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BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

November 2016

Review: November 2019

Bulletin 247: Bazedoxifene plus conjugated oetsrogens (Duavive®) for post-menopausal symptoms in women with a uterus

JPC Recommendations:

To support the East of England Priorities Advisory Committee (PAC) policy statement and recommendations (See attachment – PAC doc updated Nov 2016)

The East of England
Priorities Advisory Committee
A function of PrescQIPP

FULL EVIDENCE REVIEW

Bazedoxifene plus conjugated oestrogens (Duavive®) for post-menopausal symptoms in women with a uterus

Recommendations on the use of bazedoxifene plus conjugated oestrogens (Duavive ®) for the treatment of post-menopausal symptoms in women with a uterus

Routine commissioning of bazedoxifene plus conjugated oestrogens (Duavive®) for the treatment of post-menopausal symptoms in women with a uterus is currently NOT recommended because:

- There is insufficient evidence to quantify the risks and benefits compared to current alternative treatments
- There are no long term safety data.
- Information on cost effectiveness and cost impact is not currently available.

Recommendations will be reviewed in the light of new national guidance, new evidence and information on cost effectiveness.

Medicine	Bazedoxifene (BZA) plus conjugated oestrogens (CE), Duavive®
Proposed sector of prescribing	Primary and secondary care

Key points/Evidence level

Key points

- Bazedoxifene acetate is a third generation selective oestrogen receptor modulator (SERM), similar to raloxifene, and has oestrogen-receptor agonist effects on bone, and antagonist effects on uterine and breast tissue.
- When a SERM is paired with an oestrogen, it forms a tissue-selective estrogen complex (TSEC); a novel class of therapeutic agents, which achieve an optimal blend of estrogen receptor agonist and antagonist effects for the treatment of menopausal symptoms and prevention of osteoporosis.
- Bazedoxifene combined with conjugated estrogens has recently been approved by the Food & Drug Administration (FDA) in the United States (US) for treatment of moderate-to-severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis in women with a uterus as Duavee® and in the European Union (EU), as Duavive®, for the treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus.
- Bazedoxifene with conjugated oestrogens (BZA/CE) has been evaluated in five published Phase III Selective Estrogen Menopause and Response to Therapy (SMART) studies. These phase III trials showed that:

  - Compared with placebo, BZA/CE, demonstrated improvements in vasomotor symptoms and vulvovaginal atrophy, while protecting the endometrium, increased the Bone Mineral Density (BMD) of the lumbar spine and hip and showed decreases in bone turnover markers.
  - BZA/CE was less effective than a combination of medroxyprogesterone with conjugated oestrogens (MPA/CE) and there is insufficient data with raloxifene on which to base a definitive conclusion.
- BZA/CE was associated with an acceptable safety profile and possible improved tolerability; (lower rates of uterine bleeding and breast pain) when compared with MPA/CE, however more data is required to confirm this as the phase 3 trials were limited by the small number of patients taking MPA/CE and the overall duration of the trials. Other HRT preparations were not included in any studies and BZA was not compared to CE alone due concerns about uterine safety with unopposed estrogens.
- No apparent increased risk for serious adverse events, such as venous thromboembolism, cardiovascular events, endometrial cancer, or breast cancer, was observed with either dose strength of BZA/CE.
- There is limited data available in the following groups:
  - Use in elderly patients; studies to date have only included postmenopausal women up to the age of 65 years.
  - Use in hepatic impaired patients.
  - Use in renal impaired patients.
  - Use in patients with malignancy.
  - Use in patients with history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking.
  - Long-term (>2 years) safety data, specifically on breast protection and gynaecological cancers (endometrial and ovarian in particular)
  - Patients from ethnic minorities.
  - Patients who are morbidly obese (BMI = 34.0kg/m^2).
- There is limited comparative data with hormone replacement therapy. A formulation containing MPA/CE was included as an active control in study. However, the study was too small and too short on which to draw definitive conclusions regarding comparative efficacy between BZA/CE and MPA/CE.
- The anticipated cost of BZA/CE is unknown and the tariff status cost implications need to be confirmed.

