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REVIEW ARTICLE

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What do TSECs provide in the menopausal hormone therapy?

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ABSTRACT

Tissue-selective estrogen complex (TSEC) is projected as a progestogen-free option for the treatment of estrogen deficiency symptoms in postmenopausal, non-hysterectomized women. TSEC combines the benefits of estrogen with a selective estrogen receptor modulator (SERM), in this case bazedoxifene acetate (BZA), which has an antagonistic effect on the endometrium, thus avoiding the use of progestins. The authorized TSEC combination (conjugated estrogens [CE] 0.45 mg/BZA 20 mg) for the alleviation of vasomotor symptoms has been demonstrated in randomized clinical trials compared with placebo or menopausal hormone therapy (MHT). In addition, TSEC has shown improvements in quality of life and vaginal atrophy. In respect to MHT using progestins, the benefits of TSEC are found mainly in the bleeding pattern, amenorrhea rate, and reduction in mammary repercussion (i.e., breast tenderness and radiological density). The objective of this guide will be to analyze the efficacy and safety of TSEC consisting of CE/BZA in postmenopausal women.

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Introduction

The main components of menopausal hormone therapy (MHT) are estrogen and progestins. Estrogen-only MHT is given to hysterectomized women. Progestins are added in regimens for non-hysterectomized women to reduce the increased risk of endometrial hyperplasia and carcinoma, which occurs with unopposed estrogen. Different routes of administration can be used for individual hormones. The routes of administration are oral, transdermal (patches and gels), subcutaneous (implants), and vaginal [1,2].

Bazedoxifene (BZA), a selective estrogen receptor modulator (SERM) approved for the treatment of postmenopausal women at risk of fracture, antagonizes the effects of estrogen on the endometrium [3]. Conjugated estrogens (CE) plus BZA is a tissue-selective estrogen complex (TSEC). In Europe, the combination of 0.45 mg CE/20 mg BZA is indicated for the treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate [4]. The FDA has approved the combination for women who suffer from moderate-to-severe hot flashes (vasomotor symptoms) associated with menopause and to prevent osteoporosis after menopause [5]. Double-blind, randomized, placebo-controlled, phase 3 studies, known as the Selective estrogens, Menopause, And Response to Therapy (SMART) trials, have investigated the efficacy of CE/BZA for relieving vasomotor symptoms (VMS), the effects on bone mass, and endometrial and breast safety in postmenopausal women [6].

The objective of this guide will be to analyze the efficacy and safety of TSEC consisting of BZA/CE in postmenopausal women.

Methods

To clarify the clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used [7].

To obtain the recommendations, we searched the MEDLINE, EMBASE, PubMed, Scopus, and Cochrane databases for all articles (in any language) published in peer-reviewed journals through December 2017 using the search strategy described in the Appendix. Reference lists from papers identified by the search and key reviews were hand-searched to identify additional publications. Studies that were in press in peer-reviewed journals and available online ahead of publication were also considered. Full articles that met the inclusion criteria were reviewed in detail. Other relevant papers were used for references.

Experimental studies

Although the molecular mechanisms responsible for the anti-proliferative effect of BZA have not been completely elucidated, several hypotheses have been outlined that place it as one of the SERMs with anti-estrogenic capacity in the endometrium [8].

From a genetic perspective, studies have analyzed the effects of estrogen and progesterone on the expression of genes related to endometrial proliferation, hyperplasia, and endometrial adenocarcinoma. One of the candidate genes synthesizes fibroblast growth factor 18 (*FGF18* gene), a factor that promotes epithelial proliferation. The *FGF18* gene is increased in endometrial adenocarcinoma and inhibited by progesterone. BZA inhibits the synthesis of FGF18 in endometrial stromal cells via a method

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that differs from progesterone [9]. In addition, BZA participates in the degradation of alpha estrogen receptors, a unique effect among most SERMs [10].

Clinical trials

The efficacy and safety of TSEC with CE/BZA have been evaluated in pivotal phase III studies, including *Selective estrogens, Menopause, And Response to Therapy* (SMART) trials [11–15]. These are multicenter, randomized, double-blind, placebo-controlled trials conducted in postmenopausal women with a uterus. Four of these trials also used an active control with raloxifene (SMART-1), BZA without CE (SMART-3) or with CE combined with medroxyprogesterone acetate (CE/MPA) (SMART-4), or BZA without CE (SMART-5). Table 1 summarizes the SMART trials and their endpoints.

