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Duavee® (conjugated estrogens/ bazedoxifene): A review

Shane Reilly-Roger, Pharm.D. Candidate

Vasomotor symptoms associated with menopause are one of the most common signs of menopausal transition. Between 30% - 50% of women experience symptoms of hot flashes and night sweats during their perimenopausal period and 30% - 80% experience these symptoms during postmenopause.[1] Vasomotor symptoms can decrease quality of life by reducing sleep quality, increasing irritability, and causing difficulty concentrating.[2]

The most effective treatment for relieving vasomotor symptoms associated with menopause is conjugated estrogens. However, conjugated estrogens alone have been associated with in increased risk of endometrial hyperplasia and adenocarcinoma.[3, 4] It is recommended that all women with an intact uterus taking conjugated estrogens for hormone therapy also receive progestin to diminish this risk.[3] However, progestin is associated with side effects including endometrial bleeding, dysphoria, and an increased mammographic density.[3] In the Woman's Health Initiative, the combination of estrogen plus progestin increased the risk of breast cancer, where estrogen alone did not.[5, 6]

Originally, hormone replacement therapy was thought to decrease cardiovascular risk in postmenopausal women. However, the Women's Health Initiative estrogen plus progestin study did not find a decrease in coronary heart disease, but did find an increase in stroke and pulmonary embolism. The overall conclusion was that conjugated estrogens plus progestin should not be recommended for chronic disease prevention in postmenopausal women.[5, 6]

Low bone mineral density is common in the older population. In US women above the age of 50, it is estimated that 49% have osteopenia and 10% have osteoporosis at the femur neck.[7] Conjugated estrogens alone decrease the risk of hip fracture in women age 50-79 who have undergone hysterectomy.[5] Similarly, estrogen plus progestin decreases the risk of hip fracture in women age 50-79 with an intact uterus.[5] The decrease risk in fracture however does not appear to continue for long after discontinuation of hormone therapy.[8]

Pfizer Inc. gained FDA approval for Duavee® (0.45 mg conjugated estrogens/20 mg bazedoxifene) in October of 2013. It is a combination of conjugated estrogens and an estrogen agonist/antagonist (or selective estrogen receptor modulator) approved for women with an intact uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporo-

Inside This Issue:

sis. This article will outline the pharmacology, pharmacokinetics, clinical trials, adverse effects, and dosing of conjugated estrogens/bazedoxifene (CE/BZA).

Pharmacology & Pharmacokinetics

Conjugated estrogens act as agonists on various tissue in the body. This can have beneficial effects on bone and the prevention of vasomotor symptoms. However, estrogens can have detrimental effects, such as the increase risk of endometrial cancer. [9]

Bazedoxifene is an estrogen receptor antagonist/agonist, also known as a selective estrogen response modulator (SERM). As their name suggests, SERMs act as either agonists or antagonists depending on the tissue being affected. Different SERMs have different spectrums of agonist or antagonist activity. [10] The agonist and antagonist activity of several SERMs is reviewed in table 1. In pre-clinical trials, bazedoxifene had a positive effect on bone mineral density and appeared to have either neutral or positive effects on uterine and breast tissue. [11] When bazedoxifene is added to conjugated estrogens, it acts as an antagonist at the uterine tissue, reducing the risk of endometrial hyperplasia, which may lead to endometrial malignancy. [12, 13]

The mechanism of hot flashes is not fully understood. Vasomotor symptoms have been linked to decreased levels of estrogen. These symptoms are characterized by cutaneous vasodilation, sweating, and behavioral thermoregulation.[15]

Osteoporosis associated with menopause is thought to be due to decreased estrogen-mediated inhibition of bone resorption without a fully compensatory increase in bone formation. These effects result in decreased bone mass and an increase in facture risk.[16] Estrogen attenuates osteoblast apoptosis while stimulating osteoclast apoptosis.[17]

In post-menopausal women aged 55-85 with osteoporosis, bazedoxifene decreases bone mineral density loss and decreases incidence of vertebral fracture similar to raloxifene. Neither bazedoxifene nor raloxifene decreased risk of nonvertebral fractures.[18, 19]

High fat meals increase the AUC of bazedoxifene by 25%, but do not affect the Cmax. CE/BZA may be administered with or without food.[12]

Bazedoxifene is not metabolized through the cytochrome P450 system and is not a known inducer or inhibitor of the system.[12] Bazedoxifene is metabolized through the UGT enzymes in the intestines and liver and is susceptible to interactions with agents that affect the UGT enzyme system. If CE/BZA is coadministered with an inducer of the UGT enzyme system (e.g. rifampin, phenobarbital, carbamazepine, and phenytoin), there