Background information

The menopause, sometimes referred to as the “change of life”, is the end of menstruation, when a woman stops having periods as she reaches the end of her natural reproductive life. This is not usually abrupt, but a gradual process during which women experience perimenopause before reaching post menopause. The average age of menopause in the UK is 51. However, this varies widely and 1 in 100 women experience premature ovarian insufficiency.[1-3]

In the lead-up to the menopause, known as the perimenopause, oestrogen levels decrease, causing the ovaries to stop producing an egg each month (ovulation), this leads to irregular periods as well as vasomotor symptoms such as:[1-3]

- Hot flushes
- Night sweats
- Mood swings
- Vaginal dryness.

Other symptoms include memory and concentration loss, a lack of interest in sex, headaches, and joint and muscle stiffness. Quality of life may be severely affected.

Most women (8 out of 10) experience some symptoms, typically lasting about four years after the last period, but continuing for up to 12 years in about 10% of 14 women.[1-3]

Prolonged lack of oestrogen affects the bones and cardiovascular system and postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis.[1-3]

Hormone replacement therapy (HRT), along with bisphosphonates for those women at risk of osteoporosis, are the mainstays of current treatment.

Around a million women in the UK currently use treatment for their menopausal symptoms. The advice and support available is variable, and use of HRT varies with socioeconomic and cultural factors. The number of prescriptions for HRT almost halved after two large studies, the Women's Health Initiative (2002) and the Million Women Study (2003) which focused on the use of HRT in chronic disease prevention and highlighted the potential long-term risks but did not consider the benefits in terms of menopausal symptom relief. The overall balance of benefits and risks of HRT use therefore has yet to be confirmed.[1]

Bazedoxifene acetate is a third generation selective oestrogen receptor modulator (SERM), similar to raloxifene, and has oestrogen-receptor agonist effects on bone, and antagonist effects on uterine and breast tissue.[4,5]

It is approved for use in the European Union, but is not currently used in the UK as a monotherapy.

When a SERM is paired with an oestrogen, it forms a tissue-selective estrogen complex (TSEC); a novel class of therapeutic agents, which achieve an optimal blend of estrogen receptor agonist and antagonist effects for the treatment of menopausal symptoms and prevention of osteoporosis.[6,7]

Bazedoxifene combined with conjugated estrogens [BZA/CE] is the only TSEC for which Phase III clinical trials have been completed. It has recently been approved by the Food & Drug Administration (FDA) in the United States (US) for treatment of moderate-to-severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis in women with a uterus as Duavee® and in the European Union (EU) as Duavive® for the treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus.[5,8-10]

Formulation/Available products

Bazedoxifene 20mg plus conjugated oestrogens 0.45mg (Duavive®).[10]

Licensed indication

Treatment of oestrogen 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.[10]

Usual dosage

The recommended dose is 0.45mg conjugated oestrogens (CE) and 20mg bazedoxifene (BZA) taken as a single oral tablet, once daily.[10]

Treatment alternatives/place in therapy

Combined hormonal replacement therapies (HRT) containing both an estrogen (such as estradiol) and a progestogen (such as medroxyprogesterone -MPA). Examples include Prempak C, Premique, Elleste Duet, Kliofem.[11]

Raloxifene is licensed for the treatment and prevention of osteoporosis in postmenopausal women. It is not licensed for the management of menopausal symptoms.[12] Raloxifene is recommended as a possible treatment option for the secondary prevention of osteoporosis by NICE.[13]

Future alternatives

None known.

National guidance

NICE guideline Menopause: diagnosis and management NG23 does not provide any information regarding choice of HRT and no specific recommendation in relation to BZA/CE.[1]

Local guidance

None identified.

Evidence for use

BZA/CE has been evaluated in five published Phase III Selective Estrogen Menopause and Response to Therapy (SMART 1-5) studies.[9,14-19]

Severity and frequency of hot flushes; sleep disturbances and menopause-related quality of life and sexual function/activities were assessed in all the trials. Changes in bone mineral density (BMD) and bone turnover markers (BTM) were assessed in SMART-1, SMART-4 and SMART-5.[14,18-19] All trials were designed to provide sufficient sample sizes to power the outcomes and results were analysed on a modified intention to treat basis and were sponsored by the original manufacturer, Wyeth.

