CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-788
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	929/08
PRODUCT:	Synthetic conjugated estrogens, vaginal cream
INTENDED CLINICAL POPULATION:	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause
SPONSOR:	Duramed Pharmaceuticals Inc.
DOCUMENTS REVIEWED:	Label
REVIEW DIVISION:	Division of Reproductive and Urologic Products (HFD-580)
PHARM/TOX REVIEWER:	Krishan L. Reviewer, D.V.M., Ph.D
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	George Lyght

Date of review submission to Division File System (DFS): 11-13-08

Recommendations on Labeling: Pharmacology/Toxicology review of the original NDA submission dated 6-25-04 was entered in DFS on 2-24-05. The label is acceptable from the P/T prospective.

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/s/

Krishan L. Raheja
11/13/2008 01:26:53 PM
PHARMACOLOGIST

Lynnda Reid
11/13/2008 02:42:10 PM
PHARMACOLOGIST
I concur that 1) nonclinical data support an approval action, and 2) labeling is acceptable.

Memo to the file

Date: 9-10-08

NDA #: 21788

Date of submission: 6-25-04

Sponsor: Duramed Pharmaceuticals, Inc.

Drug Product: Cenestin vaginal cream 0.625%

Indication: Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Subject: Final Duramed Label

The original NDA submitted dated 6-25-04 was reviewed and entered in DFS on 2-4-05. From the Pharm-Tox perspective nothing has changed from the original review cycle and the original review is sufficient.

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T Supervisor: Lynnda Reid, Ph.D.

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/s/

Krishan L. Raheja
9/10/2008 12:03:55 PM
PHARMACOLOGIST

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-788
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	6/25/04
PRODUCT:	Cenestin vaginal cream 0.625%
INTENDED CLINICAL POPULATION:	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause
SPONSOR:	Duramed Pharmaceuticals Inc.
DOCUMENTS REVIEWED:	Nonclinical pharmacology and toxicology, Electronic file Item 5
REVIEW DIVISION:	Division of reproductive and urologic Drug Products (HFD-580)
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Lynnda Reide, Ph.D.
DIVISION DIRECTOR:	Dan Shames, M.D.
PROJECT MANAGER:	George Lyght

Date of review submission to Division File System (DFS): 2-24-05

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Pharmacology recommends approval of NDA 21-788 for Cenestin vaginal cream 0.625 mg/g for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

B. Recommendation for nonclinical studies: Per agreement with the Division, the Sponsor has not conducted any non-clinical pharmacology or toxicology studies for the synthetic conjugated estrogens, A formulation. Pursuant to Section 505(b)(2), the Sponsor therefore, has requested the Agency to refer to the reference-listed conjugated estrogen cream products regarding the non-clinical pharmacology, ADME and toxicology to satisfy NDA requirements for non-clinical assessment of the Cenestin (synthetic conjugated estrogens, A) vaginal cream, 0.625%. Furthermore the non-clinical pharmacology and toxicology of synthetic conjugated estrogens is expected to be similar to other short-acting oral estrogen, information, which has been incorporated in the Estrogen Class Labeling.

C. Recommendations on labeling: Labeling will be similar to Cenestin (0.3 mg, 0.45 mg, 0.625 mg and 1.25 mg strengths) tablets as daily oral regimen for the treatment of vulvar and vaginal atrophy associated with the menopause, approved under NDA 20-992.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Estrogenic effects. All nonclinical studies are referenced to approved NDA 20-992 for Cenestin (synthetic conjugated estrogens, A) tablets.

B. Pharmacologic activity: estrogenic

C. Nonclinical safety issues relevant to clinical use: Safety issues are the same as for other estrogen products. The pharmacological class of this product is that of a short-acting estrogen in a non-liquefying cream base.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-788
Review number: 1
Sequence number/date/type of submission: 000/6-25-04/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Duramed Pharmaceuticals Inc.
Manufacturer for drug substance: DPT Laboratories, San Antonio, TX 78209

Reviewer name: Krishan L. raheja, D.V.M., Ph.D
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: 1-16-05

Drug:

Trade name: Cenestin (synthetic conjugated estrogens, A) cream
Generic name: Cenestin vaginal cream 0.0625 mg/g
Chemical name: a blend of 8 estrogenic compounds listed under drug composition

Relevant INDs/NDAs/DMFs: IND 53,731, IND 65,505; NDA 20-992 (Cenestin Tablets for oral administration available in 0.3 mg, 0.34 mg, 0.625 mg, 0.9 mg and 1.25 mg strengths of synthetic conjugated estrogens); DMF# — b(4)

Drug class: estrogen

Intended clinical population: menopausal women

Clinical formulation: The active ingredients of Cenestin vaginal cream are the same as for FDA approved Cenestin (synthetic conjugated estrogens, A) tablets.