Vasomotor symptoms

Of the pivotal trials, only SMART-2 used the number and intensity of hot flashes as its main variable. The study was performed on 332 healthy postmenopausal women aged 40–65 years with moderate or intense hot flashes. At the end of the 12-week study, the mean number of moderate and severe hot flashes and the severity of these hot flashes were reduced with CE/BZA compared with placebo (-7.63 ± 0.36 vs. -4.92 ± 0.48, $p < .001$; and -0.87 ± 0.08 vs. -0.26 ± 0.11, $p < .001$, respectively) [12]. In a later analysis, an increase in the number of women who did not experience hot flashes or who experienced more days without them was noted [16].

The efficacy on hot flashes was a secondary objective of SMART-1, where reductions in their frequency and severity were observed with CE/BZA compared with placebo and raloxifene. These effects remained after 2 years of treatment [11]. However, data comparing CE/BZA and other MHT regarding the reduction in hot flashes are not available. Only one study showed a similar efficacy for relieving hot flashes between CE 0.45 mg/BZA 20 mg and CE 0.625 mg/MPA 1.5 mg, but the principal purpose of this article was to determine the effects of CE/BZA on sleep and health-related quality of life (HRQoL) [17].

Health-related quality of life

In addition to their effects on vasomotor symptoms (VMS), TSEC combinations are effective in improving sleep quality and HRQoL.

In the SMART-2 trial, the sleep scale and HRQoL improved in women treated with CE/BZA compared with placebo [12]. In addition to the reduction in hot flashes, improvement was observed in all sleep parameters (falling asleep, sleep adequacy, and sleep disturbance $p < .001$) and the total treatment-specific quality of life (MENQoL) score ($p < .001$) [18].

In another series of 459 women, improvements were similar to women treated with CE/MPA in hot flashes, sleep quality, and HRQoL after 1 year of treatment [17].

CE/BZA appears to affect sleep more directly in women who have severe VMS but more indirectly via improvements in VMS in women with less severe VMS. Similarly, benefits of CE/MPA on sleep disturbance in the overall SMART-5 population were largely attributed to the reduction in VMS [19].

Similarly, in a *post hoc* SMART-2 study, CE/BZA improved HRQoL in postmenopausal women with bothersome hot flashes [17]. Other studies that evaluated HRQoL as a secondary objective achieved similar results [18–23].

Vaginal and sexual health

The SMART-3 trial was specifically designed to evaluate the effect of CE/BZA on vulvovaginal atrophy (VVA). This trial included 664 postmenopausal women aged 40–65 years. Women who received CE/BZA exhibited improvement in the percentage of superficial vaginal cells and parabasal cells in week 12 ($p < .01$ compared with placebo). However, significant differences in the reduction in vaginal pH and improvement in the most bothersome vulvovaginal symptoms (i.e., dyspareunia, vaginal dryness)

Table 1. Main efficacy results for TSEC from the SMART trials.

Study and trial registration	Objective	Main results
SMART 1 NCT00675688 [11]	Effects on menopausal symptoms, metabolic parameters, and overall safety vs. BZA, HT (CE/MPA), and PBO	• Reduction of the moderate-severe daily hot flushes ($p < .05$ vs. PBO) and its severity ($p < .001$ vs. PBO) • Improvements in sleep parameters ($p < .05$ vs. PBO) • Improvements in lipid parameters and homocysteine levels, no changes in carbohydrate metabolism, and only minor effects on some coagulation parameters • Endometrial safety • Breast pain and adverse events similar to placebo
SMART 2 NCT00234819 [12]	Safety and efficacy treating moderate to severe vasomotor symptoms vs. BZA, HT (CE/MPA), and PBO	• Reduction in the number and severity of hot flashes ($p < .001$ vs. PBO) • Improvements in sleep parameters ($p < .05$ vs. PBO) • Improvements in satisfaction and quality of life ($p < .05$ vs. PBO)
SMART 3 NCT00238732 [13]	Efficacy and safety of two doses of TSEC vs. PBO for the treatment of moderate to severe VVA associated with menopause	• Increase in superficial and intermediate cells, and decrease in parabasal cells ($p < .01$ vs. PBO) • Improvements in satisfaction, vasomotor symptoms, sexual function, and quality of life ($p < .05$ vs. PBO)
SMART 4 NCT00242710 [14]	Endometrial safety and BMD effects vs. HT (CE/MPA) and PBO	• Endometrial safety similar to PBO • Bleeding and breast tenderness lower than HT ($p < .05$) • Improve lumbar spine and total hip BMD ($p < .001$ vs. PBO) • Favorable safety/tolerability profile over 1 year
SMART 5 NCT00808132 [15]	Endometrial safety and BMD effects vs. BZA alone, HT, and PBO	• Low endometrial hyperplasia incidence (<1%) in all groups • Cumulative amenorrhea rates similar to PBO and BZA and higher than HT ($p < .001$) • Improve lumbar spine and total hip BMD ($p < .001$ vs. PBO) • Breast tenderness similar to PBO and BZA and significantly lower than HT ($p < .01$) • Adverse event rates were similar among the groups • Serious AEs overall and AE-related discontinuation rates lower than HT