SMART 1

SMART 1: A two year double-blind, randomised, multicentre, placebo- and active- controlled phase 3 trial involved 3397 healthy women, aged 40-75 years with an intact uterus who were menopausal for at least one year. Subjects were randomly assigned to one of eight treatment regimens, including six BZA/CE doses (BZA [10, 20, or 40mg] each with CE [0.45 or 0.625mg]), raloxifene 60mg, or placebo, and were instructed to record information on hot flushes, sexual activity/dyspareunia, and breast pain. Vaginal atrophy was measured by vaginal smears at months 6, 12, 18 and 24. Primary outcomes were not well defined.[14,15]

Two sub study groups were conducted; sub study I enrolled 1454 women >5 years postmenopausal with mean baseline T-score [± SD] = -1.47 ± 0.73, and at least one additional risk factor for osteoporosis; and sub study II evaluated BMD in women (n=861) between 1–5 years postmenopausal with similar T-score and risk factor profile at baseline. See below for discussion.

SMART 2

SMART 2: A multicentre, double-blind, randomised, placebo-controlled 12 week study conducted at 43 sites in the United States involving 318 healthy women with an intact uterus with at least 12 months of spontaneous amenorrhea, or six months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) > 40 mIU/mL. Participants were randomly assigned to receive BZA 20mg with either CE 0.45mg or CE 0.625mg or placebo following a 2:2:1 randomization ratio.

The primary efficacy variables for this study were the changes from baseline in the average daily number of moderate and severe hot flushes and the severity of hot flushes at weeks 4 and 12.[16]

SMART 3

SMART 3: A phase 3, multicentre, double-blind, randomized, placebo-controlled, comparator, 12-week study conducted at 66 sites in the United States. Involving 664 healthy women aged 40-65 years, with at least 12 months of spontaneous amenorrhea or at least six months of spontaneous amenorrhea with (FSH) > 40 mIU/mL. Participants were assigned to receive BZA 20mg/CE 0.45mg, BZA 20mg/CE 0.625mg, BZA 20mg, or placebo.

The primary efficacy parameters were four co-primary endpoints comparing the BZA/CE groups with the placebo group: the proportion of vaginal superficial cells, the proportion of parabasal cells, vaginal pH, and severity of the most bothersome vulvar/vaginal symptom, assessed at week 12.[17]

SMART 4

SMART 4: A phase 3, multicentre, double-blind, randomized, active- and placebo-controlled, comparator, one year study conducted at 62 sites in the United States and Argentina involving 1061 healthy women with an intact uterus, a healthy endometrium, and at least 12 months of spontaneous amenorrhea or at least six months of spontaneous amenorrhea with (FSH) > 40 mIU/mL. Participants were assigned to receive BZA 20mg/CE 0.45mg, BZA 20mg/CE 0.625mg, CE 0.45mg/ medroxyprogesterone (MPA) 1.5mg, or placebo. [N.B. the closest UK equivalent is Premique® (conjugated oestrogen (625mcg/medroxyprogesterone acetate 5mg) or Premique® Low Dose (conjugated oestrogen 300mcg/medroxyprogesterone acetate 1.5mg)].

The primary efficacy endpoint was the incidence of endometrial hyperplasia at one year. A sub-study was also conducted to evaluate the effect of BZA/CE on postmenopausal osteoporosis and bone markers.[18]

SMART 5

SMART 5: A one year, multicentre, international, randomized, double-blind, placebo- and active-controlled phase 3 study conducted at 166 sites, involving 1866 healthy postmenopausal women, aged 40 to 65 years, seeking treatment for menopausal symptoms. Subjects were randomised to receive BZA 20mg/CE0.45 or 0.625mg, BZA 20mg, CE 0.45mg/MPA 1.5mg, or placebo at a ratio of 2:2:1:1:2.

The primary endpoint for the main study was the incidence of endometrial hyperplasia at 12 months. This trial included an osteoporosis sub study. 590 subjects received daily oral BZA/CE 20mg and 0.45 or 0.625mg, BZA 20mg, MPA 1.5mg/CE 0.45mg or placebo.[19]

Management of menopausal symptoms caused by oestrogen deficiency

Effect of BZA/CE on vasomotor symptoms

Results from SMART-1 demonstrated that all doses of BZA/CE provided significantly better relief than placebo at most time points ($p<0.01$), but not compared with raloxifene.[14,15]

In SMART-2, all groups demonstrated a significant reduction ($p< 0.001$) from baseline and also compared with placebo for the mean daily number of moderate and severe hot flushes at all-time points. In a secondary analysis at week 12, both doses of BZA/CE reduced hot flushes from baseline by 74% and 80% respectively, compared with 51% for placebo.

