

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-840

PHARMACOLOGY REVIEW



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: 21-840
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 10/21/04
PRODUCT: Seasonique (levonorgesrel/ethinyl estradiol and ethinyl estradiol)
INTENDED CLINICAL POPULATION: Women requiring oral contraceptive
SPONSOR: Duramed Research Inc. One Belmont Avenue, Bala Cynwyd, PA 19004
DOCUMENTS REVIEWED: As per the pre-NDA agreement with the Agency of 8-30-04, Duramed has referred all non-clinical pharmacology/toxicology information to that contained in the various NDA submissions for the previously approved drug products. Therefore, no new pharmacology, toxicology, or pharmacokinetic/toxicokinetic studies were considered necessary nor were performed by Duramed in support of the current NDA 21-840 application.
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 Reid, Ph.D.
DIVISION DIRECTOR: Dan Shames, M.D.
PROJECT MANAGER: Karen Kirchberg

Date of review submission to Division File System (DFS): 1-10-05

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW 4

2.6.1 INTRODUCTION AND DRUG HISTORY4

2.6.2 PHARMACOLOGY.....6

2.6.3 PHARMACOLOGY TABULATED SUMMARY6

2.6.4 PHARMACOKINETICS/TOXICOKINETICS.....6

2.6.5 PHARMACOKINETICS TABULATED SUMMARY.....6

2.6.6 TOXICOLOGY6

2.6.7 TOXICOLOGY TABULATED SUMMARY.....6

OVERALL CONCLUSIONS AND RECOMMENDATIONS.....6

APPENDIX/ATTACHMENTS7

Appears This Way
On Original

EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: Pharmacology recommends approval of Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol).
- B. Recommendation for nonclinical studies: none
- C. Recommendations on labeling: Labeling will be similar to Seasonale approved under NDA 21-544, which has the same formulation composition and dosing schedule and for similar indication.

II. Summary of nonclinical findings

A. **Brief overview of nonclinical findings:** Seasonique is an extended cycle oral contraceptive containing 84 tablets of the combination levonorgestrel 150 ug and ethinyl estradiol 30 ug as in Seasonale and 7 tablets of ethinyl estradiol 10 ug instead of 7 placebo tablets in Seasonale approved under NDA 21-544. The safety of Seasonique with new dosing regimen is supported by reference to data that already exists on the safety of Seasonale. As a result of modification in dosing regimen, patients using Seasonique would receive the same total annual dose of levonorgestrel as the patients using Seasonale and slightly higher (0.28 mg) total annual dose of ethinyl estradiol than do patients on Seasonale. The increased dose of ethinyl estradiol is still lower (10.36 vs 13.65) than total dose of ethinyl estradiol found in approved oral contraceptive Ovral and Ovral-28. Also Nordett-21 (NDA 18-668) and Portia (ANDA 75-866) are approved with the same active ingredients and the same daily doses. Many of the chronic toxicology studies to support the safety of levonorgestrel and ethinyl estradiol were done using daily dosing up to 2 years and were used for the approval of Seasonale and are thus applicable to Seasonique. There are 20 combination oral contraceptives containing levonorgestrel/ethinyl estradiol at concentrations similar to or higher than those in Seasonique were approved in United States from 1999 to 2003. No new toxicology studies are necessary and none were submitted for Seasonique.

B. Pharmacologic activity: Contraceptive

A. Nonclinical safety issues relevant to clinical use: none

Appears This Way
On Original

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-840

Review number: 1

Sequence number/date/type of submission: 000/10-21-04/New drug application

Information to sponsor: Yes () No (*)

Sponsor and/or agent: Duramed Pharmaceuticals, Inc. One Belmont Ave., 11th Floor, Bala Cynwyd, PA

Manufacturer for drug substance:

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

Division name: DRUDP

HFD #: 580

Review completion date:

Drug:

Trade name: Seasonique

Generic name: Levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets

Code name:

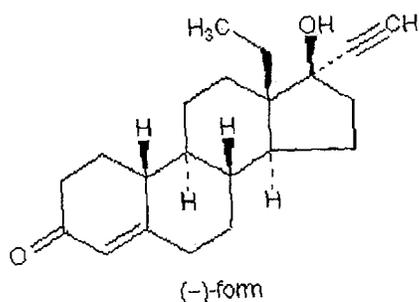
Chemical name: Levonorgestrel (18, 19-Dinorpregn-4-en-20-yn-one, 13-ethyl-17-hydroxy-, (17a)-, (-)-
Ethinyl estradiol (19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17a)-

CAS registry number: 797-63-7 (LNG); 57-36-6 (EE)

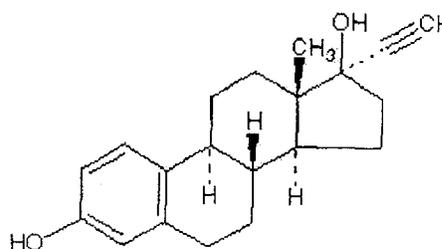
Molecular formula/molecular weight: C₂₁H₂₈O₂/312.45 (LNG); C₂₀H₂₄O₂/296.41 (EE)

Structure:

Levonorgestrel



Ethinyl estradiol



Relevant INDs/NDAs/DMFs: NDA 21-544

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

Intended clinical population: Women wishing to use extended cycle oral contraceptive

Clinical formulation: Unit formulation is given in table below:

Ingredient	Function	Active	Placebo
Levonorgestrel, USP	Active	0.15	none
Ethinyl estradiol, USP	Active	0.03	none
Anhydrous Lactose, NF	+		
Hydroxypropyl Methylcellulose 2208, USP			
Microcrystalline Cellulose			
Magnesium Stearate			
Total Core weight			
or:			
Total coated tablet weight			N/A

Active ingredients: levonorgestrel and ethinyl estradiol are both compendial drug substances

* Target weight gain

Route of administration: oral

Dosing regimen: One tablet taken daily in the following schedule: 84 active combination tablets followed by 7 ethinyl estradiol tablets.

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

[For (b)(2) applications:

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of [NDA 21-840] are owned by [Duramed Pharmaceuticals, Inc.] or are data for which [Duramed Pharmaceuticals, Inc.] has obtained a written right of reference. Any information or data necessary for approval of [NDA 21-840] 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 21-840].

Studies reviewed within this submission: No pharmacology/toxicology studies conducted or submitted. All studies referred 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.

2.6.2 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 Seasonique.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on the approval of Seasonale under NDA 21-544, which has the same formulation and dosing schedule as Seasonique, the product being reviewed under present NDA 21-840, as well as use of both active ingredients at doses equal or higher in many other approved formulations for the same indication, Pharmacology considers Seasonique is safe for the proposed indication.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of NDA 21-840 for the combination oral contraceptive Seasonique.

Suggested labeling: Labeling will be similar to that for Seasonale approved under NDA 21-544.

APPENDIX/ATTACHMENTS: NONE

Appears This Way
On Original

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

/s/

Krishan L. Raheja
1/11/05 09:40:08 AM
PHARMACOLOGIST

Lynnda Reid
1/11/05 11:34:00 AM
PHARMACOLOGIST

Appears This Way
On Original