BZA: bazedoxifene; CE: conjugated estrogen; HT: hormone therapy; MPA: medroxyprogesterone acetate; PBO: placebo; SMART: Selective estrogens, Menopause, And Response to Therapy; TSEC: tissue-selective estrogen complex; VVA: vulvar/vaginal atrophy.

($p < .05$) were observed only with a CE 0.625 mg/BZA dose and not with the commercialized dose (CE 0.45 mg) [13].

Changes in vaginal cytologies and improvement in dyspareunia were assessed as secondary objectives in the SMART-1 trial, where women treated with CE/BZA exhibited an increase in superficial and intermediate cells together with a reduction in parabasal cells ($p < .001$). The number of women who complained of dyspareunia also decreased from the 9th to 12th week ($p < .05$) [13].

Sexual function was evaluated in the SMART-3 trial with the MENQoL and the *Arizona Sexual Experiences Scale* (ASEX). Compared with placebo, any CE/BZA dose exhibited an increase in vaginal lubrication ($p < .05$) in the ASEX. The total scores reported from this questionnaire increased for the two doses of CE/BZA at 12 weeks ($p < .001$) compared with the scores reported for the group treated only with BZA, and significant improvements were also noted ($p < .05$) in the excitation, orgasm, and lubrication domains. When the MENQoL was used, sexual function improved with any CE/BZA dose compared with placebo and BZA alone ($p < .001$) [13].

A *post hoc* analysis of the SMART-3 trial examined the relationship between sexual function and the signs and symptoms of VVA, and an approximately linear relationship was noted between these factors. Sexual function improved as dyspareunia and other VVA symptoms decreased [24]. Data comparing CE/BZA and other MHTs regarding the effect on VVA are not available.

Bone effects

The efficacy of CE/BZA on bone was evaluated in the SMART-1, -4, and -5 trials. In all of these trials, a significant increase in lumbar and hip bone mineral density (BMD) was observed compared with placebo. In SMART-1, lumbar and hip BMD was also increased compared with raloxifene [11]. In SMART-5, the increase was smaller than that for CE/MPA in the spinal column; however, the dropout rate with this MHT was higher [15]. In SMART-5, the increase was smaller than that for CE/MPA in the spinal column; however, the dropout rate with this MHT was higher [15].

In a combined analysis of SMART-1 and -5, CE/BZA increased lumbar and hip BMD compared with placebo, independently of user risk, using the Fracture Risk Assessment Tool (FRAX) [25]. The results for BMD have been corroborated in Black and Latin American patients [26].

However, in Spain, the CE/BZA combination has not been approved for the treatment of postmenopausal osteoporosis [6].

Safety

Globally, the safety of CE/BZA has been analyzed in a total of 4868 postmenopausal women who participated in the five SMART trials (3322 for at least 1 year, and 1999 for 2 years). Of these, 1585 received the commercial dose (CE 0.45 mg/BZA), and 1241 received placebo. The most frequent adverse effect was abdominal pain (greater than 10% of patients) followed by vulvovaginal candidiasis, constipation, diarrhea, nausea, muscle spasms, elevated triglycerides, headache, arthralgia, myalgia, back and limb pain, nasopharyngitis, and the flu [11,27].

Endometrial effects

Endometrial hyperplasia was the main measurement of the SMART-1 and -5 trials. The minimum effective dose of BZA for preventing hyperplasia at 2 years was 20 mg [28].

In SMART-1, the incidence of endometrial hyperplasia over 2 years was <1% with any dose of CE (0.625 or 0.45 mg)/BZA (20 or 40 mg), similar to that observed with placebo. Similarly, the endometrial thickness observed with any CE/BZA dose was similar to that observed with placebo. Taken together, these data suggest endometrial safety and were appropriate for regulatory approval [4,5].

In SMART-5, a case of endometrial hyperplasia was observed in each of the CE/BZA groups and the placebo group at 12 months, whereas these cases were not observed in the groups that received only BZA or CE/MPA. No cases of endometrial carcinoma were reported [15]. Endometrial safety was also the primary endpoint in the SMART-4 trial, which reported no cases of hyperplasia with CE 0.45 mg/BZA, CE 0.45 mg/MPA, or placebo, but three cases with CE 0.625 mg/BZA (1.1%), the TSEC combination not marketed [14].