Similarly, the mean daily severity of hot flushes significantly improved ($p< 0.001$) from baseline and compared with placebo with BZA 20mg/CE 0.45 or 0.625mg at all-time points. BZA 20mg/CE 0.625mg had significantly greater reductions in hot flush severity than had BZA 20mg/CE 0.45mg from week 6 ($p=0.011$) to week 12 ($p=0.002$).

Additionally, the secondary endpoint (responder rates) showed that significantly more ($p<0.001$) BZA/CE-treated women responded at both the 75% and 50% level compared with placebo at weeks four and 12, and the median time to reach a 50% reduction in hot flushes for at least three consecutive days was significantly shorter for BZA 20mg/CE 0.45mg (15 days) and BZA 20mg/CE 0.625mg (14 days) compared with placebo ($p<0.001$).[20,21]

Effect of BZA/CE on vaginal symptoms

In SMART-1, treatment with BZA (10mg)/CE (0.625mg or 0.45mg) and BZA (20mg)/CE (0.625 or 0.45mg) was significantly more effective than placebo in increasing the mean proportion of superficial cells, intermediate cells and decreasing the proportion of parabasal cells from baseline to most time points ($p<0.001$). All BZA/CE combinations significantly reduced dyspareunia compared with raloxifene ($p<0.05$).[14,15]

SMART-3 demonstrated that compared with both placebo and BZA, BZA 20mg/CE 0.625mg and CE 0.45mg significantly increased superficial cells at week four compared with placebo and BZA ($p<0.05$); however, at week 12, only BZA 20mg/CE 0.625mg reached significance ($p<0.01$).

Parabasal cells were significantly decreased with both doses of BZA/CE at weeks 4 and 12 (p<0.001). Significant increases in intermediate cells were also observed with both BZA doses at weeks 4 and 12 (p<0.001, p<0.01, p<0.05, p<0.05 respectively).[14,17]

Mean vaginal pH significantly decreased from baseline to week 12 with both BZA/CE doses (p<0.001) compared with placebo or BZA 20mg. The mean vaginal pH decrease was significantly lower than that of the placebo group for the BZA 20 mg/CE 0.625mg group (p<0.001) but not the BZA 20mg/CE 0.45mg group (p<0.116).

At 12 weeks BZA 20mg/CE 0.625mg, but not BZA 20mg/CE 0.45mg, significantly improved the 'most bothersome symptom' (MBS) compared with placebo (p=0.05). Both strengths of BZA/CE significantly improved vaginal dryness compared with placebo (p<0.05) or BZA 20mg (p<0.001).

No significant differences were observed between either BZA/CE doses or BZA compared with placebo for itching and dryness, or for pain with intercourse with either BZA/CE dose versus placebo, but did versus BZA 20mg (p<0.05).

At 12 weeks, sexual function (ASEX) and lubrication significantly improved in both BZA/CE groups compared with placebo. However, no significant difference was observed for change from baseline in overall total ASEX score versus the placebo group.[14,17]

Effect of BZA/CE on breast tenderness

SMART-5 demonstrated a significant improvement in breast tenderness vs. the placebo and active treatment groups (p<0.001, p<0.01 for all time periods).[19] In SMART-1 and SMART-4, the percentage of subjects in the BZA/CE treatment groups had breast pain similar to that for placebo, but in SMART-4 there was a lower incidence of breast pain when compared with CE/PMA (p<0.01).[14,18]

Effect of BZA/CE on sleep and quality of life

Results from SMART-2 showed that at week 12, BZA/CE treatment significantly improved time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II, as assessed by the MOS sleep scale and improved MENQOL scores, compared with placebo (p<0.001). A significant improvement (p<0.01) in the number of hours slept each night was also observed in participants taking BZA 20mg/CE 0.625mg compared with placebo.