Table 1 | Agonist/Antagonist effect of select SERMs[10,12,14]

SERM	Agonist	Antagonist	Indication
Tamoxifene	*Endometrium*: Promotes endometrial hyperplasia and increases risk of endometrial cancer *Coagulation*: Increased risk of venous thromboembolism *Bone*: Prevents osteoporosis	*Breast*: Blocks endogenous estrogens to reduce the incidence of or treat hormone-responsive breast cancer *Vasomotor*: Increase in hot flashes	Prevention and treatment of hormone-responsive breast cancer
Raloxifene	*Bone*: Prevents osteoporosis *Coagulation*: Increased risk of venous thromboembolism	*Breast* *Vasomotor*: Increase in hot flashes	Prevention and treatment of osteoporosis in post-menopausal women
Clomiphene		*Pituitary*: Reduces negative feedback to increases FSH and LH output.	Induce ovulation in an anovulatory women
Bazedoxifene	*Bone:* Prevents osteoporosis	*Endometrium:* Prevents endometrial hyperplasia caused by exogenous conjugated estrogens *Vasomotor* : Increase in hot flashes	For women with a uterus, in combination with CE for prevention of osteoporosis and treatment of moderate to severe vasomotor symptoms associated with menopause.

may be an increased risk of endometrial hyperplasia due to a decrease in exposure to bazedoxifene, while the dose of conjugated estrogens remains the same. In postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy.[12]

Bazedoxifene is 85% eliminated through biliary excretion and likely undergoes enterohepatic recycling. Drugs that interfere with biliary excretion may decrease the systemic exposure of bazedoxifene and put the woman at a higher risk for endometrial hyperplasia. CE/BZA has not been studied in patients with hepatic impairment and is contraindicated in this population.[12]

Conjugated estrogens are metabolized at least partially through CYP3A4 and are susceptible to interactions with agents that affect CYP3A4.[12] CYP3A4 inducers may decrease the effectiveness of conjugated estrogens by reducing circulating levels. Enzyme inhibitors of CYP3A4, such as erythromycin and grapefruit juice may increase the exposure of conjugated estrogens and put the patient at a higher risk for endometrial hyperplasia. Precautions similar for the drug interactions discussed with bazedoxifene should be taken.[12]

The half-life of conjugated estrogens is 17 hours and the half-life of bazedoxifene is 30 hours. Steady state is reached by the 2nd week with once-daily administration. Conjugated estrogens and its metabolites are excreted in the urine. CE/BZA was not studied in women with renal impairment and its use in not recommended in this population.[12]

CE/BZA was not studied in women over the age of 75 and its use is not recommended in this population.[12]

Clinical Trials

Five trials evaluating the safety and efficacy of CE/BZA were completed. These trials evaluated the effects of the combined agent on moderate to severe vasomotor symptoms, bone mineral density, endometrial hyperplasia, moderate to severe vulvar/vaginal atrophy, and overall safety. Summaries of these trials are given in Table 2.

A 2-year, outpatient, randomized, double-blind, placebo- and active-controlled, phase 3 study (The Selective Estrogen Menopause and Response to Therapy [SMART]-1 trial) reported on the primary outcome of endometrial effects of CE/BZA, raloxifene , or placebo. The SMART-1 trial studied 3,397 women between 40-75 years with an intact uterus. Pickar et al, found that bazedoxifene 20 mg was the lowest effective dose in preventing endometrial hyperplasia associated with conjugated estrogens at 0.625 mg or 0.45 mg versus placebo. Endometrial hyperplasia was diagnosed by blinded pathologists using endometrial biopsies taken at 6, 12, and 24 months or more often if malignancy was suspected. Conjugated estrogens 0.625 mg and 0.45 mg with bazedoxifene 10 mg showed a statistically significant increase in incidence of endometrial hyperplasia (7.14%, 95% CI 4.19-10.09 and 2.53%, 95% CI 0.68-4.38).[20]

Several substudies were performed on the SMART 1 study population. Lobo et al found CE/BZA at all doses significantly decreased the daily number of hot flashes by 51.7% to 87.5% depending on dose compared to 17.1% for placebo (p-value <0.05 for all doses).[21] For all doses Lindsay et al reported more women had no change or an increase in bone mineral density at the lumbar spine with CE/BZA versus placebo at 12 and 24 months (63% to 76% versus 30 to 39% p-value < 0.001). Lindsay et al also reported an increase in annual percentage change in lumbar spine bone mineral density compared to a decrease seen in placebo (0.94 % versus -1.08 %, p-value <0.01).[22] Archer et al reported a similar amount of amenorrhea with CE/BZA and placebo (>83% in the first year, no p-value reported).[23]

