CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-840

CHEMISTRY REVIEW(S)

NDA 21-840

SEASONIQUE®
(levonorgestrel/ethinyl estradiol tablets) 0.15 mg/0.03 mg and (ethinyl estradiol tablets) 0.01 mg

Duramed Pharmaceuticals, Inc.

Division of Reproductive and Urologic Drug Products
(DRUDP, HFD-580)

Reviewed By:
Sarah C. Pope, Ph.D.
Pre-Marketing Assessment Division III/Branch V
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-840

2. REVIEW #2

3. REVIEW DATE: 12-MAY-2006

4. REVIEWER: Sarah C. Pope, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	10-AUG-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (Class 1 response)	24-MAR-2006
Revised C/C/labeling and PI/PPI	09-MAY-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Duramed Pharmaceuticals, Inc.
Address:	5040 Lester Road Cincinnati, Ohio 45213
Representative:	Joe Carrado, M.Sc., R.Ph.
Telephone:	(610)-747-2600

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: SEASONIQUE
   b) Non-Proprietary Name (USAN): (levonorgestrel/ethinyl estradiol tablets)

Chemistry Review Data Sheet

(ethinyl estradiol tablets)

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: estrogen/progestin for contraceptive use

11. DOSAGE FORM: Tablets

12. STRENGTHS/POTENCIES: 0.15 mg/0.03 mg levonorgestrel/ethinyl estradiol
0.01 mg ethinyl estradiol

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

_____SPOTS product

__X____Not a SPOTS product

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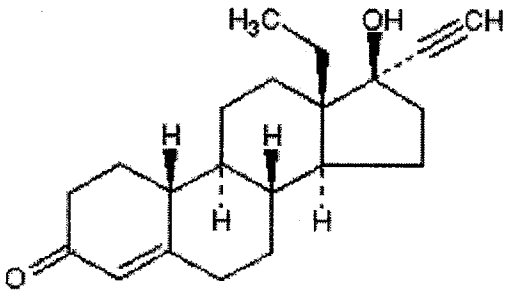
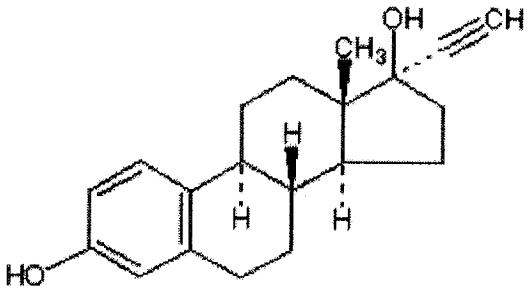
16. CHEMICAL NAMES, STRUCTURAL FORMULAE, MOLECULAR FORMULAE, MOLECULAR WEIGHTS:



Levonorgestrel
$C_{21}H_{28}O_2$
MW = 312.45 g/mole



Ethinyl estradiol
$C_{20}H_{24}O_2$
MW = 296.40 g/mole

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (no changes from CMC Review #1):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					Adequate*	31-MAY-2005	Reviewed by Dr. S. Pope
					Adequate	16-DEC-2004	Reviewed by Dr. S. Dhanesar
					Adequate	02-SEP-2003	Reviewed by Dr. N. Takiar
					Adequate	11-MAR-2002	Reviewed by Dr. D. Klein
					Adequate	14-JUN-2002	Reviewed By Dr. L. Rocca
					Adequate	27-SEP-2000	Reviewed by Dr. R. Lostritto
					Adequate	21-JAN-2004	Reviewed by Dr. D. Matecka
					Adequate	02-SEP-2003	Reviewed by Dr. B. Wu

* See attached Chemistry Review for details.