Significant improvements versus placebo for the psychosocial (p< 0.05), physical (p<0.01), and sexual function (p<0.01) scores were observed with BZA 20mg/CE 0.625mg.[6,9,16,22,23]

Post-menopausal osteoporosis

The EU licence application for the use of Duavive® for post-menopausal osteoporosis was withdrawn by Pfizer in January 2015 as European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) assessment found that, no added value was shown for the fixed-dose combination of BZA/CE over the mono-components in treatment of postmenopausal osteoporosis, and there are important potential life threatening and disabling unfavourable effects associated with its use. In its assessment the EMA acknowledged that BZA/CE demonstrated relevant increases in bone mineral density (BMD) from baseline compared to placebo and that for both components used as monotherapies, anti-fracture efficacy has been established. However, the observed increases in BMD appeared to be less than those seen with the active control of CE 0.45mg/MPA 1.5mg, although this is probably not even the most efficacious dose of CE/MPA. In addition, BZA/CE did not show superiority to BZA 20 mg in changes of BMD from baseline and for the BZA 20mg/CE 0.45mg dose even failed the pre-specified non-inferiority criterion. Furthermore, while with BZA effects on BMD increase with increasing dose, the opposite effect has been seen with BZA/CE were the lowest doses of BZA 10mg / CE showed the most pronounced increases with attenuating effects with increasing the dose of BZA indicating relevant pharmacodynamic interactions between both components.[9,14,18,19,24-27]

The EMA concluded that the fixed combination of BZA/CE has no superior efficacy on BMD compared to BZA monotherapy and appears to have inferior efficacy to CE/MPA.[9,14,18,19,24-27]

The skeletal effects of BZE/CE were evaluated in the SMART-1, SMART-4 and SMART-5 sub studies.[14,18,19]

In the SMART-1 sub study BZA/CE increased lumbar spine BMD from baseline compared with placebo and ($p<0.001$). BZA/CE significantly increased the mean percent change from baseline in lumbar spine BMD compared with raloxifene ($p<0.05$, placebo $p<0.001$) but only in women >5yrs post menopause, and significantly increased the annual percent change (slope analysis) in lumbar spine BMD compared with placebo ($p<0.005$), but apart from one strength (BZA/CE (20mg/0.45mg) ($p<0.05$) did not increase this measure when compared with placebo. BZA/CE significantly increased spine lumbar BMD responder rates compared with placebo and raloxifene ($p<0.001$ for both). But for women one to five years postmenopausal, this effect was not as significant for the BZA/CE 20mg/0.45mg strength when compared with raloxifene at 24 months ($p<0.01$).

The secondary endpoints; mean percent change from baseline and annual percent change of the total hip and femoral neck, trochanter, and intertrochanteric BMD were reported in SMART-1 and SMART-4. SMART-5 also considered change from baseline in total hip BMD. Radial BMD effects were only considered in SMART-1. BZA/CE significantly increased mean percentage changes in BMD at the femoral intertrochanteric, neck and trochanteric regions compared with placebo, but probability indices varied depending on region and age post menopause.

BZA/CE significantly increased total hip BMD compared with placebo ($p<0.001$). When compared with raloxifene, the only significant measure was increase in total hip BMD for women up to five years post menopause ($p<0.05$).

When compared with MPA/CE, increases were not statistically significant.

BZA/CE significantly increased mean percentage change in BMD in only one of three radial regions analysed at one time point only, when compared with placebo (but p-value was not stated), and did not increase radius BMD when compared with raloxifene.

Effects on the bone turnover markers (BTMS), osteocalcin and C-telopeptide were considered in SMART-1 and SMART-5 and showed BZA/CE increased median percentage changes of BTMs compared with placebo ($p<0.001$) and raloxifene ($p<0.05$). BTMS were not compared with MPA/CE.

Contraindications and precautions

Please consult current Summary of Product Characteristics (SPC) up to date prescribing recommendations for BZA/CE (Duavive®).[10]

- Hypersensitivity to the active substances or to any of the excipients.
- Known, suspected, or past history of breast cancer.
- Known, past or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer).
- Undiagnosed genital bleeding.
- Untreated endometrial hyperplasia.
- Active or past history of venous thromboembolism (e.g. deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis).
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency).
- Active or past history of arterial thromboembolic disease (e.g. myocardial infarction, stroke).
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal.
- Porphyria.
- See also Pregnancy and lactation discussion below.

For the treatment of postmenopausal symptoms, BZA/CE should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and treatment should only be continued as long as the benefit outweighs the risk.[10]

Women taking BZA/CE should not be taking progestins, additional oestrogens or selective oestrogen receptor modulators (SERMs).[10]

BZA/CE has not been studied in the treatment of premature menopause.[10]

Monitoring

Before starting or re-starting treatment, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.[10]

The following conditions, either current, occurred previously or aggravated by pregnancy or past hormonal treatment, require closer supervision as they an recur or worsen during treatment with BZA/CE.[10]

Leiomyoma (uterine fibroids) or endometriosis.

