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New Drug Update

Duavee: a tissue-selective estrogen complex for menopausal symptoms and prevention of osteoporosis

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ABSTRACT

Post-menopausal women suffer from a plethora of problems like vasomotor symptoms, vulvovaginal atrophy (VVA), bone loss, and all this can be attributed to estrogen deficiency. The conventional treatment till date for these hormone deficient manifestations have been estrogen replacement therapy in hysterectomized female or a combination of estrogen and progesterone therapy in women with an intact uterus. The reason for adding progesterone is to protect the endometrium from estrogenic stimulation. The drawback with the combination therapy was irregular vaginal bleeding and breast discomfort, which led to the discontinuation of this therapy. The United States Food and Drug Administration, has recently approved a novel tissue selective estrogen complex comprising of conjugated estrogen (0.45 mg) and a selective estrogen receptor modulator, bazedoxifene (BZA) (20 mg) for the treatment of moderate to severe vasomotor symptoms and prevention of osteoporosis in non-hysterectomized post-menopausal women. This combination retains the benefits of estrogen on vasomotor symptoms, VVA and bone density along with the protective effect of BZA on endometrium and breast tissue. The results of clinical trials have been promising but what still needs to be evaluated is the long term safety of this pair on venous thromboembolism, stroke, and breast cancer.

Keywords: Bazedoxifene, Conjugated estrogen, Menopause, Osteoporosis

INTRODUCTION

Menopause leads to decline in estrogen production which causes troublesome manifestations like vasomotor symptoms, vulvovaginal atrophy (VVA), acceleration of bone loss predisposing the women to osteoporosis along with difficulty in sleeping, mood disorders, and thus reduced quality of life (QOL). Vasomotor symptoms are characterized by hot flashes which may alternate with chilly sensations, inappropriate sweating, and has been seen in 60-90% women. VVA is reported in 50% women and it includes dryness and vaginal itching, dyspareunia, soreness, pain during urination, urgency or incontinence. Osteoporotic thinning and weakening of bones puts the postmenopausal women at an increased risk of fractures especially compression fractures of the vertebrae and minimal trauma fractures of the hip and wrist.[1-3] For amelioration of moderate to severe menopausal symptoms and prevention of osteoporosis, there are established benefits of hormone therapy which includes estrogen replacement therapy (conjugated estrogens [CE]) for hysterectomized women or combination of estrogen progestin (CE with medroxy-progesterone acetate [MPA]) therapy for women with intact uterus.[2] The rationale of combining estrogen with progesterone in non-hysterectomized women is to limit estrogen-related endometrial hyperplasia, but this pairing has its own drawbacks like vaginal bleeding, breast pain/discomfort which form an important reason for the discontinuation of this therapy.[3,4] Hence, there was a need to have a new safer option for treatment of post-menopausal symptoms which could improve the QOL of these women. Duavee which is a tissue selective estrogen complex (TSEC) comprising of a CE and bazedoxifene (BZA), a selective estrogen receptor modulator (SERM) has been approved by FDA recently for management of moderate to severe vasomotor symptoms and prevention of osteoporosis in non hysterectomized post-menopausal women.[5] This is the only TSEC to be approved by the regulatory authorities which retains the efficacy of estrogen in management of vasomotor symptoms, VVA and osteoporotic changes along with the additive protective effects of the SERM, BZA on breast and endometrial tissues.[6]

CHEMICAL STRUCTURE

CE are a mixture of sodium estrone sulfate and sodium equilin sulfate. They, also contain concomitant components like sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.[7]

BZA is available as BZA acetate and its empirical formula is C30H34N2O3·C2H4O2 (Figure 1).[7,8]

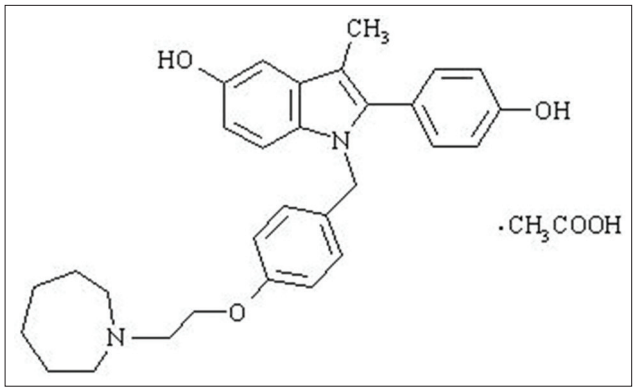

Figure 1: Bazedoxifene acetate.

