

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-609

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW



NDA 21-609

ENJUVIATM TABLETS
(Synthetic Conjugated Estrogens, B)

ENDEAVOR PHARMACEUTICALS INC.

SWAPAN K. DE

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



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Chemistry Review Data Sheet

1. NDA 21-609
2. REVIEW # 1
3. REVIEW DATE: 17-APRIL-2003(revised)
4. REVIEWER: Swapan K. De

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

See Chemistry Review #1 for NDA 21-443

Document Date

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



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Chemistry Review Data Sheet

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: 0.3 mg, 0.45 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

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

☐ SPOTS product – Form Completed
☒ 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 17 α -dihydroequilin sulfate
sodium 17 α -estradiol sulfate
sodium 17 β -estradiol sulfate
sodium 17 α -dihydroequilin sulfate
sodium 17 β -dihydroequilin sulfate
sodium $\Delta^{8,9}$ -dehydroestrone sulfate
sodium equilenin sulfate
sodium 17 α -dihydroequilenin sulfate
sodium 17 β -dihydroequilenin. sulfate



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Chemistry Review Data Sheet

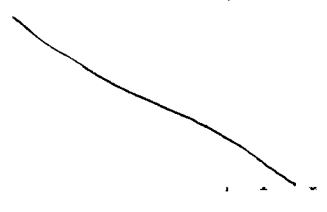
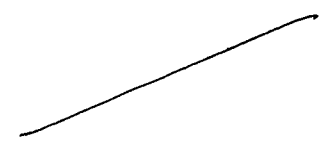
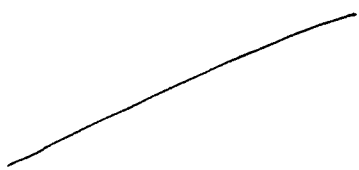
see Chemistry Review for structures (Drug Substance Section)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE ^D	COMMENTS
1	II			1	Not adequate Adequate	10/16/02 01/21/03	Reviewed by S.K.De
1	III			3	Adequate	9/15/00	Reviewed by D.N. Klein
1	III			3	Adequate	9/19/00	Reviewed by Sharon Kelly
1	III			3	Adequate	9/19/96	Reviewed by N. Ya
1	III			3	Adequate (also see Review #3)	8/27/02 (Review #3 dated 12/31/99)	Reviewed by S. Zimmerman
1	III			3	Adequate	1/10/01	Reviewed By J.D. Vidra
1	III			3	Adequate	8/3/01	Reviewed By S.P. Peri

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—	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 —**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.



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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 for NDA 21-443.

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

N/A

II. Summary of Chemistry Assessments

This NDA is an administrative split of NDA 21-443 and only refers to the 0.3 mg and 0.45 mg dosage strength drug products. However, the complete CMC review for all 4 dosage strength drug products (0.3, 0.45, 0.625 and 1.25 mg) can be found in the review for NDA 21-443.

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

Dosage form: Tablets

Strength: 0.3 mg, 0.45 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, _____ colloidal silicon dioxide NF, magnesium stearate NF, ascorbyl palmitate NF, butylated hydroxyanisole NF, and edetate disodium dihydrate USP. The film coating excipients include _____

_____ and purified water USP. The drug product is manufactured from drug substance obtained from _____ using _____ Drug product from two manufacturers _____ is included and both manufacturers are acceptable. Following packaging at _____ release testing and stability testing of the drug product is performed by (_____). The sponsor proposes to store the drug product at controlled



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Executive Summary Section

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.

12 months for both foil/foil blisters and HDPE bottles of 0.45 mg Enjuvia tablets.

9 month for foil/foil blisters and 18 month for HDPE bottles of 0.3 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).

_____, the manufacturer and supplier of the drug substance. A letter of authorization has been provided to Endeavor Pharmaceuticals Inc. to cross reference DMF _____. 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 (52.5-61.5%), sodium equilin sulfate (22.5-30.5%) and sodium 17 α -dihydroequilin sulfate (13.5-19.5%). The total of sodium estrone sulfate, sodium equilin sulfate and sodium 17 α -dihydroequilin sulfate is 90-110% of the labeled content of conjugated estrogens. The other compounds are the sodium sulfate esters of 17 α -estradiol, 17 β -estradiol, 17 α -dihydroequilin, 17 β -dihydroequilin, $\Delta^{8,9}$ -dehydroestrone, Equilenin, 17 α -dihydroequilenin and 17 β -dihydroequilenin. The proposed retest period of the drug substance of _____, 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. An initial dose of 0.625 mg daily is recommended with titration up to 1.25 mg. 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.

9 month for foil/foil blisters and 18 month for _____ bottles of 0.3 mg Enjuvia tablets.

12 months for both foil/foil blisters and _____ bottles of 0.45 mg Enjuvia tablets.

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

24 months for _____ bottles of 0.625 mg and 1.25 mg Enjuvia tablets.



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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 (bottles and foil-foil blisters) 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 compounds 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 0.625 mg and 1.25 mg dosage form. The _____ 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 0.3 mg tablets were granted only a 9 month and 18 month expiration dating period for the blister and _____ packages, respectively. The expiration dating period is 12 months for the 0.45 mg tablets packaged in both the blister and _____ packages.

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- 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 (17 α -dihydroequilenin, 17 β -dihydroequilenin, equilenin sulfate, 17 β -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)(5) 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 05:38:58 PM
CHEMIST
Signing for Swapan De.

David T. Lin
4/22/03 05:42:19 PM
CHEMIST
I concur.