



Conjugated Estrogens/Bazedoxifene (Duavee)

A Novel Agent for the Treatment of Moderate-to-Severe Vasomotor Symptoms Associated With Menopause And the Prevention of Postmenopausal Osteoporosis

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INTRODUCTION

According to the North American Menopause Society, menopause is defined as a woman's final menstrual period due to decreased functioning of the ovaries.¹ This results in diminished production of estrogen and progesterone, marking the permanent end of fertility. Menopause is confirmed only after a woman has missed her period for 12 consecutive months.¹ Natural menopause usually takes place around the age of 51 years, but it can occur anytime between 40 and 58 years of age.¹ Induced menopause can occur at any age when the menstrual period stops due to medical intervention, such as surgical removal of the ovaries, chemotherapy, or radiation. Perimenopause is defined as the menopause transition phase and begins years before the final menstrual period. Postmenopause is defined as the years following menopause. In 2000 there were an estimated 45.6 million postmenopausal women in the United States, and by 2025 the number is expected to reach 1.1 billion females worldwide.¹

During perimenopause, the ovaries begin to decrease production of estradiol (the predominant estrogen during the monthly menstrual cycle) and progesterone. The decreased production of these hormones results in elevated levels of follicle-stimulating hormone and luteinizing hormone, which stimulate the ovaries

to produce more estradiol. Eventually the ovarian follicles and estrogen will be completely depleted.

Depletion of estrogen can result in both short-term and long-term effects, including vasomotor symptoms and osteoporosis, respectively. As a result of fluctuating hormone levels during perimenopause, women may experience a variety of normal vasomotor, vaginal, and other symptoms that can vary from mild to severe (Table 1).^{5,6} While the exact mechanism is unknown, hot flashes are the direct result of the hypothalamus misreading the body's temperature because of fluctuating estrogen levels.⁹ During a hot flash the brain is trying to cool the body, resulting in blood-vessel dilation, increased blood flow to the skin surface, facial redness, flushing, sweating, and increased heart rate. The two primary long-term risks associated with decreased estrogen levels include cardiovascular disease and osteoporosis. There is a direct link between decreased estrogen and decreased bone density. Estrogen works to stimulate bone-forming cells (i.e., osteoclasts), and as estrogen production declines, the rate of bone loss increases. It is estimated that half of a woman's bone loss occurs within the first five to 10 years following menopause.⁶ As a result, a menopausal woman is at a higher risk of low bone density, osteoporosis, and fractures.

Prior to 2013, the only treatment approved by the Food and Drug Administration (FDA) for both moderate-to-

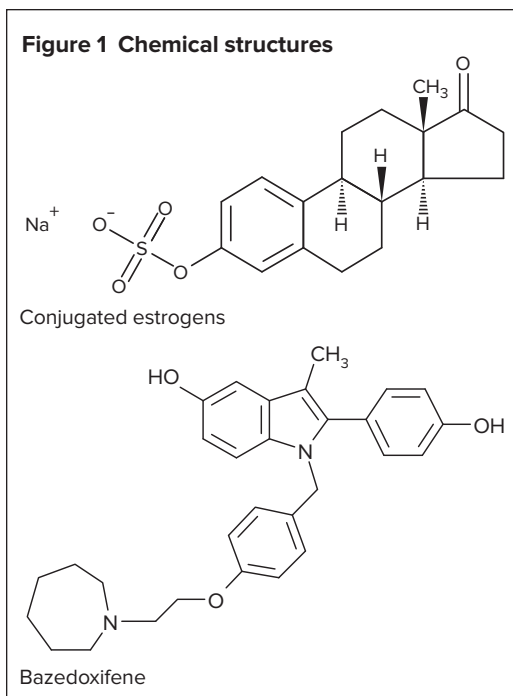
severe vasomotor symptoms and prevention of postmenopausal osteoporosis was menopausal hormone therapy (MHT), previously known as hormone replacement therapy (HRT).⁴ MHT is defined as treatment with estrogen alone or with a combination of estrogen plus a progestin. Results of the Women's Health Initiative study, which began in 1991, play a significant role in the current recommendations for use of hormonal therapy. Overall, the study showed an increased risk of cardiovascular effects and a reduced risk of fractures in the estrogen-plus-progestin and estrogen-only groups.⁴ According to the International Menopause Society, unless MHT is contraindicated or the risks outweigh the benefits, MHT remains the most effective treatment for vasomotor symptoms and the prevention and treatment of osteoporosis-related fractures in women before the age of 60 or within 10 years after menopause.³ Nonhormonal management of vasomotor symptoms includes medications such as selective serotonin reuptake inhibitor antidepressants, gabapentin, and clonidine that the FDA has not approved for this purpose.^{3,6} Bisphosphonates, raloxifene, teriparatide, denosumab, and calcitonin are nonhormonal options for prevention or treatment of postmenopausal osteoporosis.⁶ In October 2013, the FDA approved conjugated estrogens/bazedoxifene (Duavee, Pfizer Inc.) for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