MECHANISM OF ACTION

CE and BZA interact with estrogen receptors (ER) a and b, the density of which varies from tissue to tissue. ER-a is found in abundance in female reproductive tract: uterus, vagina and ovaries, and in mammary gland, hypothalamus, endothelial cells, and vascular smooth muscle. ER-b is located in prostate, ovaries, lung, brain, bone, and blood vessels.[1]

CE are agonists of ER α and β while BZA, a SERM has tissue-specific estrogenic/anti estrogenic effects. It has agonistic action on bone tissue thus preventing osteoporosis and antagonistic action at endometrium and breast tissue, where it inhibits the proliferative effects of estrogen leading to decreased incidence of endometrial hyperplasia, uterine bleeding, and breast stimulation, respectively.[6,8] The pairing of BZA with CE is based on these favorable aspects which is lacking in other SERMS like raloxifene (RLX), tamoxifene, and lasofoxifene.[9]

PHARMACOKINETICS

CE are well-absorbed from the gastrointestinal tract and attain their peak plasma concentrations in 6.5 hrs while BZA in 2.5 hrs after oral administration. There seems to be no drug-food interaction with this combination. Estrogens circulate in the blood largely bound to sex hormone binding globulin and albumin. BZA is also highly bound (98-99%) to plasma proteins. The metabolism of CE occurs mainly by hepatic enzymes, and BZA metabolizes by glucuronidation. Little cytochrome P-450 metabolism is evident. The distribution and metabolism of CE and BZA after administration of duavee have not been studied. After the administration of a single dose of duavee, CE get eliminated with a half-life of about 17 hrs compared to 30 hrs of BZA. The primary route of excretion of CE and BZA is urine and faeces respectively. BZA undergoes enterohepatic circulation, so there is a possibility of some drug interactions because of this phenomenon.[5-7]

PRECLINICAL STUDIES

The pairing of CE with BZA was based on the encouraging findings of some of the preclinical studies. Two of the other SERM/CE combinations i.e. RLX/CE and lasofoxifene/CE were also compared with BZA/CE for their effects in these animal studies. The effects of BZA, RLX, and lasofoxifene in a dose of 3 mg/kg in combination with 1 µg/kg of estradiol were studied on breast and uterine tissues of ovariectomized mice. It was seen that BZA, RLX and lasofoxifene prevented estradiol-induced increase in uterine wet weight ($p<0.05$ vs. estradiol alone). Of the three combinations, BZA-estradiol pair was more effective in antagonizing the stimulatory effects of estradiol than RLX or lasofoxifene ($p<0.05$).[3,6] Similar finding was observed in ovariectomized cynomolgus monkeys where daily doses of BZA 20 mg/CE 0.45 mg and 0.625 mg reduced endometrial proliferation.[9]

In another study with ovariectomized sexually immature mice, BZA, RLX and lasofoxifene in doses of 2 mg/kg, 10 mg/kg, and 2 mg/kg, respectively, were combined with 3 mg/kg of CE. It was seen that combinations of BZA/CE and RLX/CE were better than lasofoxifene/CE in prevention of CE induced uterine stimulation. BZA also demonstrated better estrogen antagonistic activity on breast tissue than RLX or lasofoxifene.[3] Effects on bone mineral density (BMD) of BZA (3 mg/kg)/CE (0.5-5 mg/kg) combination given for 6 weeks to ovariectomized rats were analyzed in a study. There was a significant increase in total BMD as compared to control the group for all dose combinations ($p<0.01$).[9]

All the preclinical studies demonstrated that BZA/CE combination was effective in preventing estrogen-induced uterine and breast stimulation than other SERM/CE combinations. Furthermore, the increase in BMD by BZA gave it the extra edge, and there were a lot of expectations from this pair as it entered the clinical trials. The important clinical studies for this TSEC have been discussed ahead.