In a study combining the five SMART trials, the findings of the endometrial biopsies, ultrasounds, and daily bleeding records were analyzed together. Entirely, the rate of endometrial hyperplasia was maintained below 1% [29].

Regarding endometrial cancer, there was only one case in all of the SMART studies, which occurred in a woman taking CE 0.45 mg/BZA. Consequently, the incidence rate of endometrial cancer was 0.4 per 1000 woman-years (95% confidence interval [CI] 0.0–2.4), and the risk ratio (RR) was 0.9 (95% CI 0.2–4.8) for CE 0.45 mg/BZA [29].

Similarly, the analysis of the subpopulations of these studies, particularly in Latin American women, indicates similar safety to that recorded in the general population [26].

Several randomized controlled trials (RCTs) have analyzed the degree of endometrial suppression between the levonorgestrel intrauterine system (LNG-IUS) and various other routes of progestogen administration. Although no endometrial hyperplasia was observed in any route, a greater degree of suppression of endometrial proliferation was achieved with the LNG-IUS [30]. However, no studies comparing the endometrial effect of BZA vs. progestogens are available.

In a recent systematic review including 28 studies regarding MHT and the risk of endometrial cancer, the authors concluded that use of unopposed estrogen, tibolone, and sequential combined therapy increases the risk of endometrial cancer. Continuous combined therapy seems risk-free, but this may not be the case not when micronized progesterone is used [2].

Breast effects

The data obtained in laboratory studies reveal that BZA alone or in combination with CE exerts an anti-estrogenic effect on breast tissue; however, the effect is inferior compared with other SERMs (raloxifene or lasofoxifene) [31–33].

Breast pain/tenderness are common complaints of women using traditional MHT. In contrast, in SMART-1 and SMART-5, the incidence rates of breast pain/tenderness with CE/BZA were comparable to those of placebo, whereas significantly ($p = .001$) higher rates of breast tenderness were observed with CE/MPA than CE/BZA in SMART-5 [11,34].

Similarly, while mammographic density did not change with CE/BZA, CE/MPA significantly ($p = .001$) increased breast

density compared with placebo, as it did in the Women's Health Initiative (WHI) trial [35].

In clinical studies, the incidence of breast cancer in more than 3700 women treated with CE/BZA was the same as that observed with placebo at 2 years of follow-up (SMART-1 and 5). No changes were observed in the radiological density, mastodynia, or benign pathology [36,37].

Fournier et al., using data from the French E3N cohort study, found that the association of estrogen–progestogen combinations with breast cancer risk varied significantly according to the type of progestogen. The RRs were 1.00 (0.83–1.22) for estrogen–progesterone, 1.16 (0.94–1.43) for estrogen–dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestogens. This study found no evidence of an association with risk according to the route of estrogen administration (i.e., oral or transdermal/percutaneous) [38].

There are few available studies on LNG-IUS plus estrogen. A case-control study on hormone therapy as a risk factor for breast cancer in Finland found that the use of a LNG-IUS alone ($n = 154$) (1.45; 1.97–1.77) or as a complement to estradiol ($n = 137$) (2.15; 1.72–2.68) was associated with an increased risk of breast cancer [39]. In another Finnish nationwide cohort study, LNG-IUS users had increased risks for both ductal breast cancer (standardized incidence ratio (SIR) 1.20, 95% CI 1.14–1.25) and lobular breast cancer (SIR 1.33, 95% CI 1.20–1.46) compared with the general female population [40].

A very recent study concluded that in perimenopausal women, LNG-IUS was not associated with an increased total risk of breast cancer, although in the subgroup of women in their early 40 s (40–45 years), it was associated with a slightly increased risk of invasive tumors (5-year Kaplan–Meier [KM] estimate: 0.88% vs. 0.69%, $p = .014$) [41].

Cardiovascular effects

The incidence of thrombotic events in the SMART trials was low compared with placebo, with six recorded cases out of 4868 treated women (0.069% per year, RR = 0.48, 95% CI 0.00–1.49 vs. 0.13–1.77).

In a 3-year RCT for the treatment of osteoporosis with only BZA 20 mg, the venous thromboembolism index per 1000 women-years during the study period was 2.86 in the BZA group and 1.76 in the placebo group. During the 5-year study period, it was 2.34 in the BZA group and 1.56 in the placebo group [42]. After 7 years, the venous thromboembolism indexes were 2.06 in the BZA group and 1.36 in the placebo group [4].

