

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: October 3, 2013

FROM: Julie Beitz, MD

SUBJECT: Approval Action for NDA 022247/Original 1
Duavee (conjugated estrogens 0.45 mg/bazedoxifene 20 mg)
Treatment of vasomotor symptoms
Prevention of postmenopausal osteoporosis

Complete Response Action for NDA 022247/Original 2
Duavee (conjugated estrogens 0.625 mg/bazedoxifene 20 mg)
Treatment of vulvar and vaginal atrophy
Treatment of vasomotor symptoms
Prevention of postmenopausal osteoporosis

Wyeth Pharmaceuticals, Inc.

Summary

Duavee (conjugated estrogens/bazedoxifene, hereafter referred to as CE/BZA) pairs conjugated estrogens (i.e., Premarin) with bazedoxifene. Conjugated estrogens are composed of multiple estrogens that demonstrate estrogen receptor agonist activity.¹ Bazedoxifene, a new molecular entity, demonstrates both tissue selective estrogen receptor agonist and antagonist activity. The CE/BZA combination is not currently approved in any country.

Bazedoxifene monotherapy is not currently FDA-approved. Bazedoxifene is approved in Europe (as Conbriza 20 mg) and in other countries, including Japan, for the treatment of osteoporosis. (b) (4)

Bazedoxifene monotherapy has been shown to have beneficial effects on bone mineral density and to reduce fracture risk, but offers no beneficial effect with respect to vasomotor symptoms.

Conjugated estrogens combined with BZA have net estrogen agonist activity in bone, although increasing BZA doses mitigate the effects of CE in bone. In the uterus, BZA appears to act as an estrogen antagonist and opposes the effect of CE.

The applicant submitted NDA 022247 on October 3, 2012 seeking approval for CE/BZA for three indications: treatment of moderate to severe vasomotor symptoms associated with postmenopause (VMS), treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause (VVA), and prevention of post-menopausal osteoporosis (PMO). For the VMS and PMO indications, the applicant has proposed two doses: CE 0.45/BZA 20 and CE 0.625/BZA 20. For VVA, the applicant has proposed only the CE 0.625/BZA 20 dose.

The Division of Bone, Reproductive and Urologic Products (DBRUP) has concluded that the benefits of CE 0.45/BZA 20 for 1) treatment of moderate to severe vasomotor symptoms in postmenopausal women with a uterus and 2) prevention of postmenopausal osteoporosis in women with a uterus outweigh the potential risks, and has recommended approval of this dose for these indications.

¹ Conjugated estrogens are purified from pregnant mares' urine and consist of the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine.

In addition, the Division has raised the following concerns that preclude approval of CE 0.625/BZA 20 for any indication at this time:

(b) (4)

This memo documents my concurrence with these conclusions and recommendations. NDA 022247 has been administratively split as follows:

- Original 1 will contain information supporting the use of CE 0.45/BZA 20 for the VMS and PMO indications while,
- Original 2 will contain information supporting the use of CE 0.625/BZA 20 the VVA, VMS and PMO indications.

Discussions regarding product labeling and postmarketing requirements have been satisfactorily completed and there are no inspectional issues that preclude approval of NDA 022247/Original 1 for CE 0.45/BZA 20 for the VMS and PMO indications. NDA 022247/Original 2 for CE 0.625/BZA 20 supporting the VVA, VMS and PMO indications will receive a Complete Response action.

Regulatory History

Evaluation of the combination of CE and BZA has been conducted under IND (b) (4) (prevention of postmenopausal osteoporosis, Division of Metabolism and Endocrinology Products) and under IND 062288 (treatment of vasomotor symptoms, and vulvar and vaginal atrophy, Division of Reproductive and Urologic Products).

On July 18, 2007, a pre-NDA meeting was held jointly with the two review divisions. At that meeting it became apparent that Study 304, supporting the PMO indication and endometrial protection claim, utilized a drug product formulation that was not bioequivalent to the formulation used in another phase 3 trial supporting the PMO indication (Study 303), and that an unacceptable rate of endometrial hyperplasia was observed.

