CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

OTHER REVIEW(S)

MEMORANDUM

To: **Pam Lucarelli**
Division of Reproductive and Urology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **September 26, 2008**

Re: **Comments on draft labeling for Lo Seasonique (levonorgestrel/ ethinyl estradiol and ethinyl estradiol) tablets, NDA 22-262**

We have reviewed the proposed label for Lo Seasonique (FDA version dated 9/23/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Is the tradename for this product "Lo Seasonique" or "Lo Seasonique Tablets"? Please verify and ensure use of the correct name throughout the label.

- The main section numbers should not have periods after the numbers (i.e., use "1 Indications and Usage" instead of "1. Indications and Usage"). These changes need to be made throughout Contents and the Full Prescribing Information (FPI).

HIGHLIGHTS

- *"HIGHLIGHTS OF PRESCRIBING INFORMATION"*

  Please delete the space at the beginning of this line at the top of Highlights.

- *"Lo Seasonique Tablets (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets) for oral use"*

  If "Tablets" is not part of the trade name, the word should appear after the parentheses in lower case lettering.

- *"Initial U.S. Approval: 1982"*

Please ensure that this is the date of the first approved product with this combination of active ingredients, regardless of dosage form.

Indications and Usage

- We note that the "limitation of use" about decreased efficacy with incorrect use has been retained in the FPI. If it appears there, it should also appear in Highlights.

Warnings and Precautions

- After the "title" of the risk in each bullet, please use a colon instead of a period for ease of reading.
- *"Start Lo Seasonique no earlier than 4 weeks after delivery, in women who are not breastfeeding."*

  We suggest deleting the comma in this sentence for grammatical correctness.

Use in Specific Populations

- Please insert a bullet after "production" in the Nursing bullet.

Patient Counseling statement

- *"See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."*

  Please revise this sentence slightly per the regulations to read (in bolded type):

  > See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revision Date

- The month should filled in upon approval and should be flush-right within the column.

CONTENTS

Contents should appear in a two-column format as is done for Highlights. This will allow the entire section to appear at the bottom of page 1.

- Once the FPI has been finalized, Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.

FULL PRESCRIBING INFORMATION

- In the FPI, some cross-references use all upper-case lettering for the section title, and some do not. While either presentation is acceptable, please select one format and use consistently throughout the FPI.

Boxed Warning

- *"Combined oral contraceptives (OCs) should not be used by women who are over 35 years old and smoke. (4)"*

  The cross-reference is not in the proper format for the FPI. It should read (all in italics), "*[see Contraindications (4)]*."

1 Indications and Usage

- *"Limitations of use: Incorrect use of OCs decreases their efficacy."*

  During team labeling discussions for (b) (4)), the Division seemed to be leaning toward not including the phrase (b) (4) to introduce this concept. Has this decision been reconsidered?

3 Dosage Forms and Strengths

- The NDC number should be deleted from the text in this section. It appears (correctly) under "How Supplied/Storage and Handling."

5.1 Vascular Events

- *"Start OCs no earlier than 4 weeks after delivery, in women who are not breast-feeding."*

  As noted in Highlights, please delete the comma after "delivery."

5.9 Interference with Laboratory Tests

- *"Women dependent on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase."*

  This sentence seems incomplete. Should it end with, "with the use of OCs" or something similar?

6 Adverse Reactions

- We suggest that "Clinical Trial Experience" get a subheading of 6.1 to improve its prominence. This will also facilitate the addition of a section "6.2 Postmarketing Experience" should it be needed in the future.

7.1 Changes in Contraceptive Effectiveness Associated with Co-administration of Other Products

- Please delete (b) (4) from the list of interacting drugs. It is no longer on the market, based on a review of The Orange Book and drugs@fda.

- Please correct the spelling of "topiramate" in the list.

8.5 Geriatric Use

- Please consider if this section should appear at all in the label. The regulations allow deletion of a section if it is irrelevant for a particular label.

12.3 Pharmacokinetics

- Table 3

  In the table title, please change the first word "MEAN" to "Mean."

- *"Following repeated daily dosing of combination levonorgestrel/ethinyl estradiol OCs, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose kinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity."*

  In this sentence under the "Distribution" subheading, is (b) (4) correct, or should it be "pharmacokinetics"?

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

- In general, a section should contain some text, instead of just a cross-reference. Please consider adding a sentence or two summarizing the relevant issues, and then retaining the cross-reference. Additionally, please revise the cross-reference to the correct formatting as:

  "[see Warnings and Precautions (5.2, 5.3)]."

14 Clinical Studies

- *"The pregnancy rate (Pearl Index) in women aged 18 to 35 years was 2.74 per 100 women-years (95% confidence interval 1.92 – 3.78), based on 36 pregnancies that occurred, after the onset of treatment and within 14 days after the last combination pill and based on cycles in which no other form of contraception was used."*

Please delete the comma after "occurred" for grammatical correctness.

17 Patient Counseling Information

- The title for section 17 must be "Patient Counseling Information."
- *"See FDA-approved Patient Labeling (17.2)"*

  This sentence should not be in bolded type.

- Please note that patient labeling is not the subject of this review.

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/s/

Iris Masucci
9/30/2008 03:43:32 PM
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