Berlex Laboratories, Inc.

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

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Chemistry Review Data Sheet

1. NDA 21-355

2. REVIEW #: 4

3. REVIEW DATE: 17-AUG-2004

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS:
   Chemistry Reviews # 1, 2, and 3

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document/DFS Date
Amendment AZ	18-MAR-2004
Amendment BC	18-MAR-2004
Amendment BC	16-APR-2004
Amendment BC	26-APR-2004
Amendment C	26-APR-2004
Amendment BC	28-APR-2004
Amendment BL	28-APR-2004
Amendment BC	4-AUG-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Berlex Laboratories, Inc.
Address: 340 Changebridge Road
PO Box 1000
Montville NJ 07045
Representative: Not Applicable
Telephone: 973-487-2184

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: Angeliq Tablets 1 mg/1 mg
b) Non-Proprietary Name (USAN): drospirenone and estradiol
c) Code Name/# (OGD only): Not Applicable
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Hormone Replacement Therapy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY:
    1 mg drospirenone and 1 mg estradiol per tablet

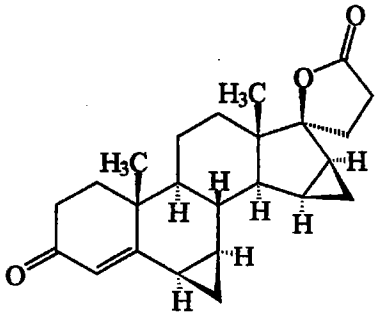
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    __x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

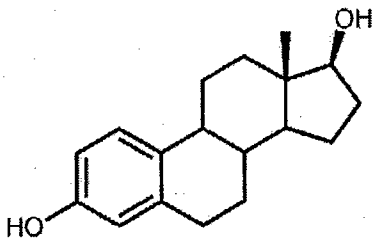


Drospirenone

Drospirenone (USAN name):

1. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5*H*)-furan]-3,5′(2*H*)-dione
2. 17-hydroxy-6β,7β,15 β,16 β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone

CAS-67392-87-4
Molecular formula: $C_{24}H_{30}O_3$
Molecular weight: 366.50



Estradiol

Estradiol (USAN name)

1. Estra-1,3,5(10)-triene-3,17-diol, (17β)
2. Estra-1,3,5(10)-triene-3,17 β -diol

CAS-50-28-2
Molecular formula: $C_{18}H_{24}O_2$
Molecular weight: 272.38

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
12138	II	Schering AG	Drospirenone	1	Adequate	11-MAY-2004	Reviewed by S. Tran
4684	II	Schering AG	Estradiol	3	Adequate	12-SEP-2002	Reviewed by J. Salemme
[redacted]	III	[redacted]	[redacted]	3	Adequate	15-OCT-2001	Reviewed by D. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	11-MAR-2002	Reviewed by D. Klein
[redacted]	III	[redacted]	[redacted]	4	N/A		21 CFR 175.300
[redacted]	III	[redacted]	[redacted]	4	N/A		21 CFR 175.300
[redacted]	III	[redacted]	[redacted]	7	N/A		21 CFR 175.105, 175.300, 176.170, 176.180, 177.1210

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-098	Yasmin (3 mg drospirenone and 0.030 mg ethinyl estradiol) Tablets
IND	53,842	drospirenone and estradiol tablets
IND	[redacted]	[redacted]
IND		

18. STATUS:

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**ACCEPTABLE**	16-AUG-2004	S. Adams
Pharm/Tox	*Not Applicable*		
Biopharm	**ACCEPTABLE**	4-JUN-2002	V. Jarugula
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs for verification.		
EA	*Not Applicable*		
Microbiology	*Not Applicable*		

19. ORDER OF REVIEW (OGD Only)

Not Applicable

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is Approval.

Refer to the Basis for Approvability in Section C below for details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

- On 17-OCT-2002, a Non-Approval letter was issued for this NDA for clinical deficiencies. At the time of the action, all chemistry were satisfactorily resolved (see Chem. Review #3). Labeling was not yet reviewed by the Division. Packaging labels were finalized by this reviewer and DMETS (10-SEP-2002 and 30-SEP-2002 amendments).
- On 18-MAR-2004, an amendment was submitted with the information requested in the 17-OCT-2002 letter. The amendment was accepted by FDA to be a Complete Response (NDA resubmission), with a review clock of 6 months. The Complete Response includes a [redacted] strength 3.0 mg drospirenone/1.0 mg estradiol.
- Along with the 18-MAR-2004 Complete Response addressing the clinical deficiencies, the applicant submitted a separate amendment for a change in the primary (product-contact) container/closure system of the drug product, [redacted] blister packs. This change was made in compliance with the Poison Prevention Packaging Requirements (1-NOV-2002 Federal Register) for hormone therapy products packaged on or after 1-NOV-2002. Stability data and a new expiration dating period accompanied the change in packaging. In addition, a new packaging site was added for the blister packaging. A new EER was submitted for the NDA for a GMP evaluation of all the sites currently listed in the NDA.

