Drug Use Research & Management Program
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New Drug Evaluation: Delayed Release Duavee® (conjugated estrogens/bazedoxifene)

Month/Year of Review: November 2014
Generic Name: conjugated estrogens/bazedoxifene
PDL Class: HRT-Estrogen, Oral

End date of literature search: March 1, 2014
Brand Name (Manufacturer): Duavee® (Wyeth)
Dossier Received: Pending

United States Food and Drug Administration (FDA) Approved Indication:
Conjugated estrogens/bazedoxifene (CE/BZA) is indicated for treating moderate to severe vasomotor symptoms associated with menopause or for preventing postmenopausal osteoporosis in women with a uterus. [1]

Research Questions:
- Is there evidence CE/BZA is superior to hormone therapy (e.g. conjugated estrogens/medroxyprogesterone acetate [CE/MPA]) in treating postmenopausal vasomotor symptoms or improving health-related quality of life or menopause-related quality of life (MSQOL) for postmenopausal women with vasomotor symptoms?
- Is there evidence CE/BZA is safer than hormone therapy for treating postmenopausal vasomotor symptoms?
- Is CE/BZA superior to bisphosphonates, other selective estrogen receptor modulators (SERMs), or hormone therapy for preventing osteoporosis and hip, vertebral, or other fractures?
- Is CE/BZA safer than bisphosphonates, other SERMs, or hormone therapy for preventing osteoporosis?
- Are there sub-groups where CE/BZA is more effective or safer than current therapies for postmenopausal symptoms or osteoporosis prevention?

Conclusions:
- CE/BZA has not been compared with current therapies for postmenopausal vasomotor symptoms. Only one phase 3 poor quality trial (SMART 2) and one supportive poor quality sub-study (SMART 1) comparing CE/BZA with placebo provide low quality evidence. CE/BZA significantly reduced the number and severity of hot flushes (mean difference in the daily number of moderate and severe hot flushes between CE/BZA and placebo was –2.71 in SMART 2 and -6.29 in sub-study SMART 1).

- Evidence that CE/BZA improves health-related quality of life (HRQOL) is insufficient. One combined analysis provides low quality evidence that CE/BZA, vs placebo, results in a meaningful change in the vasomotor functioning score of MSQOL.

- The poor quality SMART 5 trial provides low quality evidence CE/BZA significantly increases lumbar spine and total hip bone mineral density (BMD) compared with placebo (placebo subtracted difference 1.51% for the lumbar spine and 1.21% for the total hip). However, the researchers observed no statistically significant difference between the CE/MPA subgroup and CE/BZA and did not evaluate fracture risk.

- Clinical trials provide low quality evidence for the CE/BZA indications: treatment of vasomotor symptoms and prevention of osteoporosis. The incidences of all-cause mortality, serious adverse events, venous thromboembolism (VTE), and endometrial hyperplasia or endometrial malignancy in patients taking CE/BZA were similar to placebo. However, the adverse effects associated with use in a general, menopausal population remain unexplored. The potential implications of

discontinuing CE/BZA, such as the rapid bone loss associated with CE-alone use, are unclear. CE/BZA comes with the CE-related risk of VTE and ischemic stroke, and the benefits of oral hormone therapy (HT) are more likely to outweigh the risks before age 60 or within 10 years of menopause.

- According to prescribing information and National Osteoporosis Foundation (NOF) guidelines, CE/BZA use should be limited to women at significant risk of osteoporosis after considering alternatives not containing estrogen. The Global Consensus Statement on Menopausal Hormone Therapy places further limitations on the use of hormonal therapy by stating menopausal hormone therapy is effective and appropriate for preventing osteoporosis-related fractures in at-risk women who are <60 years of age or within 10 years of the start of menopause.

Recommendations:

- Make CE/BZA non-preferred due to insufficient evidence comparing it with currently available therapies and low quality evidence of efficacy compared with placebo.
- Limit use to women who
  - are postmenopausal and are within 10 years of menopause
  - are <60 years of age
  - have an intact uterus
  - failed or contraindicated to
    - conventional hormone therapy(for Prevention of vasomotor symptoms), OR
    - bisphosphonates (for Prevention of osteoporosis)

Reason for Review:
The tissue specific estrogen complex CE/BZA was approved by the FDA October 3, 2013.

Background:
CE/BZA is the first FDA-approved estrogen/SERM combination. The drug's estrogen component provides vasomotor symptom relief and increases bone density, while the SERM potentially mitigates the endometrial cancer risk that arises when women who have a uterus receive estrogen unopposed by a progestogen. The SERM also may mitigate the risk of breast cancer. BZA monotherapy has been approved in 35 countries and marketed in six countries—including Japan, Korea, Canada, and Australia—for the treatment and prevention of post-menopausal osteoporosis. [2, 3]

Treatment of Vasomotor Symptoms:
Women with menopause-related vasomotor symptoms experience reduced sleep quality, irritability, difficulty concentrating, and reduced quality of life.[4, 5] Several studies have reported the use of HT can improve menopause-related symptoms.[4, 6, 7]

Estrogen therapy (ET) with a progestogen, which is required in women with a uterus, or without a progestogen is considered the most effective treatment for moderate to severe menopause-related vasomotor symptoms and their consequences.[5 ,8] The risk of VTE and ischemic stroke increases with oral HT, but the absolute risk is rare in those <60 years old. Therefore, the benefits are more likely to outweigh the risks in women <60 years of age or within 10 years of menopause.[8, 9]

Postmenopausal Osteoporosis Prevention:
Based on 2010 statistics, an estimated 10.2 million Americans ≥50 years old have osteoporosis, and 42.5 million have low bone mass at the femoral neck or lumbar spine. Combined, these figures represent about 54% of the population who are >50 years old. . [10]

Osteoporosis diagnosis is established by bone mineral density (BMD) measurement or the occurrence of adulthood hip or vertebral facture, in the absence of metabolic bone diseases and major trauma. Osteoporosis is defined by BMD at the hip or lumbar spine that is ≤2.5 standard deviations (SD) below the mean BMD of a young-adult reference population as measured by dual-energy x-ray absorptiometry (DXA), which assesses bone density at various skeletal sites using radiation exposure. [10]

Although those with the lowest BMD have the highest fracture risk, patients with low bone mass, rather than those with osteoporosis, have the most factures. The most common fractures occur at the spine, hip (proximal femur), and wrist. [10]

NOF guidelines[10] recommend pharmaceutical treatment for women with:

- clinical or asymptomatic hip or vertebral fractures;
- DXA T-scores ≤ –2.5 SD at the femoral neck, lumber spine, and total hip; or
- postmenopausal women with low bone mass (DXA T-score between –1 and –2.5 SD) at the femoral neck, total hip, or lumbar spine and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on US-adapted WHO absolute fracture risk (FRAX). [10]

FDA-approved options for osteoporosis prevention are bisphosphonates, SERMs, and HT. Non-pharmacologic recommendations include adequate calcium and vitamin D and weight-bearing and muscle-strengthening exercise.[10] The NOF guidelines state that approved non-estrogen treatment is first-line, before considering HT when solely used for preventing osteoporosis.[10] According to the Global Consensus Statement on Menopausal Hormone Therapy, menopausal HT is effective and appropriate for preventing osteoporosis related fractures in at-risk women who are <60 years of age or within 10 years after menopause.[8] According to the North American Menopause Society (NAMS), when alternate osteoporosis therapies are not appropriate or cause adverse effects, the extended use of HT is an option for women at high risk for osteoporosis-related fractures. The NAMS also considers HT or oral contraceptives, unless contraindicated, appropriate for women who have early menopause and need to prevent bone loss, until reassessment when they reach the normal age of menopause.[5] However, the benefits of HT on bone mass and fracture rapidly wane after discontinuing treatment, requiring transition to osteoporosis treatments that preserve bone mass. In the WHI, the ET and placebo groups had the same cumulative incidence of hip fracture within a few years of discontinuing ET.[5] In contrast, bisphosphonates may have residual effects after treatment is discontinued.[10] The NOF recommends CE/BZA's use for women who are at significant risk of osteoporosis after considering alternatives that do not contain estrogen, while other guidelines have yet to address this product.[10]

According to the NOF, the need for continuing osteoporosis medication should be reviewed annually.[10] After the initial three to five years of treatment, a comprehensive risk assessment should be performed. Comprehensive assessment should include fracture history, new chronic diseases or medications, height measurement, BMD testing, and vertebral imaging if there has been any documented height loss during the treatment period.[10]

Clinical Efficacy:

Clinical efficacy data is included only for the approved dose (CE 0.45 mg/BZA 20 mg). The acronym CE/BZA refers to the approved dose. The dosage for unapproved dosage forms are noted when addressed.

