CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-443

Chemistry Review(s)

NDA 21-443

ENJUVIA™ TABLETS
(Synthetic Conjugated Estrogens, B)

DURAMED PHARMACEUTICALS INC.

SWAPAN K. DE

DIVISION OF REPRODUCTIVE & UROLOGIC DRUG PRODUCTS (HFD-580)

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA 21-443

2. REVIEW # 2

3. REVIEW DATE: 05-MAY-2004

4. REVIEWER: Swapan K. De

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	22-MAR-2002
Amendment #012 (updated stability data)	04-OCT-2002
Amendment #013 (DMF authorization letters)	10-OCT-2002
Amendment #016 (deficiencies to IR letter)	05-DEC-2002
Amendment #020 (acceptance criteria of drug product)	11-FEB-2003
Amendment #021 (stability data)	11-FEB-2003
Amendment #023 (correction of stability data)	28-FEB-2003
Amendment #025 (stability database SAS 5.0 format)	20-MAR-2003
Amendment #026 (Related to FDA 483	24-MAR-2003
Amendment #027 (labeling & mock-ups)	27-MAR-2003
Amendment #030 (Shelf life/dissolution/stability spec.)	21-APR-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #034 (Transfer of ownership)	24-NOV-2003
Resubmission	09-MAR-2004
Submission (e-mail)	03-MAY-2004
Submission (e-mail)	04-MAY-2004
Submission	05-MAY-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Duramed Pharmaceuticals, Subsidiary of Barr Pharmaceuticals, Inc.
Address:	One Bala Plaza, Suite 324 Bala Cynwyd, PA 19004
Representative:	Joseph A. Carrodo, M.Sc., R.Ph.
Telephone:	(610) 668-2989

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ENJUVIA™ Tablets
b) Non-Proprietary Name (USAN): Synthetic Conjugated Estrogens, B
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of moderate to severe vasomotor symptoms associated with menopause

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.625 mg, and 1.25 mg

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:

The active drug substance for this product is composed of 10 estrogenic components:
sodium estrone sulfate
sodium equilin sulfate
sodium 17α-dihydroequilin sulfate
sodium 17α-estradiol sulfate
sodium 17β-estradiol sulfate
sodium 17β-dihydroequilin sulfate
sodium $\Delta^{8,9}$-dehydroestrone sulfate
sodium equilenin sulfate
sodium 17α-dihydroequilenin sulfate
sodium 17β-dihydroequilenin sulfate

see Chemistry Review #1 for structures (Drug Substance Section)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFER-ENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Drug substance (Conjugated estrogens)	1	Adequate	01/21/03	Reviewed by S.K.De
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/15/00	Reviewed by D.N. Klein
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/19/00	Reviewed by Sharon Kelly
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/19/96	Reviewed by N. Ya
[redacted]	III	[redacted]	[redacted]	3	Adequate	8/27/02	Reviewed

		[redacted]	[redacted]		(also see Review #3)	(Review #3 dated 12/31/99)	by S. Zimmerman
[redacted]	III	[redacted]	[redacted]	3	Adequate	1/10/01	Reviewed By J.D. Vidra
[redacted]	III	[redacted]	[redacted]	3	Adequate	8/3/01	Reviewed By S.P. Peri
[redacted]	IV	[redacted]	[redacted]	1	Adequate	2/6/03	Reviewed by S.K.De
[redacted]	IV	[redacted]	[redacted]	3	Adequate	12/9/02	Reviewed by N. Chidambaram
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/27/00	Reviewed by R. Lostritto

[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: IND 57-111

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Adequate (stability data analysis)	4/8/03	Moh-Jee Ng, Ph.D.
EES	acceptable	4/15/03	Office of Compliance
Pharm/Tox	Adequate	1/22/03	Alex Jordan, Ph.D.
Biopharm	Adequate	4/10/03	Jarugula Venkat, Ph.D.
LNC	Adequate (see appendix for correspondence with Dan Boring)	4/08/02	Dan Boring, Ph.D.
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	03/31/04	Carol Holquist, R.Ph.
EA	Categorical exclusion granted	4/15/03	Swapan K. De, Ph.D.
Microbiology	N/A		

The application submission(s) covered by this review was taken in the date order of receipt. X Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-443

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The previous pending labeling issues have been resolved satisfactorily and, therefore, from chemistry, manufacturing, and controls point of view, this NDA may be approved.

