CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

CHEMISTRY REVIEW(S)

NDA 21-788

Synthetic Conjugated Estrogens, A
Vaginal Cream 0.625 mg/g

Duramed Pharmaceuticals, Inc.

Bogdan Kurtyka, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

CMC REVIEW OF NDA 21-788
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

CMC Review Data Sheet

1. NDA 21-778

2. REVIEW #: 3

3. REVIEW DATE: 26-NOV-2008

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: CMC Review #2

Submission(s) Reviewed	Document Date
Amendment	10-SEP-2008
Amendment	29-JUL-2008
Amendment	09-JUN-2008
Complete Response	12-MAR-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Class I resubmission – labeling update	26-SEP-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Duramed Pharmaceuticals, Inc.
Address:	One Belmond Avenue, 11th Floor Bala Cynwyd, PA 19004
Representative:	Charlene A. Bruno
Telephone:	(610) 747-2737

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name: Synthetic conjugated estrogens, A
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Estrogen, treatment of moderate to severe vasomotor symptoms of vulvar and vaginal atrophy associated with

menopause.

11. DOSAGE FORM: Vaginal cream

12. STRENGTH/POTENCY: 0.625 MG/G

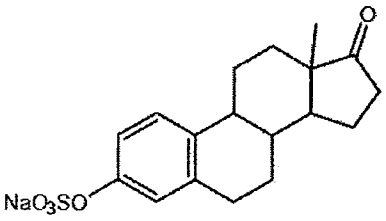
13. ROUTE OF ADMINISTRATION: Vaginal

14. Rx/OTC DISPENSED: __√__Rx ____OTC

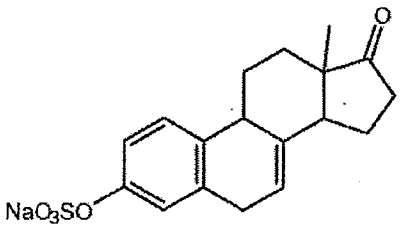
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

16. CHEMICAL NAMES, STRUCTURAL FORMULAE, MOLECULAR FORMULAE, MOLECULAR WEIGHTS:



Sodium estrone sulfate
$C_{18}H_{21}O_5NaS$
MW = 372.42 g/mole



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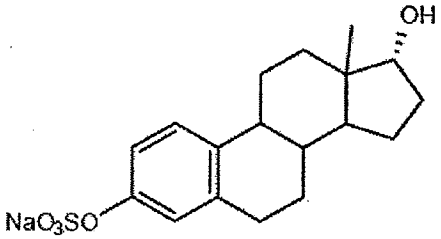

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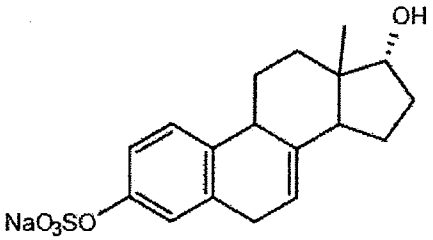

Sodium 17α-dihydroequilin sulfate
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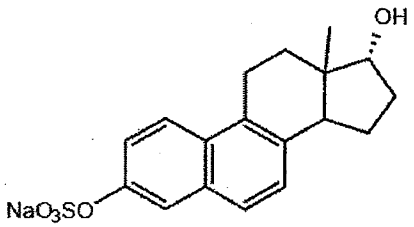
CMC Review Data Sheet



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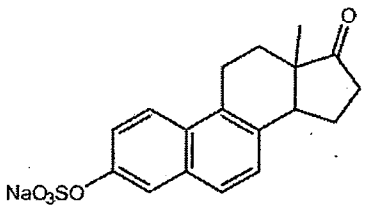

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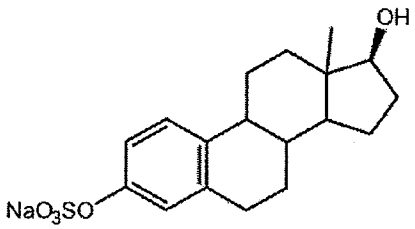

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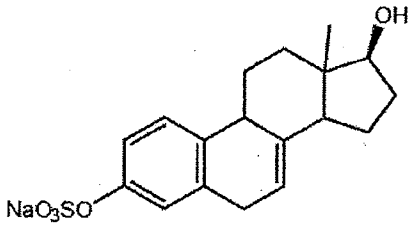

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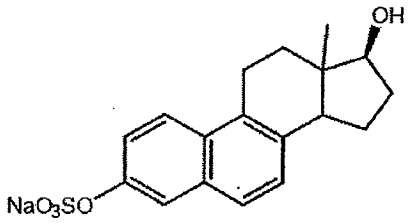

Sodium 17β-dihydroequilenin sulfate
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MW = 370.41 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	01-Apr-2008	
					Adequate	08-May-2008	
					Adequate	11-Mar-2005	See CMC Review #1 for NDA 21-788

b(4)

CMC Review Data Sheet

[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
None		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	27-MAY-2008	Bogdan Kurtyka
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	Established name used instead of trade name		
EA	Categorical exclusion granted		See Review #1
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The CMC Review for NDA 22-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities are in compliance with cGMP and labels have required information.
Therefore, from a CMC perspective, this NDA is recommended for "Approval".