Treatment of Vasomotor Symptoms:

Approval of CE/BZA for treating moderate to severe vasomotor symptoms was based on pivotal Trial 305 (Selective Estrogens, Menopause, And Response to Therapy 2 or SMART 2), with supporting evidence from a sub-study of Trial 303 (SMART 1 sub-study). [2]

In SMART 2 (Trial 305)—a poor quality study—CE/BZA significantly reduced the number and severity of hot flushes over 12 weeks. SMART2 was a multicenter, double-blind, three parallel group, placebo-controlled study that randomized 332 (n=310 modified intent to treat [mITT], defined below) healthy postmenopausal women who were age 40 to 65 and had intact uteruses. The women sought treatment for hot flushes and reported seven moderate to severe hot flushes per day or 50 per week. Subjects were randomized 2:2:1 to received daily CE 0.625 mg/BZA 20 mg, CE/BZA, or placebo. The co-primary endpoints were reduction in the average daily number of moderate and severe hot flushes and reduction in daily severity of hot flushes at weeks 4 and 12 compared with placebo. The daily severity score was calculated as follows: [(# mild hot flushes) + (# moderate hot flushes x 2) + (# severe hot flushes x 3)] ÷ [total # hot flushes]. The mITT population and last observation carried forward (LOCF) were used for the primary analysis at weeks 4 and 12. The mITT population was defined as those who had taken ≥1 dose, had ≥5 days of data at baseline, and had ≥5 days of data for ≥1 on-therapy week. At week 12, CE/BZA reduced the average number of daily moderate and severe hot flushes from baseline by 74% (mean change from baseline –7.63) vs 47%] (mean change from baseline –4.92) for placebo, resulting in a difference from placebo of –2.71 (CI: –3.84 to –1.57, p<0.001). This exceeded the >2 hot flushes per day criterion in 2003 FDA Guidance. The FDA noted the magnitude of effect was numerically lower than approved

CE/progestogen preparations: CE/MPA mean reduction of –10.8 hot flushes per day for a placebo-subtracted decrease of –4.8. With regard to severity of hot flushes, CE/BZA reduced the average daily severity from baseline by 38% (mean change from baseline –0.87) vs 11% (mean change from baseline –0.26) for placebo (difference from placebo –0.60, CI: –0.86 to –0.35, p<0.001). The greatest mean decrease in symptoms (frequency and severity) occurred 5 to 6 weeks after treatment onset.[2,11]

SMART 1 was a poor quality supportive study evaluating the effects of CE/BZA on menopausal symptoms. The main study of this multicenter, double-blind, placebo- and active-controlled phase 3 trial enrolled 3,397 healthy, primarily white women who had been postmenopausal for at least 1 year, were ages 40 to 75, and had an intact uterus. Subjects were randomized 1:1:1:1:1:1:1:1 to receive CE (0.625 mg or 0.45 mg)/BZA (10mg, 20mg, or 40 mg) or raloxifene 60 mg or placebo. Subjects also were directed to maintain a consistent daily intake of dietary and supplemental calcium (1000 to 1600 mg) and vitamin D (200 to 400 IU). The primary endpoint of the main study was the incidence of endometrial hyperplasia at 12 months, while the primary endpoint for the indication was the mean change in the number of hot flushes from baseline at week 12 using LOCF for the efficacy evaluable population (EE1, n=216), defined as subjects who had taken at least 1 dose, had screening endometrial biopsy, or had hyperplasia diagnosed before the time point and who reported at least seven moderate or severe hot flushes daily or 50 weekly during screening. Subjects recorded hot flushes in daily diaries and the mean daily number of hot flushes was calculated using moderate and severe hot flushes and the mean daily severity of hot flushes was calculated using mild, moderate, and severe (assigned intensities of 1, 2, and 3, respectively). At baseline, the mean number of hot flushes were 11.44, 12, and 14.32 for the CE/BZA (n=28), raloxifene (n=24), and placebo (n=33) arms and the mean severity of hot flushes was 2.45, 2.37, and 2.37, respectively. CE/BZA significantly reduced the frequency and severity of hot flushes compared with placebo. At week 12, the mean daily change in the number of hot flushes from baseline were –8.74, –5.29, and –2.45 for CE/BZA, raloxifene, and placebo, resulting in percentage decreases of 76%, 44%, and 17%, respectively. The mean change in severity of hot flushes was –1, –0.22, and –0.21, respectively, for a placebo subtracted difference of –0.60 (CI: –0.86 to –0.35) for CE/BZA.[2, 12]

Abraham et al[13] analyzed the changes in total and domain scores on the 29-item self-administered Menopause-specific Quality of Life questionnaire (MENQOL) across SMART 1, SMART 2, and SMART 5 (a trial for the approved osteoporosis indication), as well as SMART 3, a trial conducted for the unapproved indication vulvar/vaginal atrophy. MSQOL was prospectively evaluated among several secondary endpoints in these studies, mostly without adjusting for multiplicity. The studies reported scores for the vasomotor, physical, sexual, and psychosocial functioning domains and the aggregated score for CE/BZA. Subjects indicated their symptom experiences in the last month on a scale from 1 (not experienced) to 8 (extremely bothered). The differences in total MENQOL and physical, psychosocial, and sexual functioning domains between CE/BZA and placebo did not exceed the defined Clinically Important Differences (CID). The differences in vasomotor functioning exceeded the CID for SMART 2 at 3 months (–1.69, p<0.001) and SMART 5 at 12 months (–1.65, p<0.001), but not for SMART 1 at any time point and not for SMART 5 at 3 months.

The evidence for CE/BZA's efficacy in treating vasomotor symptoms is of low quality. The evidence is comprised of one main study and one sub-study with small patient numbers, with the average number of patients per treatment arm per study center being less than one for the SMART 1 sub-study and less than three for SMART 2. Although CE/BZA is indicated for women who are post-menopausal up to the age of 75, the populations in the studies were generally healthy and likely would not reflect a true population. High discontinuation rates across the SMART 1 main study's treatment arms (29.8% for CE/BZA, 35.7% for RAL, and 35.4% for PLA) indicate CE/BZA's usefulness may be limited. Also a fixed-dose formulation of CE/BZA may limit its use in women who require higher or lower doses of estrogen. Numerous internal validity concerns also were evident in these studies:

- Mild hot flushes were included in the assessment of the change in moderate and severe hot flushes, which may inflate the baseline severity.
- A clinically significant reduction in the severity of hot flushes was not defined. 31.3% of subjects had protocol violations in SMART 1 and 25.2% in SMART 2.
- The SMART 2 mITT population had subjects who did not meet the entry criteria for the requisite number of hot flushes.
- The distribution by race/ethnicity was uneven across study groups for the SMART 1 sub-study
- An imbalance in the number of hot flushes at baseline existed across study groups in the SMART 1 sub-study.
- Enrollment in the SMART1 main study was not based on hot flush frequency or severity requirement.
- The number of subjects in the SMART 1 sub-study was not predefined.

