CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

CHEMISTRY REVIEW(S)

NDA 22-262

Lo Seasonique

Duramed Pharmaceuticals Inc.

Bogdan Kurtyka, Ph.D.

Review Chemist

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

CMC REVIEW OF NDA 22-262
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

CMC Review Data Sheet

1. NDA 22-262

2. REVIEW #: 1

3. REVIEW DATE: 15-SEP-2008

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	26-DEC-2007
Amendment – Environmental Assessment	27-MAR-2008
Amendment – Response to the IR Letter	06-JUN-2008
Amendment – Labeling Changes	26-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Duramed Pharmaceuticals, Inc.
Address:	One Belmond Avenue 11th Floor Bala Cynwyd, PA 19004
Representative:	Joseph A. Carrado
Telephone:	610-747-2600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lo Seasonique

b) Non-Proprietary Name: (a) Levonorgestrel/Ethinyl Estradiol tablets
(b) Ethinyl Estradiol tablets

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/Progesting for contraceptive use

11. DOSAGE FORM: Tablet, film coated CODE: 504

CMC Review Data Sheet

12. STRENGTH/POTENCY: a. Levonorgestrel 0.1mg/Ethinyl Estradiol 0.02mg
b. Ethinyl Estradiol 0.01mg

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

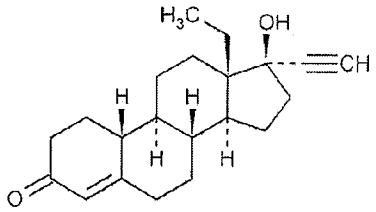
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed
__√__Not a SPOTS product

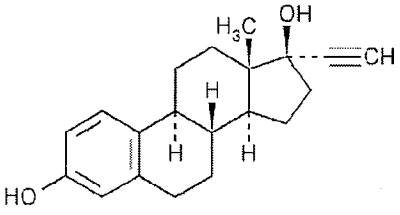
16. CHEMICAL NAMES, STRUCTURAL FORMULAE, MOLECULAR FORMULAE, MOLECULAR WEIGHTS:

Chemical Name: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-
USAN Name: Levonorgestrel
CAS Number: CAS-797-63-7
Structural Formula:



Molecular Formula: $C_{21}H_{28}O_2$
Molecular Weight: 312.4

Chemical Name: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-
USAN Name: Ethinyl Estradiol
CAS Number: CAS-57-63-6
Structural Formula:



Molecular Formula: $C_{20}H_{24}O_2$
Molecular weight: 296.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	02/22/2008	
	II			3	Adequate	02/01/2008	Reviewed to support ANDA (b) (b)
	III			1	Adequate	03/06/2008	
	III			1	Adequate	03/06/2008	
	III			3	Adequate	11/12/2007	Reviewed for all (b) (4) types

[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: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	04/14/2008	Bogdan Kurtyka
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	Pending		
EA	Categorical exclusion granted (see review)	04/15/2008	Bogdan Kurtyka
Microbiology	N/A		

The CMC Review for NDA 22-262

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. Facilities are in compliance with cGMP. Labels/labeling 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

No recommendations at this time.

II. Summary of CMC Assessments

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

(1) Drug Substance

Lo Seasonique uses two drug substances, Levonorgestrel and Ethinyl Estradiol. Both drug substances are controlled by USP monographs.
The applicant references DMF(b) (4)) for details on the description, characterization, manufacture, packaging, quality control testing, and stability of Levonorgestrel. The Letter of Authorization is provided in the application. DMF(b) (4) has been reviewed and found ADEQUATE to support this application.
The applicant references DMF(b) (4)) for details on the description, characterization, manufacture, packaging, quality control testing, and stability of Ethinyl Estradiol. The Letter of Authorization is provided in the application. DMF(b) (4) has been last reviewed on February 1, 2008 (review #20) and found ADEQUATE to support ANDA(b) (4) . Since the last review the DMF has not been updated.

(2) Drug Product

The drug product consists of two kinds of tablets. The first type of tablet contains two active drug substances, Levonorgestrel and Ethinyl Estradiol, in the amount of 0.1 mg and 0.02 mg per dosage form, respectively. The second type of tablet contains only Ethinyl Estradiol in the amount of 0.01 mg per tablet.
The drug product is a continuation of a family of approved contraceptives

manufactured by the applicant, including Seasonale and Seasonique. The combination (Levonorgestrel and Ethinyl Estradiol) tablet is a low-strength version of approved Seasonique. The Ethinyl Estradiol tablet is identical to the single component tablet of Seasonique.
Both types of tablets are manufactured (b) (4) using standard compendial excipients.
The container closure system is a pouch with 2 blister cards each containing 4 rows of 7 Levonorgestrel and Ethinyl Estradiol tablets and 1 blister card containing 4 rows of 7 Levonorgestrel and Ethinyl Estradiol tablets and 1 row of 7 Ethinyl Estradiol tablets.
Specifications include identification, assay, and content uniformity of active ingredients, dissolution, impurities, and water level.
The application includes results of 24 months long-term stability studies. There were no significant changes in any lot. The applicant has proposed an 18 month expiration date when stored at controlled room conditions.