Risk factors for thromboembolic disorders, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, if immobilisation is to follow elective surgery temporarily stopping BZA/CE four to six weeks earlier is recommended.

Risk factors for oestrogen-dependent tumours, e.g. 1st degree heredity for breast cancer, hypertension, liver disorders (e.g. liver adenoma).

- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headacher
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis.

Therapy should be discontinued immediately if the following conditions occur: venous thromboembolism, stroke, pregnancy, jaundice or deterioration in liver function, significant increase in blood pressure, new onset of migraine-type headache.[10]

BZA/CE can cause raised triglycerides, annual monitoring of serum triglyceride levels should be considered and women with pre-existing hyper-triglyceridaemia should be followed closely.[10,28-31]

Safety and tolerability

BZA/CE was generally well tolerated in clinical trials and demonstrated a safety profile which was in line with individual constituents. The incidence of AEs, serious AEs, and study discontinuations due to AEs was similar across all treatment groups. Treatment with BZA/CE was not associated with an increased risk of VTEs or cardiovascular AEs or estrogen sensitive cancers; however, a longer period of observation in a larger population of subjects would provide definitive risk information regarding

possible adverse systemic lupus erythematosus (SLE), and cancer. Prophylactic measures need be considered to prevent VTE following surgery.[9,10,30-32]

BZA/CE were associated with a favourable lipid profile with the exception of an increase in triglyceride levels, which was similar to that reported for estrogen progestin-containing HRT. No other clinically significant changes in clinical laboratory tests were noted.[9,10,28-31]

There were no significant differences in the adjusted mean change in body weight with either BZA/CE dose compared with placebo at one year or at the final on-therapy evaluation. Changes from baseline in mean systolic blood pressure were similar to those observed for the placebo group

There were no differences among treatment groups in the incidences of selected cardiac events or cerebrovascular events.[9,10]

Effect of BZA/CE on endometrial safety

In SMART-5 the BZA/CE and CE/MPA groups showed significantly greater increases from baseline in endometrial thickness vs. placebo: ($p<0.5$ to 0.001). The incidence of proliferative endometrium at 12 months was low (<1%) and similar among the groups. The incidence of endometrial polyps was low in all groups but was significantly higher for the BZA 20mg/CE0.45mg and CE/MPA groups vs placebo ($p<0.05$ for both).[19,31,34,35]

There were no cases of endometrial hyperplasia reported in the SMART-4 trial in the BZA 20mg/CE 0.45mg, CE 0.45mg/MPA 1.5mg, and placebo groups, and three cases in the BZA 20mg/CE 0.625mg group.

In SMART-4 and SMART-5, BZA/CE treatment was associated with significantly higher rates of amenorrhea and lower incidences of breast pain compared with MPA/CE. Significantly higher percentages of subjects in the MPA/CE group discontinued the study due to bleeding-related adverse events (AEs) compared with the BZA/CE and placebo groups. These results are consistent with tolerability concerns associated with combined HRT, including breast tenderness and irregular vaginal bleeding. Therefore BZA/CE may have an improved tolerability profile compared with conventional combined HRT.[31,34,35]

Endometrial hyperplasia and carcinoma

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on duration of treatment and oestrogen dose. After stopping treatment, risk may remain elevated for at least 10 years. Women taking BZA/CE should not take additional oestrogens as this may increase the risk of endometrial hyperplasia and endometrial carcinoma.

The addition of bazedoxifene in BZA/CE reduces the risk of endometrial hyperplasia, which may be a precursor of endometrial carcinoma.

Break-through bleeding and spotting may occur during treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.[9,35,36]

Breast safety

The effect of BZA/CE on the risk of breast cancer is remains unknown.[9,10,36,37]

The effect of BZA/CE regimens on the incidence of breast pain/tenderness was evaluated in SMART-1, SMART-2, and SMART-5.

In these studies, breast pain/tenderness was measured by daily subject diaries. Both the BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg dose strengths demonstrated an incidence of breast pain/tenderness that was not significantly different compared with placebo, raloxifene 60mg, and BZA 20mg.