Finally, CE/BZA's ability to improve quality of life has not been adequately demonstrated. One poorly quality assessment of MSQOL has been performed. This assessment equivocally supports the vasomotor symptom indication; however, it does not support CE/BZA's ability to improve other measures of the MSQOL and does not address HRQOL.

Postmenopausal Osteoporosis Prevention: [2]
An osteoporosis sub-study (OSS) of SMART 5 (Trial 3307) and two supportive sub-studies (OP1 and OP2) of SMART 1 (Trial 303) served as the basis for CE/BZA's indication for the prevention of postmenopausal osteoporosis. The primary endpoints for the sub-studies were the mean changes in BMD at the lumbar spine at month 12 for SMART 5 OSS and at 24 months for the SMART1 OP1 and OP2.

SMART 5 was a poor quality, multicenter, randomized, double-blind, and placebo- and active-controlled study in generally healthy women who were age 40 to 64, had an intact uterus, were ≤5 years postmenopausal, and were seeking treatment for menopausal symptoms. The study evaluated the endometrial safety and BMD effects of daily CE (0.45 mg or 0.625 mg)/BZA 20 mg vs BZA 20 mg alone, CE 0.45 mg/MPA 1.5 mg, and placebo. The primary endpoint for the main study was incidence of endometrial hyperplasia. The percent change in lumbar spine BMD and in total hip BMD from baseline at month 12 were primary and secondary endpoints, respectively, of the OSS. The OSS was performed at sites with DXA machines and included 119 of 445, 56 of 230, 59 of 220, and 139 of 474 subjects in the CE/BZA, BZA, CE/MPA, and placebo arms of the main study, respectively.

The CE/BZA, BZA, and CE/MPA subgroups had significantly greater increases in lumbar spine and total hip BMD compared with the placebo subgroup at 12 months:
OSS lumbar spine: 0.24% for CE/BZA ($p<0.001$), 0.07% for BZA ($p=0.0026$), 1.30% for CE/MPA ($p< 0.001$), –1.28% for placebo
OSS total hip: 0.50% for CE/BZA ($p< 0.001$); 0.47% for BZA ($p< 0.001$); 0.71% for CE/MPA (p-value not reported); –0.72% for placebo

The placebo subtracted mean percent change in BMD at the lumbar spine and total hip for the CE/MPA subgroup was numerically greater than for the CE/BZA subgroup but was not statistically different: 2.57% (CI: 1.72 to 3.43) vs 1.51% (CI: 0.82 to 2.2), respectively, for the spine and 1.42% (CI: 0.85 to 1.99) vs 1.21% (CI: 0.76 to 1.67) for the hip. The placebo group had progressive bone loss over 12 months.

SMART 1—a poor quality, 24-month, multicenter, placebo- and active-controlled study—evaluated the effects of CE/BZA on BMD in women at risk for osteoporosis. Included were healthy postmenopausal women who were age 40 to 75 and had intact uteruses and acceptable endometrial biopsy at baseline. The subjects were randomized 1:1:1:1:1:1:1:1 into eight groups: CE (0.45 mg or 0.625 mg)/BZA (10 mg, 20 mg, or 40 mg), raloxifene 60 mg, and placebo. Subjects were prospectively enrolled into one of two sub-studies based on menopausal status: (1) Osteoporosis Prevention I sub-study (OPI 1) if >5 years post-menopausal and a BMD T-score at the lumbar spine or total hip between –1 and –2.5 and ≥1 additional osteoporosis risk factor (2) Osteoporosis Prevention 2 and Metabolic sub-study (OP2) if ≤5 years postmenopausal and ≥1 osteoporosis risk factor. Baseline characteristics were similar across study groups except for maternal history of fracture: 5.56% for CE/BZA, 6.95% for raloxifene, 8.15% for placebo group for OP1 and 3.6% for CE/BZA, 7.5% for raloxifene, 6.5% for placebo group for OP2. The mean years since menopause for OP1 was about 11 years and for OP2 was about 3 years, the mean age of subjects was 58 for OP1 and 52 for OP2, the mean age of the last menses was about 48 for OP1 and 50 for OP2, the baseline mean lumbar spine T-score was –1.47 for OP1 and in the normal range (–0.83) for OP2. About 55% of women in OP2 were osteopenic by T-score. Subjects in both sub-studies had their daily calcium and vitamin D intake assessed at baseline and received calcium carbonate 600 mg plus vitamin D_3 if their calcium intake was <1000 mg.

The primary endpoint of the main study was the incidence of endometrial hyperplasia after 1 year—a surrogate endpoint for endometrial cancer—using the EE population (subjects who had taken at least 1 dose, had screening endometrial biopsy, or had hyperplasia diagnosed before the time point). The main secondary endpoint evaluated by the FDA was the mean percent change from baseline BMD of the lumbar spine after 2 years of therapy between CE/BZA groups and placebo using the mITT population (subjects who took ≥1 dose and had baseline and ≥1 on-therapy BMD) and LOCF. Among the other secondary endpoints was BMD of the hip (mean percent change at all time points). Responder rates were compared between CE/BZA groups and placebo using mITT, defined as all subjects who took at least one dose and had baseline and at least one on-therapy BMD.

In both sub-studies, the CE/BZA group had a significantly greater least square (LS) mean percent change in lumbar spine and total hip BMD from baseline to 24 months than the placebo group and a significantly greater percent change in lumbar spine BMD than the raloxifene group ($p\leq0.001$ for all vs placebo):

- OP1 lumbar spine: 1.64% for CE/BZA, 0.75% for raloxifene, –1.47% for placebo

total hip: 1.07% for CE/BZA, 0.87% for raloxifene, 1.53% for placebo

- OP2 lumbar spine: 1.72% for CE/BZA, 0.13% for raloxifene, –1.90% for placebo
  total hip: 0.46% for CE/BZA, –0.27% for raloxifene, –1.41% for placebo

The responder rates for no change or increase in BMD for the lumbar spine at month 24 were significantly greater for CE/BZA and RAL than PLA: 68% and 59% vs. 30%, respectively, ($p<0.001$ for both). The FDA did not use responder figures in their review.

The evidence for the efficacy of CE/BZA in preventing osteoporosis is of low quality. The indication is based on sub-studies with small patient numbers and surrogate, secondary, and sub-study endpoints. Also, the efficacy of CE/BZA in improving fracture risk has not been addressed. CE/BZA is indicated for women with osteoporosis who are up to age 75. At this age, many women are likely to have acquired or be subject to a variety of health issues. However, the populations used in the CE/BZA studies were generally healthy women who had been prescreened for endometrial abnormalities. Furthermore, women primarily ≤65 years of age served as subjects in the SMART 1 trial; 45% of subjects in SMART 1 OP2 had a mean lumbar T-score within the normal range; the maximum years of age and years since menopause of patients in SMART 5 were about 62 and 5.5, respectively; and the mean T-score was within the normal range for SMART 5. Also limiting external validity were high discontinuation rates across the SMART 1 main study's treatment arms (29.8% for CE/BZA, 35.7% for RAL, and 35.4% for PLA) and the use of two different formulations for phase 3 trials, neither of which was the marketed formulation. However, the FDA was satisfied the formulations were bioequivalent. Internal validity concerns included an uneven history of maternal fracture across study groups for SMART 1 OP1 and OP2, an imbalance in discontinuation rates in SMART 5, and a lack of direct statistical comparisons between CE/MPA and raloxifene and CE/BZA.
Outstanding questions: How long should therapy be continued? What is CE/BZA's place in therapy relative to other osteoporosis prevention therapies? Is CE/BZA more safe and effective than CE/MPA for long-term use?