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug product –
  Refer to Chem. Reviews #1, 2, and 3 for detailed information.

  Name: Angeliq Tablets (drospirenone/estradiol)
  Strengths: 1.0 mg drospirenone/1.0 mg estradiol
  Dosage form: immediate release tablet for oral administration; non-sterile

Indication: Hormone Replacement Therapy
Packaging: 28 tablets in a foil-backed ——— blister pack.
Formulation - All inactive ingredients are compendial excipients. Inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.
The only differences between the clinical batches and the drug product intended for marketing are the color of the film coats and the embossing of the commercial tablets. Comparative dissolution data are provided for the clinical and commercial batches.
The 1 mg drospirenone/1 mg estradiol tablet is ———

- Drug substances – USANs: drospirenone and estradiol;
  Reference is made to Drug Master Files 4684 and 12138 for all chemistry reviews of these drug substances. Refer to Chem. Reviews #1, 2, and 3 for detailed information.

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: oral
- Dosing schedule: one tablet per day
- Dosage strength: 1 mg drospirenone/1 mg estradiol per tablet
- Expiry: ——— s when stored at room temperature. This expiry is based on ——— stability data at 25 °C/60% RH for three full-scale commercial tablet batches in the blister packaging intended for marketing.

C. Basis for Approvability or Not-Approval Recommendation

- All chemistry deficiencies have been satisfactorily resolved in the first cycle of the NDA review (refer to Chem. Reviews #1, 2, and 3).
- A recommendation from the Office of Compliance is "Acceptable" (16-AUG-2004 by S. Adams of HFD-322).
- The change from — packaging (reviewed in the first review cycle) to blister packaging (reviewed in the second review cycle) is adequately supported by manufacturing information and documentation on the safety and suitability of the blister packaging components.
- The proposed expiry of ——— when stored at room temperature is acceptable. This expiry is based on ——— stability data at 25 °C/60% RH for three full-scale commercial tablet batches in the blister packaging intended for marketing.
- Labeling: On 28-APR-2004, new packaging labels (mock-ups) were submitted. The new labels are acceptable because they are essentially the same as the previous labels

found to be acceptable in the previous Chem. Review #3, with the only differences in the description of packaging (necessary because of the change [redacted] blister packaging), colors, and graphics. The colors and graphics are deemed to be acceptable because they do not obscure or detract from the drug information.

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

3 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3

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

/s/

Suong Tran
8/17/04 04:27:45 PM
CHEMIST

paper sign-off 8/17/04

Moo-Jhong Rhee
8/17/04 04:40:31 PM
CHEMIST
I concur

NDA 21-355

Angeliq Tablets
(drospirenone/estradiol)
1 mg/1 mg
3 mg/1 mg

Berlex Laboratories, Inc.

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-355

2. REVIEW #: 3

3. REVIEW DATE: 8-OCT-2002

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS:
   Not Applicable

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document/DFS Date
Amendment (labeling)	30-SEP-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Berlex Laboratories, Inc.
Address: 340 Changebridge Road
PO Box 1000
Montville NJ 07045
Representative: Not Applicable
Telephone: 973-487-2184

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Angeliq Tablets 1 mg/1 mg and 3 mg/1 mg
b) Non-Proprietary Name (USAN): drospirenone and estradiol
c) Code Name/# (OGD only): Not Applicable
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 4
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Hormone Replacement Therapy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY:
    1 mg drospirenone and 1 mg estradiol per tablet, or
    3 mg drospirenone and 1 mg estradiol per tablet

13. ROUTE OF ADMINISTRATION: oral

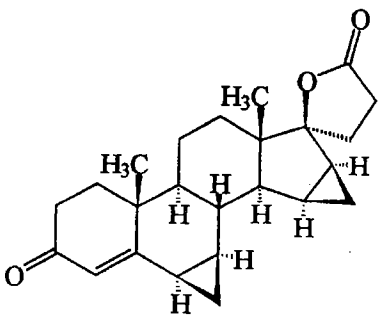
14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note21]:

    _____SPOTS product – Form Completed

    __x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

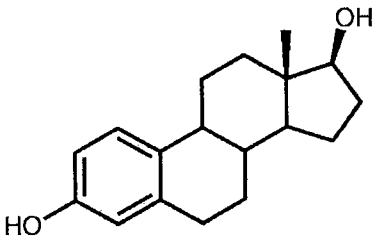


Drospirenone

Drospirenone (USAN name):

1. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5*H*)-furan]-3,5′(2*H*)-dione

2. 17-hydroxy-6β,7β,15 β,16 β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone
CAS-67392-87-4
Molecular formula: $C_{24}H_{30}O_3$
Molecular weight: 366.50