A Type C meeting was held on February 12, 2008, to discuss product quality, clinical pharmacology, and clinical issues related to formulation changes that occurred during development. At that meeting, FDA noted that based on the available data 1) (b) (4) (b) (4) d, and 2) that endometrial protection had been demonstrated for CE 0.45/BZA 20 (b) (4)

The applicant submitted a new trial supporting the PMO indication and endometrial protection claim (Study 3307) under a Special Protocol Assessment request in August 2008. Agreement was reached that Study 3307 would be an acceptable replacement for Study 304.

On October 27, 2008, IND (b) (4) was transferred to the Division of Reproductive and Urologic Products (later renamed DBRUP).

On February 17, 2010, the Division provided written comments to Wyeth regarding the results of bioequivalence studies conducted to demonstrate bridging of the to-be-marketed CE/BZA tablet formulation with clinical Formulations A and B used in the phase 3 trials. The Division also provided preliminary comments for a pre-NDA meeting scheduled for September 26, 2011; the sponsor cancelled the meeting following receipt of the comments.

In January 2012, Wyeth requested a Type C meeting with the Division and the Office of Scientific Investigations (OSI). Following review of the meeting package submitted on March 30, 2012, OSI requested additional information regarding monitoring procedures during the conduct of the clinical trials, methods used to select sites for third party audits, the extent of missing source documents at various sites, and the impact of audit findings on the trial results. Wyeth provided the requested information in May and June 2012. After reviewing this information, OSI provided additional comments to Wyeth on September 11, 2012, requesting that the NDA submission contain: 1) a tabular accounting of the availability of source documentation for all investigational sites enrolling subjects in each trial, 2) information regarding monitoring and oversight of each trial, and 3) third party audit reports for the phase 3 trials. At a meeting held on September 14, 2012, the sponsor agreed to submit this information.

NDA 022247 was received on October 3, 2012, and reviewed in accordance with timelines specified in The Program. The application was granted a standard 12-month review. Information regarding missing source documents was received on February 19, 2013. The Late-Cycle Meeting (LCM) was held on June 26, 2013. An advisory committee meeting was not held because outside expertise was not deemed necessary.

Product Quality Considerations

(b) (4)

The following substantive review issues were raised at the LCM with the applicant, and subsequently addressed during the review:

1) (b) (4) dissolution failures were discovered during FDA's drug product manufacturing site inspection. Additional information is required (b) (4)

The applicant stated (b) (4)
(b) (4) Release testing and 3-month stability data on confirmatory batches were submitted on July 31, 2013, and met acceptance criteria for both CE and BZA dissolution. (b) (4)
(b) (4) Thus, the Agency's concerns were adequately addressed.

2) Environmental Assessments (EA) for CE and BZA have not been submitted. The applicant was advised to submit an EA for BZA; the EA for conjugated estrogens could be literature-based using data available on estrogens, estradiol equivalents and exposure models to assess the risks to ecological species. The applicant agreed to provide the requisite EAs, but without information on estradiol, by July 31, 2013. The applicant also proposed to provide additional CE information from GLP study reports on March 31, 2015. On July 3, 2013, the applicant submitted the proposed content for its EAs which was found acceptable. Review of the EAs submitted on July 31, 2013 found that approval of CE/BZA is not expected to have a significant impact on the human environment. Thus, the Agency's concerns were adequately addressed.

3) A test and acceptance criterion for (b) (4) bazedoxifene in the drug product is needed. The applicant's June 4, 2012 amendment adequately addressed this request.

Inspections of manufacturing facilities were conducted; on August 14, 2013, the Office of Compliance determined the facilities to be acceptable.

Clinical Pharmacology

After administration of a single dose of CE/BZA, baseline-adjusted total estrone (representing CE) is eliminated with a half life of approximately 17 hours. Bazedoxifene is eliminated with a half life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration.