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Table 1 Short-Term Effects Related to Menopause

Vasomotor Symptoms	Vaginal Symptoms	Other
<ul style="list-style-type: none"> • Hot flashes • Skin flushing • Night sweats 	<ul style="list-style-type: none"> • Vaginal discharge • Irritation • Burning • Itchiness • Pain with or without sexual activity • Urine leakage 	<ul style="list-style-type: none"> • Sleep disturbances • Mood swings • Decreased libido • Joint aches • Headaches • Thinning hair



PHARMACOLOGY

Conjugated estrogens/bazedoxifene (CE/BZA) is the first FDA-approved medication that combines conjugated estrogens with an estrogen agonist/antagonist, bazedoxifene. Conjugated estrogens are an estrogen replacement therapy and work to supplement depleted estrogen levels as a woman reaches menopause. Bazedoxifene is classified as a selective estrogen receptor modulator (SERM). The chemical structures of conjugated estrogens and bazedoxifene are shown in Figure 1.

The combination of CE/BZA has been labeled the tissue selective estrogen complex (TSEC) in the literature. It exerts

estrogenic activity on the bone but displays antiestrogenic activity on the uterus and breast. Bazedoxifene helps to reduce the risk of endometrial hyperplasia, which can occur with estrogen replacement therapy. Therefore, CE/BZA is only indicated for those women with an intact uterus.⁷ Bazedoxifene was approved in April 2009 in Europe for the treatment of postmenopausal osteoporosis. Other SERMs currently available include tamoxifen and toremifene (Fareston, ProStrakan), used for the treatment of breast cancer, and raloxifene (Evista, Lilly), which is approved for the treatment and prevention of osteoporosis and reduction of breast cancer risk. Prior to the approval of CE/BZA, preclinical data

showed that bazedoxifene might have the potential for fewer uterine and vasomotor effects compared with the other SERMs.¹⁰

PHARMACOKINETICS

Although the pharmacokinetics of CE/BZA have not been evaluated in women with renal or hepatic impairment, the product is not recommended for use in women with renal impairment and is contraindicated in patients with hepatic impairment.⁷ Reduced exposure to the bazedoxifene component and a potential increased risk of endometrial hyperplasia may be observed in women with a body mass index greater than 27 kg/m².⁷ Major routes of excretion are urinary and biliary

for the conjugated estrogen and bazedoxifene components, respectively. Based on pharmacokinetic studies, it appears that bazedoxifene undergoes enterohepatic recycling from the gut into circulation.^{7,11} No drug interaction studies have been conducted with CE/BZA; however, the individual components have shown potential interactions *in vitro* and *in vivo*. Estrogens are partially metabolized by CYP3A4, so inducers and inhibitors of CYP3A4 may affect the metabolism of estrogens.⁷ Use of CYP3A4 inhibitors may increase the risk of endometrial hyperplasia.⁷ Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and the liver. Those drugs known to induce UGT (i.e., rifampin, phenobarbital, carbamazepine, and phenytoin) may increase the patient's exposure to bazedoxifene.^{7,11}