Estradiol

Estradiol (USAN name)
1. Estra-1,3,5(10)-triene-3,17-diol, (17β)
2. Estra-1,3,5(10)-triene-3,17 β -diol
CAS-50-28-2
Molecular formula: $C_{18}H_{24}O_2$
Molecular weight: 272.38

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
12138	II	Schering AG	Drospirenone	1	Adequate	14-JUN-2002	Reviewed by S. Tran
4684	II	Schering AG	Estradiol	3	Adequate	26-AUG-1999	Reviewed by R. Patel
	III			3	Adequate	12-FEB-2001	Reviewed by D. Klein
	III			3	Adequate	19-SEP-2001	Reviewed by S. Kelly
	III			3	Adequate	14-AUG-2001	Reviewed by R. Uppoor

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-098	Yasmin (3 mg drospirenone and 0.030 mg ethinyl estradiol) Tablets
IND	53,842	drospirenone and estradiol tablets
IND		
IND		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**ACCEPTABLE**	4-FEB-2002	M. Garcia
Pharm/Tox	*Not Applicable*		
Biopharm	**ACCEPTABLE**	4-JUN-2002	V. Jarugula
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs for verification.		
ODS	**ACCEPTABLE** for the proprietary name "Angeliq". Revisions to the container labels are recommended.	9-JUL-2002	J. Fan
EA	*Not Applicable*		
Microbiology	*Not Applicable*		

19. ORDER OF REVIEW (OGD Only)

Not Applicable

The Chemistry Review for NDA 21-355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is **APPROVAL**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug product –
  Name: Angeliq Tablets (drospirenone/estradiol)
  Strengths: 1.0 mg drospirenone/1.0 mg estradiol, or
  3.0 mg drospirenone/1.0 mg estradiol
  Dosage form: immediate release tablet for oral administration; non-sterile
  Indication: Hormone Replacement Therapy
  Packaging: [redacted]

  Formulation - All inactive ingredients are compendial excipients. The two dosage strengths differ by the relative amounts of drug substances and lactose, and by the color ingredients. Inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.

  The only differences between the clinical batches and the drug product intended for marketing are the color of the film coats and the embossing of the commercial tablets. Comparative dissolution data are provided for the clinical and commercial batches.

The 1 mg drospirenone/1 mg estradiol tablet is

The 3 mg drospirenone/1 mg estradiol tablet is

- The initial Chemistry Review of the original submission dated 14-DEC-2001 and of the 14-JAN-2002, 1-FEB-2002, and 15-FEB-2002 amendments found deficiencies which were conveyed to the applicant. Subsequently, the applicant submitted amendments in response which satisfactorily resolved the chemistry deficiencies.
- Of the chemistry deficiencies found in the original submission and amendments, the more germane issues are as follows:
  - The drug product specifications originally did not include a full description of the tablets stating the shape, color, and embossment. NDA revisions were made per FDA's request to include this testing and acceptance criteria.
  - Release testing of the drug product originally did not include testing for impurities and degradation products. In addition, the proposed acceptance criteria for impurities/degradants were wide and did not reflect batch analysis and stability data. NDA revisions were made per FDA's request to include release testing and acceptance criteria for impurities/degradants and to tighten these criteria.
  - The dissolution acceptance criteria were originally proposed to be estradiol Q=—% at —minutes and drospirenone Q= —% at —minutes for both dosage strengths. This Chemistry reviewer and the Clin. Pharm. Reviewer (V. Jarugula) finalized these criteria to be estradiol Q=' — at 30 minutes and drospirenone Q= — % at 30 minutes for both dosage strengths. The applicant accepted these final criteria in the 26-JUL-2002 amendment.
  - The post-approval stability commitment originally did not include a full stability study design for post-approval changes. The applicant's proposed matrixing design is acceptable only for routine monitoring of the drug product. In addition, any extension of the expiry should be based on real-time data from three production batches and a full study design. NDA revisions were made per FDA's request to incorporate in the stability commitment a full stability study design for post-approval changes and a statement that any extension of the expiry will be based on real-time data from three production batches and a full study design.

- The release testing of the drug product is performed on the bulk tablets by Schering GmbH prior to final packaging by [redacted] This is deemed acceptable because: 1) adequate procedures are established per FDA Compliance requirements (see attached emails) for release testing performed on the bulk product: procedures for receipt and handling of incoming bulk tablets, procedures for repackaging the bulk tablets into market containers, and release procedures to ensure that all packaging and labeling specifications are met prior to release; 2) Berlex QA performs a visual inspection of the tablets before and after packaging; 3) Berlex QA monitors the packaging operations and reviews the packaging batch records; 4) FDA Compliance has an acceptable profile on the packaging contractor [redacted] 5) photostability data of unprotected tablets, and 24-month stability data at 25 °C/60% RH and [redacted] stability data at 40 °C/75% RH for tablets in bulk containers show that the product quality is maintained during storage, shipping, and it is not affected by the increase in temperature and humidity or exposure to light; and 6) the same procedures for release testing of the bulk product and packaging/distributing of the final product are approved for Betapace Tablets (see 25-MAR-2002 meeting minutes).