II. Summary of Chemistry Assessments

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

See chemistry review #1.

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

See chemistry review #1.

C. Basis for Approvability or Not-Approval Recommendation

From chemistry, manufacturing, and controls point of view, this NDA may be approved since the sponsor has addressed all the deficiencies noted during the review cycle (see chemistry review #1) and pending labeling issues are now resolved (see next page, chemistry assessment).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/S. K. De, Ph.D.
HFD-580/ Moo-Jhong Rhee, Ph.D.

C. CC Block

HFD-580/Division File/NDA 21-343
HFD-580/S. K. De, Ph.D.
HFD-580/Moo-Jhong Rhee, Ph.D.
HFD-580/GLyght

3 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Swapan De
5/7/04 02:54:07 PM
CHEMIST

Moo-Jhong Rhee
5/7/04 03:01:13 PM
CHEMIST
I concur

CHEMISTRY REVIEW

NDA 21-443

ENJUVIA™ TABLETS
(Synthetic Conjugated Estrogens, B)

ENDEAVOR PHARMACEUTICALS INC.

SWAPAN K. DE

DIVISION OF REPRODUCTIVE & UROLOGIC DRUG PRODUCTS (HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-443

2. REVIEW # 1

3. REVIEW DATE: 17-APRIL-2003(revised)

4. REVIEWER: Swapan K. De

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	22-MAR-2002
Amendment #012 (updated stability data)	04-OCT-2002
Amendment #013 (DMF authorization letters)	10-OCT-2002
Amendment #016 (deficiencies to IR letter)	05-DEC-2002
Amendment #020 (acceptance criteria of drug product)	11-FEB-2003
Amendment #021 (stability data)	11-FEB-2003
Amendment #023 (correction of stability data)	28-FEB-2003
Amendment #025 (stability database SAS 5.0 format)	20-MAR-2003
Amendment #026 (Related to FDA 483)	24-MAR-2003
Amendment #027 (labeling & mock-ups)	27-MAR-2003
Amendment #030 (Shelf life/dissolution/stability spec.)	21-APR-2003

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Endeavor Pharmaceuticals, Inc.
Address:	127 Racine Drive, Suite 202 Wilmington, NC 28403
Representative:	John B. West, Jr.
Telephone:	(910) 202-3544

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ENJUVIA™ Tablets
b) Non-Proprietary Name (USAN): Synthetic Conjugated Estrogens B
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of moderate to severe vasomotor symptoms associated with menopause

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.625 mg, and 1.25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

_____SPOTS product – Form Completed
___x__Not a SPOTS product

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

The active drug substance for this product is composed of a 10 component estrogen mixture: sodium estrone sulfate

sodium equilin sulfate
sodium 17α-dihydroequilin sulfate
sodium 17α-estradiol sulfate
sodium 17β-estradiol sulfate
sodium 17α-dihydroequilin sulfate
sodium 17β-dihydroequilin sulfate
sodium $\Delta^{8,9}$-dehydroestrone sulfate
sodium equilenin sulfate
sodium 17α-dihydroequilenin sulfate
sodium 17β-dihydroequilenin. sulfate

see Chemistry Review for structures (Drug Substance Section)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Drug substance (Conjugated estrogens)	1	Not adequate Adequate	10/16/02 01/21/03	Reviewed by S.K.De
[redacted]	III	[redacted]		3	Adequate	9/15/00	Reviewed by D.N. Klein
[redacted]	III	[redacted]		3	Adequate	9/19/00	Reviewed by Sharon Kelly
[redacted]	III	[redacted]		3	Adequate	9/19/96	Reviewed by N. Ya
[redacted]	III	[redacted]		3	Adequate (also see Review #3)	8/27/02 (Review #3 dated 12/31/99)	Reviewed by S. Zimmerman

Chemistry Review Data Sheet

[ ]	III	[ ]	3	Adequate	1/10/01	Reviewed By J.D. Vidra
[ ]	III	[ ]	3	Adequate	8/3/01	Reviewed By S.P. Peri
[ ]	IV	[ ]	1	Adequate	2/6/03	Reviewed by S.K.De
[ ]	IV	[ ]	3	Adequate	12/9/02	Reviewed by N. Chidambaram
[ ]	III	[ ]	3	Adequate	9/27/00	Reviewed by R. Lostritto