[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
Original IND	IND 63,735	Active since 30-NOV-2001

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	03-JAN-2005	S. Adams (see CMC Review #1)
Biopharm	Dissolution criteria acceptable.	10-AUG-2005	Dr. J. Bullock (see CMC Review #1)
LNC	N/A	N/A	N/A
Methods Validation	Acceptable.	30-JUN-2005	Dr. S. Pope (see CMC Review #1)
ODS	Original DMETS comments Second cycle DMETS comments DMETS comments conveyed Revised C/C labels received	21-OCT-2004 14-APR-2006 01-MAY-2006 09-MAY-2006	F. Duffy F. Duffy
EA	Categorical exclusion claimed.	11-MAR-2005	Dr. S. Pope (see CMC Review #1)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-840

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this NDA can be approved.

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)

This second-cycle Chemistry Review addresses only labeling (PI/PPI and Container/Carton) and the Sponsor's proposal for a post-approval filing mechanism. All other information may be found in the first-cycle CMC review (10-AUG-2005). A discussion of the Sponsor's proposed post-approval filing strategy is located in the "Drug Substance – Regulatory Specifications and Analytical Procedures" section of this review.

Drug Product

SEASONIQUE® (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets) consists of two tablet formulations. The first 84 tablets are combination tablets containing levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg). The subsequent 7 tablets contain ethinyl estradiol as the sole active pharmaceutical ingredient. This NDA proposes the combination of both tablet types in a 91-day dosing regimen for the prevention of pregnancy.

The proposed LVG/EE tablet is nearly identical in formulation and manufacture to that of the currently approved SEASONALE active tablet. The tablets are different only in color coating, as well as debossing code. The EE tablet is not parallel to the SEASONALE product, as the EE tablet contains an API (and is therefore not chemically considered a placebo). There is no placebo tablet used in SEASONIQUE.

The container/closure system for Seasonique is as follows: one carton contains a full physician's package insert and three aluminum pouches; each pouch contains a patient insert, a dessicant pack, and a plastic dispenser; one tablet dispenser opens (like a book) to present three plastic leaves, each leaf containing one blister card; the top two blister cards each contains 28 blue-green LVG/EE (combination) tablets, and the third blister card contains 28 blue-green LVG/EE tablets followed by 7 yellow EE (single entity) tablets.

The drug product is manufactured by Barr Laboratories. Acceptable specifications have been provided to ensure product quality at release.

Once released, the drug product will be packaged in a 91-day blister pack. The relevant DMFs for the container/closure system have been reviewed and determined to be adequate for this drug product.

Based on the stability data provided in the first review cycle for this NDA, a [redacted] expiry has been granted for storage at [redacted] (controlled room temperature).

Drug Substance (levonorgestrel):
Levonorgestrel is a compendial (USP) drug substance. All of the pertinent CMC information is cross-referenced to DMF [redacted] This DMF was reviewed and was determined to be adequate in support of this NDA (see Chemistry Review #10 dated 31-MAY-2005 by Dr. S. Pope).

Drug Substance (ethinyl estradiol):
Ethinyl estradiol is a compendial (USP) drug substance. All of the pertinent CMC information is cross-referenced to DMF [redacted] This DMF was previously reviewed and was determined to be adequate (see Chemistry Review #15 dated 16-DEC-2004 by Dr. S. Dhanesar).

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

The drug product consists of 91 tablets for oral administration. There are two tablet types (0.15/0.03 mg LVG/EE and 0.01 mg EE). The overall dosing regimen includes the administration of the combination (LVG/EE) tablet for 84 days, followed by administration of the single-entity (EE) tablet for seven days.

C. Basis for Approvability or Not-Approval Recommendation

There are no outstanding Chemistry, Manufacturing and Controls issues for this NDA. Acceptable container/carton labels have been provided, and the proposed Package Insert and Patient Information labeling is acceptable.

III. Administrative

A. Reviewer's Signature

Sarah C. Pope, Ph.D., Chemistry Reviewer

B. Endorsement Block

Moo-Jhong Rhee, Ph.D., Branch Chief

C. CC Block

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Withheld Track Number: Chemistry-1

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/s/

Sarah Pope
5/12/2006 02:02:54 PM
CHEMIST

Moo-Jhong Rhee
5/12/2006 02:56:11 PM
CHEMIST
Chief, Branch III

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NDA 21-840

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2. REVIEW #1

3. REVIEW DATE: 10-AUG-2005

4. REVIEWER: Sarah C. Pope, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	28-JUL-2005
Amendment	14-JUL-2005
Amendment	15-APR-2005
Amendment	01-DEC-2004
Amendment	11-NOV-2004
Original	21-OCT-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Duramed Pharmaceuticals, Inc.