- Drug substances – USANs: drospirenone and estradiol;
  Reference is made to Drug Master Files 4684 and 12138 for all chemistry reviews of these drug substances.
  The physico-chemical properties of the drug substances are included in the NDA.
  Drospirenone is a white to off-white crystalline powder that has a melting range of [redacted] °C, an optical rotation [redacted]

  [redacted]

  Due to the confidentiality nature of Drug Master Files, review issues regarding the drug substances cannot be divulged in this NDA review. Reference is made to the chemistry reviews of the Drug Master Files for details.

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: oral
- Dosing schedule: one tablet per day
- Dosage strength: [redacted]
- Expiry: [redacted] when stored at room temperature. This expiry is based on [redacted] stability data at 25 °C/60% RH for three full-scale embossed-tablet batches for each dosage strength in each container/closure system intended for marketing.

Chemistry Review Data Sheet

1. NDA 21-355

2. REVIEW #: 2

3. REVIEW DATE: 27-SEP-2002

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS:

   Not Applicable

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document/DFS Date
Amendment (labeling)	10-SEP-2002
Amendment (labeling)	16-SEP-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Berlex Laboratories, Inc.
Address:	340 Changebridge Road PO Box 1000 Montville NJ 07045
Representative:	Not Applicable
Telephone:	973-487-2184

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Angeliq Tablets 1 mg/1 mg and 3 mg/1 mg
   b) Non-Proprietary Name (USAN): drospirenone and estradiol
   c) Code Name/# (OGD only): Not Applicable
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 4
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Hormone Replacement Therapy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY:
    1 mg drospirenone and 1 mg estradiol per tablet, or
    3 mg drospirenone and 1 mg estradiol per tablet

13. ROUTE OF ADMINISTRATION: oral

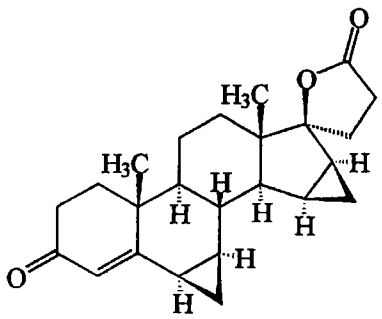
14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note21]:

    _____SPOTS product – Form Completed

    __x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

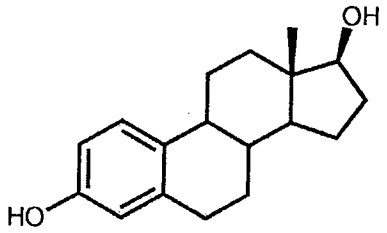


Drospirenone

Drospirenone (USAN name):

1. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5*H*)-furan]-3,5′(2*H*)-dione
2. 17-hydroxy-6β,7β,15 β,16 β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone

CAS-67392-87-4
Molecular formula: $C_{24}H_{30}O_3$
Molecular weight: 366.50



Estradiol

Estradiol (USAN name)
1. Estra-1,3,5(10)-triene-3,17-diol, (17β)
2. Estra-1,3,5(10)-triene-3,17 β -diol

CAS-50-28-2
Molecular formula: $C_{18}H_{24}O_2$
Molecular weight: 272.38

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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4684	II	Schering AG	Estradiol	3	Adequate	26-AUG-1999	Reviewed by R. Patel
	III			3	Adequate	12-FEB-2001	Reviewed by D. Klein
	III			3	Adequate	19-SEP-2001	Reviewed by S. Kelly
	III			3	Adequate	14-AUG-2001	Reviewed by R. Uppoor

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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-098	Yasmin (3 mg drospirenone and 0.030 mg ethinyl estradiol) Tablets
IND	53,842	drospirenone and estradiol tablets
IND		
IND		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**ACCEPTABLE**	4-FEB-2002	M. Garcia
Pharm/Tox	*Not Applicable*		
Biopharm	**ACCEPTABLE**	4-JUN-2002	V. Jarugula
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs for verification.		
ODS	**ACCEPTABLE** for the proprietary name "Angeliq". Revisions to the container labels are recommended.	9-JUL-2002	J. Fan
EA	*Not Applicable*		
Microbiology	*Not Applicable*		

19. ORDER OF REVIEW (OGD Only)

Not Applicable

Chemistry Review Data Sheet

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is **APPROVABLE** pending satisfactory labeling (container labels).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