The active ingredients of Cenestin (synthetic conjugated estrogens, A) Vaginal Cream are blend of 9 synthetic estrogenic substances. These estrogenic substances include sodium estrone sulfate, sodium equilin sulfate, sodium 17a-dihydroequilin sulfate, sodium 17a-estradiol sulfate, sodium 17B-dihydroequilin sulfate, sodium 17a-dihydroequilenin sulfate, sodium 17B-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17B-estradiol sulfate.

The inactive ingredients for the Cenestin tablet and Cenestin vaginal cream differ as follows:

The tablet inactive ingredients consist of ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pre-gelatinized starch, titanium dioxide, and triethyl citrate.

The inactive for the Cenestin vaginal cream in a non-liquefying base are: benzyl alcohol, – wax, cetyl alcohol, cetyl esters wax, glycerin, glyceryl monostearate, light mineral oil, methyl stearate, propylene glycol monostearate, sodium hydroxide, sodium lauryl sulfate and sodium phosphate dibasic anhydrous. b(4)

Route of administration: intravaginal twice a week

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-788 are owned by Duramed Pharmaceuticals, Inc. or are data for which Duramed Pharmaceutical Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-788 that Duramed Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Duramed Pharmaceuticals Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-788.

Studies reviewed within this submission: none submitted

2.6.2 PHARMACOLOGY

Referred to NDA 20-992 for Cenestin (synthetic conjugated estrogens, A) tablets with 0.3 mg, 0.45 mg, 0.625 mg and 1.25 mg strengths approved for similar indications as for present NDA 21-788.

2.6.3 PHARMACOLOGY TABULATED SUMMARY :

None submitted

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

As shown in table below, the systemic exposure to unconjugated estrogens was significantly higher with FDA approved and marketed Cenestin tablets compared to Cenestin vaginal cream when administered similar doses:

PK parameters of unconjugated estrogens following a dose of 2 x 0.625 mg Cenestin tablets in healthy postmenopausal women under fasting conditions:

Estrogen	C_{max} (pg/ml) CV%	T_{max} (h) CV%	AUC_{0-72hr} (pg.hr/ml) CV%
Baseline adjusted free estrone	84.5 (41.7)	8.25 (35.6)	1749 (43.8)
Equilin	45.6 (47.3)	7.78 (28.8)	723 (67.9)

Healthy postmenopausal women under fasting conditions were enrolled.

PK parameters for unconjugated estrogens following twice-weekly 2 gm Cenestin cream containing 1.25 mg conjugated estrogens

Estrogen	C_{max} (pg/ml) CV%	T_{max} (h) CV%	AUC_{0-72hr} (pg.hr/ml) CV%
Baseline adjusted free estrone	35.7 (31.2)	7.3 (32.7)	637.3(49.9)
Equilin	9.6 (19.5)	6.4 (34.8)	97.6 (52.4)

Note: All PK parameters were determined from steady state observations.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NONE SUBMITTED

2.6.6 TOXICOLOGY

none submitted

2.6.7 TOXICOLOGY TABULATED SUMMARY

None submitted

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: No new preclinical toxicology studies were required. All pharmacology and toxicology information was referred to studies submitted for the approval of NDA 20-992 for Cenestin (synthetic conjugated estrgens, A) tablets. Both Cenestin (synthetic conjugated estrogens, A) tablets and Cenestin (synthetic conjugated estrogens, A) vaginal cream the same active ingredients i.e., both are formulated with a blend of 9 estrogenic compounds. Both the Cenestin tablets and Cenestin Cream have the same therapeutic indication.

The inactive ingredients are different for Cenestin tablets and Cenestin vaginal cream, however, all are compendial or are listed in FDA Inactive Ingredients list.

No toxicological concern is also based on the observation that the systemic exposure to unconjugated estrogens is significantly higher with the approved Cenestin tablets compared to Cenestin vaginal cream given equivalent doses.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of NDA 21-788 for Cenestin (synthetic conjugated estrogens, A) cream.

Suggested labeling: Labeling will be similar to that for NDA 20-992 for Cenestin (synthetic conjugated estrogens, A) tablets.

APPENDIX/ATTACHMENTS

none

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/s/

Krishan L. Raheja
2/24/05 10:32:57 AM
PHARMACOLOGIST

Lynnda Reid
3/1/05 07:06:35 PM
PHARMACOLOGIST