Clinical Safety: [1]
CE/BZA's safety was evaluated in four phase 3 clinical trials including a total of 1,224 patients treated with CE/BZA and 1,069 patients treated with placebo, as well as calcium (600-1200 mg) and vitamin D (200-400 IU) daily in SMART 1 and 5. The incidences of all-cause mortality and serious adverse events were 0% and 3.5%, respectively, in the CE/BZA group and 0.2% and 4.8%, respectively, in the placebo group. The percentage of subjects discontinuing treatment due to adverse reactions was 7.5% in the CE/BZA group and 10% in the placebo group. Hot flush, upper abdominal pain, and nausea were the most common adverse reactions leading to discontinuation. The most common adverse reactions (incidence ≥ 5%) more frequently reported in subjects treated with CE/BZA than placebo are presented in the appendix table Adverse Reactions.

SMART 1 and SMART 5 assessed the effects of CE/BZA on endometrial hyperplasia or endometrial malignancy and on uterine bleeding or spotting. The EE population (patients who had taken at least one dose of CE/BZA, had baseline and post-baseline endometrial biopsies, or had been diagnosed with hyperplasia) had an incidence of endometrial hyperplasia or malignancy <1% at 24 months and 12 months for SMART 1 and 5, respectively. The cumulative amenorrhea at 12 months was 83% and 88% for the CE/BZA groups in SMART 1 and 5, respectively, vs 85% and 84% for the placebo groups.

VTE was reported in 0% of patients taking CE/BZA and 0.1% of patients taking placebo. Because both groups had low VTE event rates, conclusions cannot be drawn about the risk of VTE with CE/BZA relative to that seen with other estrogen therapies.

The risks associated with the use of CE alone should be assumed to be similar for CE/BZA until shown otherwise.

Unanswered safety questions include the following:
What effects does discontinuing therapy have on bone loss? What are the risks of long-term use of CE/BZA and are the risks different depending on the age of the patient, number of years of use, and years since the start of menopause? What are the risks of developing hyperplasia for patients with significantly higher BZA clearance? Will women who take CE/BZA initially for vasomotor symptoms experience rapid bone loss upon discontinuation due to resolution of vasomotor symptoms?

What are the risks of CE/BZA use in the general population of postmenopausal women, including those who may not be healthy, have not had uterine biopsy prior to use, and are older and are several years past the start of menopause?

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COMPARATIVE CLINICAL EFFICACY

Treatment of Vasomotor Symptoms: [2, 11, 12]

Relevant Endpoints:
1) Health Related Quality of Life and Menopause Specific Quality of Life (see Clinical Efficacy section regarding MSQOL)
2) Serious adverse reactions
3) Mean daily number of moderate and severe hot flashes
4) Mean daily severity of hot flushes

Primary Study Endpoint:
1) Incidence of endometrial hyperplasia at 12 months (primary endpoint of the SMART 1 main study)
2) Mean change from baseline in average daily number of moderate and severe hot flushes at week 4 (SMART 2) and week 12 (SMART 1 sub-study and SMART 2)
3) Mean change from baseline in average daily severity of hot flushes at week 4 (SMART 2) and week 12 (SMART 1 sub-study and SMART 2): [(# mild hot flushes) + (# moderate hot flushes x 2) + (# severe hot flushes x 3)] ÷ [total # hot flushes]

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (p-values), LOCF	ARR/ NNT	Safety Results (CI, p-values)	ARR, NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. SMART 1 (Trial 303) supportive sub-study Lobo (2009) and FDA Med Review Phase 3, MC (94), DB, PC, AC, RCT Note: This study included 8 arms, 6 for CE/BZA, 1 for RAL, and 1 for PLA. Only the	1. CE 0.45 mg/BZA 20 mg daily 2. RAL 60 mg daily 3. PLA daily Duration: 12 weeks Note: SMART1 evaluated CE/BZA for treating vasomotor symptoms and preventing osteoporosis, so 3397 were randomized, but only patients meeting EE1 criteria (n=216	**Demographics:** SMART 1 EE1 population (CE/BZA, RAL, PLA, respectively): ・ Age (mean): 54.6, 55.6, 54 ・ Ethnic origin (%) White: 82.1, 87.5, 87.9 Black: 14.3, 4.2, 3 Other: 3.6, 8.3, 6.1 (1 subject missing from data for PLA ethnicity) ・ BMI (mean): 25.7, 25.7, 24.7 ・ Years since last menstruation (mean):	**EE1** 1. 28 2. 24 3. 33 Total trial randomization: N=3544 CE 0.625 mg/BZA 10 mg: 430 CE 0.625 mg/BZA 20 mg: 414 CE 0.625 mg/BZA 40 mg: 417 CE 0.45 mg/BZA	**Mean daily change in # of moderate and severe hot flushes at week 12:** 1. CE/BZA: –8.74, SE 1.14 (p=0.001) 2. RAL: –5.53, SE 1.18 (p=0.049) 3. PLA: –2.45, SE 1.02 (Efficacy is a difference of	NA	For the safety population (CE/BZA n=433, RAL n=423, PLA n=427): **Any SAE at month 24:** CE/BZA: 6% RAL: 7.6% PLA: 8% **Any TEAE at month 24:** CE/BZA: 92.6% RAL: 92.4%	NA NA	**Quality rating:** Poor-Fair **Internal Validity:** <u>Selection:</u> ・ The distribution by race/ethnicity is uneven across study groups ・ An imbalance in the number of hot flushes at baseline existed across groups with 11.4 hot flushes for CE/BZA and 14.3 for PLA. ・ Subjects who had ≥7 moderate o severe hot flushes per day or ≥50 per week during the screening week were prospectively included

approved dose (CE 0.45 mg/BZA 20 mg) is addressed in this efficacy evaluation.	total) were selected for the evaluation of vasomotor symptoms post-randomization. The safety evaluation includes all subjects taking the approved CE/BZA dose, raloxifene, and placebo.	6.7, 6.6, 6.8 · Mean # mod + severe HF: 11.44, 12, 14.32 · Mean severity HF: 2.45, 2.37, 2.39 **Inclusion Criteria:** · Healthy, postmenopausal women, age 40 to 75, with intact uterus · FSH >30 IU/mL and 17β-estradiol <183.5 pmol/L · Last menstruation ≥12 months before screening · BMI ≤32.2 kg/m^2 · Acceptable endometrial biopsy results at screening · ≥7 to 10 moderate or severe hot flushes daily or ≥50 weekly during the screening week · ≥5 years postmenopausal **Exclusion Criteria:** · Estrogen-dependent neoplasia · Endometrial hyperplasia · Malignancy in last 10 y, except basal cell skin cancer · Thrombophlebitis, thrombosis, thromboembolic disorders · Cerebrovascular accident, stroke, or TIA	10 mg: 417 CE 0.45 mg/BZA 20 mg: 433 CE 0.45 mg/BZA 40 mg: 423 RAL 60 mg: 423 PLA: 427	>2 hot flushes daily) **in severity of hot flushes at week 12:** 1. CE/BZA: –1, SE 0.15 (<0.001) 2. RAL: –0.22, SE 0.17 3. PLA: –0.21, SE 0.14	NA	PLA: 91.8% **Venous thromboembolism at month 24:** CE/BZA: <1% RAL: <1% PLA: <1% **Cardiovascular AEs at month 24:** CE/BZA: <1% RAL: <1% PLA: <1% **Discontinuation due to AEs:** CE/BZA: 10.6% RAL: 13.9% PLA: 14.3%	NA NA NA	in the sub-study. However, the number of subjects was not predefined. <u>Performance:</u> · 31.3% of subjects had protocol violations, including use of prohibited medications affecting lipids or coagulation and use of prohibited medications affecting bone metabolism. · Blinding of researchers was described for the main study but not the sub-study <u>Detection:</u> <u>Attrition:</u> · The discontinuation rate was high across all 8 arms for the main study, ranging from 29.8% to 35.7%, and was 29.8% for CE 0.45 mg/BZA 20 mg, 35.7% for RAL, and 35.4% for PLA specifically. Discontinuation rates for the sub-study were: 28% CE 0.45 mg/BZA 10 mg; 14% CE 0.45 mg/BZA 20 mg; 38% CE 0.625 mg/BZA 40 mg; 57% PLA; 25% RAL · Used LOCF **External Validity:** <u>Recruitment:</u> <u>Patient Characteristics:</u> · The study was limited to healthy postmenopausal women who had uterine biopsy performed <u>Setting:</u> · The average number of patients per study center was very small. Therefore, any determinations about setting are likely not