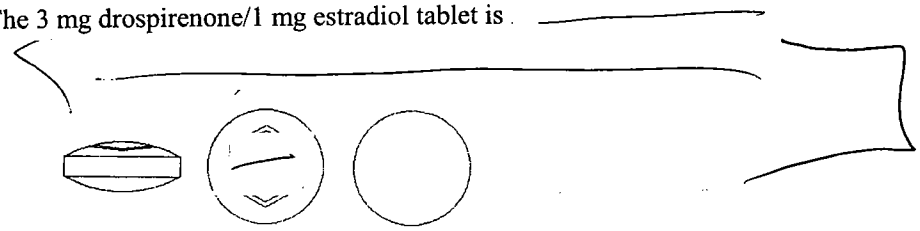
- Drug product –
  Name: Angeliq Tablets (drospirenone/estradiol)
  Strengths: 1.0 mg drospirenone/1.0 mg estradiol, or
  3.0 mg drospirenone/1.0 mg estradiol
  Dosage form: immediate release tablet for oral administration; non-sterile
  Indication: Hormone Replacement Therapy
  Packaging: [redacted]

  Formulation - All inactive ingredients are compendial excipients. The two dosage strengths differ by the relative amounts of drug substances and lactose, and by the color ingredients. Inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.

  The only differences between the clinical batches and the drug product intended for marketing are the color of the film coats and the embossing of the commercial tablets. Comparative dissolution data are provided for the clinical and commercial batches.

The 1 mg drospirenone/1 mg estradiol tablet is

The 3 mg drospirenone/1 mg estradiol tablet is



- The initial Chemistry Review of the original submission dated 14-DEC-2001 and of the 14-JAN-2002, 1-FEB-2002, and 15-FEB-2002 amendments found deficiencies which were conveyed to the applicant. Subsequently, the applicant submitted amendments in response which satisfactorily resolved the chemistry deficiencies.
- Of the chemistry deficiencies found in the original submission and amendments, the more germane issues are as follows:
  - The drug product specifications originally did not include a full description of the tablets stating the shape, color, and embossment. NDA revisions were made per FDA's request to include this testing and acceptance criteria.
  - Release testing of the drug product originally did not include testing for impurities and degradation products. In addition, the proposed acceptance criteria for impurities/degradants were wide and did not reflect batch analysis and stability data. NDA revisions were made per FDA's request to include release testing and acceptance criteria for impurities/degradants and to tighten these criteria.
  - The dissolution acceptance criteria were originally proposed to be estradiol Q= ——— minutes and drospirenone Q= ——— minutes for both dosage strengths. This Chemistry reviewer and the Clin. Pharm. Reviewer (V. Jarugula) finalized these criteria to be estradiol Q= —% at 30 minutes and drospirenone Q= —% at 30 minutes for both dosage strengths. The applicant accepted these final criteria in the 26-JUL-2002 amendment.
  - The post-approval stability commitment originally did not include a full stability study design for post-approval changes. The applicant's proposed matrixing design is acceptable only for routine monitoring of the drug product. In addition, any extension of the expiry should be based on real-time data from three production batches and a full study design. NDA revisions were made per FDA's request to incorporate in the stability commitment a full stability study design for post-approval changes and a statement that any extension of the expiry will be based on real-time data from three production batches and a full study design.

- The release testing of the drug product is performed on the bulk tablets by Schering GmbH prior to final packaging by [redacted] This is deemed acceptable because: 1) adequate procedures are established per FDA Compliance requirements (see attached emails) for release testing performed on the bulk product: procedures for receipt and handling of incoming bulk tablets, procedures for repackaging the bulk tablets into market containers, and release procedures to ensure that all packaging and labeling specifications are met prior to release; 2) Berlex QA performs a visual inspection of the tablets before and after packaging; 3) Berlex QA monitors the packaging operations and reviews the packaging batch records; 4) FDA Compliance has an acceptable profile on the packaging contractor [redacted]); 5) photostability data of unprotected tablets, and 24-month stability data at 25 °C/60% RH and [redacted] stability data at 40 °C/75% RH for tablets in bulk containers show that the product quality is maintained during storage, shipping, and it is not affected by the increase in temperature and humidity or exposure to light; and 6) the same procedures for release testing of the bulk product and packaging/distributing of the final product are approved for Betapace Tablets (see 25-MAR-2002 meeting minutes).

- Drug substances – USANs: drospirenone and estradiol;
  Reference is made to Drug Master Files 4684 and 12138 for all chemistry reviews of these drug substances.
  The physico-chemical properties of the drug substances are included in the NDA.
  Drospirenone is a white to off-white crystalline powder that has a melting range [redacted] °C, an optical rotation [redacted]

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: oral
- Dosing schedule: one tablet per day
- Dosage strength: [redacted]
- Expiry: [redacted] when stored at room temperature. This expiry is based on [redacted] stability data at 25 °C/60% RH for three full-scale embossed-tablet batches for each dosage strength in each container/closure system intended for marketing.