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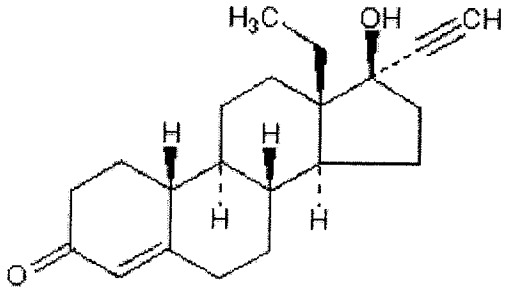

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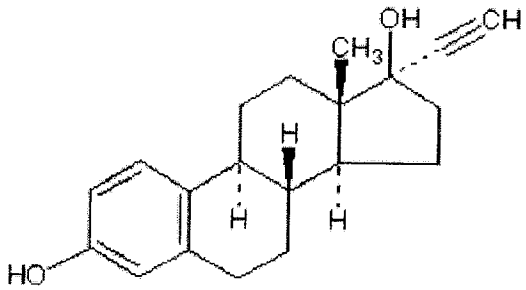

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LNC	N/A	N/A	N/A
Methods Validation	Methods will be submitted post-approval.	30-JUN-2005	Dr. S. Pope
ODS	DMETS comments pending	21-OCT-2004	F. Duffy
EA	Categorical exclusion claimed.	11-MAR-2005	Dr. S. Pope
Microbiology	N/A		

The Chemistry Review for NDA 21-840

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this NDA is approvable pending the resolution of final labeling, including the Patient Information and Physician's Package Insert, and the submission of acceptable container/carton 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

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The drug product is manufactured by Barr Laboratories. Acceptable specifications have been provided to ensure product quality at release (need Sponsor to confirm criteria for the EE tablets).

Once released, the drug product will be packaged in a 91-day blister pack. The relevant DMFs for the container/closure system have been reviewed and determined to be adequate for this drug product.

Based on the stability data provided in the first review cycle for this NDA, a [redacted] expiry has been granted for storage at [redacted] (controlled room temperature).

Drug Substance (levonorgestrel):
Levonorgestrel is a compendial (USP) drug substance. All of the pertinent CMC information is cross-referenced to DMF [redacted] This DMF was reviewed and was determined to be adequate in support of this NDA (see Chemistry Review #10 dated 31-MAY-2005 by Dr. S. Pope).

Drug Substance (ethinyl estradiol):
Ethinyl estradiol is a compendial (USP) drug substance. All of the pertinent CMC information is cross-referenced to DMF [redacted] This DMF was previously reviewed and was determined to be adequate (see Chemistry Review #15 dated 16-DEC-2004 by Dr. S. Dhanesar).

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The drug product consists of 91 tablets for oral administration. There are two tablet types (0.15/0.03 mg LVG/EE and 0.01 mg EE). The overall dosing regimen includes the administration of the combination (LVG/EE) tablet for 84 days, followed by administration of the single-entity (EE) tablet for seven days.

C. Basis for Approvability or Not-Approval Recommendation

In order for this NDA to be recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint, the following two items need to be satisfactorily resolved:

a) Acceptable container/carton labels should be submitted.
b) Acceptable final labeling, including the Physicians' Package Insert and Patient Information, should be submitted.

III. Administrative

A. Reviewer's Signature

Sarah C. Pope, Ph.D., Chemistry Reviewer

B. Endorsement Block

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader

C. CC Block

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/s/

Sarah Pope
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CHEMIST

Moo-Jhong Rhee
8/10/05 06:09:11 PM
CHEMIST
I concur