		· Neuro-ocular disorder · MI or ischemic heart disease · Chronic renal or hepatic disease · Gall bladder disease · Use of oral estrogen, progestin, androgen, or SERM medications withou washout · Presence of unresolved abnormal mammogram or pap smear; endocrine disease; LFT >1.5xULN; BP >160/100; alcohol or drug abuse						possible. <u>Outcomes:</u> · This study is of insufficient duration to assess or support the assessment of CE/BZA efficacy or safety beyond 12 weeks. · What constitutes a clinically meaningful reduction in the severity of hot flushes was not defined. · These results are from a sub-study of a main study investigating the incidence of endometrial hyperplasia. · Enrollment in the total sub-study was small (n=216 over 94 study centers). · Enrollment in the main study was not based on hot flush frequency or severity requirement. · Mild hot flushes were included in the assessment of the severity of hot flushes, which may inflate the baseline severity and confound the efficacy results, because mild hot flushes usually respond without treatment. · Safety is difficult to determine because of exclusion of subjects with conditions that may predispose them to unwanted side effects of estrogen therapy **Analysis:** · The results of this sub-study supports the indication with regard to the reduction in the number moderate and severe hot flashes by >2 per day. While this sub-study also supports a statistically significant

								improvement in severity of hot flushes, no indication of the clinical significance of this is evident. ・This sub-study is of insufficient duration to support the assessment of CE/BZA efficacy beyond 12 weeks or to assess the effect of discontinuation on severity of menopausal symptoms. Furthermore, the study population is unlikely to reflect the population considered for this therapy. ・This sub-study is of insufficient duration to assess or support the assessment of CE/BZA safety.
2. SMART 2 (Trial 305) Pinkerton (2009) and FDA Med Review Phase 3, MC (43), DB, PC, RCT	1. CE 0.45 mg/BZA 20 mg daily 2. PLA daily Duration: 12 weeks	CE/BZA (n=127), PLA (n=63), respectively, for safety population: ・ Age (mean): 53.6, 53.6 ・Ethnic origin (%) White: 88.2, 84.1 Black: 8.7, 11.1 Hispanic: 7.9, 4.8 Other: 3.2, 4.8 ・BMI (mean): 26.4, 26 ・Years since last menstruation (mean): 4.7, 4.8 for mITT population: ・Daily # mod + severe hot flushes (mean±SD): 10.3±5.38, 10.5±4.96 ・Daily severity score of hot flushes (mean±SD): 2.3±0.31, 2.3±0.33	**mITT** 1. 122 2. 63 Total randomized: CE 0.45 mg/ BZA 20 mg: 133 CE 0.625 mg/ BZA 20 mg: 133 PLA: 66	**Mean daily change in # moderate and severe hot flushes at week 4:** 1. CE/BZA: –5.9, (p=0.001) 2. PLA: – 2.84 Difference: –3.07 (–4.40 to –1.73) (Efficacy is a difference of >2 hot flushes per day) **in severity of hot flushes at week 4:** 1. CE/BZA: –0.58 (p<0.001) 2. PLA: –0.09	NA	**SAE:** CE/BZA: 2% PLA: 0% **Venous thromboembolism:** CE/BZA: 0% PLA: 0% **Discontinuation due to AEs:** CE/BZA: 3.9% PLA: 9.5%	NA NA NA	**Quality rating:** Poor-Fair **Internal Validity:** <u>Selection:</u> ・The mITT population had subjects who did not meet the entry criteria for the requisite number of hot flushes. <u>Performance:</u> ・25.2% (n=80) of subjects had protocol deviations. 23.3% (n=74) had protocol deviations due to inclusion/exclusion violations. 8.8% (n=28) had protocol violations while on study drug. There was an uneven distribution of overall deviations across treatment groups. ・6.3% of subjects were taking concomitant therapy to treat VMS symptoms. ・ Blinding of researchers was not described.

		Inclusion Criteria: · Age: 40 to 56 · Intact uterus · At least 12 months postmenopausal · Seeking treatment for hot flushes · Experienced ≥7 moderate to severe hot flushes daily or ≥50 weekly · BMI ≤34 kg/m^2 **Exclusion criteria:** · history of disease (e.g., endometrial hyperplasia, estrogen-dependent neoplasia; undiagnosed vaginal bleeding; chronic renal or hepatic disease; thromboembolic disorders; cerebrovascular accident; neuro-ocular disorders; ischemic heart disease; gallbladder disease; malignancy, except skin cancer · endometrial thickness >4 mm, focal endometrial abnormality, ovarian cyst complex or >20 mm · active endocrine disease, alcohol or drug abuse, heavy smoking, use of an IUD w/in 12 weeks before screening		Difference: –0.48 (–0.70 to –0.27) **Mean daily change in # moderate and severe hot flushes at week 12; mean difference from PLA (CI):** 1. CE/BZA: –7.63 (p<0.001) 2. PLA: – 4.92 Difference: –2.71 (–3.84 to –1.57) **in severity of hot flushes at week 12:** 1. CE/BZA: –0.87 (p<0.001) 2. PLA: –0.26 Difference: –0.60 (–0.86 to –0.35)	NA NA NA			Attrition: For the safety population: 11%, 13%, and 16% of those taking CE 0.45 mg/BZA 20 mg (n=127), CE 0.625 mg/BZA 20 mg (n=128), and PLA (n=66) discontinued, respectively. **External Validity:** Recruitment: Patient Characteristics: · The population was generally healthy and had been assessed for endometrial hyperplasia. Setting: · The average number patients per study center was very small. Therefore, any determinations about setting are likely not possible. Outcomes: · The study enrolled small patient numbers spread over numerous centers · The study was of short duration **Analysis:** · The results of this sub-study supports the indication with regard to the reduction in the number of moderate and severe hot flashes by >2 per day. While this sub-study also supports a statistically significant improvement in severity of hot flushes, no indication of the clinical significance of this is

		・use of oral estrogen-, progestin-, androgen-, or SERM-containing drugs within 8 weeks before screening; vaginal hormone products within 4 weeks; or estrogen or progestin implants/injectables within 6 mo. ・estrogen-, progestin-, androgen-, or SERM-containing medications and treatments for vasomotor symptoms prohibited during study						evident. Furthermore, the study population is unlikely to reflect the population considered for this therapy. ・This sub-study is of insufficient duration to support the assessment of CE/BZA efficacy beyond 12 weeks or to assess the effect of discontinuation on severity of menopausal symptoms. Furthermore, the study population is unlikely to reflect the population considered for this therapy. ・This sub-study is of insufficient duration to assess or support the assessment of CE/BZA safety.