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. In postmenopausal women, a significant proportion of circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

The metabolic disposition of BZA has been determined following oral administration of 20 mg of radiolabeled bazedoxifene. Bazedoxifene is extensively metabolized; glucuronidation is the major metabolic pathway.

Drug interactions. *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by CYP3A4. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in an increased risk for endometrial hyperplasia.

Bazedoxifene undergoes little or no CYP P450-mediated metabolism and does not induce or inhibit the activities of major CYP isoenzymes. *In vitro* data suggest that BZA is unlikely to interact with co-administered drugs via CYP-mediated metabolism. Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver. The metabolism of BZA may be increased by concomitant use of substances known to induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin. A reduction in BZA exposure may be associated with an increased risk of endometrial hyperplasia.

Because of the potential for loss of uterine protection when exposures to conjugated estrogens increase relative to exposures to bazedoxifene, the applicant will be required to conduct a drug-drug interaction trial post-approval to characterize the pharmacokinetic profile of conjugated estrogens when co-administered with a strong CYP3A4 inhibitor.

Formulation changes. Over the 10-year period of drug development, several formulation changes occurred. Formulation A (the original formulation) was used in Study 303 (PMO indication). Formulation B was used in Study 305 (VMS indication) and Study 306 (VVA indication). Study 304 used both Formulations B and C, however the BZA component of Formulation C was found to be 18% less bioavailable than the BZA component of Formulation A. In a written response dated October 10, 2008, to a Special Protocol Assessment, the Division agreed that Study 3307, which used Formulation A, could replace Study 304 in support of the PMO indication and endometrial protection claim.

Effect of body weight. The Agency's population PK analysis of dense PK data found that BZA clearance increased with body weight. Subjects over 75 kg were observed to have an average clearance that was 17% higher than those with lower body weight (less than or equal to 75 kg). Accordingly, a 17% decrease in BZA exposure is expected in this group of women. This decrease in BZA exposure could result in loss of endometrial protection.

QT Assessment. In a thorough QT study that evaluated up to 120 mg of BZA, no QTc prolongation was observed.

Pediatric Use. The pharmacokinetic profile of CE/BZA has not been evaluated in a pediatric population; the product is not indicated for use in children.

The following substantive review issues were raised at the LCM with the applicant, and subsequently addressed during the review:

1) Inadequate information is available related to the bridging of clinical trial formulations to the final to-be-marketed formulation. A June 19, 2013, amendment was under review at the time of the LCM. In this submission, the applicant demonstrated that clinical trial Formulations A and B bridge to the final to-be-marketed CF Formulation.

2) At the LCM, the Division noted that product use would not be recommended in labeling for women with renal or hepatic impairment, or in women > 75 years of age. The basis for these recommendations is as follows:

Renal impairment. The pharmacokinetics of CE/BZA have not been evaluated in women with renal impairment. The **Dosing and Administration** section, **Use in Patients with Renal Impairment** subsection, of the product label will recommend against product use in women with renal impairment.

Hepatic impairment. The pharmacokinetics, safety, and efficacy of CE/BZA have not been evaluated in women with hepatic impairment. No pharmacokinetic studies with CE were conducted in women with hepatic impairment.

In a pharmacokinetic study of BZA 20 mg alone, C_{max} and AUC increased 67% and 143%, respectively, in women with mild hepatic impairment (Child Pugh Class A, N=6), compared to healthy subjects. The C_{max} and AUC of BZA increased 32% and 109%, respectively, in women with moderate hepatic impairment (Child Pugh Class B, N=6). The C_{max} and AUC of BZA increased 20% and 268%, respectively, in women with severe hepatic impairment (Child Pugh Class C, N=6). The half-life of BZA was prolonged from 32 to 50 hours in women with severe hepatic impairment.

The use of CE/BZA in women with hepatic impairment will be contraindicated in product labeling.