CLINICAL STUDIES

Duavee has been evaluated in various Phase III trials which were randomized, double-blind, placebo and active-controlled and are termed as selective estrogen, menopause, and response to therapy (SMART) trials. There have been five SMART trials conducted with duavee for evaluation of various efficacy and safety parameters in healthy,

postmenopausal women with an intact uterus and normal endometrial biopsy. SMART-1 trial was conducted in 3397 generally healthy postmenopausal women (age 40-75 years) for 24 months. The BZA/CE combination was compared with placebo as well as an active comparator RLX to evaluate the incidence of endometrial hyperplasia at the end of 1 year. Effects on bone marrow density were evaluated in two sub-studies under SMART 1 trial in women with >5 years of menopause and the other with women between 1 and 5 years since menopause (Figure 2). It was seen that the lowest effective dose of BZA to be combined with CE 0.45 mg/0.625 mg for protection from endometrial stimulation was 20 mg and hence the subsequent trials were carried on with this dose (Figure 2).[2,3]

SMART-2 trial (n=318) was conducted in healthy, postmenopausal women (age 40-65 years) with an intact uterus who had seven or more than seven episodes of moderate to severe hot flashes per day. The study duration was 12 weeks and the effects of BZA/CE combination was evaluated on vasomotor symptoms, sleep quality and QOL of the patients (Figure 2).[9]

SMART-3 trial was conducted on 652 healthy, postmenopausal women (age 40-65 years) with an intact uterus who had one or more than one symptom of moderate to severe symptom of VVA at screening. The study was conducted for 12 weeks and effect of BZA/CE combination was evaluated on measures of VVA in comparison to BZA alone or placebo (Figure 2).[2-4]

SMART-4 trial (n=1061) was conducted on healthy, postmenopausal women (age 40-65 years) with an intact uterus for 1 year. The combination of BZA/CE was compared with CE/MPA or placebo for incidence of endometrial hyperplasia and the change in lumbar spine BMD at 1 year.[10] SMART-5 trial (n=1886) was conducted on healthy, postmenopausal women (age 40-75 years) with an intact uterus for 1 year. The combination of BZA/CE was compared with CE/MPA or BZA 20 mg or placebo for effectiveness on uterine protection, prevention of osteoporosis, and effects on breast density (Figure 2).[4,10]

IMPORTANT EFFICACY RESULTS

Vasomotor symptoms

SMART 1 trial demonstrated a significant reduction in frequency of hot flashes with all doses of BZA/CE (−51.7% to −85.7%) versus placebo (−17.1%) ($p<0.05$). The severity of hot flashes with BZA 10 and 20 mg/CE 0.45 and 0.625 mg reduced significantly as compared to placebo ($p<0.001$).[3] Similarly SMART 2 study also showed a significant reduction in number of hot flashes with BZA 20 mg/CE 0.45 mg and 0.625 mg by 74% and 80%, respectively, as