The SMART-2 trial was an outpatient, multicenter, double-blind, randomized, placebo-controlled study of 12-week duration carried out in 332 women between 40-65 years with moderate to severe hot flashes (>7/day or 50/week). Previously bazedoxifene at various doses taken alone was found to increase the incidence of hot flashes compared to placebo (20 to 24% versus 14% p-value <0.05).[10] However with the combination CE/BZA at various doses, Pinkerton et al reported a significant reduction in number of hot

Table 2 | Summary of Phase-III clinical trials for BZA/CE

Reference	Treatment Arms	Main Outcome	Results for CE/BZA 0.45 mg/20 mg (FDA approved dose)	Authors Conclusion
Pickar[20], 2009	CE/BZA dosed at 0.45 mg/ 10 mg 0.45 mg/ 20 mg 0.45 mg/ 40 mg 0.625 mg/ 10 mg 0.625 mg/ 20 mg 0.625 mg/ 40 mg Raloxifene 60 mg Placebo	Incidence of endometrial hyperplasia at 12 mo in the efficacy evaluable population	Cases: 0 (One sided 97.5% confidence interval: 0.00-1.09) Difference vs placebo: 0 (95% CI: 0.00-0.00) Difference vs raloxifene: 0 (95% CI: 0.00-0.00)	When combined with CE 0.625 mg or 0.425 mg, BZA at 20 mg was the lowest effective dose for preventing endometrial hyperplasia over 2 yr of study.
Lobo[21], 2009	CE/BZA dosed at 0.45 mg/ 10 mg 0.45 mg/ 20 mg 0.45 mg/ 40 mg 0.625 mg/ 10 mg 0.625 mg/ 20 mg 0.625 mg/ 40 mg Raloxifene 60 mg Placebo	Hot flashes, breast pain, vaginal atrophy, metabolic parameters, and adverse events	*Hot flashes*: average daily reduction from baseline for all doses of CE/BZA ranged from -5.53 – -8.98 vs -2.45 with placebo (P <0.01) *Vaginal atrophy*: CE/BZA 0.45 mg/20 mg + effect vs placebo (P<0.001) *Dyspareunia*: Significantly less than placebo during weeks 9-12 (P<0.05) *Sexual activity*: No between group differences *Breast pain*: No between group differences. *Metabolic*: Significant decrease vs placebo in total cholesterol 3.7% vs 0.2% (P<0.05); significant increase in triglycerides vs placebo 23.1 % vs 6.1 % (P<0.01)	Overall CE/BZA at 0.625 or 0.45 mg/20 mg is an effective and safe treatment for menopausal symptoms.
Lindsay[22], 2009	CE/BZA dosed at 0.45 mg/ 10 mg 0.45 mg/ 20 mg 0.45 mg/ 40 mg 0.625 mg/ 10 mg 0.625 mg/ 20 mg 0.625 mg/ 40 mg Raloxifene 60 mg Placebo	Change in bone mineral density of the lumbar spine	CE/BZA 0.45 mg/20 mg vs placebo: Substudy I: 0.94 vs -1.08 (P<0.001) Substudy 2: 1.01 vs -1.41 (P<0.001)	CE/BZA combinations decreased bone turnover and bone loss in postmenopausal women at increased risk for osteoporosis.
Archer[23], 2009	CE/BZA dosed at 0.45 mg/ 10 mg 0.45 mg/ 20 mg 0.45 mg/ 40 mg 0.625 mg/ 10 mg 0.625 mg/ 20 mg 0.625 mg/ 40 mg Raloxifene 60 mg Placebo	Cumulative amenorrhea profiles and the incidence of bleeding or spotting over 2 yr	CE/BZA 0.45 mg/20 mg: amenorrhea (>83% during the 1st yr) and bleeding and spotting were similar to placebo	Postmenopausal women treated with BZA 20 or 40 mg or CE 0.625 or 0.45 mg had right rates of cumulative amenorrhea that were similar to those reported with placebo
Pinkerton[24], 2009	CE/BZA dosed at 0.45 mg/ 20 mg 0.625 mg / 20 mg Placebo	Efficacy in treating moderate to severe vasomotor symptoms	At wk 12, CE/BZA 0.45 mg/20 mg reduced hot flashes from baseline by 74% vs 51% with placebo (P<0.001)	CE 0.45 or 0.625 mg with BZA 20 mg is effective, with short term safety, for treating vasomotor symptoms in postmenopausal women.

