CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-873

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

Date: 8/7/06
NDA #: 21-873
Date of submission: 3-1-06
Sponsor: Berlex Laboratories, Inc.
Drug Product: YAZ (Drospirenone 3 mg/ethinylestradiol 0.02 mg tablets)
Indication: Premenopausal dysphoric disorder (PMDD)
Subject: Class 1 Resubmission.

NDA 21-873 was originally submitted on 12-22-04 for PMDD. The same drug product was also reviewed under the NDA 21-098, submitted on 10/16/03. Both NDAs were acceptable from clinical pharmacology and biopharmaceutics perspective. The primary Clinical Pharmacology reviewers for these NDAs were Julie Bullock, Pharm.D and Leslie Kenna, Ph.D. The original reviews are posted in DFS.

Recommendation: Labeling for YAZ is acceptable and no further action is indicated from Clinical Pharmacology perspective.

Ameeta Parekh, Ph.D
Team Leader, DCP3, Office of Clinical Pharmacology

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Ameeta Parekh
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BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA	**21-676 & 21-873**
Submission Date	December 22, 2004 June 15, 2004
Brand Name	YAZ™
Generic Name	Drospirenone (DRSP) 3mg/Ethinyl Estradiol (EE) 0.02mg
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Berlex, Inc.
Submission Type; Code	Standard
Dosing regimen	Once Daily
Indication	21-676: Oral Contraception 21-873: Premenstrual dysphoric disorder (PMDD)

Briefing on November 18th attended by John Hunt, and Ameeta Parekh

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1 Executive Summary

YAZ is a 24-day oral contraceptive combination with 24 active tablets containing 3mg Drospirenone (DRSP) and 0.02 mg Ethinyl Estradiol (stabilized by betadex as a clathrate) and 4 inert film coated placebo tablets for use as an oral contraceptive and for the treatment of premenstrual dysphoric disorder.

YAZ tablets are a reduced estrogen version of YASMIN tablets (DRSP 3mg/EE 0.03mg) which were approved on May 11, 2001 for oral contraception (NDA 21-098). The main differences between YAZ and Yasmin® are below

	YAZ™	Yasmin®
Active Tablets	24	21
Placebo Tablets	4	7
Estrogen	0.02 mg EE as a betadex clathrate.	0.03 mg EE free steroid

Both YAZ and YASMIN contain DRSP, a novel progestin and derivative of 17α-spirolactone. DRSP possesses progestogenic and aldosterone-antagonist properties which differentiate DRSP from other currently marketed progestin's.

Berlex developed YAZ in the US under INDs —— (oral contraceptives, OC) and 61,304 (premenstrual dysphoric disorder, PMDD). An NDA for the indication of oral contraception alone was submitted on October 16, 2003 (NDA 21-676; Reviewer: Leslie Kenna, Ph.D) and was found acceptable from a Clinical Pharmacology perspective. An approvable action was received on November 17, 2004 in which DRUDP stated in the approvable letter that the sponsor needed to demonstrate a clinical benefit for the 24-day regimen over that provided by the 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/EE. The sponsor resubmitted a response to the NDA 21-676 approvable action on June 15, 2005. No new clinical pharmacology studies were submitted in the response to the approvable action

Berlex submitted a new NDA 21-873 on December 22, 2005 to demonstrate that the 24-day regimen is safe and effective for the secondary indication of the treatment of PMDD symptoms. PMDD is a medical disorder characterized by debilitating mood and behavioral changes, and frequently somatic complaints in the week preceding menstruation. The currently approved treatments for PMDD consist of various Selective Serotonin Re-uptake inhibitors which main indications are for the treatment of depression. The clinical development program of YAZ for the treatment of PMDD symptoms consists of two pivotal studies.

No new pharmacokinetic studies were submitted under NDA 21-873. Reference to NDA 21-676 was made for the Human Pharmacokinetics and Bioavailability section. During the initial review cycle for NDA 21-676 the NDA was deemed acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. In the NDA 21-873 for the PMDD indication, the sponsor has not made any changes which could impact the Clinical Pharmacology and Biopharmaceutics review. There has been no change in dose, nor has there in any change in drug formulation. The formulation used in the clinical trials was identical to the formulation used in NDA 21-676, which was equivalent to the to-be-marketed formulation.