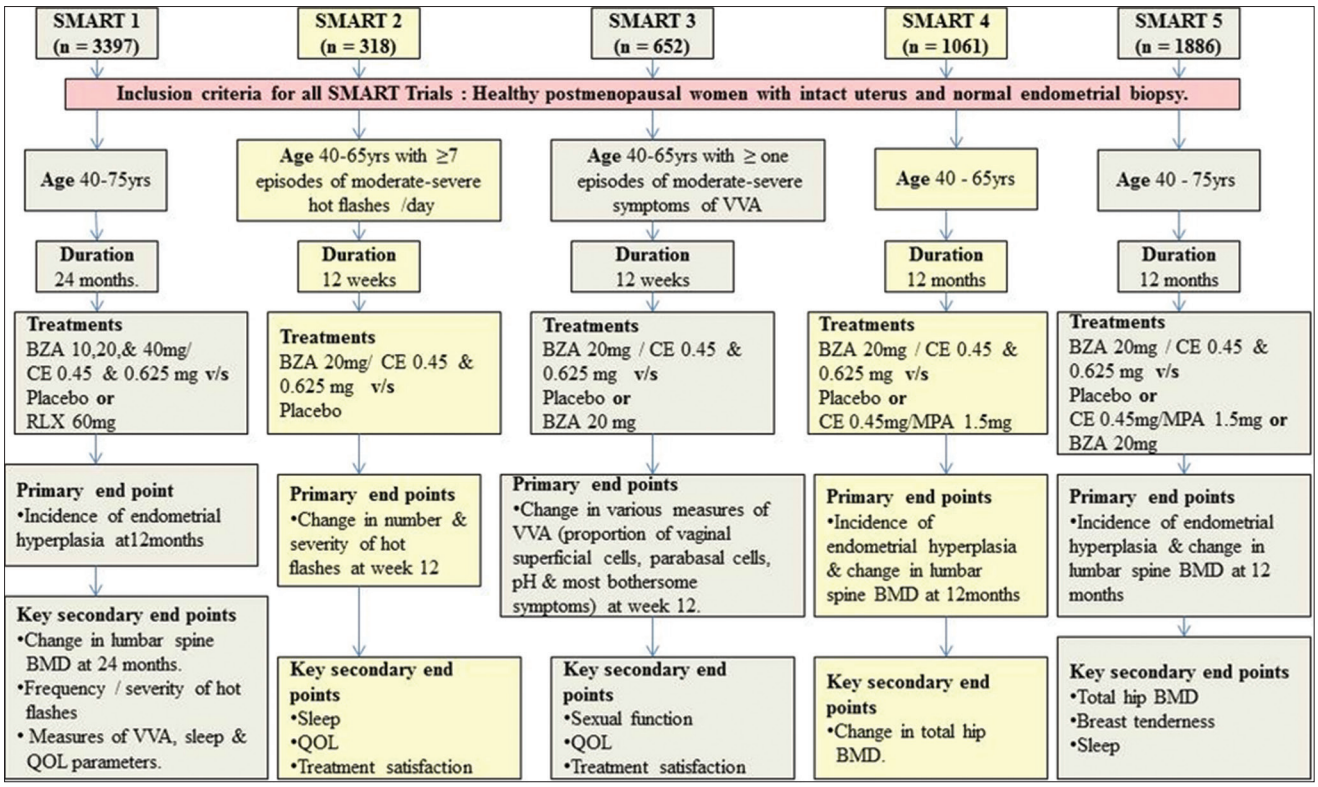

Figure 2: Study designs of Phase III SMART Trials of Duavee (BZA/CE).[2-4] BMD: Bone mineral density, BZA: Bazedoxifene, CE: Conjugated estrogens, MPA: Medroxyprogesterone acetate, QOL: Quality-of-life, RLX: Raloxifene, VVA: Vulvovaginal atrophy, SMART: Selective estrogen, menopause, and response to therapy.

compared to 51% with placebo (p<0.001).[10,11] The severity of hot flashes also was significantly lower with BZA 20 mg/CE 0.45 mg and 0.625 mg in comparison with placebo-treated women (p<0.001).[2,3]

Vulvovaginal atrophy (VVA)

The effect on VVA is measured by improvement in vaginal maturation index (VMI), pH of the vagina and the most bothersome symptom like vaginal dryness, irritation, dyspareunia, etc. The premenopausal vaginal pH is between 3.5 and 4.5 while after menopause, it becomes 5.0-7.5 hence predisposing a woman to vaginal infection. VMI, which indicates the relative proportion of parabasal cells, intermediate cells, and mature superficial cells of the vaginal squamous epithelium, is calculated based on the following formula: VMI =0.5(X_2) + 1(X_3), where X_2=%age of intermediate cells and X_3=%age of superficial cells. The VMI is 0-49% in patients with an absent or low estrogenic effect, 50-64% in patients with a moderate estrogenic effect, and 65-100% in patients with a high estrogenic effect.[12]

SMART 1 trial demonstrated a significant increase in proportion of superficial cells at 24 months with BZA 10 and 20 mg/CE 0.45 mg and 0.625 mg in comparison with placebo-treated women (p<0.01). An increase in proportion of intermediate cells with decrease in parabasal cells was seen with BZA 10 and 20 mg/CE 0.45 mg and 0.625 mg versus placebo and both results were statistically significant (p<0.001).[2,3]

In SMART 3 trial, similar significant results were seen with BZA 20 mg/CE 0.45 mg and 0.625 mg i.e. increase in superficial and intermediate cells, decrease in parabasal cells when compared to placebo (p<0.05).[2] In addition, in SMART 3 trial, there was significant decrease in vaginal pH from baseline (p<0.001) with BZA 20 mg/CE 0.45 mg and 0.625 along with improvement in most bothersome vaginal symptoms.[4]