DOSAGE AND ADMINISTRATION

CE/BZA tablets contain conjugated estrogens 0.45 mg and bazedoxifene 20 mg. This combination is approved for once-daily dosing both for vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis. CE/BZA should be limited to those women who are at a significant risk of osteoporosis. Nonestrogen medications should be considered first-line therapy for those women not at high risk of postmenopausal osteoporosis. Women taking CE/BZA for postmenopausal osteoporosis should be instructed to take calcium and vitamin D supplementation. CE/BZA tablets can be taken without regard to meals and should be swallowed whole. If a dose of CE/BZA is missed,

Table 2 Warnings and Precautions for Conjugated Estrogens/Bazedoxifene		
Boxed Warnings	Contraindications	Warnings
<ul style="list-style-type: none"> Do not take additional estrogens. There is an increased risk of endometrial cancer in women with a uterus who use unopposed estrogens. Estrogen therapy should not be used for the prevention of cardiovascular disease or dementia. Use the lowest effective estrogen dose for the shortest duration based on individual treatments goals and risks. 	<ul style="list-style-type: none"> Undiagnosed abnormal uterine bleeding Known, suspected, or past history of breast cancer or estrogen-dependent neoplasia Active or past history of deep vein thrombosis or pulmonary embolism Active or past history of arterial thromboembolic (i.e., stroke, myocardial infarction) or thrombophilic disease (protein C, protein S, antithrombin) Hypersensitivity to estrogens, bazedoxifene, or other ingredients Known hepatic impairment or hepatic disease Pregnancy and nursing 	<ul style="list-style-type: none"> Patients should not take additional estrogens, progestins, or estrogen agonists/antagonists. Estrogens or bazedoxifene may increase the risk of cardiovascular disease (i.e., deep vein thrombosis, pulmonary embolism, and stroke) or retinal vascular thrombosis. Estrogen alone may increase the risks of endometrial, breast, or ovarian cancer; the effect of conjugated estrogens/bazedoxifene is unknown. Exercise caution in patients with a history of gallbladder disease, thyroid disease, hypertriglyceridemia, or jaundice

the patient should take it as soon as she remembers. Women should be advised not to take two doses at the same time.

ADVERSE EFFECTS AND PRECAUTIONS

The most common adverse drug events (with an incidence of at least 5%) associated with CE/BZA have included muscle spasms, dizziness, nausea, diarrhea, dyspepsia, upper abdominal pain, neck pain, and throat pain.⁷ The most common reactions that have led to the discontinuation of CE/BZA were hot flashes, abdominal pain, and nausea.⁷ CE/BZA has the same boxed warnings, precautions, and contraindications as other estrogen-containing medications (Table 2).^{3,4,7} Patients taking CE/BZA should be monitored for any signs and symptoms of thromboembolic events, and they should report abnormal vaginal bleeding to their health care provider.

CLINICAL TRIALS

The approval of CE/BZA (Duavee) was based on five pivotal phase 3 trials. The Selective Estrogen, Menopause, and Response to Therapy (SMART) trials¹²⁻¹⁶ 1 to 5 evaluated CE/BZA's safety and efficacy in the management of moderate-

to-severe vasomotor symptoms, bone mineral density, endometrial hyperplasia, moderate-to-severe vulvar/vaginal atrophy, and overall safety. At this time CE/BZA is not approved for vulvar atrophy (SMART-3),¹⁴ and this paper will focus on the SMART-1¹² and SMART-2¹³ trials. Overall conclusions of the SMART-3, SMART-4, and SMART-5 trials can be found in Table 3.