Effect of age. The pharmacokinetic profile of CE/BZA has not been evaluated in the elderly. Clinical trials of CE/BZA did not enroll women > 75 years of age.

The pharmacokinetics of a single 20 mg dose of BZA were evaluated in postmenopausal women. Compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC, and women \geq 75 years of age (n=8) showed a 2.6-fold increase in AUC. This increase in BZA exposure could result in loss of CE efficacy.

The **Dosing and Administration** section, **Use in the Elderly** subsection, of the product label will recommend against product use in women over 75 years.

Retention of Source Documents

Due to natural disaster, clerical errors, or unknown random events, source documentation was partially or completely missing in approximately 8% of subjects in Study 303 (PMO indication), in 1.5% of subjects in Study 305 (VMS indication), (b) (4)

The following substantive review issue was raised at the LCM with the applicant and addressed during the review as follows:

Concerns regarding the reliability of data from Study 303 were raised due to the recent (May 23, 2013) submission of adverse event reports from a trial that was completed in 2006. The Division asked why approximately ten percent of the subject files from Site 447 in Brazil appeared to be missing at random.

The applicant explained that Site 447 was inspected in January 2013 and four discrepancies between source files and case report forms were noted, but that none of these recently reported adverse events changed the overall adverse event profile of the product. The applicant attributed the missing subject files to closure of the site and movement of those files between the site and the storage facilities. The applicant stated that they conducted both internal and third-party quality assurance inspections and determined that the pattern of missing subject files was random in nature, but that they were unable to identify the reason(s) for the missing files.

On August 2, 2013, the Office of Scientific Investigations finalized its recommendations regarding the clinical site inspection findings. The Division was advised to consider the implications of missing records in its assessment of efficacy. Re-analyses of efficacy removing data from participants with missing source documentation were performed; removal of these data did not adversely affect the efficacy findings from either Study 303 (PMO indication) or Study 305 (VMS indication). (b) (4)

Efficacy

Treatment of vasomotor symptoms (VMS). The efficacy of CE 0.45/BZA 20 as a treatment for moderate to severe vasomotor symptoms associated with menopause was established in a 12-week randomized, double-blind, placebo-controlled trial (Study 305). A total of 318 women, ages 42-64 (mean age 53 years) with an intact uterus who had at least 7 moderate to severe hot flushes per day or at least 50 per week at baseline were evaluated. Of these, 127 women were assigned to CE 0.45/BZA 20, (b) (4), and 63 women were assigned to placebo.

Treatment with either CE/BZA dose significantly reduced the number and severity of hot flushes, as measured by the daily severity score, compared with placebo at Weeks 4 and 12 ($p < 0.001$ for each efficacy measure at each time point). A re-analysis of efficacy endpoints with removal of data from subjects with missing records did not alter the results. (b) (4)

(b) (4)
NDA 022247/Original 2 containing information supporting the use of CE 0.625/BZA 20 for VMS will receive a Complete Response action.

Prevention of postmenopausal osteoporosis (PMO). The efficacy of CE 0.45/BZA 20 for the prevention of postmenopausal osteoporosis was established in two randomized controlled trials that assessed changes in bone mineral density.²

Study 303 was a 24-month, double-blind, randomized, placebo- and active-controlled trial evaluating multiple combinations of CE/BZA (including CE 0.45/BZA 20) and placebo on bone mineral density. A total of 3,397 women ages 40-75 (mean age 56 years) with an intact uterus were evaluated.

Prevention of osteoporosis was assessed in two subgroups: 1) 1454 women at least 5 years from their last menstrual period (mean 11 years), and 2) 861 women between 1 and 5 years since menopause (mean 3 years). Women in these subgroups had a mean age of 59 and 52 years, and a mean baseline lumbar spine

² In general, for all agents except estrogens, fracture efficacy must be demonstrated prior to accepting changes in bone mineral density as the endpoint for a prevention indication. Based on epidemiologic data, estrogens have been shown to have fracture efficacy. Based on clinical trial data, BZA 20 mg monotherapy has been shown to reduce the risk of fractures.