In the original 21-873 NDA submission, the sponsor has provided the results of two large clinical trials:

- 304049: A multi-center, randomized, parallel group, study consisting of 2 qualifying menstrual cycles and 3 treatment cycles. The objective of this study was to evaluate the effectiveness of YAZ in the treatment of women with symptoms of PMDD. Primary efficacy variable was the change from baseline in the PMDD symptoms as measured by subject-recorded symptoms on the Daily Rating Severity of Symptoms (DRSP) scale. 450 subjects were randomized to YAZ or placebo.
- 305141: A multi-center, randomized, crossover study. A total of 64 subjects completed 2 qualification cycles, 3 treatment cycles with YAZ or placebo, a washout cycle, and 3 treatment cycles with YAZ or placebo. The objective of the study was to evaluate the effectiveness of YAZ in the treatment of women with symptoms of PMDD. The primary efficacy variable was the change from baseline in the PMDD symptoms as measured by the DRSP scale.

Refer to the NDA 21-676; YAZ for oral contraception for detailed information on the products clinical pharmacology and biopharmaceutics characteristics.

In addition please reference the submission made on March 31, 2005 for NDA 21-355 (Angeliq) which contains a Phase 1 drug-drug interaction study to evaluate the potential of DRSP to inhibit CYP3A4 using midazolam as a marker substrate for CYP3A4. The review of this study was completed by Julie Bullock, Pharm.D. (Review in DFS).

In brief, the study was a placebo controlled steady state crossover study to assess drospirenone's potential to inhibit CYP3A4. Each subject received DRSP 3mg or placebo to steady state and a single dose of midazolam was given on Days 7 and 9. The primary target variable was the mean of Days 7 and Day 9 AUC for Midazolam and its hydroxy-metabolite, 1-hydroxy-midazolam. The 90% confidence intervals for the geometric mean fell within the 80-125% confidence intervals needed for bioequivalence for AUC (see Table 1). A BE analysis for Cmax was not provided by the sponsor. An analysis using WinNonlin was performed by the reviewer and the average of Days 7 and 9 fell within the 90% confidence interval limit (see Table 2). The study concluded that DRSP at doses up to 3 mg per day does not potently inhibit CYP3A4 and that dose reductions for substrates of CYP3A4 would be clinically un-necessary.

TABLE 1: AUC 90% confidence intervals for assessment of bioequivalence

Primary target variable	Mean ratio	Lower confidence limit	Upper confidence limit
Mean of AUC(0-tlast) of MDZ at Day 7 and Day 9	97.9%	90.9%	105.4%
Mean of AUC(0-tlast) of 1'OH-MDZ at Day 7 and Day 9	96.1%	87.4%	105.8%

TABLE 2: Cmax 90% confidence intervals for assessment of bioequivalence (calculated by reviewer)

Primary target variable	Mean ratio	Lower confidence limit	Upper confidence limit
Mean of Cmax of MDZ at Day 7 and Day 9	101.9%	89.7%	115.7%
Mean of Cmax of 1'OH-MDZ at Day 7 and Day 9	97.1%	83.6%	112.8%

Recommendation

NDA 21-676, YAZ for Oral Contraception is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

NDA 21-873, YAZ for PMDD is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

Julie M. Bullock, Pharm.D.

Ameeta Parekh, Ph.D., Team Leader

2 Summary of Clinical Pharmacology and Biopharmaceutics

Refer to the review of YAZ for oral contraception NDA 21-676 by Leslie Kenna, Ph.D.

3 Detailed Labeling Recommendations

Changes to the label will be posted in DFS separately when complete.

4 Appendices

4.1 Cover Sheet and OCPB Filing / Review Form

Please see previous DFS submission by Julie Bullock

4.2 Review of YAZ for Oral contraception

Refer to previous submission to DFS for NDA 21-676 by Leslie Kenna

4.3 Review of Yasmin

Refer to a previous submission to DFS for NDA 21-098 by Venkat Jarugula.

4.4 Review of Study 036946

Refer to DFS review of Angeliq (NDA 21-355) complete response by Julie Bullock

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Julie Bullock
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Ameeta Parekh
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