SMART-1

SMART-1 was a two-year, randomized, phase 3 trial that evaluated the effects of CE/BZA on endometrial tissue and bone mineral density (BMD). The study enrolled 3,544 patients who were randomized into eight groups. The treatment groups included CE/BZA (0.625/10 mg, 0.45/10 mg, 0.625/20 mg, 0.45/20 mg, 0.625/40 mg, and 0.45/40 mg), raloxifene 60 mg, and placebo. The study included postmenopausal women between 40 and 75 years of age with an intact uterus. Patients with a history of thromboembolic disease, ischemic heart disease, stroke, and estrogen-dependent cancers were excluded from the study. The primary outcome measure was the incidence of endometrial hyperplasia, which was evaluated at 12 months. An acceptable rate of

hyperplasia was defined as less than 2%. Endometrial hyperplasia was observed in the 0.625/10-mg group (n = 13, 3.81%) and in the 0.45/10-mg group (n = 3, 0.94%). Hyperplasia was not observed in either of the 40-mg BZA groups or the raloxifene and placebo groups. One patient (0.32%) developed endometrial hyperplasia in the 0.625/20-mg CE/BZA group and no cases of hyperplasia were observed in the 0.45/20-mg CE/BZA group. At 12 months, the increase in endometrial thickness was not statistically different in the 20-mg or 40-mg BZA groups compared with placebo and raloxifene. Compared with placebo and raloxifene, a significant increase from baseline in endometrial thickness was observed in both of the BZA 10-mg groups ($P < 0.01$). Patients enrolled in the SMART-1 study were also evaluated for the change in BMD of the lumbar spine and the hip. Women who were more than five years postmenopausal were assessed in Substudy I; those between one and five years past menopause were enrolled in Substudy II. Women received supplements of Caltrate 600 plus vitamin D. Substudy I enrolled 1,454 participants, while 861 subjects were enrolled in Substudy II. At the end of the trial, 1,295 women (89%)

Table 3 SMART Trial Overview

Trial	Outcome Measure	Methods	Results	Conclusion
SMART-3	Treatment of moderate-to-severe vulvar/vaginal atrophy associated with menopause	For 12 weeks, 664 patients used: <ul style="list-style-type: none"> • BZA/CE 20/0.625 mg • BZA/CE 20/0.45 mg • BZA 20 mg • Placebo 	BZA/CE 20/0.625 mg or 20/0.45 mg improved vaginal maturation ($P < 0.01$) and vaginal dryness ($P < 0.05$); BZA/CE 20/0.625 mg improved vaginal pH ($P < 0.05$)	BZA/CE was effective in treating moderate-to-severe vulvar/vaginal atrophy and other vaginal symptoms.
SMART-4	Endometrial safety and effects on BMD	For 1 year, 1,061 patients used: <ul style="list-style-type: none"> • BZA/CE 20/0.625 mg • BZA/CE 20/0.45 mg • CE/MPA 0.45/1.5 mg • Placebo 	Three cases (1.1%) of endometrial hyperplasia were reported with BZA/CE 20/0.625 mg compared with none for BZA/CE 20/0.45, CE/MPA, or placebo Compared with CE/MPA, both BZA/CE doses increased total hip BMD ($P \leq 0.05$) and lumbar spine BMD ($P < 0.05$)	Both doses of BZA/CE improved BMD and maintained endometrial safety.
SMART-5	Effects of BZA/CE on breast density and other breast parameters	For 1 year, 1,843 patients used: <ul style="list-style-type: none"> • BZA/CE 20/0.625 mg • BZA/CE 20/0.45 mg • BZA 20 mg • CE/MPA 0.45/1.5 mg • Placebo 	Breast density as determined by mammograms decreased from baseline with both BZA/CE doses, BZA, and placebo. CE/MPA increased breast density from baseline ($P < 0.001$). Both doses of BZA/CE showed rates of breast tenderness similar to placebo and significantly lower than CE/MPA ($P < 0.001$)	Both doses of BZA/CE showed a favorable breast safety profile and did not increase breast density.

BMD = bone mineral density; BZA = bazedoxifene; CE = conjugated estrogens; MPA = medroxyprogesterone acetate

in Substudy I and 783 (91%) in Substudy II had received at least one dose of the study medication and were included in the modified intent-to-treat (MITT) analysis. In the MITT population for both substudies, patients randomized to BZA had a statistically significant difference in mean percent change ($P < 0.001$) in lumbar spine BMD from baseline compared with placebo regardless of the BZA dose. In Substudies I and II, the total hip BMD was significantly higher ($P < 0.001$) with all CE/BZA doses at months 12 and 24 from baseline versus placebo.