T-score of -1.47 and -0.83, respectively. Women in both groups took calcium (600-1200 mg) and vitamin D (200-400 IU) daily.

Treatment with either CE/BZA dose significantly increased lumbar spine BMD at 24 months compared to placebo in both groups of postmenopausal women ($p < 0.001$). Treatment with either CE/BZA dose also increased total hip bone mineral density in both groups. A re-analysis of efficacy endpoints with removal of data from subjects with missing records did not alter the results. (b) (4)

Study 3307 was a 12-month, double-blind, randomized, placebo- and active-controlled trial; a total of 1,843 women, ages 41-64 (mean age 54 years) were evaluated. Of these, 590 women were less than 5 years postmenopausal (mean 2.5 years). The mean baseline lumbar spine T-score was -0.91 in women treated with CE 0.45/BZA 20 (b) (4) and -0.95 in women in the placebo group. Women took calcium (600 mg) and vitamin D (400 IU) daily.

Treatment with either CE/BZA dose significantly increased mean lumbar spine bone mineral density at 12 months compared to placebo in women who had been postmenopausal between 1 and 5 years (mean 2.5 years). Total hip bone mineral density was also increased with CE/BZA treatment relative to placebo. (b) (4)

Fracture efficacy for CE/BZA was not formally assessed in this development program. Fractures were captured as adverse events; the incidence of fractures was low in both CE/BZA- and placebo-treated women.

Only the CE 0.45/BZA 20 dose is recommended for approval. The **Indications and Usage** section, **Limitation of Use** subsection, will include language that is consistent with the labeling for other conjugated estrogens, namely, that product use only for the prevention of postmenopausal osteoporosis should be limited to women at significant risk of osteoporosis after non-estrogen alternatives have been carefully considered.

(b) (4)
NDA 022247/Original 2 containing information supporting the use of CE 0.625/BZA 20 for PMO will receive a Complete Response action.

Treatment of vulvar and vaginal atrophy (VVA). (b) (4)

(b) (4)

The following substantive review issue was raised at the LCM with the applicant and has been addressed as follows:

(b) (4)
NDA 022247/Original 2 containing information supporting the use of CE 0.625/BZA 20 for VVA will receive a Complete Response action.

Safety

The safety of CE/BZA was evaluated in four phase 3 clinical trials ranging from 12 weeks to 24 months in duration and enrolling 6,210 postmenopausal women ages 40 to 75 years (mean age 55 years). Among these, 1,224 women were treated with CE 0.45/BZA 20, and 1,069 women received placebo.

The incidence of all cause mortality, serious adverse events, and neoplasia was low in both CE/BZA and placebo-treated women. The percentage of women who withdrew from treatment due to adverse events was 7.5% and 10% in CE/BZA- and placebo-treated women, respectively. The most common adverse events leading to discontinuation were hot flushes, abdominal pain, and nausea.

Venous and arterial thromboembolism (VTE and ATE). Venous thromboembolism and arterial thrombotic events (including stroke and myocardial infarction) are known to occur with administration of both conjugated estrogens and estrogen agonist/antagonists. The incidence of VTE and arterial thrombotic events was low in both CE/BZA- and placebo-treated subjects.

Consistent with the labeling for other products containing CE, use of CE/BZA will be contraindicated in women with an active or a past history of VTE or arterial thrombotic events.

At the LCM, the Division noted that estrogen class labeling would be included in product labeling for CE/BZA. This would include standard wording for the contraindications, boxed warnings, and warnings and precautions sections, as well as descriptions of the results of the Women's Health Initiative estrogen-alone substudies.