[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: IND 57-111

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Adequate (stability data analysis)	4/8/03	Moh-Jee Ng, Ph.D.
EES	Pending		Office of Compliance
Pharm/Tox	Adequate	1/22/03	Alex Jordan, Ph.D.
Biopharm	Adequate	4/10/03	Jarugula Venkat, Ph.D.
LNC	Adequate (see appendix for correspondence with Dan Boring)	4/08/02	Dan Boring, Ph.D.
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	12/11/02	Carol Holquist, R.Ph.
EA	Categorical exclusion granted	4/15/03	Swapan K. De, Ph.D.
Microbiology	N/A		

The application submission(s) covered by this review was taken in the date order of receipt. X Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-443

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls point of view, this NDA is approvable. The NDA may be approved pending the labeling issues delineated in the Labeling section of the review.

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

N/A

II. Summary of Chemistry Assessments

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

Dosage form: Tablets
Strength: 0.625 mg, and 1.25 mg
Route of Administration: Oral

Description:
ENJUVIA™ tablets contains a drug substance mixture which is composed of sodium sulfate esters of 10 different estrogen compounds and the following excipients, lactose monohydrate NF, hyoxypropyl methylcellulose — USP, colloidal silicon dioxide NF, magnesium stearate NF, ascorbyl palmitate NF, butylated hydroxyanisol NF, and edetate disodium dihydrate USP. The film coating excipients include [ ] opadry clear [ ] opadry color [ ] and purified water USP. The drug product is manufactured from drug substance obtained from [ ] using [ ] processes. Drug product from two manufacturers [ ] is included and both manufacturers are acceptable. Following [ ] at [ ] of the drug product is performed by [ ] The sponsor proposes to store the drug product at controlled room temperature (25°C/60% RH) and based on the stability data provided, the following expiration dating period is granted.
12 months for foil/foil blister packages of 0.625 mg and 1.25 mg Enjuvia tablets.
24 months for HDPE bottles of 0.625 mg and 1.25 mg Enjuvia tablets.
[ ]
[ ]

The tradename, ENJUVIA™, has been accepted by OPDRA, and adequate chemistry information is presented in the labeling and labels of the primary as well as the secondary packaging. In addition, the established name, synthetic conjugated estrogens, B, is consistent with a previously approved product and also determined to be acceptable by the Labeling and Nomenclature Committee (LNC).

[redacted] is the manufacturer and supplier of the drug substance. A letter of authorization has been provided to Endeavor Pharmaceuticals Inc. to cross reference DMF [redacted] The drug substance, synthetic 10-component conjugated estrogen (CE10) contains 10 estrogenic compounds which are present as the sodium sulfate esters. The drug substance characterization includes identification and acceptance criterion for each compound, limits of free steroids, water content and microbial limit tests. The three major estrogenic compounds in CE10 are sodium estrone sulfate [redacted] sodium equilin sulfate [redacted] and sodium 17α-dihydroequilin sulfate [redacted] The total of sodium estrone sulfate, sodium equilin sulfate and sodium 17α-dihydroequilin sulfateis [redacted] of the labeled content of conjugated estrogens. The other compounds are the sodium sulfate esters of 17α-estradiol, 17β-estradiol, 17α-dihydroequilin, 17β-dihydroequilin, $\Delta^{8,9}$-dehydroestrone, Equilenin, 17α-dihydroequilenin and 17β-dihydroequilenin. The proposed retest period of the drug substance of [redacted] when stored at 8-15°C, is acceptable.

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

For treatment of moderate-to-severe vasomotor symptoms associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. [redacted] Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

Recommended storage conditions for the drug product is 25°C (77°F); excursions are permitted are permitted to 15-30°C (59°-86°F) [USP Controlled Room Temperature]. The expiration dating period for different dosage forms and packages granted are shown below.

[redacted]

12 months for foil/foil blister packages of 0.625 mg and 1.25 mg Enjuvia tablets.
24 months for HDPE bottles of 0.625 mg and 1.25 mg Enjuvia tablets.