Similarly, among users of CE 0.45 mg/BZA, the percentage of ictus was 0.06% compared with 0% in placebo users. The incidence of ischemic heart disease and myocardial infarction was similar among users of CE 0.45 mg/BZA and placebo (0.3% and 0.2% vs. 0.2% and 0.2%, respectively). In parallel, systolic blood pressure increased by an average of 1.15 mm Hg in the CE 0.45 mg/BZA user group [43].

There are no RCTs evaluating the cardiovascular effects of CE/BZA vs. other MHTs, but upon comparing CE 0.45 mg/BZA 20 mg with historical data from the WHI trial with CE/MPA, nonsignificant differences were observed between both groups of similar age in venous thromboembolism (0.3 vs. 1.9), coronary heart disease (2.6 vs. 2.2), and ictus (0.4 vs. 1.5) [43].

Metabolic effects

No RCTs comparing the metabolic effects of CE/BZA vs. MHT are available. Preclinical and clinical studies suggest that estrogens increase insulin sensitivity, but this effect is countered by progestins, which are associated with hyperinsulinemia and decreased insulin sensitivity [44]. Effects of CE/BZA on insulin sensitivity have not been reported.

Progestins: risks and benefits

Apart from micronized progesterone, there are several types of progestins whose biological activities and effects depend on their chemical structures, particularly with respect to pharmacokinetics and potency. The oral route is the most common route of progestin administration for MHT, but different parenteral routes have been used to avoid first-pass hepatic metabolism. The potential risk of progestins, along with the associated intolerance and the side effects they produce, has resulted in the search for a progestin with a better tolerance or a progestin-free treatment. A summary of the most important side effects attributed to progestins is shown in Table 2.

In its last recommendations, the International Menopause Society even stated that breast cancer could be associated with progestins [58]. However, many of these effects are based on limited data, and there are no double-blind randomized trials comparing long-term safety for breast cancer and cardiovascular risk among them. Short-term clinical studies and observational

Table 2. Breast and cardiovascular effects of the different progestins.

Progestins	Breast effects	CV effects
Micronized progesterone [38,45]	No	No
Pregnane derivatives no acetylated		
Dydrogesterone [38,46,47]	No	No
Pregnane derivatives acetylated		
MPA [46–51]	BC risk	CV risk (no in recent menopause)
Megestrol acetate [52]	No	No
Chlormadinone acetate [49,51]	Tenderness	No
Cyproterone acetate [51,53]	Tenderness	No
19-Nortesterone derivated: Entranes		
NET [46]	BC risk	
NETA [52,54,55]	BC risk	CV risk (no in recent menopause)
Tibolone [56]	No	No
19-Nortesterone derivated: Gonanes		
LNG [52]	BC risk	
Spyrolactone derivated		
DRSP [57]	Tenderness	Antihypertensive

BC: breast cancer; CV: cardiovascular; DRSP: drospirenone; LNG: levonorgestrel; MPA: medroxyprogesterone acetate; NET: norethisterone; NETA: norethisterone acetate.

and experimental studies indicate that micronized progesterone and dydrogesterone are the safer progestins with acceptable metabolic profiles and are associated with a lower risk profile of breast cancer than progestins when they are used in MHT [59].

TSEC user profile

The treatment of vasomotor symptoms remains the main indication for MHT of any type, including TSEC. Reciprocally, the first option for treatment of this symptomatology is MHT of any type. The question then is whether TSEC is another option within the range of possible MHTs or presents advantages/added risks compared with other MHTs with progestins that permit delineating a user profile.

Clarifying this idea, the efficacy of the authorized TSEC combination (CE 0.45 mg/BZA 20 mg) for the alleviation of hot flashes has been demonstrated in SMART-2. Other studies have also demonstrated efficacy similar to MHT with regard to bone, vaginal, or metabolic parameters. However, for the treatment of VVA, the first course of action is the use of topical estrogens, and comparative data are not available between these agents and TSEC.

The possible benefits of TSEC are found mainly in the bleeding pattern and amenorrhea rate, which are more favorable for TSECs. The benefits also include reduced mammary repercussion achieved with respect to MHT with progestins and reduced mastodynia. In addition, TSEC exhibits a reduced increase in mammary radiological density; hence, not seeing an increase is at least reassuring.

In addition, some studies show that some progestins in MHT users are associated with hyperinsulinemia and decreased insulin sensitivity [46]. These effects have not been reported with CE/BZA treatment.