Effects on bone

These effects were evaluated by measuring the changes in BMD as seen with dual energy X-ray absorptiometry, changes in bone turnover markers. The bone effects were studied in SMART1, SMART 4, and SMART 5 clinical trials. In SMART 1 sub-studies , it was seen that all doses of BZA/CE significantly increased the lumbar spine (p<0.001 in women 1-5 years post-menopause)and total hip BMD (p<0.01 in women 1-5 years post menopause and p<0.001 in women > 5 years post menopause) as compared to placebo.[3] Compared to RLX 60 mg, significant increase in lumbar spine BMD was seen with BZA 20 mg/CE 0.45 and 0.65 mg from baseline to months 12 (p<0.001) and 24 (p=0.002 and p=0.001, respectively).[4] Similar positive results were seen in SMART 4 and SMART 5 trials. In SMART 4 trial, both doses of BZA/CE showed a significant increase in lumbar BMD (p<0.001 with placebo and p<0.05 with CE 0.45mg/MPA 1.5 mg) and total hip BMD (p<0.001with placebo and p<0.05 with CE 0.45mg/MPA 1.5 mg).[10] In SMART 5, both doses of BZA/CE showed similar efficacy to CE/MPA while better effect than BZA 20 mg on lumbar and total hip BMD.[4]

Effect on sleep, QOL, and treatment satisfaction

Effect of treatment on sleep in the study population was assessed in SMART1 using daily diaries and SMART2 trial using Medical outcomes study sleep scale, for various parameters of sleep like time taken to fall asleep, quality of sleep etc. The BZA 20 mg/CE 0.45 mg and 0.625 mg showed significant improvement in sleep parameters versus placebo (p<0.05 in SMART 1 and p<0.001 in SMART 2).[3]

QOL was assessed in SMART 1, SMART 2, and SMART 3 studies using Menopause specific QOL (MENQOL) questionnaire. Significant improvement in vasomotor functions and total MENQOL scores was seen in all these trials with BZA 20 mg/CE 0.45 mg and 0.625 mg versus placebo (p<0.001). In SMART 3 trial, sexual functions were assessed using Arizona Sexual Experiences scale and there was a significant improvement in ease of lubrication with both doses of BZA/CE as compared to placebo (p<0.05).[2,3]

Treatment satisfaction in SMART 2 and SMART 3 studies was evaluated using Menopause Symptoms Treatment Satisfaction Questionnaire and the results of SMART 2 study showed that 73.5% of women who took BZA 20 mg/CE 0.45 mg and 78.2% of BZA 20 mg/CE 0.625 mg treated women were overall satisfied with treatment as compared to 44.4% with placebo (p<0.001). The treatment satisfaction in SMART 3 trial, with BZA 20 mg/CE 0.45 mg was 62.6% and with BZA 20 mg/CE 0.625 mg, it was 69.4%. This was significantly higher than the placebo group where 47.5% women were satisfied with the treatment (p<0.001). The satisfaction with treatment was because of improvement in vasomotor symptoms, mood and quality of sleep.[3]

SAFETY PARAMETERS

Endometrial safety

BZA 20 mg/CE 0.45 mg and 0.65 mg showed decreased incidence of endometrial hyperplasia (<1%) in SMART 1 and SMART 5 trials which was comparable to placebo. The dose combinations of BZA 10 mg/CE 0.45 and 0.625 mg demonstrated few cases of endometrial hyperplasia which does not seem acceptable.[10,13] Hence, this dose pair of BZD 10 mg/CE 0.45 and 0.625 mg was not included in clinical studies further.[3] Estrogen itself carries a risk of

endometrial cancer if used for a prolonged period hence the combination of any other estrogen therapy with duavee is not advised.[14]

Breast safety

All the three trials, SMART 1, SMART 2 and SMART 3 demonstrated that incidence of breast related adverse events (breast pain/discomfort, increase mammographic density) were low and similar to placebo/RLX 60 mg/BZA 20 mg.[2,3,10] In SMART 5 trial, the incidence of breast tenderness with BZA/CE was significantly lower than CE 0.45 mg/MPA 1.5 mg ($p<0.001$).[2,9,10] The effect of BZA/CE on breast cancer is not known yet. Therefore periodical evaluation for it during the treatment duration should be carried out.

Cardiovascular safety

Incidence of venous thromboembolic events (VTE) was 0.75/1000 woman-years for BZA 20 mg/CE 0.45 and 0.625 mg groups and 1.56/1000 woman-years for placebo-treated group.[3] Cardiovascular adverse events like myocardial infarction, coronary artery disease, and coronary artery insufficiency did occur among different treatment groups in SMART 1 trial and therefore it becomes imperative to evaluate the risk of cardiovascular accidents in patients receiving this therapy for a long period of time.[2,4]

Other adverse drug effects

The common adverse reactions reported with the use of BZA/CE tablets in placebo-controlled trials included muscle spasms, nausea, diarrhea, dyspepsia, abdominal pain upper, oropharyngeal pain, dizziness, and neck pain.[6,10]

WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS

The warnings and precautions for use of duavee in various medical conditions are described in Table 1.

