

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022247Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: June 4, 2013

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

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Drug Name(s): conjugated estrogens/bazedoxifene

Therapeutic Class: estrogen/SERM combination

Dosage and Route: 0.625/20 mg, 0.45/20 mg by mouth once daily

Application Type/Number: NDA 22247

Applicant/sponsor: Wyeth Pharmaceuticals

OSE RCM #: 2012-2814

## 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates the risk management plan submitted by Wyeth received on September 26, 2012 with the new drug application (NDA) 22247 submission; and determines if a REMS is necessary to ensure the benefits of conjugated estrogens/bazedoxifene (CE/BZA) 0.45/20 mg and 0.625/20 mg outweigh its risks. Division of Bone, Reproductive, and Urologic Products (DBRUP) recognizes CE as the primary component of this combination product and attributes the primary action of the product to CE. BZA is a selective estrogen receptor modulator (SERM) that has both estrogen agonist and antagonist effects.

Wyeth did not propose a risk evaluation and mitigation strategy (REMS).

### 1.1 BACKGROUND

On September 26, 2012, Wyeth submitted CE/BZA taken once daily by mouth for the following proposed indications:

- Treatment of moderate to severe vasomotor symptoms, (VMS)
- Treatment of moderate to severe vulvar and vaginal atrophy (VVA), and
- Prevention of postmenopausal osteoporosis (PMO)

### 1.2 REGULATORY HISTORY

(b) (4)

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## 2 MATERIALS REVIEWED

The following materials were reviewed:

- Wyeth's risk management plan. Submitted September 26 and received October 3, 2013.
- Whitaker M, Bienz S, Willet G, Voss S. Clinical Review [draft]; version dated June 4, 2013.
- Premarin [package insert]. Philadelphia PA: Pfizer; 2012.

## 3 RESULTS OF REVIEW

### 3.1 OVERVIEW OF CLINICAL PROGRAM

The CE/BZA NDA relies on pivotal data from Studies 303 (2 years), 305 (12 weeks), 306 (12 weeks), and 3307 (1 year), all phase 3 double-blind, randomized, placebo and/or active-controlled trials. All of these trials were conducted in healthy postmenopausal

women age 40 to 65. A total of 6041 patients received various combinations of BZA and CE for up to 2 years. The CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg 1089 and (b) (4) subjects have been treated for at least 6 months respectively and 987 and (b) (4) for a year. According to the clinical review, these trials support that CE/BZA 0.45/20 mg is safe and effective for the treatment of VMS and prevention of PMO. However, there are two main issues regarding the review of this product:

- Data integrity issues: missing source documentation was identified requiring DBRUP to exclude data from certain patients, sites, and studies in their analyses.
- Drug reformulation: The drug product required several reformulations for a variety reasons during the clinical trials. At the time of this review, the Sponsor has not provided sufficient information to demonstrate a “bridge” between the various formulations and the “to be marketed” product. The chemistry, manufacturing and controls (CMC) review is not recommending approval unless information to assure the identity, strength, purity, and quality of the product are satisfactorily resolved.

The DBRUP clinical review does not recommend approving the CE/BZA 0.625/20 mg dose for any indication (b) (4)

Further, the review does not recommend approval of the VVA indication (b) (4)

For comprehensive assessment of these issues, refer to the clinical review.

### 3.2 SAFETY CONCERNS

As part of the NDA, Wyeth submitted a risk management plan in the format that is required as part of the marketing application for the European Union.

#### 3.2.1 Risks Identified by the Sponsor

Wyeth identified the following risks associated with CE/BZA:

- Venous thromboembolism (VTE)
- Increased serum triglycerides

Both these risks are established risk with CEs. The approved labeling for CEs includes a Boxed Warning for the increased risk of stroke and VTE among other risks and a Precaution for hypertriglyceridemia.

#### 3.2.2 Risks Identified by FDA

The safety review focused on the narrow therapeutic window of bazedoxifene and the degree of endometrial protection provided by BZA. Data analyzed from Study 303 for the probability of hyperplasia at 24 months demonstrated a steep dose-response relationship from 10 to 40 mg of BZA in combination with CE 0.625 mg. While no hyperplasia concerns were noted with CE/BZA 0.45/20mg dose, these findings indicated that an adequate level of BZA exposure is necessary to reduce the risk of endometrial hyperplasia and the issues with drug reformulation summarized in Section 3.1 are more problematic.

The clinical review of the deaths, non-fatal SAEs, neoplasms, and adverse events leading to withdrawal were similar between groups.

#### **4 DISCUSSION**

CEs (monotherapy) are approved for treatment of VVA, VMS, and PMO. As stated in the clinical review, unopposed estrogen increases the risk of endometrial cancer in a woman with a uterus. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. BZA has both estrogen agonist and antagonist effects. In the uterus, it appears to act as an estrogen antagonist and opposes the effect of CE. Therefore, the BZA in this combination product is a substitute for progestin; an adjunctive agent intended to provide endometrial protection.

DBRUP recognizes CE as the primary component; attributing the primary action of the product to CE. As such, the risk management approach should be consistent with other CE products - labeling, including a Boxed Warning and patient package insert.<sup>1</sup>

#### **5 CONCLUSION**

DRISK concurs with DBRUP that, based on the available data and the potential benefits and risks of treatment, a REMS is not required for CE/BZA. A risk management approach consistent with other combination CE products (labeling including a Boxed Warning and patient package insert) is appropriate. If a new indication or new safety concern arises, the need for a REMS should be re-evaluated.

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<sup>1</sup> 21 CFR 310.515 – Patient package inserts for estrogens.

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/s/  
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