Among the possible risks, the lack of long-term endometrial safety has been noted. However, in SMART-1, CE/BZA was associated with rates of endometrial hyperplasia of less than 1%, which are similar to those observed with placebo. These rates are consistently lower than the 2 and 4% rates at 12 or 24 months, respectively, that the European and American drug agencies set as endometrial protection requirements for products that contain estrogens [4,5]. Therefore, healthy postmenopausal women with a uterus can use CE/BZA for the treatment of menopausal symptoms and the prevention of bone loss with peace of mind for 2 years in terms of their endometrial profile.

Regarding breast cancer risk, the short duration of the pivotal studies should be noted so as not to guarantee long-term breast safety. However, there is no reason to think that TSECs increase breast cancer risk. In our recommendations, we included that before the prescription of TSEC, no other additional tests are necessary for population screening.

Furthermore, we do not have data on the use of TSECs in women with risk factors or a family history of breast cancer, but nothing suggests that their existence requires depriving these women of the possibility of being treated with TSEC. We have no evidence of its use in women surviving breast cancer, so we kept the same recommendations already written for these patients [60].

Final considerations and future perspectives

The SMART trials were performed in healthy, non-obese, mainly Caucasian women without considering other cardiovascular, endometrial cancer, or breast cancer risk factors. The long-term safety of TSEC is not clearly established due to the limited duration of these studies, and the risks associated with its use by women over 65 years of age are not identified.

Therefore, additional safety studies are needed in other women over the long term. For example, it would be necessary to assess its effect on obese patients (with higher cardiovascular, endometrial, and mammary risk). Thus, a 2A recommendation grade could be achieved according to Grade criteria (we have high quality evidence, but the degree of recommendation requires long-term studies and assessment in other medical conditions). Regarding age, we do not think that analyses are necessary in women over 65 years of age, bearing in mind that the latest recommendations for any type of MHT do not include initially administering this regimen in women of this age.

Summary and recommendations

- TSEC is associated with a clinically significant reduction in the number and severity of hot flashes (GRADE 2A). This efficacy is similar to that recorded with MHT.
- TSEC is associated with clinically significant improvements in health- and sleep-related quality of life (GRADE 2B). These improvements are similar to those observed with MHT.
- TSEC decreases dyspareunia and reduces vaginal dryness compared to placebo. In addition, the use of TSEC involves significant improvements in sexual health. However, isolated VVA is not an approved indication for TSEC.
- TSEC is associated with a safe breast profile with the same incidence rates of breast tenderness and effect on mammary density as placebo (GRADE 2A).
- TSEC achieves high amenorrhea rates compared with placebo and significantly higher rates compared with MHT (GRADE 2A).
- TSEC exhibits a favorable endometrial safety profile with an incidence of hyperplasia similar to that of placebo (GRADE 2A).

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References

[1] Valera MC, Gourdy P, Trémollières F, et al. From the women's health initiative to the combination of estrogen and selective estrogen receptor modulators to avoid progestin addition. Maturitas. 2015;82:274–277.

[2] Sjögren LL, Mørch LS, Løkkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. Maturitas. 2016;91:25–35.

