# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-873**

# PHARMACOLOGY REVIEW(S)

# Pharmacology/Toxicology Review

**Date:** 5-17-06

**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. P/T prospective about the approval of the NDA

NDA 21-873 originally submitted on 12-22-04 was reviewed on 2-24-05. All pharmacology, ADME, general toxicology, genotoxicity studies, reproductive toxicity studies and carcinogenicity studies reviewed under NDA 21-098 for the approval of Yasmin supported the safety of combination of drospirenone/ethinyl estradiol for the contraception indication. The primary difference between Yasmin and Yasmin 20 (YAZ) is that the reduced amount of ethinyl estradiol in YAZ is complexed with B-cyclodextrin as the EE-B-cyclodextrin clathrate to ensure shelf stability at low concentrations. No new toxicology studies were requested or submitted for NDA 21-873.
Labeling for YAZ is similar to that for approval of NDA 21-098 for Yasmin.

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

**Through P/T Supervisor:** Lynnda Reid, Ph.D.

**Regulatory action:** Based on review and approval of NDA 21-098 for Yasmin, Pharmacology recommends approval of NDA 21-873 for YAZ.

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/s/

Krishan L. Raheja
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PHARMACOLOGIST

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5/19/2006 02:46:41 PM
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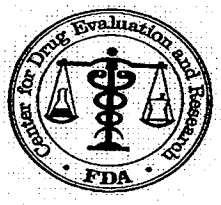


**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

| | |
|---|---|
| NDA NUMBER: | 21873 |
| SERIAL NUMBER: | 000 |
| DATE RECEIVED BY CENTER: | 12/23/04 |
| PRODUCT: | Yaz (drospirenone 3 mg/ethinyl estradiol 0.02 mg) |
| INTENDED CLINICAL POPULATION: | Contraceptive and PMDD |
| SPONSOR: | Berlex Pharmaceuticals, Inc. |
| DOCUMENTS REVIEWED: | Nonclinical Pharmacology and Toxicology, Section 5 (Electronic File: pharmtox\pharmtox.pdf) |
| 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: | Charlene Williamson |

Date of review submission to Division File System (DFS): 2-24-05

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# *EXECUTIVE SUMMARY*

## I. Recommendations

A. **Recommendation on approvability:** This NDA is similar in composition and indication to the sponsor's NDA 21-676 (YAZ containing drospirenone 3 mg/ethyinyl estradiol 0.02 mg tablets) and NDA 21-098 (Yasmin containing 0.3 mg drospirenone/0.03 mg ethinyl estradiol tablets), both approved for oral contraception. Under NDA 21-873 the sponsor has evaluated YAZ for the treatment of premenopausal dysphoric disorder (PMDD).
Based on the similarity in composition and intended treatment populations with the sponsor's previously approved products, Pharmacology recommends approval of NDA 21-873.

B. **Recommendations for nonclinical studies:** None

C. **Recommendations on labeling:** Labeling will be similar to that for NDAs 21-098 and 21-676.

## II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Nonclinical pharmacology and toxicology studies are referenced to NDA 21-098 and NDA 21-676, which are approved for similar indications. As such referenced studies are acceptable to support NDA 21-873.

B. Pharmacologic activity : Drospirenone has mainly progestogenic, antiandrogenic and antimineralocorticoid activity.

C. Nonclinical safety issues relevant to clinical use: none

# *2.6 PHARMACOLOGY/TOXICOLOGY REVIEW*

## 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number**: 21-873
**Review number**: 1
**Sequence number/date/type of submission**: 000/12-23-04
**Information to sponsor**: Yes ( ) No ( *)
**Sponsor and/or agent**: Berlex Laboratories, Inc. P.O.Box 1000, Montville, NJ 07045
**Manufacturer for drug substance**: Schering GmbH and Co. Germany

**Reviewer name**: Krishan L. Raheja, D.V.M., Ph.D.
**Division name**: Reproductive and Urologic Drug Products
**HFD #**: 580
**Review completion date**:

**Drug**:

Trade name: YAZ
Generic name: drospirenone (DRSP) 3 mg/ethinyl estradiol (EE) 0.02 mg tablets
Code name: ZK 30595 (drospirenone) ZK 4944 (ethinyl estradiol)
Chemical name: DRSP = (6B, 7B; 15B-dimethylene-3-oxo-17a-pregn-4-ene-21 -17-carbolactonne (IUPAC)
EE= 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diiol,(17a)
CAS registry number: 67392-87-4 (DRSP); 57-63-6 (EE)
Molecular formula/molecular weight: $C_{24}H_{30}O_3$/366.5 (DRSP); $C_{20}H_{24}O_2$/296.4 (EE)
Structure: Referred to NDA 21-098

**Relevant INDs/NDAs/DMFs**: IND 51,693; DMF 12138 (DRSP) and DMF 1985 (EE); NDA 21-098 (Yasmin) and NDA 21-676 (YAZ).

**Drug class**: DRSP (progestin); EE (estrogen)

**Intended clinical population**: as contraceptive and for PMDD

PMDD (premenopausal dysphoric disorder) is described as a distinct clinical entity with clear onset and offset of symptoms closely linked to the menstrual cycle and prominence of emotional symptoms.

**Clinical formulation**: tablets with composition as under NDA 21-676

**Route of administration**: oral

**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 21-873 are owned by Berlex Laboratories, Inc. or are data for which Berlex Laboratories, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-873 that Berlex Laboratories, 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 Berlex Laboratories, 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 21-873.

**Studies reviewed within this submission:** None. All nonclinical studies are referenced to NDAs 21-098 and 21-676

**Studies not reviewed within this submission**: -

## 2.6.2 PHARMACOLOGY

Drospirenone is progestational agent with antiandrogenic and antimineralocorticoid activity. Drospirenone in combination with ethinyl estradiol acts by suppression of gonadotropins. Although the primary mechanism of action is inhibition of ovulation, other alterations include changes in cervical mucus (which increases the difficulty of sperm entry in to the uterus) and in the endometrium (which reduces the likelihood of implantation).

PHARMACOLOGY TABULATED SUMMARY: **none submitted**

## 2.6.3 PHARMACOKINETICS/TOXICOKINETICS

Referred to NDAs 21-098 and 21-676

## 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NONE SUBMITTED

## 2.6.6 TOXICOLOGY

All referred nonclinical studies were reviewed under NDAs 21-098 and 21-676

## 2.6.7 TOXICOLOGY TABULATED SUMMARY

NONE SUBMITTED

## OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** Based on the sponsor's approved NDAs 21-098 and 21-676 having the same composition and a similar intended population for NDA 21-873, Pharmacology has no safety concerns.

Unresolved toxicology issues (if any): None

**Recommendations:** Pharmacology recommends approval of NDA 21-873 for contraception and PMDD indications.

**Suggested labeling:** Labeling will be similar to that for NDAs 21-098 and 21-676

**APPENDIX/ATTACHMENTS**: NONE

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/s/

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2/24/05 10:36:01 AM
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