Contraindications

Duavee is contraindicated in women with undiagnosed abnormal uterine bleeding, known/suspected/past history of breast cancer, known/suspected estrogen-dependent cancer, deep venous thrombosis, pulmonary embolism, history of or active stroke, myocardial infarction, hypersensitivity to estrogens/BZA, known hepatic dysfunction, known protein C/protein S/antithrombin deficiency or other known thrombophilic disorders.[5,6,10,14]

Drug Interactions

Estrogens are metabolized partially by CYP3A4 enzymes hence the concomitant use of duavee tablets with CYP3A4 inhibitors or inducers may interfere with its serum concentrations. Hence various risks like endometrial hyperplasia, VTE may be enhanced. BZA is metabolized by uridine diphosphate glucuronosyltransferase enzymes and drugs like rifampin, phenobarbitone, carbamazepine, phenytoin which are inducers of this enzyme could reduce serum concentrations of BZA and therefore increase the risk of endometrial hyperplasia with duavee.[5-7]

Dosage and Administration

The US FDA has approved duavee which contains BZA 20 mg/CE 0.45 mg in fixed-dose combination. It is supplied in 2 blisters containing 15 tablets each. The recommended dosage is one tablet once daily with or without food.[7,10]

Table 1: Warnings and precautions with duavee (BZA/CE).[6,7]

Conditions	Action taken	Reason
Sudden partial/complete loss of vision Sudden onset of proptosis/diplopia/migraine	Discontinue therapy till further examination	Risk of retinal vascular thrombosis with estrogen
Suspected stroke	Discontinue therapy immediately	Increased risk of VTE with BZA/CE
Severe hypertriglyceridemia	Discontinue therapy	Can lead to pancreatitis
Cardiac dysfunction (CHF)	Careful monitoring	Risk of fluid retention with estrogen
Hypoparathyroidism	Careful monitoring	Estrogen can cause hypocalcemia
Patient with thyroid disorder (hypothyroidism)	Increase the dose of thyroid replacement therapy	Increase TBG levels with estrogen
Asthma Diabetes mellitus Epilepsy Hemangiomas Migraine	Cautious use	Estrogen can exacerbate these conditions

CHF: Congestive cardiac failure, TBG: Thyroid binding globulin, VTE: Venous thrombo-embolism, BZA: Bazedoxifene

Use in Specific Populations

Pregnant/lactating women

Duavee is a category X drug, therefore not to be used in women who are or may become pregnant. Duavee should not be used by nursing mothers as it is not known whether this drug is excreted in human milk.[6,7]

Children

Duavee is not indicated for use in children.[7]

Geriatric use

Duavee is not recommended for use in women greater than 75 years of age as clinical data in this population is lacking. In a study done on women over 65 years of age taking CE (0.625 mg) daily, an increased risk of dementia is reported.[10,15]

Hepatic and renal impairment

Duavee is not recommended for use in patients with renal or hepatic impairment as pharmacokinetics of duavee is not studied in such patients.[7]

SUMMARY

Duavee is a first compound of a novel class of menopausal therapy called 'TSEC' which combines the favorable effects of estrogens on vasomotor symptoms, vaginal atrophic changes, and BMD along with uterine and breast protective effects of a SERM, BZA to treat moderate to severe vasomotor symptoms in postmenopausal women along with prevention of postmenopausal osteoporosis. The FDA has approved this drug combination in a dose of BZA 20 mg/CE 0.45 mg which has been associated with greater benefit to risk ratio so far. This combination is aimed to replace the conventional estrogen-progesterone hormonal therapy for menopausal symptoms which carried a risk of irregular vaginal bleeding and breast discomfort leading to discontinuation among the patients. All the preclinical and clinical study data have shown positive results with duavee where risk of endometrial hyperplasia was significantly lowered without any increase in breast density and breast tenderness. As long-term safety trials are yet not conducted with this combination, hence the risk of VTE, stroke or breast cancer in patients who will be on prolonged therapy with duavee needs to be further evaluated. In light of these findings, we can say that it is better to use duavee for the shortest possible duration in every patient after performing their risk-benefit assessment with the aim of maximizing the drug benefits and minimizing the adverse effects of hormonal treatment.

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