[3] Peng L, Luo Q, Lu H. Efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e8659.
[4] http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_Product_Information/human/002314/WC500181566.pdf
[5] FDA Guidance: www.fda.gov/downloads/drugs/guidancecompliancere-gulatory information/guidances/ucm071643.pdf
[6] Mirkin S, Komm BS. Tissue-selective estrogen complexes for post-menopausal women. Maturitas. 2013;76:213–220.
[7] http://cebgrade.mcmaster.ca/
[8] Kharode Y, Bodine PV, Miller CP, et al. The pairing of a selective estrogen receptor modulator, bazedoxifene, with conjugated estrogens as a new paradigm for the treatment of menopausal symptoms and osteoporosis prevention. Endocrinology. 2008;149:6084–6091.
[9] Flannery CA, Fleming AG, Choe GH, et al. Endometrial cancer-associated FGF18 expression is reduced by bazedoxifene in human endometrial stromal cells *in vitro* and in murine endometrium. Endocrinology. 2016;157:3699–3708.
[10] Han SJ, Begum K, Foulds CE, et al. The dual estrogen receptor α inhibitory effects of the tissue-selective estrogen complex for endo-metrial and breast safety. Mol Pharmacol. 2016;89:14–26.
[11] Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril. 2009;92:1025–1038.
[12] 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. Menopause. 2009;16:1116–1124.
[13] Kagan R, Williams RS, Pan K, et al. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treat-ment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause. 2010;17:281–289.
[14] Mirkin S, Komm BS, Pan K, Chines AA. Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women. Climacteric. 2013;16:338–346.
[15] Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab. 2014;99:E189–E198.
[16] Yu H, Racketa J, Chines AA, et al. Hot flush symptom-free days with bazedoxifene/conjugated estrogens in postmenopausal women. Climacteric. 2013;16:252–257.
[17] Pinkerton JV, Pan K, Abraham L, et al. Sleep parameters and health-related quality of life with bazedoxifene/conjugated estrogens: a randomized trial. Menopause. 2014;21:252–259.
[18] Utian W, Yu H, Bobula J, et al. Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. Maturitas. 2009;63:329–335.
[19] Pinkerton JV, Bushmakin AG, Racketa J, et al. Evaluation of the direct and indirect effects of bazedoxifene/conjugated estrogens on sleep disturbance using mediation modeling. Menopause. 2014;21:243–251.
[20] Bushmakin AG, Abraham L, Pinkerton JV, et al. Evaluation of the measurement model and clinically important differences for meno-pause specific quality of life associated with bazedoxifene/conjugated estrogens/bazedoxifene treatment on quality of life in postmenopausal women. Maturitas. 2016;94:173–179.
[21] Abraham L, Pinkerton JV, Messig M, et al. Menopause-specific quality of life across varying menopausal populations with conjugated estrogens/bazedoxifene. Maturitas. 2014;78:212–218.
[22] Gallagher JC, Shi H, Mirkin S, et al. Changes in bone mineral density are correlated with bone markers and reductions in hot flush severity in postmenopausal women treated with bazedoxifene/conjugated estrogens. Menopause. 2013;20:1126–1132.
[23] Bachmann G, Bobula J, Mirkin S. Effects of bazedoxifeno/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. Climacteric. 2010;13:132–140.
[24] Pinkerton JV, Bushmakin AG, Komm BS, et al. Relationship between changes in vulvar-vaginal atrophy and changes in sexual functioning. Maturitas. 2017;100:57–63.
[25] Gallagher JC, Palacios S, Ryan KA, et al. Effect of conjugated estrogens/bazedoxifene on postmenopausal bone loss: pooled analysis of two randomized trials. Menopause. 2016;23:1083–1091.
[26] Palacios S, Arias L, Lavenberg J, et al. Evaluation of efficacy and safety of conjugated estrogens/bazedoxifene in a Latin American population. Climacteric. 2016;19:261–267.
[27] Pinkerton JV, Abraham L, Bushmakin AG, et al. Evaluation of the efficacy and safety of bazedoxifene/conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the Selective estrogens, Menopause and Response to Therapy (SMART) trials. J Womens Health. 2014;23:18–28.
[28] Pickar JH, Yeh IT, Bachmann G, et al. Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. Fertil Steril. 2009;92:1018–1024.
[29] Mirkin S, Pinkerton JV, Kagan R, et al. Gynecologic safety of conjugated estrogens plus bazedoxifene: pooled analysis of five phase 3 trials. J Womens Health. 2016;25:431–442.
[30] Depypere H, Inki P. The levonorgestrel-releasing intrauterine system for endometrial protection during estrogen replacement therapy: a clinical review. Climacteric. 2015;18:470–482.
[31] Peano BJ, Crabtree JS, Komm BS, et al. Effects of various selective estrogen receptor modulators with or without conjugated estrogens on mouse mammary gland. Endocrinology. 2009;150:1897–1903.
[32] Song Y, Santen RJ, Wang JP, et al. Inhibitory effects of a bazedoxi-fene/conjugated equine estrogen combination on human breast cancer cells in vitro. Endocrinology. 2013;154:656–665.
[33] Madak-Erdogan Z, Gong P, Katzenellenbogen BS. Differential utiliza-tion of nuclear and extranuclear receptor signaling pathways in the actions of estrogens, SERMs, and a tissue-selective estrogen complex (TSEC). J Steroid Biochem Mol Biol. 2016;158:198–206.
[34] Pinkerton JV, Harvey JA, Pan K, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. Obstet Gynecol. 2013;121:959–968.
[35] Crandall CJ, Aragaki AK, Cauley JA, et al. Breast tenderness after-initiation of conjugated equine estrogens and mammographic density change. Breast Cancer Res Treat. 2012;131:969–979.
[36] Pinkerton JV, Taylor H, Pan K, et al. Breast parameters with bazedox-ifene/conjugated estrogens in randomized, controlled trials of post-menopausal women. Menopause 2010;17:1221–1222.
[37] Harvey JA, Pinkerton JV, Baracat EC, et al. Breast density changes in a randomized controlled trial evaluating bazedoxifene/conjugated estrogens. Menopause. 2013;20:138–145.
[38] Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107:103–111.
[39] Lyytinen HK, Dyba T, Ylikorkala O, et al. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intra-uterine system carries a risk as well. Int J Cancer. 2010;126:483–489.
[40] Soini T, Hurskainen R, Grénman S, et al. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: a nationwide cohort study. Acta Oncol. 2016;55:188–192.
[41] Siegelmann-Danieli N, Katzir I, Landes JV, et al. Does levonorgestrel-releasing intrauterine system increase breast cancer risk in peri-menopausal women? An HMO perspective. Breast Cancer Res Treat. 2017;167:257–262.
[42] Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxi-fene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008;23:1923–1934.
[43] Komm BS, Thompson JR, Mirkin S. Cardiovascular safety of conjugated estrogens plus bazedoxifene: meta-analysis of the SMART trials. Climacteric. 2015;18:503–511.
[44] Sites CK, L'Hommedieu GD, Toth MJ, et al. The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2005;90:2701–2707.
[45] Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Ann Intern Med. 2014;161:249–260.
[46] Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmeno-pausal women using estradiol-progestogen therapy. Obstet Gynecol. 2009;113:65–73.
[47] Schneider C, Jick SS, Meier CR. Risk of cardiovascular outcomes in users of estradiol/dydrogesterone or other HRT preparations. Climacteric. 2009;12:445–453.
[48] Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310:1353–1368.
[49] Krämer EA, Seeger H, Krämer B, et al. The effect of progesterone, testosterone and synthetic progestogens on growth factor- and estradiol-treated human cancerous and benign breast cells. Eur J Obstet Gynecol Reprod Biol. 2006;129:77–83.
[50] Chlebowski RT, Rohan TE, Manson JE, et al. Breast cancer after use of estrogen plus progestin and estrogen alone: analyses of data from 2