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

None.

II. Summary of CMC Assessments

NDA 21-788 was originally submitted on 25-JUN-2004. In the original submission the drug product name was Cenestin® (synthetic conjugated estrogens, A) vaginal cream. The application was found "Approvable" from a CMC perspective, pending the submission of acceptable container/carton labeling. The overall "Not Approved" letter was issued on 25-APR-2005.
On 12-MAR-2008 Duramed submitted a complete response that included new clinical and PK study results, labeling, and new CMC information.
When Review #2 was completed, labeling issues were still pending. The labeling update is the subject of this review.

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

See Review #2.

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

See Review #2.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of Synthetic Conjugated Estrogens, A Vaginal Cream over the proposed shelf life (18 months) when stored as labeled.
Adequate controls for raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity, strength, quality, and

purity of the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration date. Labeling is acceptable.
This NDA is recommended for "Approval" from a CMC perspective.

III. Administrative

A. Reviewer's Signature: *(See appended electronic signature page)*

Bogdan Kurtyka

B. Endorsement Block: *(See appended electronic signature page)*

Moo-Jhong Rhee, Branch Chief, Branch #3,
Division 2, ONDQA

C. CC Block: entered electronically in DFS

APPEARS THIS WAY
ON ORIGINAL

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Bogdan Kurtyka
11/26/2008 04:06:56 PM
CHEMIST

Moo-Jhong Rhee
11/26/2008 04:09:16 PM
CHEMIST
Chief, Branch III

NDA 21-788

Bijuva®
(Synthetic Conjugated Estrogens, A)
Vaginal Cream 0.625 mg/g

Duramed Pharmaceuticals, Inc.

Bogdan Kurtyka, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

CMC REVIEW OF NDA 21-788
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

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ON ORIGINAL

CMC Review Data Sheet

1. NDA 21-778

2. REVIEW #: 2

3. REVIEW DATE: 11-SEP-2008

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: CMC Review #1

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10-SEP-2008
Amendment	29-JUL-2008
Amendment	09-JUN-2008
Complete Response	12-MAR-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Duramed Pharmaceuticals, Inc.
Address:	One Belmond Avenue 11th Floor Bala Cynwyd, PA 19004
Representative:	Charlene A. Bruno
Telephone:	(610) 747-2737

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bijuva® Vaginal Cream
b) Non-Proprietary Name: Synthetic conjugated estrogens, A
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Estrogen, treatment of moderate to severe vasomotor symptoms of vulvar and vaginal atrophy associated with menopause.

CMC Review Data Sheet

11. DOSAGE FORM: Vaginal cream

12. STRENGTH/POTENCY: 0.625 MG/G

13. ROUTE OF ADMINISTRATION: Vaginal

14. Rx/OTC DISPENSED: __√__Rx ____OTC

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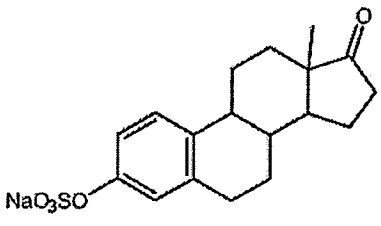

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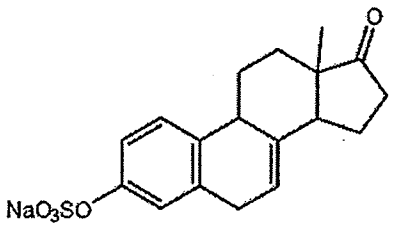

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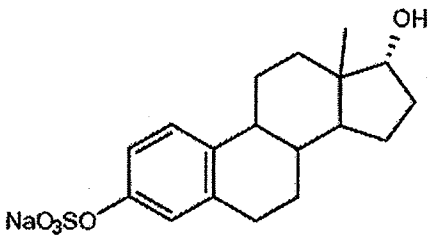

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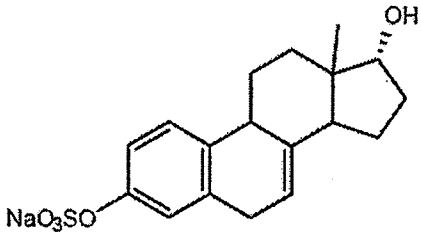

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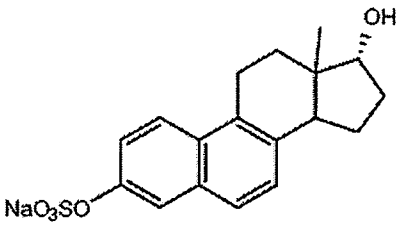