In SMART-5, the incidence of breast tenderness in subjects treated with BZA/CE was significantly lower than that in subjects treated with CE 0.45mg/MPA 1.5mg ($p<0.001$). These results are consistent with the relative incidences of adverse events related to breast pain/tenderness and discontinuation rates due to breast pain/tenderness reported by participants in the SMART trials. In SMART-5, the BZA 20mg/CE 0.45mg and BZA 20mg/CE 0.625mg treatment groups demonstrated non-inferiority compared with placebo with regards to mammographic breast density. By contrast, the CE 0.45mg/MPA 1.5mg treatment group exhibited a significant increase in breast density compared with the placebo group. BZA/ CE treatment did not affect age-related changes in mammographic breast density (i.e. natural reduction in breast density throughout the years of menopause). The results demonstrated that, unlike estrogen progestin-containing HRT, BZA 20mg/CE 0.45mg, and BZA 20mg/CE 0.625mg have a neutral (similar to placebo) effect on breast density.[36,37]

Ovarian cancer

The effect of BZA/CE on the risk of ovarian cancer is unknown.[9,10]

Drug interactions

No interaction studies have been performed with BZA/CE. The following is known about the constituents when used as monotherapies.[9,10]

Oestrogens

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of oestrogens. Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.

Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase plasma concentrations of oestrogens and may result in adverse reactions.[9,10]

Bazedoxifene

Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver. The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampicin, phenobarbital, carbamazepine, and phenytoin, potentially leading to decreased systemic concentrations of bazedoxifene. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.[9,10]

Bazedoxifene undergoes little or no cytochrome P450 (CYP)-mediated metabolism. Bazedoxifene does not induce or inhibit the activities of major CYP isoenzymes, and is unlikely to interact with co-administered medicinal products via CYP-mediated metabolism.

There were no significant pharmacokinetic interactions between bazedoxifene and the following medicinal products: ibuprofen, atorvastatin and azithromycin or an antacid containing aluminium and magnesium hydroxide. Based on in vitro bazedoxifene plasma protein-binding characteristics, interactions with warfarin, digoxin or diazepam are unlikely.[9,10]

Pregnancy and lactation

BZA/CE is only indicated for use in postmenopausal women and must not be taken by women of childbearing potential.[9,10]

There are no data from the use of BZA/CE in pregnant women. If pregnancy occurs during treatment with BZA/CE, it should be withdrawn immediately.[9,10]

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.[9,10]

In studies conducted in rabbits, bazedoxifene alone has shown reproductive toxicity. The potential risk for humans is unknown.[9,10]

It is not known whether bazedoxifene is excreted in human milk. Detectable amounts of oestrogens have been identified in the milk of mothers receiving CE. Oestrogen administration to breast-feeding mothers has been shown to decrease the quantity and quality of the milk.[9,10]

Costs/Tariff status/Activity costs

Comparative costs (BNF and Drug Tariff April 2015). Costs are indicative only and do not imply therapeutic equivalence.

The pricing of BZA/CE is unknown.[5]

Likely HRG included (i.e. in tariff).[5]

Many preparations are available for menopausal symptoms. Bazedoxifene plus conjugated oestrogens (BZA/CE) is another option and, as a single tablet, could be attractive. Current 28-day treatment costs range from £1.10 (alendronate 70mg/week) to £17.06 (raloxifene 60mg/day) and £25.60 (strontium ranelate 2g/day). Conjugated oestrogens for HRT cost around £2-£6 for three months treatment. BZA/CE is likely to be priced competitively.[5]

Cost effectiveness (if available)

Unknown

Impact per 100,000 population

Unknown. The number of patients who may request BZA/CE is not clear from current data, but potentially BZA/CE could be used in all women once they reach the menopause to alleviate symptoms.

Affordability/Considerations

It is difficult to estimate financial impact of this treatment as the number of eligible patients and place in therapy in relation to other hormone replacement treatments cannot be established on existing data.

Decisions from other bodies

NICE. Not assessed. NICE guideline Menopause: diagnosis and management NG23 published November 2015 does not provide any information regarding choice of HRT and no specific recommendation in relation to BZA/CE.[1]

SMC Not assessed to date (October 2016).

AWMSG. No evidence submission received from product license holder to date, therefore currently not recommended for use within NHS Wales (October 2016).