Women's Health Initiative randomized clinical trials. JAMA Oncol. 2015;1:296–305.
[51] Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115:840–845.
[52] Mirkin S, Wong BC, Archer DF. Effect of 17 beta-estradiol, progesterone, synthetic progestins, tibolone, and tibolone metabolites on vascular endothelial growth factor mRNA in breast cancer cells. Fertil Steril. 2005;84:485–491.
[53] Lundström E, Wilczek B, Von Palffy Z, et al. Mammographic breast density during hormone replacement therapy: effects of continuous combination, unopposed transdermal and low-potency estrogen regimens. Climacteric. 2001;4:42–48.
[54] Stuedal A, Ma H, Bjørndal H, et al. Postmenopausal hormone therapy with estradiol and norethisterone acetate and mammographic density: findings from a cross-sectional study among Norwegian women. Climacteric. 2009;12:248–258.
[55] Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ. 2012;345:e6409.
[56] Mendoza N, Abad P, Baró F, et al. Spanish Menopause Society position statement: use of tibolone in postmenopausal women. Menopause. 2013;20:754–760.
[57] Archer DF. Drospirenone and estradiol: a new option for the postmenopausal woman. Climacteric. 2007;10:3–10.
[58] 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;16:316–337.
[59] Palacios S, Mejía A. Progestogen safety and tolerance in hormonal replacement therapy. Expert Opin Drug Saf. 2016;15:1515–1525.
[60] Sánchez-Borrego R, Mendoza N, Beltrán E, et al. Position of the Spanish menopause society regarding the management of menopausal symptoms in breast cancer patients. Maturitas. 2013;75:294–300.

Appendix. Search strategy

((‘tissues’[MeSH Terms] OR ‘tissues’[All Fields] OR ‘tissue’[All Fields]) AND selective[All Fields] AND (‘estrogen’[All Fields] OR ‘estrogens’[Pharmacological Action] OR ‘estrogens’[MeSH Terms] OR ‘estrogens’[All Fields] OR ‘estrogen’[All Fields]) AND (‘therapy’[Subheading] OR ‘therapy’[All Fields] OR ‘therapeutics’[MeSH Terms] OR ‘therapeutics’[All Fields])) AND ((‘therapy’[Subheading] OR ‘therapy’[All Fields] OR ‘therapeutics’[MeSH Terms] OR ‘therapeutics’[All Fields]) AND (‘menopause’[MeSH Terms] OR ‘menopause’[All Fields])) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR doublé-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (‘clinical trial’ [tw] OR ((singl* [tw] OR blind* [tw])) OR (‘latin square’ [tw] OR placebo [mh]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer* [tw] NOT (animal [mh] NOT human [mh])).