Women randomized to BZA also had a statistically significant difference in mean percent change ($P < 0.05$) in BMD over 24 months compared with women randomized to raloxifene in all BZA doses except BZA 40 mg. The increases in lumbar spine BMD tended to be greater with the higher CE dose (0.625 mg). Irrespective of the CE dose, the increase in BMD was largest for the regimen with the lowest dose of BZA (10 mg). The higher BZA doses were associated with diminishing effect on the increase in BMD. Compared with raloxifene only, CE/BZA 0.625/10 mg, 0.45/10 mg, and 0.625/20 mg resulted in significantly higher ($P < 0.05$) hip BMD at 24 months.

The incidence of adverse events, including venous thromboembolism, cardiovascular events, and breast pain, was similar between the CE/BZA and placebo groups. The majority of treatment-emergent adverse events were mild to moderate in severity and not considered related to the study drug. Overall, the SMART-1 trial showed that CE 0.625 or 0.45 mg and BZA 20 mg was the lowest effective dose to prevent endometrial hyperplasia.

SMART-2

SMART-2 was a 12-week, phase 3 trial designed to assess the safety and efficacy of CE/BZA for the treatment of moderate-to-severe vasomotor symptoms associated with menopause. This study randomized 332 postmenopausal women with moderate-to-severe hot flashes to BZA/CE 20/0.45 mg, BZA/CE 20/0.625 mg, or placebo once daily. Patients were enrolled in the study if they experienced seven or more moderate-to-severe hot flashes per day or more than 50 moderate-to-severe hot flashes per week. The daily number

of moderate-to-severe hot flashes was the primary efficacy endpoint. The severity of hot flashes was also assessed at weeks 4 and 12. The results of the trial showed a significant ($P < 0.001$) decrease in the mean number of daily moderate-to-severe hot flashes. At week 12, hot flashes were reduced from baseline by 74% in the BZA/CE 20/0.45-mg group and by 80% in the BZA/CE 20/0.625-mg group compared with a 51% reduction in the placebo group. At all time points, the mean severity of daily hot flashes improved significantly ($P < 0.001$) in both BZA/CE groups from baseline. No significant difference in treatment-emergent adverse events was observed in the BZA/CE and placebo groups. The most common reported treatment-emergent adverse effects were infection, pain, arthralgia, and headache. The study did not report any cases of thromboembolic and cerebrovascular events. Overall, the SMART-2 trial concluded that BZA 20 mg in combination with CE 0.45 or 0.625 mg is effective for short-term treatment of vasomotor symptoms in postmenopausal women.

NONPHARMACOLOGICAL OPTIONS

In addition to medication, patients should be made aware of lifestyle modifications that can be implemented to help alleviate bothersome vasomotor symptoms. Wearing layered clothing, the use of fans, cool drinks, relaxation techniques, and avoiding triggers (i.e., spicy foods, alcohol, smoking, or caffeine) are important in the nonpharmacological management of postmenopausal symptoms. Women who experience insomnia should maintain good sleep hygiene, avoid daytime naps, and limit extensive exercise before bedtime. The varying mood swings that can arise may be managed through physical activity, support groups, and individualized therapy. Calcium and vitamin D supplementation is an important and necessary part of the prevention of osteoporosis. Regular weight-bearing exercise, as well as limiting alcohol and caffeine, is essential in preventing osteoporosis.