Comments sought from

PAC members and Consultants via PAC members.

Evidence strengths and limitations

There is limited data available in the following groups:[9]

- Use in elderly patient; studies to date have only included postmenopausal women up to the age of 65 years.
- Use in hepatic impaired patients.
- Use in renal impaired patients.
- Use in patients with malignancy.
- Use in patients with history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, coronary heart disease, angina), diabetes or obesity or long-term smoking.
- Long-term (>2 years) safety data, specifically on breast protection and gynaecological cancers (endometrial and ovarian in particular).
- Patients from ethnic minorities.[38]
- Patients who are morbidly obese (BMI= 34.0kg/m^2)[9,10]

There is limited comparative data with hormone replacement therapy, a formulation containing conjugated oestrogens and medroxyprogesterone acetate was included as an active control in the study, however the study was too small and too short on which to draw definitive conclusions regarding comparative efficacy between BZA/CE and CG/MPA. Other HRT preparations were not included in any studies and BZA was not compared to CE alone due concerns about uterine safety with unopposed estrogens.

A high placebo effect was observed in SMART 3; which may have attenuated the difference in improvements between the placebo and BZA/CE groups. In particular, this limited conclusions that could be drawn from changes in "most bothersome symptom (MBS) and pain with intercourse with BZA/CE. One possible explanation may be due to the relatively large number of participants who did not engage in sexual activity during the study among women who selected pain with intercourse as their MBS at baseline; this resulted in loss of power to detect a statistical difference between groups. Although patient-reported MBS may be the best clinical reflection of treatment benefit, it may have no reliable distributional characteristics, being an overstatement of the expectations of treatment, and representing a selected patient population, which may be considered to be a limitation. Also, MBS was different for the BZA/CE, BZA, and placebo groups at baseline.

Options considered by PAC

Option 1. Not recommended.

Option 2: Recommended only for women in whom quality of life is seriously impaired due to menopausal symptoms and who have not tolerated combined hormone replacement therapy.

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

***Consult Summary of Prescribing Characteristics for full prescribing details.**

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Author: Katie Taylor & Vicky Gibson on behalf of PAC

Document history

PAC approval date	12th October 2015
Consultation process	PAC members and Consultant Gynaecologists across the East of England.
Version	v1 Evidence base reviewed October 2016 by Gemma Dowell on behalf of PAC - no new evidence published
QA process	Katie Smith, Regional Medicines Information Director, East Anglia Medicines Information Service, 6th January 2016

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Assessment against ethical and commissioning principles

Treatment assessed (May 2015)	Bazedoxifene plus conjugated oestrogens
East of England PAC recommendation	Routine commissioning of bazedoxifene plus conjugated oestrogens (Duavive®) for the treatment of post-menopausal symptoms in women with a uterus is currently NOT recommended.
1. Clinical effectiveness	Bazedoxifene with conjugated oestrogens (BZA/CE) has been evaluated in five published Phase III Selective Estrogen Menopause and Response to Therapy (SMART) studies. These phase III trials showed that compared with placebo, the TESC, BZA/CE, significantly increases BMD of the lumbar spine and hip and decreases bone turnover markers. However, when compared with raloxifene, results are overall less convincing, and BZA/CE was less effective than a combination of medroxyprogesterone with conjugated oestrogens (MPA/CE). BZA/CE is generally well tolerated and demonstrates a safety profile similar to that of placebo, and other comparators. There is limited comparative data with hormone replacement therapy, a formulation containing MPA/CE was included as an active control in study, however the study was too small and too short on which to draw definitive conclusions regarding comparative efficacy between BZA/CE and MPA/CE. Other HRT preparations were not included in any studies and BZA was not compared to CE alone due concerns about uterine safety with unopposed estrogens.
2. Cost effectiveness	Not available
3. Equity	No issues identified.
4. Needs of the community	The current lack of data on cost and cost effectiveness means that it is not possible to calculate the impact of funding this treatment, or to assess the potential need for disinvestment in other treatment areas.
5. Need for healthcare (incorporates patient choice and exceptional need)	Women have a universal right to access hormone replacement therapy if their quality of life is impaired to a significant extent. Alternative treatment options are available, so the need for healthcare is small. BZA/CE may be a useful option for patients who cannot tolerate conventional HRT.
6. Policy drivers	None identified
7. Disinvestment	None identified

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

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