AC: active controlled, AEs: adverse events, CE/BZA: conjugated estrogens/bazedoxifene, DB: double blind, D/C: discontinuation, EE1: the subset of efficacy evaluable population who have moderate to severe vasomotor symptoms (see “Clinical Efficacy” section for definition); HF: hot flushes, LOCF: last observation carried forward, mITT: modified intent to treat (those who had taken ≥1 dose, ≥5 days of data at baseline, and ≥5 days of data for ≥1 on-therapy week), NA: not applicable, NR: not reported, MC: multicenter, PC: placebo controlled, PLA: placebo, RAL: raloxifene, RCT: randomized controlled trial, SAE: serious adverse event, TEAE: treatment-emergent adverse event, VMS: vasomotor symptom

Prevention of Osteoporosis: [2, 14, 15]

Relevant Endpoints:
1) Vertebral, hip, or other fractures
2) Serious adverse reactions
4) Serious adverse reactions

Primary Study Endpoint:
1) Incidence of endometrial hyperplasia at 12 months (primary endpoint of the SMART 1 and SMART 5 main studies)
2) Mean percent change in BMD at the lumbar spine at 12 months and 24 months (as evaluated by the FDA) for SMART 5 and for SMART 1, respectively (endpoint of SMART 1 sub-studies, OP1 and OP2, and SMART 5 sub-study, OSS)

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results LOCF	ARR, NNT	Safety Results (CI, p-values)	ARR, NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. SMART 1 (Trial 303) supportive sub-studies Lindsay (2009) and FDA Med Review Phase 3, MC (94), DB, PC, AC, RCT Note: This study included 8 arms, 6 for CE/BZA, 1 for RAL, and 1 for PLA. Only the approved dose (CE 0.45 mg/BZA 20 mg) is addressed in this efficacy evaluation.	1. CE 0.45 mg/BZA 20 mg daily 2. RAL 60 mg daily 3. PLA daily Duration: 24 months	**Demographics:** CE/BZA, RAL, PLA, respectively, for OP1 sub-study (>5 y postmenopausal): · Age (mean): 58.4, 58.5, 58.3 · Ethnic origin (%) White: 79.7, 79.3, 71.7 Black: 19.2, 19.7, 26.6 Hispanic: 0.6, 0, 0.5 Other: 0.6, 1.1, 1.1 · BMI (mean): 25.7, 25.7, 26.1 · Years since last menstruation (mean): 11.3, 11, 11.4 · Age at last menstruation (mean): 47.6, 47.9, 47.5 · Baseline lumbar spine T-score (mean): –1.43, –1.48, –1.52 · Maternal history of fracture (%): 5.56%, 6.95%, 8.15% for OP2 sub-study (1 to 5 y postmenopausal): · Age (mean): 52.1, 52.3, 52.3	**mITT** **SA** OP1 1. 155 2. 157 3. 151 OP2 1. 95 2. 90 3. 95 Total trial randomization: N=3544 CE 0.625 mg/BZA 10 mg: 430 CE 0.625 mg/BZA 20 mg: 414 CE 0.625 mg/BZA 40 mg: 417 CE 0.45 mg/BZA 10 mg:	OP1 **LS mean % change in BMD at lumbar spine (p-value vs PLA); mean difference from PLA (CI) at 24 months:** 1. CE/BZA: 1.64 (p<0.001); 3.11 (2.29 to 3.93) 2. RAL: 0.75 (p<0.001); 2.22 (1.40 to 3.04) 3. PLA: –1.47 **LS mean % change in BMD at total hip; mean difference from PLA at 24 months** 1. CE/BZA: 1.07	NA	For the safety population (CE/BZA n=433, RAL n=423, PLA n=427): **Any SAE at month 24:** CE/BZA: 6% RAL: 7.6% PLA: 8% **Any TEAE at month 24:** CE/BZA: 92.6% RAL: 92.4% PLA: 91.8% **Endometrial hyperplasia/neoplasia:** CE/BZA: 0.68% RAL: 0% PLA: 0% **Venous thromboembolism at month 24:** CE/BZA: <1% RAL: <1% PLA: <1%	NA NA NA NA	**Quality rating:** Poor Selection: · The percentage of subjects within each treatment group with a maternal history of fracture varied across treatment groups. · The mean T-score for the OP2 group was within the normal range, with 45% of subjects having a T-score in the normal range Performance: · Blinding of researchers was described for the main study but not the sub-studies Detection: · These results are from two sub-studies of a main study investigating the incidence of endometrial hyperplasia. Therefore, secondary and sub-study endpoints were used.

		· Ethnic origin (%) White: 82, 77.6, 81.5 Black: 9.9, 15, 10.2 Hispanic: 7.2, 6.5, 8.3 Other: 1, 1, 0 · BMI (mean): 26, 26.2, 25.5 · Years since last menstruation (mean): 3, 3, 3 · Age at last menstruation (mean): 49.7, 50, 49.9 · Baseline lumbar spine T-score (mean±SD): –0.81±1.11, –0.81±1.1 –0.94±1.06 · Maternal history of fracture (%): 3.6%, 7.5%,6.5% **Inclusion Criteria:** · Same as SMART 1 "Treatment of Vasomotor Symptoms" Comparative Clinical Efficacy table plus the following: · for OP1: >5 years postmenopausal and BMD T-score between –1 and –2.5 and one additional risk factor for osteoporosis · for OP2: 1 to 5 years postmenopausal and one additional risk factor for osteoporosis **Exclusion Criteria:** · Same as SMART 1 "Treatment of Vasomotor Symptoms" Comparative Clinical Efficacy table plus the following: · for OP sub-studies: History of osteoporotic fracture; use of glucocorticoids, calcitonin, anabolic steroids, parathyroid hormones,	430 CE 0.45 mg/BZA 20 mg: 433 CE 0.45 mg/BZA 40 mg: 423 RAL 60 mg: 423 PLA: 427	(p<0.001); 1.73 (1.17 to 2.28) 2. RAL: 0.87 (p<0.001); 1.53 (0.97 to 2.08) 3. PLA: –0.65 OP2 **LS mean % change in BMD at lumbar spine; mean difference from PLA at 24 months:** 1. CE/BZA: 1.72 (p<0.001); 3.62 (2.64 to 4.6) 2. RAL: 0.13 (p<0.001); 2.03 (1.03 to 3.02) 3. PLA: –1.90 **LS mean % change in BMD at total hip; mean difference from PLA at 24 months:** 1. CE/BZA: 0.46 (p<0.001); 1.87 (1.19 to 2.54) 2. RAL: –0.27 (p=0.0011); 1.14 (0.45 to	NA NA	**Cardiovascular AEs at month 24:** CE/BZA: <1% RAL: <1% PLA: <1% **Discontinuation due to AEs:** CE/BZA: 10.6% RAL: 13.9% PLA: 14.3%	NA NA	Attrition: · The discontinuation rate was high across all 8 arms for the main study, ranging from 29.8% to 35.7%, and was 29.8% for CE 0.45 mg/BZA 20 mg, 35.7% for RAL, and 35.4% for PLA specifically. No discontinuation rate for the sub-study could be found. · A small number of patients were enrolled in the sub-studies **External Validity:** Recruitment: Patient Characteristics: · The study was limited to healthy postmenopausal women who had had uterine biopsy performed · Subjects were primarily 65 years of age or younger. Setting: · The average number patients per study center was very small. Therefore, any determinations about setting are likely not possible. Outcomes: · A surrogate endpoint was used · The sub-studies do not address the efficacy or effectiveness in improving fracture risk. ·The studies were of short duration compared with the length of use of drugs for bone loss.