COST AND FORMULARY CONSIDERATIONS

CE/BZA (Duavee) is available as a 20-mg/0.45-mg tablet in a package con-

taining a 30-day supply. The average wholesale price for a month's supply is \$146.25 (\$4.87 per tablet).¹⁷ With a median expected treatment duration of about one to two years, CE/BZA may not place a substantial financial burden on patients or institutions. Since CE/BZA has shown a significant benefit for patients with menopausal symptoms and a decreased risk of osteoporosis, adding this agent to outpatient formularies should be considered. However, no published pharmacoeconomic analyses confirm the value of using the combination regimen of CE/BZA as a cost-effective treatment option. These analyses would be valuable to help guide P&T committees with their formulary decisions.

CONCLUSION

The guidelines and recommendations on menopausal hormone therapy and preventive strategies for midlife health (i.e., osteoporosis) of the International Menopause Society (IMS) were updated in 2013 and included BZA. According to the IMS, the BZA/CE combination has been shown to alleviate vasomotor symptoms, reduce bone turnover rates, and prevent bone loss. The report adds that while future studies are necessary, the SERMs have been shown to inhibit endometrial hyperplasia, similar to combination MHT (estrogen plus progestin), but without adversely affecting the breast. In 2014, the North American Menopause Society recommendations for the clinical care of midlife women noted CE/BZA to be an option for vasomotor symptoms as well as for prevention of osteoporosis. Both reports stated that the type of therapy chosen, length of treatment, and dosing should be individualized for each patient depending on the severity of menopausal symptoms and patient characteristics.

REFERENCES

1. North American Menopause Society. Overview of menopause. In: *Menopause Practice: A Clinician's Guide*, 4th ed. Mayfield Heights, Ohio: North American Menopause Society; 2010:1–5.
2. North American Menopause Society. The 2012 hormone therapy position statement of the North American Menopause Society. *Menopause* 2012;19(3):257–271.
3. De Villiers TJ, Pines A, Panay N, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013;16(3):316–337.

4. Goodman NF, Cobin RH, Ginzburg SB, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. 2011. Available at: www.aace.com/sites/default/files/menopause.pdf. Accessed October 10, 2014.
5. Office on Women's Health, U.S. Department of Health and Human Services. Menopause. September 2010. Available at <http://www.womenshealth.gov/menopause/menopause-basics/index.html>. Accessed October 10, 2014.
6. Cleveland Clinic. Menopause. Available at: http://my.clevelandclinic.org/health/diseases_conditions/hic-what-is-perimenopause-menopause-postmenopause. Accessed October 10, 2014.
7. Duavee (conjugated estrogens/bazedoxifene) prescribing information. Philadelphia, Pennsylvania; Pfizer Inc.; October 2013.
8. Medical News Today. Osteoporosis drug bazedoxifene stops growth of breast cancer cells. June 2013. Available at: <http://www.medicalnewstoday.com/articles/262039.php>. Accessed October 10, 2014.
9. Breastcancer.org. All about hot flashes. May 2013. Available at: http://www.breastcancer.org/tips/menopausal/facing/hot_flashes. Accessed October 10, 2014.
10. Gennari L, Merlotti D, De Paola V, et al. Bazedoxifene for the prevention of postmenopausal osteoporosis. *Ther Clin Risk Manag* 2008;4(6):1229–1242.
11. Shen Li, Ahmad S, Park S, et al. In vitro metabolism, permeability, and efflux of bazedoxifene in humans. *Drug Metab Dispos* 2010;38(9):1471–1479.
12. Pickar JH, Yeh IT, Bachmann G, et al. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. [SMART-1] *Fertil Steril* 2009;92(3):1018–1024.
13. Pinkerton JV, Utian WH, Constantine GD, et al. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. [SMART-2] *Menopause* 2009;16(6):1116–1124.
14. Kagan R, Williams RS, Pan K, et al. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. [SMART-3] *Menopause* 2010;17(2):281–289.
15. Mirkin S, Komm BS, Pan K, et al. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. [SMART-4] *Climacteric* 2013;16(3):338–346.
16. Pinkerton JV, Harvey JA, Pan K, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. [SMART-5] *Obstet Gynecol* 2013;121(5):959–968.
17. Red Book Online. Ann Arbor, Michigan; Truven Health Analytics. Accessed February 12, 2015. ■