C. Basis for Approvability or Not-Approval Recommendation

- All chemistry deficiencies delineated in the 21-MAR-2002 chemistry letter have been satisfactorily resolved.
- Office of Compliance issued an "Acceptable" recommendation on 4-FEB-2002 in the establishment evaluation report.
- On 4-JUN-2002, this Chemistry reviewer and the Clin. Pharm. Reviewer (V. Jarugula) finalized acceptance criteria for dissolution to be estradiol Q=— % at 30 minutes and drospirenone Q=—% at 30 minutes for both dosage strengths. The applicant accepted these final criteria in the 26-JUL-2002 amendment.
- Office of Drug Safety found the proprietary name "Angeliq" acceptable on 9-JUL-2002 (J. Fan).
- Chemistry comments regarding the 14-DEC-2001 labeling were sent to the applicant in the 21-MAR-2002 chemistry letter, and the comments from the Office of Drug Safety were sent on 1-AUG-2002. The 15-AUG-2002 amendment was submitted for the revised container labels (color mock-ups), which incorporated the FDA comments. However, the 15-AUG-2002 revised container labels had new items that were different from the original labels. Subsequently, additional chemistry comments regarding the 15-AUG-2002 container labels (as well as comments regarding the original package insert) were sent to the applicant on 26-AUG-2002. Except for the issue of the height of the text of the established name relative to that of the proprietary name, all other labeling issues were satisfactorily resolved in the 10-SEP-2002 amendment as follows:
  - Replace "Angeliq" with "Angeliq Tablets". The 10-SEP-2002 labeling includes this revision and is acceptable.
  - Change the height of the text of the established name to be at least half the height of "A" in "Angeliq" and change the color of the text of the established name to a darker color, such as black, to make the text more legible. The 10-SEP-2002 labeling has the text of the established name and quantitative statement in ——— background and is acceptable. However, the height of the text of the established name (approx. 1 mm) is less than half the height of "A" (approx. 6 mm) in "Angeliq" and less than half the height of the other letters (approx. 3 mm) in "Angeliq." On 25-SEP-2002, this reviewer informed the applicant the height requirement for the established name must be met per 21 CFR 201.10(g)(2). The applicant explained that the requirement cannot be met due to the lack of space on the labels. However, this explanation is not acceptable because the space on the labels can be redesigned to accommodate the text.
    Deficiency: Change the height of the text of the established name to be at least half the height of "A" in "Angeliq" per 21 CFR 201.10(g)(2).
  - Change the color of the highlight for ——— to a brighter shade of ——— The 10-SEP-2002 labeling includes the text '——— in a ——— color and is acceptable.
  - State the lot number and expiry on the ——— labels. The 10-SEP-2002 labeling includes this revision and is acceptable.
  -

- For the [redacted] to the top of the labels (underneath the NDC and above "Angeliq Tablets".) The 10-SEP-2002 labeling includes this revision and is acceptable.
- Revised title of the Physician's Insert: The 10-SEP-2002 and 16-SEP-2002 labeling includes this revision and is acceptable.

  ANGELIQ TABLETS
  (drospirenone and estradiol)

- Revised How Supplied section of the Physician's Insert: The 10-SEP-2002 labeling includes this revision and is acceptable.

  HOW SUPPLIED
  ANGELIQ TABLETS (drospirenone and estradiol) [redacted]

  Store at 25° C (77° F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
  REFERENCES FURNISHED UPON REQUEST

  Manufactured for:
  BERLEX [redacted]
  Manufactured in Germany
  Berlex Component Code #

(Note: no revision of the package insert has been sent to the applicant from DRUDP other than the chemistry comments on the Description and How Supplied sections.)

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

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

/s/

Suong Tran
9/27/02 03:02:03 PM
CHEMIST

per discussion on 9/27/02

Moo-Jhong Rhee
9/27/02 03:06:48 PM
CHEMIST
I concur

NDA 21-355

Angeliq Tablets
(drospirenone/estradiol)
1 mg/1 mg
3 mg/1 mg

Berlex Laboratories, Inc.

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-355

2. REVIEW #: 1

3. REVIEW DATE: 28-AUG-2002

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS:
   Not Applicable

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document/DFS Date
Original	14-DEC-2001
Amendment	14-JAN-2002
Amendment	1-FEB-2002
Amendment	15-FEB-2002
Amendment	13-MAY-2002
Amendment	10-JUN-2002
Amendment	14-JUN-2002
Amendment	22-JUL-2002
Amendment	26-JUL-2002
Amendment	15-AUG-2002
Amendment	19-AUG-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Berlex Laboratories, Inc.
Address: 340 Changebridge Road
PO Box 1000
Montville NJ 07045
Representative: Not Applicable
Telephone: 973-487-2184

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Angeliq Tablets 1 mg/1 mg and 3 mg/1 mg
b) Non-Proprietary Name (USAN): drospirenone and estradiol
c) Code Name/# (OGD only): Not Applicable
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Hormone Replacement Therapy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY:
1 mg drospirenone and 1 mg estradiol per tablet, or
3 mg drospirenone and 1 mg estradiol per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