Abbreviations used: CE = conjugated estrogens, BZA = bazedoxifene, vs = versus, wk = week, mo = month, yr = year, BMD = Bone mineral density.

Table 2 continued | Summary of Phase-III clinical trials for BZA/CE

Reference	Treatment Arms	Main Outcome	Results for CE/BZA 0.45 mg/20 mg (FDA approved dose)	Authors Conclusion
Bachmann[25], 2010	CE/BZA dosed at 0.45 mg/ 20 mg 0.625 mg / 20 mg BZA 20 mg Placebo	Effects of BZA/CE on sexual function and quality of life	At wk 12 CE/BZA 0.45 mg/ 20 mg (FDA approved) showed: No change in total ASEX scale vs placebo; Improvement in overall score on the MENQOL questionnaire vs placebo (P<0.001); Significantly greater overall satisfaction with treatment on the MS-TSQ (P<0.05).	BZA/CE for 12 wk was shown to significantly improve sexual function and quality-of-life measures in symptomatic postmenopausal women.
Mirkin[26], 2013	CE/BZA dosed at 0.45 mg / 20 mg 0.625 mg / 20 mg CE 0.45 mg/ medroxyprogesterone acetate 1.5 mg Placebo	CE/BZA endometrial safety and effects on BMD vs CE/MPA	*Endometrial hyperplasia*: 0 cases in CE/BZA 0.45 mg/20 mg, CE/MPA, and placebo. 3 cases in the CE/BZA 0.625 mg/20 mg group. *Increase in Lumbar Spine BMD*: CE/BZA 0.45 mg/ 20 mg vs CE/MPA: 0.80% vs 2.22% (P<0.05). (Placebo: -1.56%, P<0.001). *Total hip*: CE/BZA 0.45 mg/ 20 mg vs CE/MPA 0.62% vs 1.47% (P<0.05) (Placebo: -0.99, P<0.001)	CE/BZA 0.45 or 0.625 /20 mg significantly improved BMD while maintaining endometrial safety and showed a favorable safety/tolerability profile over 1 yr.
Pinkerton[27], 2013	CE/BZA dosed at 0.45 mg / 20 mg 0.625 mg / 20 mg CE 0.45 mg/ medroxyprogesterone acetate 1.5 mg BZA 20 mg Placebo	Mammographic breast density and other breast parameters at 12 mo	Mammographic breast density decreased from baseline with CE/BZA 0.45 mg/65 mg and placebo (Mean -0.38% and -0.32%, no p-value given). Breast tenderness rates similar to placebo (5.8-9.4%, P>.546-.821 for both doses) No differences in incidence of breast-related adverse events were identified.	CE/BZA 0.45 or 0.625mg/20 mg did not increase mammographic breast density or tenderness over the course of 1 yr with a favorable breast-related safety profile.

Abbreviations used: CE = conjugated estrogens, BZA = bazedoxifene, vs = versus, wk = week, mo = month, yr = year, BMD = Bone mineral density.

flashes at weeks 4 and 12 from baseline compared with placebo (74% to 80% versus 51%, p-value <0.001).[24]

The SMART-3 trial was a 12-week double-blind placebo-controlled study in 652 postmenopausal, non-hysterectomized women with symptoms of moderate to severe vulvar/vaginal atrophy. The study evaluated CE/BZA's effect on sexual function and quality of life. The results were measured using the Arizona Sexual Experiences scale (ASEX), the Menopause-Specific Quality of Life (MENQOL) scale, and the Menopause Symptoms Treatment Satisfaction Questionnaire (MS-TSQ). There was no difference in the change in total ASEX score. There was a significant improvement in vasomotor function according to ASEX score for CE/BZA 0.45 mg/20 mg and 0.625 mg/20 mg (1.33 to 1.67 versus 0.51, p-value <0.001) and total MENQOL score (1.09 to 1.18 versus 0.67, p-value <0.001). There was a significantly greater overall satisfaction with treatment versus placebo according to the MS-TSQ (62.6% to 69.4% versus 47.4%, p-value <0.05). There was also significantly greater satisfaction with control of hot flashes during the day (58.9% to 65.8% versus 35.1%, p-value <0.001) and night (55.9% to 63.3% versus 38.3%, p-value <0.001) and satisfaction with the effect of treatment on quality of sleep (50.3% to 50.5% versus 27.7%, p-value < 0.001).[25] CE/BZA is not approved for the treatment of vulvar/vaginal atrophy.

