CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

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:	**22-262**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**Dec. 26, 2007**
PRODUCT:	**Lo Seasonique**
INTENDED CLINICAL POPULATION:	**Women who elect to use oral contraceptives as a method of contraception**
SPONSOR:	**Duramed Research, Inc.**
DOCUMENTS REVIEWED:	Duramed has referenced the non-clinical pharmacology/toxicology information contained in various NDA submissions for previously approved drug products including NDA 21-840, Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol). Therefore, no new pharmacology, toxicology or pharmacokinetic/toxicokinetic studies were necessary to support the current NDA 22-262 application.
REVIEW DIVISION:	**DRUP**
PHARM/TOX REVIEWER:	**Alex Jordan**
PHARM/TOX SUPERVISOR:	**Lynnda Reid**
DIVISION DIRECTOR:	**Scott Monroe**
PROJECT MANAGER:	Kassandra Sherrod

Date of review submission to Division File System (DFS):

Appears This Way on Original

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Pharmacology recommends approval of Lo Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol).

B. Recommendation for nonclinical studies None

C. Recommendations on labeling Labeling will be similar to Seasonique approved under NDA 21-840, which has the same formulation composition and dosing schedule and is used for a similar indication.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Lo Seasonique is an extended regimen oral contraceptive consisting of levonorgestrel (0.10 mg) and ethinyl estradiol (0.02 mg) to be taken orally for 91 days (84 days of the combination followed by 7 days of 0.10 mg EE alone).
Seasonique is an approved drug (NDA 21-840), with the same duration but with higher doses. The regimen is 84 days of 0.15 mg levonorgestrel and 0.30 mg ethinyl estradiol followed by seven days of 0.10 mg EE alone.
The chronic toxicology studies to support the safety of levonorgestrel and ethinyl estradiol were done using daily dosing for up to 2 years and are sufficient to support the safety of Lo Seasonique. No new toxicology studies are necessary and none were submitted.

B. Pharmacologic activity: Contraception

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-262
Review number: 1
Sequence number/date/type of submission: 000/12-26-07/New Drug Application
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Duramed Research, Inc, Bela Cynwyd, Pa.
Manufacturer for drug substance:

Reviewer name: Alex Jordan, PhD
Division name: DRUP

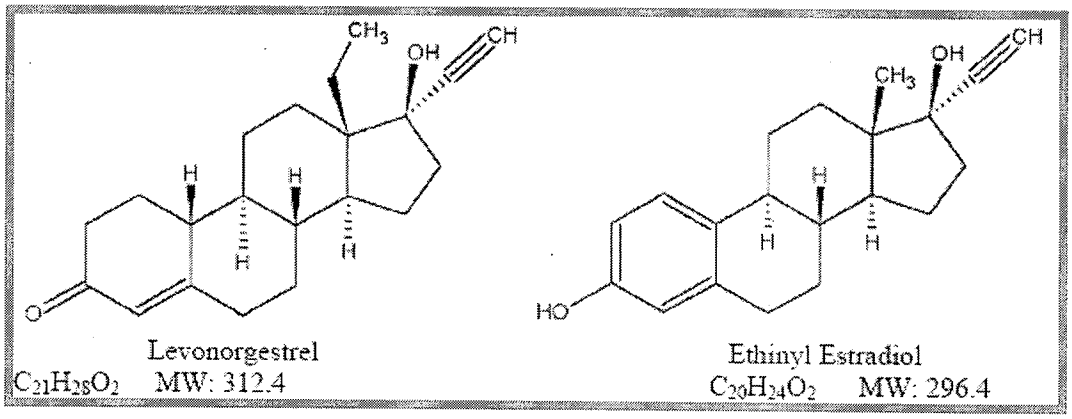
Review completion date: 1/23/2008

Drug:

Trade name: Lo Seasonique
Generic name: Levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets
Code name:
Chemical name: Levonorgestrel (18, 19-dinorpregn-4-en-20-yn-one, 13-ethyl-17-hydroxy-, (17a)-,(-)-ethinyl estradiol (19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17a)-

CAS registry number: 797-63-7 (LNG); 57-36-6 (EE)
Molecular formula/molecular weight: $C_{21}H_{28}O_2$/312.45 (LNG); $C_{20}H_{24}O_2$/296.41 (EE)

Structure:



Relevant INDs/NDAs/DMFs: NDA 21-840

Drug class: LNG (progestin); EE (estrogen)

Intended clinical population: Women wanting to use extended cycle oral contraception

Clinical formulation:

Ingredient	Function	Reference to Standard
Tablet (b) (4)		
Levonorgestrel,USP (Micronized)	Active	USP
Ethinyl Estradiol, USP(Micronized)	Active	USP
Anhydrous Lactose, NF(b) (4)	(b) (4)	NF
Hydroxypropyl Methylcellulose (b) (4), USP (b) (4))		USP
Microcrystalline Cellulose, NF (b) (4))		NF
Starch, NF (Corn Starch) (b) (4) (b) (4)		NF
Magnesium Stearate, NF		NF
(b) (4) :		
(b) (4) Consisting of: Lactose monohydrate, NF (b) (4) / Hypromellose (b) (4) , USP Titanium Dioxide, NF Triacetin, USP (b) (4) ; FD&C Yellow #6 Aluminum Lake		In-House*

* In-House means the material is neither USP nor NF.

Route of administration: oral
Dosing regimen: One tablet taken daily: 84 combination tablets followed by 7 ethinyl estradiol tablets.

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 22-262 are owned by Duramed or are data for which Duramed has obtained a written right of reference. Any information or data necessary for approval of NDA 22-262 that Duramed 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 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 22-262.

Studies reviewed within this submission: No pharmacology/toxicology studies were conducted or submitted. All studies refer to approved contraceptive products containing levonorgestrel and ethinyl estradiol.

Studies not reviewed within this submission: None submitted

2.6.2 PHARMACOLOGY

Pharmacology of levonorgestrel and ethinyl estradiol is well established and both ingredients have been approved in many combined oral contraceptives.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None submitted

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

None submitted

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted

2.6.6 TOXICOLOGY

None submitted

2.6.7 TOXICOLOGY TABULATED SUMMARY

No new toxicology studies submitted. Safety is supported by reference to approved combination oral contraceptives containing levonorgestrel and ethinyl estradiol at dose levels equal or higher than those in Lo Seasonique

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on the approval of Seasonique under NDA 21-840, which has the same formulation and dosing schedule as Lo Seasonique, as well as use of both active ingredients at doses equal or higher in many other approved formulations for the same indication, Pharmacology considers Lo Seasonique safe for the proposed indication.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of NDA 22-262 for Lo Seasonique.

Suggested labeling: Labeling will be similar to that for Seasonique.

APPENDIX/ATTACHMENTS None

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/s/

Alexander W. Jordan
1/28/2008 02:50:12 PM
PHARMACOLOGIST

Lynnda Reid
1/28/2008 03:05:52 PM
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PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

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

Drug Name: Lo Seasonique **NDA Type:**

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

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?			NA
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?			NA
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?			NA
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			NA

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			NA
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			NA
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)			NA
11	Has the sponsor addressed any abuse potential issues in the submission?			NA
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments:

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

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/s/

Alexander W. Jordan
1/28/2008 02:51:48 PM
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1/28/2008 03:04:02 PM
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