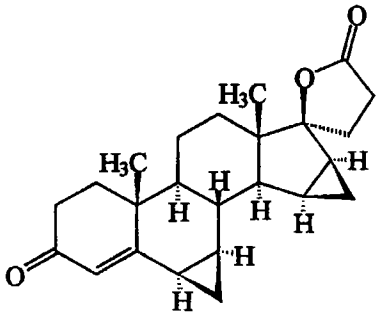
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note21]:

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

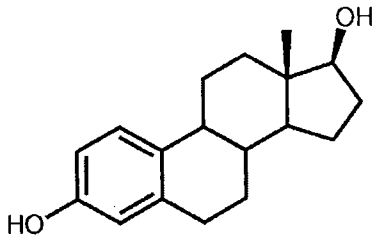


Drospirenone

Drospirenone (USAN name):

1. (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5*H*)-furan]-3,5′(2*H*)-dione
2. 17-hydroxy-6β,7β,15 β,16 β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone

CAS-67392-87-4
Molecular formula: $C_{24}H_{30}O_3$
Molecular weight: 366.50



Estradiol

Estradiol (USAN name)

1. Estra-1,3,5(10)-triene-3,17-diol, (17β)
2. Estra-1,3,5(10)-triene-3,17 β -diol

CAS-50-28-2
Molecular formula: $C_{18}H_{24}O_2$
Molecular weight: 272.38

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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4684	II	Schering AG	Estradiol	3	Adequate	26-AUG-1999	Reviewed by R. Patel
[redacted]	III	[redacted]	[redacted]	3	Adequate	12-FEB-2001	Reviewed by D. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	19-SEP-2001	Reviewed by S. Kelly
[redacted]	III	[redacted]	[redacted]	3	Adequate	14-AUG-2001	Reviewed by R. Uppoor

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-098	Yasmin (3 mg drospirenone and 0.030 mg ethinyl estradiol) Tablets
IND	53,842	drospirenone and estradiol tablets
IND	[redacted]	[redacted]
IND		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**ACCEPTABLE**	4-FEB-2002	M. Garcia
Pharm/Tox	*Not Applicable*		
Biopharm	**ACCEPTABLE**	4-JUN-2002	V. Jarugula
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs for verification.		
ODS	**ACCEPTABLE** for the proprietary name "Angeliq". Revisions to the container labels are recommended.	9-JUL-2002	J. Fan
EA	*Not Applicable*		
Microbiology	*Not Applicable*		

19. ORDER OF REVIEW (OGD Only)

Not Applicable

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-355

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is **APPROVABLE** pending satisfactory labeling (physician's package insert and container labels).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug product –
  Name: Angeliq Tablets (drospirenone/estradiol)
  Strengths: 1.0 mg drospirenone/1.0 mg estradiol, or
  3.0 mg drospirenone/1.0 mg estradiol
  Dosage form: [redacted] tablet for oral administration; non-sterile
  Indication: Hormone Replacement Therapy
  Packaging: [redacted]

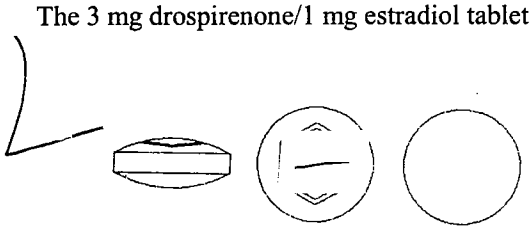
  Formulation - All inactive ingredients are compendial excipients. The two dosage strengths differ by the relative amounts of drug substances and lactose, and by the color ingredients. Inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.

  The only differences between the clinical batches and the drug product intended for marketing are the color of the film coats and the embossing of the commercial tablets. Comparative dissolution data are provided for the clinical and commercial batches.