Effects on the endometrium. The role of bazedoxifene in the CE/BZA combination is to provide endometrial protection in lieu of a progestational agent. Adequate protection is defined as an endometrial hyperplasia rate after 12 months of $\leq 1\%$ (with the upper bound of the one-sided 95% CI $\leq 4\%$).³

In Study 303, the probability of endometrial hyperplasia was assessed for combinations of CE 0.45 mg and BZA 10, 20, or 40 mg, and for combinations of CE 0.625 mg and BZA 10, 20, or 40 mg. At month 12, the endometrial hyperplasia rate exceeded (b) (4) for CE 0.625/BZA 10 (b) (4) at month 24, the endometrial rate exceeded 1% for CE 0.45/BZA 10 and CE 0.625/BZA 10 (at 2.5% and (b) (4), respectively).

In Study 303, combinations of CE with BZA 20 or 40 mg had acceptable endometrial hyperplasia rates. This finding was replicated in Study 3307 (which used the same formulation); the endometrial hyperplasia rate at month 12 in this trial was less than 1% for both CE 0.45/BZA 20 and CE 0.625/BZA 20.

In Study 304, during the second year, subjects were switched from Formulation B to Formulation C, which contained a BZA component that was less bioavailable than that of Formulation A used in Study 303 and 3307. In Study 304, women with 12 and 24 month exposures to CE 0.425/BZA 20 had acceptable endometrial hyperplasia rates; (b) (4). These data raise concerns that a relatively small decrement in BZA bioavailability could have a dramatic increase in the endometrial hyperplasia rate. (b) (4)

The following substantive review issue was raised at the LCM with the applicant and addressed during the review as follows:

(b) (4)

³ See Draft Guidance for Industry: *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations of Clinical Evaluation*, 2003.

Vaginal Bleeding. Vaginal bleeding and spotting are known to occur with use of combination conjugated estrogen/medroxyprogesterone acetate products. Similarly, the combination of CE with an estrogen agonist-antagonist such as BZA may provide incomplete protection from vaginal bleeding and spotting. Vaginal bleeding was reported with similar frequency in subjects on CE 0.45/BZA 20, CE 0.625/BZA 20, and placebo (4-5%).

Fractures. Fractures were reported with similar frequency in subjects on CE 0.45/BZA 20, on CE 0.625/BZA 20, and on placebo (1-2%). The most common types of fractures reported were foot, rib, and wrist fractures.

Pregnancy and Nursing Considerations

CE/BZA will be designated as Pregnancy Category X and must not be used in women who are or may become pregnant.

No studies were performed on animals to evaluate the effects on reproduction with CE/BZA.

Administration of BZA to rats at maternally toxic dosages ≥ 1 mg/kg/day (≥ 0.3 times the human AUC at the 20 mg dose) resulted in reduced numbers of live fetuses and/or reductions in fetal body weights. No fetal developmental anomalies were observed. In studies conducted with pregnant rabbits treated with BZA, abortion and an increased incidence of heart (ventricular septal defect) and skeletal system (ossification delays, misshapen or misaligned bones, primarily of the spine and skull) anomalies in the fetuses were present at maternally toxic dosages of ≥ 0.5 mg/kg/day (twice the human AUC at the 20 mg dose).

Duavee should not be used by lactating women. It is not known whether the drug is excreted in human milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

Tradename Review

On June 18, 2013, the applicant was notified that the proposed tradename “Duavee” is acceptable.

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The pediatric study requirement for this application will be waived because necessary studies are impossible or highly impracticable as the approved indications apply to conditions that do not occur in the pediatric population.

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of increased concentrations of conjugated estrogens in the presence of a strong CYP3A4 inhibitor. These increased concentrations may increase the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of increased concentrations of conjugated estrogens in the presence of a strong CYP3A4 inhibitor. These increased concentrations may increase the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Therefore, based on appropriate scientific data, FDA has determined that the applicant will be required to conduct a pharmacokinetic trial evaluating the effect of a strong CYP3A4 inhibitor on the exposure of conjugated estrogens and bazedoxifene in obese and non-obese women.

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/s/

JULIE G BEITZ
10/03/2013