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/s/

Margaret Kober
9/13/2005 05:47:59 PM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-873

Berlex, Inc.
Attention: Nancy Velez, Manager Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone 3 mg/ ethinyl estradiol 0.02 mg) Tablets.

We also refer to your August 30, 2005, correspondence, received September 2, 2005, requesting a meeting to discuss the Agency's decision to extend this application's User Fee Date for an additional 3 months. We have considered your request and concluded that the meeting is now unnecessary based on the series of telephone calls between Joseph Sonk and Margaret Kober that has occurred in the interim.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
9/13/2005 07:32:29 PM

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: August 5, 2005

TO: Charlene Williamson, Regulatory Project Manager
Lisa Soule, Medical Officer
Gerald Willett, Medical Officer
Division of Reproductive and Urologic Products, HFD-540

THROUGH: Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-873

PROTOCOL(s): Protocol #304049 entitled: "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg Ethinyl Estradiol 20 µg (as Beta-Cyclodextrin Clathrate), in the Treatment of Premenstrual Dysphoric Disorder (PMDD)", and

Protocol #305141 entitled: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 µg (as Beta-Cyclodextrin Clathrate), in the Treatment of Premenstrual Dysphoric Disorder (PMDD)"

SPONSOR: Berlex, Inc.

DRUG: YAZ

INDICATION: Treatment of premenstrual dysphoric disorder (PMDD)

CHEMICAL CLASSIFICATION: 2

**THERAPEUTIC
CLASSIFICATION:** S

INSPECTION SUMMARY GOAL DATE: August 12, 2005

ACTION GOAL DATE: October 23, 2005

I. BACKGROUND:

In this NDA application, the sponsor included results of Protocols 304049 and 305141 for the use of YAZ[®] (drospirenone 3 mg/ethinyl estradiol 20 µg) in the treatment of PMDD. The objective of the study was to determine the efficacy of YAZ[®] in women experiencing PMDD.

This inspection of the sites of Drs. Moreines and Drosman was requested by the reviewing division because these sites were among the higher enrolling sites.

The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site):

NAME	CITY	STATE/ COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
Robert Moreines, M.D.	Kenilworth	New Jersey	29 Mar 05	17 Jun 05	NAI/011540
Steven Drosman, M.D.	San Diego	California	29 Mar 05	22 Jul 05	VAI/011577

Site # 27

Robert Moreines, M.D.
1700 Galloping Hill Road
ClinSearch, Inc.
Kenilworth, New Jersey 07033

Protocol #304049, 15 subjects

See **Overall Assessment and Recommendations**, below

- a. 15 subjects were randomized to the study with 4 subjects dropping out and 11 completing the study. Source documents for five of the subjects were reviewed in depth, including, but not limited to consent forms, test article accountability, safety assessments, adverse event reporting, and concomitant medications.
- b. There were no limitations to the inspection.

c. A Form FDA 483 was not issued. No significant deviations from regulations were noted.

Site # 8

Steven Drosman, M.D.
3651 Fourth Avenue, Suite 200
Genesis Center for Clinical Research
San Diego, California 92103

Protocol # 304049, 40 subjects
Protocol # 305141, 14 subjects

See **Overall Assessment and Recommendations**, below

- a. 40 subjects completed study protocol 304049 and 14 subjects completed study protocol 305141. Records for sixteen subjects were reviewed in depth for protocol 304049 and records for six subjects were reviewed in depth for protocol 305141.
- b. There were no limitations to the inspection.
- c. A Form FDA 483 was issued noting that the following adverse events were assessed by the study coordinator, not the investigator as required by protocol:

Patient	Adverse Event	Date
840049	melancholy	8/21/03
840049	dry mouth	8/21/03
840049	URI	9/17/03
840049	breast tenderness	9/17/03
840049	eye irritation/dryness	10/21/03
840071	breast tenderness	10/7/03
840071	increased anxiousness	10/7/03
840071	nausea	10/31/03
840071	chest cold	11/24/03

The Form 483 noted that the following subjects had pregnancy tests performed at various visits with expired test kits:

Patient Identification	Date of Test	Recorded Expiration Date of Kit
840009	6/30/03	2/1/03
840071	7/14/03	2/1/03
840069	6/17/03	2/1/03
080009	6/21/02	1/11/02

Subject 840069 was not excluded despite a daily regimen of tetracycline.

Three subjects received physical/gynecologic al examinations by a nurse practitioner not identified on the Form 1572.

Of note was subject 840056 who complained of bilateral leg numbness. The protocol specifically addresses this adverse event as possibly signaling thrombotic events that may require the subject's exclusion from the study at the investigator's discretion. This event was apparently not assessed by the investigator until approximately four months after resolution of the complaint. The subject completed the study.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this application by Dr. Moreines appear adequate in support of the relevant submission.

The data submitted in support of this application by Dr. Drosman appear adequate in support of the relevant submission despite a lack of timely assessment and reporting of adverse events. The review division medical officer should determine whether the data from subject 840069 who was on a daily antibiotic regimen should be excluded from study analysis.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
HFD-580/Doc. Rm. NDA 21-873
HFD-45/Program Management Staff (electronic copy)
HFD-46/RF
HFD-46/c/r/s
HFD-46/Blay

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/s/

Roy Blay
8/8/05 04:15:31 PM
CSO

Ni Aye Khin
8/8/05 05:32:42 PM
MEDICAL OFFICER

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: May 20, 2005

To: Charlene Williamson, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products (DRUDP)
HFD-580

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
HFD-042

Subject: NDA 21-873
DDMAC carton labeling comments for YAZ Tablets

DDMAC has reviewed the proposed carton labeling submitted in a consult request by DRUDP on April 7, 2005, for YAZ Tablets and we have no comments at this time.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Michelle Safarik
5/20/05 09:47:23 AM
DDMAC REVIEWER