

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-045**

**ENVIRONMENTAL ASSESSMENT**

## MEMORANDUM

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

**DATE:** January 23, 2007

**TO:** Mildred Wright, Project Manager (HFD-540)

**CC:** Linda Athey, Victoria Lutwak, Moo-Jhong Rhee

**FROM:** Shulin Ding, Pharmaceutical Assessment Lead (ONDQA)

**CONCURRENCE:** Moo-Jhong Rhee, Chief, Branch 3 (ONDQA)

**SUBJECT:** **NDA 22-045: Review of Environmental Assessment**

The applicant requests in an amendment dated Jan. 15, 2007 a categorical exclusion per 21 CFR 25.31(b) for the environmental assessment of NDA 22-045.

The request of categorical exclusion is based on the projected highest quantity of the active moiety expected to be produced for direct use within five year of the expected launch of the proposed product. The projected quantity provided in the amendment covers all related applications: YAZ (3.0 mg DRSP/0.02 mg EE), Yasmin (3.0 mg DRSP/0.03 mg EE), Angeliq (0.5 mg DRSP/1 mg E2), and Angeliq (2 mg DRSP/1 mg E2).

The sponsor claims that the projected quantity would result in a concentration of less than 1 part per billion (ppb) for both drug substances, drospirenone (DRSP) and ethinyl estradiol (EE), at the point of entry into the aquatic environment.

### **Reviewer's Evaluation:**

A review of the projected quantity and calculation confirms that the concentration at the point of entry into the aquatic environment is well below 1 ppb for both drospirenone and ethinyl estradiol. **The request of waiver for an environmental assessment is, therefore, acceptable.**

The applicant uses an outdated POTW flow value of  $1.214 \times 10^{11}$  liters per day in the calculation of the concentration at the point of entry into the aquatic environment. POTW flow value has been updated to  $1.321 \times 10^{11}$  liters per day. This discrepancy, however, does not change the overall assessment and conclusion for the applicant's request of categorical exclusion.

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/s/

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Shulin Ding  
1/24/2007 01:34:37 PM  
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Moo-Jhong Rhee  
1/25/2007 09:57:07 AM  
CHEMIST  
Chief, Branch III

## Consultation

**Application #** NDA 22-045  
**To** Division of Dermatology and Dental Products  
**From** Gerald Willett MD, Medical Officer,  
Division of Reproductive and Urologic Products;  
**Through** Lisa Soule, MD, Clinical Team Leader  
Scott Monroe MD, Acting Division Director.  
**Type of Document** Type 6 NDA  
**Name of Drug** Yaz (drospirenone 3mg/ethinyl estradiol 0.02mg)  
**Re:** Safety and Labeling

### Background:

YAZ is an oral contraceptive containing 3mg of drospirenone and 0.02 mg of ethinyl estradiol. It was approved for the indication of prevention of pregnancy (NDA 21-676) on March 16, 2006. Subsequently, on October 4, 2006, YAZ was approved for the secondary indication of premenstrual dysphoric disorder (PMDD) for women who also planned to use an oral contraceptive as their contraceptive method (NDA 21-873). The primary clinical reviews in DFS for the contraceptive and PMDD indications are listed in the following table:

**NDA Submissions for YAZ**

<b>NDA / Review Description</b>	<b>Author</b>	<b>Date</b>	<b>Safety Information</b>
21-676 / Medical Officer Review (MOR)	Gerald Willett	11/16/2004	Review of submission for the initial cycle for prevention of pregnancy
21-676 / MOR of complete response	Gerald Willett	3/14/2006	Review of complete response and recommendation for approval for prevention of pregnancy
21-873 / MOR of PMDD	Lisa Soule	1/23/2006	Review of submission for the initial cycle for PMDD secondary indication
21-873 / MOR of complete response	Gerald Willett	9 /28/2006	Review of complete response and recommendation for approval of PMDD as a secondary indication

On October 18, 2006 the Division of Dermatology and Dental Products (DDDP) sent a consultation request to the Division of Reproductive and Urologic Products (DRUP) that consisted of the following two requests:

- 1) Provide consultative advice regarding the safety of this drug as per the clinical studies conducted in the NDA.
- 2) Provide consultative advice regarding appropriate language for labeling.

**DRUP Consultation Response Comments:**

1) DRUP reviewed safety data from NDA 22-045 (Phase 3 studies 306820 and 306996 submitted to that NDA for the secondary indication of acne) as part of its safety review for approval of the contraceptive indication (NDA 21-676). The safety findings in general in those studies were similar to safety findings encountered with all oral contraceptives. The potassium safety findings which were studied due to the drospirenone component of the pill were similar to other reviewed studies containing potassium findings for YAZ. In summary, there were no safety issues from the Phase 3 acne studies (306820 and 306996) that precluded approval of YAZ for its contraceptive indication.

YAZ and all other combination oral contraceptives have safety risks that have to be balanced against their benefits with regard to the primary contraceptive indication. These safety risks need to be considered when approving a secondary indication to determine if the risks may be increased in the population likely to use the drug for the secondary indication. DRUP is not aware of factors, per se, that are likely to increase the risks associated with the use of YAZ in women with acne, assuming that the risk factors in these women are otherwise the same as those in the subjects in the clinical trials that investigated YAZ for the prevention of pregnancy and PMDD.

2) Labeling negotiations for the secondary indication of acne are ongoing between the Applicant and DDDP. DRUP believes that there should be a single label for YAZ which includes the primary and all secondary indications. There should also be a single proprietary name for the drug product.

**Gerald Willett, MD, DRUP**

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/s/

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Gerald Willett  
12/20/2006 11:00:00 AM  
MEDICAL OFFICER

Lisa Soule  
12/20/2006 03:14:30 PM  
MEDICAL OFFICER

Scott Monroe  
12/20/2006 08:48:11 PM  
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I concur.