		therapeutic fluoride, bisphosphonates, anticoagulants, or antihyperlipidemics without washout; diseases affecting bone metabolism; ≥2 abnormal lumbar vertebrae; baseline lumbar spine or total hip BMD T-score > 2.5 SD below the mean for healthy young women		1.82) 3. PLA: –1.41 **% responders lumbar spine BMD at 24 months:** 1. CE/BZA: 68% (p<0.001) 2. RAL: 59% (p<0.001) 3. PLA: 30%	NA 2.6 3.4			**Analysis:** · The results of the study support the indication, as CE/BZA significantly increases BMD at the lumbar spine and total hip. However, the study population was narrower in age than the intended population fo the indication. The study population, a generally healthy one, also is unlikely to reflect th general population considered for this treatment. · The duration of use is insufficient to make a determination regarding safety for long-term use.
2. SMART 5 Trial (3307) sub-study Pinkerton (2014) and FDA Med Review Phase 3, MC (166), DB, AC, PC, RCT	1. CE 0.45 mg/BZA 20 mg daily 2. BZA 20 mg daily 3. CE 0.45 mg/MPA 1.5mg daily 4. PLA daily Duration: 12 months	**Demographics:** CE/BZA, BZA, CE/MPA, PLA, respectively, for OSS population: · Age (mean; range): 53.1 (46 to 60), 53 (45 to 62), 52.8 (43 to 61), 53.1 (42 to 62) · Ethnic origin (%) White: 91.9, 94.5, 88.6, 91.8 Black: 5.9, 5.5, 8.6, 5.7 Other: 2.2, 2.9, 2.5, 1.9 · BMI (mean): 25.7, 26.5, 26.8, 25.5 · Years since last menstruation (mean): 2.42 (0.51 to 5.4), 2.43 (0.55 to 5.3), 2.49 (0.53 to 4.97), 2.63 (0.53	**mITT** 1. 119 2. 56 3. 59 4. 139	**LS mean % change in BMD at lumbar spine (p-value); mean difference from PLA (CI) at 12 months:** 1. CE/BZA: 0.24 (p<0.001); 1.51 (0.82 to 2.20) 2. BZA: 0.07 (p=0.0026); 1.34 (0.47 to 2.21) 3. CE/MPA:	 NA	For the safety population (CE/BZA n=445, BZA n=230, CE/MPA n=220, PLA n=474): **Any SAE at month 12:** 1. CE/BZA: 3.6% 2. BZA: 2.2% 3. CE/MPA: 5.9% 4. PLA: 3.8% **Any TEAE at month 12:** 1. CE/BZA: 84.3% 2. BZA: 84.3% 3. CE/MPA: 85% 4. PLA: 82.7%	 NA NA	**Quality rating:** Poor **Internal Validity:** <u>Selection:</u> · Mean years since menopause was 2.5 years. · Mean T-score was within the normal range. · Small patient numbers. <u>Attrition:</u> · High discontinuation rate and imbalance in discontinuation rate for the CE/MPA group (27.1%) and BZA 20 mg groups (24.7%) compared with CE/BZA

		to 20.87) ・T-score (mean±SD; range): –0.91±0.77 (–2.4 to 1.5) –0.82±0.75 (–2.2 to 0.8), –0.77±0.78 (–2.4 to 1.25), –0.95±0.91 (–2.6 to 2.65) ・FRAX major osteoporotic fracture score (mean±SD): 5.2±2.6, 4.6±1.8, 4.4±1.8, 5±1.8 ・FRAX hip fracture score (mean±SD): 0.38±0.38, 0.33±0.35, 0.29±0.34, 0.42±0.42 **Inclusion Criteria:** ・Healthy ・Intact uterus ・BMI ≤34 kg/m^2 ・Normal endometrial biopsy results ・≤5 y since their last menstruation ・2 evaluable BMD scans of the lumbar spine and hip at screening differing by <5% and <7.5%, respectively **Exclusion Criteria:** Similar to SMART 1 plus the following: ・Subjects w/ lumbar spine or total hip T-scores < –2.5 at screening or a current/history of osteoporosis or low-impact traumatic fracture		1.30 (p< 0.001); 2.57 (1.72 to 3.43) 4. PLA: –1.28 **LS mean % change in BMD at total hip; mean difference from PLA at 12 months:** 1. CE/BZA: 0.50 (p< 0.001); 1.21 (0.76 to 1.67) 2. BZA: 0.47 (p< 0.001); 1.19 (0.61 to 1.77) 3. CE/MPA: 0.71 (NR); 1.42 (0.85 to 1.99) 4. PLA: –0.72	NA	**Endometrial hyperplasia/neoplasm:** 1. CE/BZA: 0.3% (UL 1-sided CI: 1.41) 2. BZA: 0% (UL 1-sided CI: 1.76) 3. CE/MPA: 0% (UL 1-sided CI: 1.99) 4. PLA: 0.28% (UL 1-sided CI: 1.33) **Venous thromboembolism at month 12:** 1. CE/BZA: 0% 2. BZA: 0% 3. CE/MPA: 0.5% 4. PLA: 0% **Cardiovascular AEs at month 12:** 1. CE/BZA: 0.2% 2. BZA: 0% 3. CE/MPA: 0% 4. PLA: 0.4% **Breast cancer:** 1. CE/BZA: 0.4% 2. BZA: 0% 3. CE/MPA: 0.5% 4. PLA: 0.2% **Discontinuation due to AEs:** 1. CE/BZA: 7.6% 2. BZA: 7% 3. CE/MPA: 14.1% 4. PLA: 7%	NA NA NA NA NA	(19.3%) and PLA (18.4%) groups for the sub-study. **External Validity:** <u>Patient Characteristics:</u> ・The study does not address the efficacy and safety of CE/BZA in women older than 62 and more than 5.5 years postmenopausal. ・The study was limited to healthy postmenopausal women who had had uterine biopsy performed. <u>Setting:</u> ・The average number of patients per study center was very small. Therefore, any determinations about setting are likely not possible. <u>Outcomes:</u> ・A surrogate endpoints was used. ・The study was of short duration compared with the length of use of drugs for bone loss. <u>Analysis:</u> ・Same as SMART 1 sub-studies above.

AC: active controlled, AEs: adverse events, CE/BZA: conjugated estrogens/bazedoxifene, DB: double blind, D/C: discontinuation, LOCF: last observation carried forward, mITT: modified intent to treat (subjects who took ≥1 dose, had lumbar spine BMD values at baseline and ≥1 value on-therapy within 60 days of the last dose of study drug), LS: least square, MPA: medroxyprogesterone acetate, NA: not applicable, NR: not reported, MC: multicenter, OP1: osteoporosis prevention sub-study 1, OP2, osteoporosis prevention sub-study 2, OSS: osteoporosis sub-study, PC: placebo controlled, PLA: placebo, RAL: raloxifene, RCT: randomized controlled trial, SA: FDA sensitivity analysis (excludes 8.1% of patients with missing source documentation) SAE: serious adverse event, TEAE: treatment-emergent adverse event, UL: upper limit

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY [1]

Conjugated estrogens (CE) and bazedoxifene (BZA) bind to and activate estrogen receptors (ER). CE are agonists of ER-α and –β, while BZA is an estrogen agonist in some estrogen-sensitive tissues and an antagonist in others, such as the uterus. CE paired with BZA produces a composite effect specific to each target tissue. BZA reduces the risk of endometrial hyperplasia that can occur with the CE component.

PHARMACOKINETICS [1]

The following information is based on monotherapy studies:

Parameter	**CE Result**	BZA Result
Oral Bioavailability		6%
Protein Binding		98-99%
Elimination	Urine	biliary excretion, then feces (~85%), and < 1% urine*
Half-Life	17 hours	30 hours
Metabolism	Partially CYP3A4	Glucuronidation

*BZA is expected to undergo enterohepatic recycling

Note: In a single-dose, crossover study in 23 postmenopausal women given CE 0.625 mg/BZA 20 mg with a high fat/high calorie meal, food increased $AUC_{0-\infty}$ of BZA 25%. The C_{max} was unchanged.

DOSE & AVAILABILITY [1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Tablet with CE 0.45 mg/BZA 20 mg	oral	once daily	CE 0.45 mg/BZA 20 mg	Use in patients with renal impairment is not recommended. The pharmacokinetics have not been evaluated in patients with renal impairment.	Use is contraindicated in patients with hepatic impairment. The pharmacokinetics, safety, and efficacy have not been evaluated in patients with hepatic impairment.*	CE/BZA is not intended for nor has it been studied in this population.	Use in patients ≥75 years old is not recommended. CE/BZA has not been studied in this population.	• Swallow tablets whole • Add supplemental calcium and/or vitamin D if daily dietary intake is inadequate. Based on a PK model from four phase 1 studies, a 17% reduction in BZA exposure was predicted in women with BMI > 27 kg/m^2 vs those with BMI ≤ 27 kg/m^2. This could be associated with an increased risk for endometrial hyperplasia.