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

The drug product should be taken orally, one Levonorgestrel and Ethinyl Estradiol tablet daily for 84 days, followed by one Ethinyl Estradiol tablet daily for 7 days.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of Lo Seasonique 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. Facilities are in compliance with cGMP.
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

38 Page(s) Withheld

__X____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Bogdan Kurtyka
9/15/2008 12:46:30 PM
CHEMIST

Moo-Jhong Rhee
9/15/2008 01:25:02 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-262
Applicant:	Duramed Pharmaceuticals, Inc.
Stamp Date:	26-Dec-2007
PDUFA Date:	26-Oct-2008
Trademark:	LoSeasonique
Established Name:	(levonorgestrel/ethinyl estradiol and ethinyl estradiol)
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Contraception
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	☐
Comments for 74-Day Letter	☐	x

Summary and Critical Issues:

A. Summary

Lo Seasonique (Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg; and Ethinyl Estradiol Tablets, 0.1 mg) are indicated for the prevention of pregnancy in women who elect to use oral contraception as a method of contraception. The dosing regimen consists of a 13 week supply. Each extended-regimen tablet dispenser contains 84 orange, round, film-coated, biconvex, unscored tablets with a debossed "b" on one side and "28" on the other (LNG/EE) and 7 yellow, round, biconvex, unscored tablets with a debossed "b" on one side and "556" on the other side (EE). Sponsor states that the Lo Seasonique LNG/EE tablets are identical to the Barr generic product Lessina (ANDA 75-803) except for color of the non-functional film coat, and that the EE tablets are identical to the marketed Seasonique formulation (NDA 21-840).

Full information on the drug substances is provided in referenced DMFs. Levonorgestrel is provided in DMF (b) (4) and Ethinyl Estradiol in DMF (b) (4)

The sponsor seeks **18 months of expiry** based on up to 24 months data at Controlled Room Temperature (CRT) (25°C/60%RH) on 4 batches on the LNG/EE tablets and 2 batches of the EE tablets. Data up to six months is available on a third batch of the EE tablets and is ongoing. Bulk product data is available through 12 months at CRT.

B. Critical issues for review

The DMFs may require review, depending on whether updates to the DMFs have been submitted since the last review.

Drug product specifications should be compared to the approved product NDA 21-840 to ensure that similar specifications are approved.

C. Comments for 74-Day Letter

There are no CMC comments for the 74-day letter.

D. Recommendation:

This NDA is fileable from a CMC perspective. A single reviewer, Bogdan Kurtyka, Ph.D., has been assigned.

Donna F. Christner, Ph.D.

NDA Number: 22-262 **Applicant: Duramed** **Stamp Date: 26-Dec-2007**

Drug Name: LoSeasonique **NDA Type: 3S**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		CE as per 21 CFR 25.15(a). REQUESTED FROM SPONSOR ON 28-Jan-2008
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		DMFs (b) (4) and (b) (4)
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	N/A		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Chemist Date

Team Leader/Supervisor Date

Filing Checklists

A. Administrative Checklists;

YES	NO		Comments
X		On its face, is the section organized adequately?	
X		Is the section indexed and paginated adequately?	
X		On its face, is the section legible?	
X		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
X		Has an environmental assessment report or categorical exclusion been provided?	CE as per 21 CFR 25.15(a). REQUESTED FROM SPONSOR ON 28-Jan-2008

B. Technical Checklists;

1. Drug Substance

X		Does the section contain synthetic scheme with in-process parameters?	DMFs
X		Does the section contain structural elucidation data?	DMFs
X		Does the section contain specifications?	DMFs
X		Does the section contain information on impurities?	DMFs
X		Does the section contain validation data for analytical methods?	DMFs
X		Does the section contain container and closure information?	DMFs
X		Does the section contain stability data?	DMFs

(b) (4)

2. Drug Product

X		Does the section contain manufacturing process with in-process controls?	
X		Does the section contain quality controls of excipients?	
X		Does the section contain information on composition?	
X		Does the section contain specifications?	
X		Does the section contain information on degradation products?	
X		Does the section contain validation data for analytical methods?	
X		Does the section contain information on container and closure systems?	
X		Does the section contain stability data with a proposed expiration date?	
X		Does the section contain information on labels of container and cartons?	
X		Does the section contain tradename and established name?	

C. Review Issues

X		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	X	Is a team review recommended?	
X		Are DMFs adequately referenced?	

DMF No.	Holder	Description	LOA	Status
(b) (4)			Yes	**Adequate** on 31-May-2007 by U. Atwal. Amendments submitted since last review. May need review.
			Yes	**Adequate** on 11-Oct-2006 by M. Cooper. Annual Reports submitted since last review. May require review.
			Yes	See ONDC Policies on Bottles and Blisters*
			Yes	Adequate on 27-Sep-2000 by R. Lostritto
				Adequate on 25-Aug-2004 by A. Schroeder
			Yes	(b) (4) Adequate on 10-Jan-2007 by G. Lunn. Amendments submitted since last review. May need review.

**Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001*
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

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✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-***2**

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

/s/

Donna Christner
2/21/2008 10:27:23 AM
CHEMIST

Hard copy signed

Moo-Jhong Rhee
2/21/2008 10:54:43 AM
CHEMIST
Chief, Branch III