The SMART-4 trial was a 1 year, multicenter, double-blind, randomized placebo- and active-controlled trial in 1061 non-hysterectomized, postmenopausal women aged 40-65 years. The study compared CE/BZA, conjugated estrogens/medroxyprogesterone acetate, and placebo. CE/BZA at 0.45 mg/20 mg (approved by the FDA) did

not cause an increase in endometrial hyperplasia, similar to placebo and conjugated estrogens/ medroxyprogesterone acetate. No cases of endometrial hyperplasia occurred in these three groups. The combination of CE/BZA with the higher dose of conjugated estrogens (0.625 mg, not the FDA approved dose) did cause 3 cases (1.1%) of endometrial hyperplasia. Both doses of CE/BZA showed a significant increase compared to placebo in mean bone mineral density at lumbar spine (0.80 % versus-1.56 %, p-value <0.001) and total hip (0.62 % to 0.84 % versus -0.99 %, p-value <0.001).[26]

The SMART-5 trial was a 1-year, multicenter, randomized, double-blind, placebo- and active-controlled study in 1843 postmenopausal women age 40-65 years with an intact uterus, a BMI ≤34.0, and who were seeking treatment for menopausal symptoms. The study found that CE/BZA did not increase frequency of abnormal mammograms, compared to placebo (CE 0.45 mg/BZA 20 mg: 0.9%, CI: 0.2%-2.3%; CE 0.625 mg/BZA 20 mg: 0.4%, CI: 0.1%-1.5%, placebo: 0.2%, CI: 0.0-1.2%). Conjugated estrogens/ medroxyprogesterone acetate did significantly increase breast denisty from baseline compared with placebo (1.4%, CI: 0.3-3.9%).[27]

Adverse Events and Safety

In the women's health initiative conjugated estrogens alone at 0.625 mg daily increase the risk of venous thromboembolism (deep vein thrombosis or pulmonary embolism) in women vs placebo (28 vs. 21 per 10 000 person-years). Only the increase risk of DVT was statistically significant (p-value = 0.03).[5] The incidence of venous thromboembolism during trials for CE/BZA was too low (0.0% in CE/BZA and 0.1% with placebo) to determine if the risk is different versus conjugated estrogens alone.[12]

In the Women's Health Initiative Memory ancillary studies, an increase in probable dementia was reported in women 65 years of age using daily conjugated estrogens (0.625 mg) alone or in combination with progestin.[28]

The use of conjugated estrogens has been linked to endometrial cancer, with the greatest risk being after 5-10 years of treatment.[12] The addition of bazedoxifene to conjugated estrogens decreases the risk of endometrial hyperplasia. With increased doses of conjugated estrogens endometrial hyperplasia may still occur, so women taking CE/BZA should not take additional estrogens or estrogen agonists/antagonists. Women with undiagnosed persistent or recurring abnormal genital bleeding should undergo diagnostic measures to rule out endometrial malignancy.[12]

Table 3 | Adverse Reactions (Incidence ≥5%) More Common in the BZA/CE Treatment Group in Placebo -controlled Trials[12]

	Conjugated Estrogens/ Bazedoxifene (N=1224)	Placebo (N=1069) (No p-values given)
Nausea	8%	5%
Diarrhea	8%	5%
Dyspepsia	7%	6%
Abdominal pain (upper)	7%	5%
Muscle Spasms	9%	6%
Neck pain	5%	4%
Dizziness	5%	3%
Oropharyngeal pain	7%	6%

Estrogens alone have been associated with increased rates of abnormal mammograms, but they have not been associated with increased risk of invasive breast cancer. The effect of CE/BZA on the risk of breast cancer is currently unknown.[12]

Other side effects that have been reported with the use of estrogens alone that women on CE/BZA may experience include increased risk of gallbladder disease, visual abnormalities, elevated blood pressure, fluid retention, hypocalcaemia, and exacerbation of several disease states including hypertriglyceridemia, hypothyroidism, hereditary angioedema, asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas.[12]

Summary

The combination drug Duavee® [conjugated estrogens/bazedoxifene] provides the benefits of conjugated estrogens while pre-

venting endometrial hyperplasia associated with conjugated estrogens alone. It is approved in women with a uterus for treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis. Endometrial hyperplasia may lead to endometrial malignancy. Even so, this agent should be used for the shortest duration possible consistent with treatment goals and risk for an individual woman. CE/BZA is not approved to treat osteoporosis. Alternative agents should be considered if osteoporosis prevention without moderate to severe vasomotor symptoms is the only indication. Many side effects associated with conjugated estrogens alone in women without a uterus have been included in warnings for the combination agent. Venous thromboembolism risk and breast cancer risk have not been fully evaluated. CE/BZA is not approved for the treatment of vulvar/vaginal atrophy.

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