Executive Summary Section

The 1 mg drospirenone/1 mg estradiol tablet is

The 3 mg drospirenone/1 mg estradiol tablet is



- The initial Chemistry Review of the original submission dated 14-DEC-2001 and of the 14-JAN-2002, 1-FEB-2002, and 15-FEB-2002 amendments found deficiencies which were conveyed to the applicant. Subsequently, the applicant submitted amendments in response which satisfactorily resolved the chemistry deficiencies.
- Of the chemistry deficiencies found in the original submission and amendments, the more germane issues are as follows:
  - The drug product specifications originally did not include a full description of the tablets stating the shape, color, and embossment. NDA revisions were made per FDA's request to include this testing and acceptance criteria.
  - Release testing of the drug product originally did not include testing for impurities and degradation products. In addition, the proposed acceptance criteria for impurities/degradants were wide and did not reflect batch analysis and stability data. NDA revisions were made per FDA's request to include release testing and acceptance criteria for impurities/degradants and to tighten these criteria.
  - The dissolution acceptance criteria were originally proposed to be estradiol Q= minutes and drospirenone Q= minutes for both dosage strengths. This Chemistry reviewer and the Clin. Pharm. Reviewer (V. Jarugula) finalized these criteria to be estradiol Q= at 30 minutes and drospirenone Q= at 30 minutes for both dosage strengths. The applicant accepted these final criteria in the 26-JUL-2002 amendment.
  - The post-approval stability commitment originally did not include a full stability study design for post-approval changes. The applicant's proposed matrixing design is acceptable only for routine monitoring of the drug product. In addition, any extension of the expiry should be based on real-time data from three production batches and a full study design. NDA revisions were made per FDA's request to incorporate in the stability commitment a full stability study design for post-approval changes and a statement that any extension of the expiry will be based on real-time data from three production batches and a full study design.

- The release testing of the drug product is performed on the bulk tablets by Schering GmbH prior to final packaging by [redacted] This is deemed acceptable because: 1) adequate procedures are established per FDA Compliance requirements (see attached emails) for release testing performed on the bulk product: procedures for receipt and handling of incoming bulk tablets, procedures for repackaging the bulk tablets into market containers, and release procedures to ensure that all packaging and labeling specifications are met prior to release; 2) Berlex QA performs a visual inspection of the tablets before and after packaging; 3) Berlex QA monitors the packaging operations and reviews the packaging batch records; 4) FDA Compliance has an acceptable profile on the packaging contractor [redacted]; 5) photostability data of unprotected tablets, and 24-month stability data at 25 °C/60% RH and [redacted] stability data at 40 °C/75% RH for tablets in bulk containers show that the product quality is maintained during storage, shipping, and it is not affected by the increase in temperature and humidity or exposure to light; and 6) the same procedures for release testing of the bulk product and packaging/distributing of the final product are approved for Betapace Tablets (see 25-MAR-2002 meeting minutes).

- Drug substances – USANs: drospirenone and estradiol;
  Reference is made to Drug Master Files 4684 and 12138 for all chemistry reviews of these drug substances.
  The physico-chemical properties of the drug substances are included in the NDA. Drospirenone is a white to off-white crystalline powder that has a melting range of [redacted] °C, an optical rotation [redacted] Due to the confidentiality nature of Drug Master Files, review issues regarding the drug substances cannot be divulged in this NDA review. Reference is made to the chemistry reviews of the Drug Master Files for details.

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: oral
- Dosing schedule: one tablet per day
- Dosage strength: [redacted]
- Expiry: [redacted] when stored at room temperature. This expiry is based on [redacted] stability data at 25 °C/60% RH for three full-scale embossed-tablet batches for each dosage strength in each container/closure system intended for marketing.

C. Basis for Approvability or Not-Approval Recommendation

- All chemistry deficiencies delineated in the 21-MAR-2002 chemistry letter have been satisfactorily resolved.
- Office of Compliance issued an "Acceptable" recommendation on 4-FEB-2002 in the establishment evaluation report.
- On 4-JUN-2002, this Chemistry reviewer and the Clin. Pharm. Reviewer (V. Jarugula) finalized these criteria to be estradiol Q= % at 30 minutes and drospirenone Q= % at 30 minutes for both dosage strengths. The applicant accepted these final criteria in the 26-JUL-2002 amendment.
- Office of Drug Safety found the proprietary name "Angeliq" acceptable on 9-JUL-2002 (J. Fan).
- PENDING: The NDA is recommended "Approvable" pending satisfactory resolution of the labeling issue. Labeling, including container labels and package inserts, has not been finalized by the applicant. Chemistry comments regarding the 14-DEC-2001 labeling were sent to the applicant in the 21-MAR-2002 chemistry letter, and the comments from the Office of Drug Safety were sent on 1-AUG-2002. The 15-AUG-2002 amendment was submitted for the revised container labels (color mock-ups), which incorporated the FDA comments. However, the 15-AUG-2002 revised container labels had new items that were different from the original labels. Subsequently, the following chemistry comments regarding the 15-AUG-2002 container labels (as well as comments regarding the original package insert) were sent to the applicant on 26-AUG-2002:
  - Replace "Angeliq" with "Angeliq Tablets".
  - Change the height of the text of the established name to be at least half the height of "A" in "Angeliq" and change the color of the text of the established name to a darker color, such as black, to make the text more legible.
  - Change the color of the highlight for " to a brighter shade of
  - State the lot number and expiry on the labels.
  -
  -

(Note: no revision of the package insert has been sent to the applicant from DRUDP other than the chemistry comments on the Description and How Supplied sections.)

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

32 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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

/s/

Suong Tran
9/5/02 10:17:10 AM
CHEMIST

paper signed 9/5/02

Moo-Jhong Rhee
9/5/02 12:39:16 PM
CHEMIST
I concur