*In a pharmacokinetic studies of BZA 20 mg alone, the C_{max} increased 67%, 32%, 20% and the AUC increased 143%, 109%, 268% in women with mild, moderate, and severe hepatic impairment, respectively. No pharmacokinetic studies with CE were performed in women with hepatic impairment.

DRUG SAFETY [1]

Serious (REMS, Black Box Warnings, Contraindications):

Black box warning:

- Women taking CE/BZA should not take additional estrogens.
- Women who have a uterus and use estrogen-alone therapy (ET) are at increased risk of endometrial cancer.
- ET should not be used for preventing cardiovascular disease or dementia.
- The Women's Health Initiative (WHI) estrogen-alone sub-study reported increased risks of stroke and deep vein thrombosis (DVT).
- The WHI Memory Study reported an increased risk of probable dementia in postmenopausal (PM) women ≥65 years old.

Without comparable data for CE/BZA, these risks should be assumed to be similar for other CE doses and dosage forms. Estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with the patient's treatment goals and risks.

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Contraindication: CE/BZA use in women with hepatic impairment.

Warnings and Precautions:

Women taking CE/BZA should not take progestins, additional estrogens, or additional estrogen agonist/antagonists.

- Increased risk of cardiovascular disorders, including thromboembolism (TE), have been reported with ET and estrogen agonists/antagonists. CE/BZA should be discontinued if TE occurs or is suspected. Risk factors for arterial vascular disease or TE should be managed. If feasible, CE/BZA should be discontinued during periods of prolonged immobilization or at least 4 to 6 weeks before a surgery associated with an increased risk of TE.
- ET has been associated with an increased risk of endometrial cancer in women who have a uterus, with the greatest risk associated with prolonged ET use. BZA reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer and can occur with the CE component. Therefore, women taking CE/BZA should not take additional estrogens, as this may increase the risk of endometrial hyperplasia. The effect of CE/BZA on breast and ovarian cancer risk is unknown. However, ET has been associated with an increase in abnormal mammograms, but not with invasive breast cancer, and has been inconsistently associated with ovarian cancer.
- Estrogen use in postmenopausal (PM) women has been associated with an increased risk of gallbladder disease requiring surgery.
- Discontinue CE/BZA if papilledema or retinal vascular lesions occur. In a small number of case reports, increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In women with pre-existing hypertriglyceridemia, estrogens may be associated with plasma triglyceride elevations leading to pancreatitis. Consider discontinuing CE/BZA if pancreatitis occurs. Estrogens may be poorly metabolized in women with impaired liver function. On average, women with hepatic impairment treated with BZA alone, vs controls, have shown a 4.3-fold increase in overall exposures. Exercise caution for women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, and discontinue CE/BZA in the case of recurrence.
- Estrogen use increases thyroid-binding globulin levels. Therefore, women on thyroid hormone replacement who are using estrogens may require increased thyroid replacement.
- Estrogens may cause fluid retention. Because of this, patients who have conditions such as cardiac dysfunction or renal impairment warrant careful observation when using estrogens. CE/BZA use in patients with renal impairment is not recommended.
- Women with hypoparathyroidism should use estrogens cautiously as estrogen-induced hypocalcemia may occur.
- Estrogens exacerbate asthma, symptoms of angioedema, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- CE\BZA use is not recommended for premenopausal women.

Monitoring:

Monitoring is as follows for CE/BZA use: diagnostic measures to rule out malignancy in PM women with undiagnosed persistent or recurring abnormal genital bleeding; thyroid function tests in women on thyroid replacement therapy; yearly breast examinations by a healthcare provider; appropriately scheduled mammography; and monthly breast self-examinations.

Drug-Laboratory Test Interactions:

- accelerated prothrombin, partial thromboplastin, and platelet aggregation times;
- increased platelet count; fibrinogen and fibrinogen activity levels; plasminogen antigen and activity levels; and factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin;
- decreased antifactor Xa and antithrombin III and antithrombin III activity levels;
- increased thyroid-binding globulin and changes in related thyroid hormone levels;
- possibly decreased free hormone concentrations, such as testosterone and estradiol;
- possibly elevated binding proteins in serum (e.g., corticosteroid binding globulin and sex hormone-binding globulin and changes in related hormone levels) and plasma proteins (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin);
- increased plasma HDL and HDL2, reduced LDL, and increased triglyceride levels;
- impaired glucose tolerance.

Drug-Drug interactions:
In vitro and *in vivo* studies and clinical studies have been conducted only with the individual components of CE/BZA as follows:

- CYP3A4 inducers (e.g., St. John's Wort, phenobarbital, carbamazepine, and rifampin) may reduce CE plasma concentrations. CYP3A4 inhibitors (e.g., erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice) may increase the exposure of CEs. Therefore, diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be taken to rule out malignancy in postmenopausal women who receive CYP3A4 inhibitors and CE/BZA concurrently for >30 days and have undiagnosed persistent or recurring abnormal genital bleeding.
- UGT inducers (e.g., rifampin, phenobarbital, carbamazepine, and phenytoin) may increase BZA metabolism. Therefore, diagnostic measures should be taken to rule out malignancy as described in the previous paragraph.

Food-Drug Interactions: Not reported

Allergy/Cross Reactive Substances: None reported

Pregnancy/lactation rating: Category X. Women who are or may become pregnant must not use CE/BZA. No animal studies have been conducted to evaluate the CE/BZA's effects on reproduction; however, rats given BZA ≥ 0.3 times the human AUC at the 20 mg dose had lower numbers of live fetuses and fetuses with reduced body weights but no observable developmental anomalies. The fetuses of treated pregnant rabbits experienced abortion and an increased incidence of heart and skeletal system anomalies at 2 times the human AUC at the 20 mg dose. CE/BZA should not be used by lactating women. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE alone, and estrogen decreases the quantity and quality of the milk in nursing mothers.

Carcinogenesis/Mutagenesis: Studies of carcinogenicity and mutagenicity with CE/BZA have not been conducted. In some animal species, long-term continuous administration of natural and synthetic estrogens increases the frequency of breast, uterus, cervix, vagina, testis, and liver carcinomas. Female transgenic mice receiving BZA 150 or 500 mg/kg/day for 6 months had a drug-related increased incidence of benign, ovarian granulosa-cell tumors. Female rats receiving 0.03% and 0.1% BZA concentrations for two years experienced a drug-related marked increased incidence of benign, ovarian granulosa-cell tumors. Systemic BZA AUC was 3 and 8 times that observed in postmenopausal women administered 20 mg/day. Male rats had drug-related renal tumors, in the presence of renal toxicity, at 0.06 to 5 times the clinical BZA AUC at a dose of 20 mg. BZA alone was not genotoxic or mutagenic in *in vitro* and *in vivo* bacterial and animal tests.

Impairment of Fertility: Studies of impairment of fertility studies have not been conducted with CE/BZA. BZA at 0.03 to 10 times the human AUC at the 20 mg dose adversely affects the fertility of female rats.

Dose Index (efficacy/toxic): No specific antidote exists for overdose, so treatment should be symptomatic.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

NME Drug Name	Lexicomp	Clinical Judgment
LA/SA for conjugated estrogens/bazedoxifene	none	None
LA/SA for Duavee	none	Duovent

ADVERSE REACTIONS [1]

The most common adverse reactions (incidence ≥ 5%) more frequently reported in women treated with CE/BZA than placebo in clinical trials.

	DUAVEE (N=1224) n (%)	Placebo (N=1069) n (%)
Gastrointestinal disorders		
Nausea	100 (8)	58 (5)
Diarrhea	96 (8)	57 (5)
Dyspepsia	84 (7)	59 (6)
Abdominal pain upper	81 (7)	58 (5)
Musculoskeletal and connective tissue disorders		
Muscle spasms	110 (9)	63 (6)
Neck pain	62 (5)	46 (4)
Nervous system disorders		
Dizziness	65 (5)	37 (3)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	80 (7)	61 (6)