C. Basis for Approvability or Not-Approval Recommendation

From chemistry, manufacturing, and controls point of view, this NDA may be approved pending final labeling. The CMC labeling issues pertaining to the physician insert and the container/carton labels are delineated in the Labeling section of the review. These issues were previously communicated to the sponsor on April 17, 2003 and a response is currently pending. However, the sponsor has addressed all other CMC deficiencies noted during the review cycle.

The sponsor's submission of amendment #012 (04-Oct-2002) includes the updated stability information. Amendment #013 (10-Oct-2002) includes DMF reference letters of authorization from suppliers associated with the manufacturing and packaging [ ] of ENJUVIA™ Tablets, which were not sent with the original submission. Amendment #016 (05-Dec-2002) includes a response to the deficiencies sent to the sponsor on November 8, 2002. Amendment #20 (7-Feb-2003) contains meeting minutes of T-con dated January 13 and 15, 2003 and an update of the drug product acceptance criteria. Some major issues with stability of the drug product, dissolution specification were resolved later. The stability data were incorrectly reported and following a T-con (dated 13-Jan-2003), the sponsor submitted updated stability data (amendment #021 dated 11-Feb-2003). However, the sponsor's justification of the out-of-specification results was determined to be unacceptable. The sponsor submitted amendment #23 dated February 28, 2003 to clarify the discrepancies in amendment #21. The amendment #25 (dated 20-Mar-2003) and amendment #28 (dated 2-Apr-2003) contain stability data for statistical analysis in SAS format. The sponsor submitted amendment #26 in response to a T-con on March 18, 2003 to provide more information on the HPLC method used for the release of drug product and stability testing. The sponsor submitted amendment #27 on March 27, 2003 that contain package insert and samples of proposed labeling for Enjuvia tablets. The dissolution acceptance criteria, updated stability specifications and expiration dating period were discussed with the sponsor during a T-con on April 15, 2003 and the issues were finalized on April 21, 2003 (Amendment #30). Some of the major issues raised during review of this NDA are discussed below.

- Drug product impurity profiles did not contain specified and unspecified impurities. Specified impurities [ ] were added to the drug product specifications following ICH guidelines. These [ ] were identified and they are [ ] respectively. The sponsor proposed a total impurities acceptance criterion of NMT – but based on the stability results it was reduced to —
- Major deficiencies were noted in the stability data. The sponsor had to update the stability data multiple times to correct the data and to update in an acceptable format. The stability data for the blister package configuration had problems with total related substances and dissolution and thus, only 12 months of expiration dating period is granted for [ ] 1.25 mg dosage form. The HDPE bottle packaging showed better stability and a 24 month expiration dating period is granted for 0.625 mg and 1.25 mg dosage form based on statistical analysis. The expiration dating period for [ ]
- The Office of Compliance issued a 'Withhold" recommendation for the NDA based on a 'FDA form 483' issued to one of the contract manufacturers for the drug product [ ] The issue was mainly on the HPLC method for impurities/degradants used during release and stability testing of the drug product. I reviewed the sponsor's response to the 483 letter and recommended to the Office of Compliance that the response to the deficiency noted for the HPLC method was acceptable based on the nature of the product and the reliability of the method.
- The product contains 10 synthetic estrogenic substances and in the original submission all 10

components were not listed in the identification tests for the release specifications. The sponsor responded by including all ten compounds in the release specifications and also documented by including chromatograms. The lower limits of some (17α-dihydroequilenin, 17β-dihydroequilenin, equilenin sulfate, 17β-estradiol sulfate and $\Delta^{8,9}$-dehydroestrone) estrogen substances were not initially specified in the drug product specifications, but were later included based on the batch data.

- The dissolution acceptance criteria were initially too wide and tightened based on batch analysis and stability data. In addition, the sponsor proposed to have different acceptance criteria for release and stability. However, finally the sponsor agreed to use the same acceptance criteria for release and stability.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/S. K. De, Ph.D.
HFD-580/D. T. Lin, Ph.D.

C. CC Block

HFD-580/Division File/NDA 21-343
HFD-580/S. K. De, Ph.D.
HFD-580/D. T. Lin, Ph.D.
HFD-580/GLyght

90 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

David T. Lin
4/22/03 04:42:50 PM
CHEMIST
Signing for Swapan De.

David T. Lin
4/22/03 04:46:52 PM
CHEMIST
I concur.