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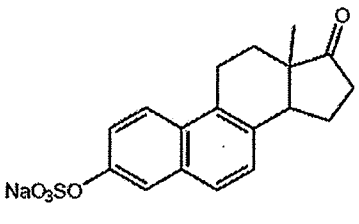

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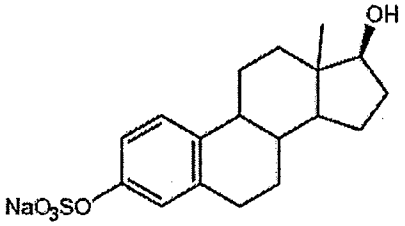

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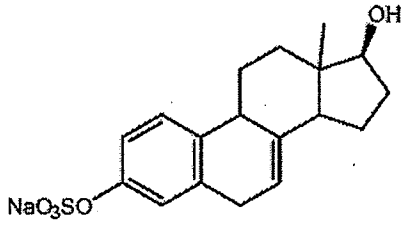

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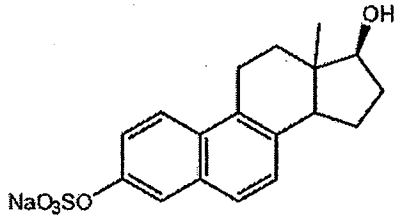

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	01-Apr-2008	
				1	Adequate	08-May-2008	
				3	Adequate	11-Mar-2005	See CMC Review #1 for NDA 21-788

b(4)

CMC Review Data Sheet

[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
None		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable		Bogdan Kurtyka
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	Trade name not approved, under negotiations	19-AUG-2008	Richard Abate
EA	Categorical exclusion granted		See Review #1
Microbiology	N/A		

The CMC Review for NDA 22-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. At the time this review is written, the trade name is still being negotiated with the applicant. However, from a CMC perspective, this NDA is recommended for "Approval".

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

None.

II. Summary of CMC Assessments

NDA 21-788 was originally submitted on 25-JUN-2004. In the original submission the drug product name was Cenestin® (synthetic conjugated estrogens, A) vaginal cream. The application was found "Approvable" from a CMC perspective, pending the submission of acceptable container/carton labeling. The overall "Not Approved" letter was issued on 25-APR-2005.
On 12-MAR-2008 Duramed submitted a complete response that included new clinical and PK study results, labeling, and new CMC information. This re-submission is the subject of this review.

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

(1) Drug Substance

The drug substance is synthetic conjugated estrogens, A, manufactured by —— . It is used in approved CENESTIN (synthetic conjugated estrogens, A) tablets. All Chemistry, Manufacturing, and Controls information for the drug substance has been cross-referenced to DMF —— This DMF was reviewed and was determined to be adequate in support of this NDA. b(4)

(2) Drug Product

BIJUVA® (synthetic conjugated estrogens, A) vaginal cream is a semisolid formulation intended for treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. The proposed strength is 0.625 mg/g.

BIJUVA consists of the active pharmaceutical ingredient (synthetic conjugated estrogens, A), along with the following inactive excipients: —— wax, benzyl alcohol, cetyl alcohol, cetyl esters wax, glycerin, glyceryl monostearate, light mineral oil, methyl stearate, propylene glycol monostearate, purified water, sodium hydroxide, sodium lauryl sulfate, and sodium diphosphate dibasic. b(4)
The drug product is manufactured at DPT Laboratories, Inc. (San Antonio, TX).
Acceptable specifications have been provided to ensure product quality at release.
Once released, the drug product will be packaged in 30-gram aluminum tubes containing ——— The tubes will then be co-packaged with vaginal applicators to be used for product application. The relevant DMFs for the container/closure system (including the tubes, ——— have been reviewed and determined to be adequate for this drug product.
Based on the stability data provided in this NDA, an eighteen month expiry has been granted for storage at 25°C/60% RH (controlled room temperature).

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

BIJUVA is administered intravaginally. One gram (1 full applicator) is applied daily for one week followed by 1 gram (1 full applicator) twice a week.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of BIJUVA® (synthetic conjugated estrogens, A) vaginal cream over the proposed shelf life (18 months) when stored as labeled.
Adequate controls for raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity, strength, quality, and purity of the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration date.
Although the trade name is still under negotiations, labeling is acceptable.
This NDA is recommended for "Approval" from a CMC perspective.

III. Administrative

A. Reviewer's Signature: *(See appended electronic signature page)*

Bogdan Kurtyka

B. Endorsement Block: *(See appended electronic signature page)*

Moo-Jhong Rhee, Branch Chief, Branch #3,
Division 2, ONDQA

C. CC Block: entered electronically in DFS

28 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Bogdan Kurtyka
9/11/2008 03:10:50 PM
CHEMIST

Donna Christner
9/11/2008 03:25:27 PM
CHEMIST
I concur for Dr. Moo-Jhong Rhee in his absence.
Hard-copy of the review was signed by him
on 11-Aug-2008 and minor updates made after that
date.