

Oestrogen deficiency symptoms in postmenopausal women: conjugated oestrogens and bazedoxifene acetate

Evidence summary

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[nice.org.uk/guidance/es3](https://www.nice.org.uk/guidance/es3)

Key points from the evidence

The content of this evidence summary was up-to-date in December 2016. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In a [randomised controlled trial](#) (RCT; n=332), at week 12, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg statistically significantly reduced the average daily number of moderate and severe hot flashes from baseline compared with placebo. In another RCT (n=664) in women with vulvar or vaginal atrophy, at week 12, there were statistically significant improvements compared with placebo in some but not all primary outcomes in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group. Statistically significant improvements in certain elements of quality of life compared with placebo were seen in both RCTs. However, no active comparator was included, making it difficult to establish the effectiveness of conjugated oestrogens and bazedoxifene 0.45 mg/20 mg compared with existing treatments. Because of the small number of women exposed and short duration of exposure, the available safety data do not allow for assessment of whether the incidence of rare but important adverse events including cardiovascular or cerebrovascular events, venous thromboembolism or cancer (including breast or ovarian cancer)

are increased in women taking conjugated oestrogens and bazedoxifene compared with placebo, or other treatments.

Regulatory status: conjugated oestrogens and bazedoxifene modified release tablets (Duavive, Merck Sharp and Dohme limited) were launched in the UK in July 2016. They are licensed for 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.

Effectiveness	Safety
<ul style="list-style-type: none">• Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg statistically significantly reduced the average daily number of moderate and severe hot flushes from a baseline of 10.3 to 2.8 at week 12. In the placebo group, hot flushes were reduced from 10.5 hot flushes at baseline to 5.4 at week 12. The difference between the groups was statistically significant ($p < 0.001$) (1 RCT, n=332).• In women with vulvar or vaginal atrophy, at week 12, there was a statistically significantly greater increase in vaginal superficial cells, and decrease in parabasal cells from baseline in women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with women in the placebo group. Decreases in vaginal pH and changes in the severity of the most bothersome vulvar or vaginal symptom were not statistically significantly different between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and the placebo group (1 RCT, n=664).• Statistically significant improvements in total score and some domains of the menopause-specific quality of life questionnaire (secondary endpoints) were seen in both trials in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with the placebo group.	<ul style="list-style-type: none">• In the 3 RCTs discussed in this evidence summary, common treatment-emergent adverse events in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group included headache (13.3%–18.7%), pain (7.9%–11.4%), and back pain (9.6%–9.7%).• In an RCT (n=1,886), at 12 months there was 1 case (0.3%) of endometrial hyperplasia in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group, 1 case (0.28%) in the placebo group and no cases in the conjugated oestrogens and medroxyprogesterone acetate group.• In an RCT (n=1,886), cumulative amenorrhoea rates were reported to be high and similar to placebo in the bazedoxifene and conjugated oestrogens group.• The European Public Assessment Report (EPAR) for conjugated oestrogens and bazedoxifene states that because the number of women exposed, lack of data in older women, and duration of treatment, the available safety data do not allow for assessment of whether the incidence of rare but important adverse events (such as cardiovascular or cerebrovascular events, venous thromboembolism or cancer) is increased in women taking conjugated oestrogens and bazedoxifene compared with placebo, or historical data for conjugated oestrogens and medroxyprogesterone.

Patient factors	Resource implications
<ul style="list-style-type: none">Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg are available as a modified release tablet which is taken once daily.	<ul style="list-style-type: none">Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets cost £15.00 for a pack of 28 tablets excluding VAT (MIMS, December 2016).

Introduction and current guidance

Menopause is a biological stage in a woman's life when she enters the end of her reproductive phase and is marked by the cessation of menstruation. A woman is defined as postmenopausal from 1 year after her last period. The changes associated with menopause and the perimenopause (the years leading up to the menopause) occur when ovarian function diminishes and ceases. This includes the cessation of both egg (oocyte) maturation and sex hormone (principally oestrogen and progesterone) secretion (NICE full guideline on [menopause: diagnosis and management](#)).

Many women experience a range of symptoms during the menopause and perimenopause and these symptoms are often short lived and lessen or disappear over time. The most common include vasomotor symptoms (for example hot flushes and sweats), effects on mood (for example low mood) and urogenital symptoms (for example vaginal dryness) (NICE full guideline on [menopause: diagnosis and management](#)).

NICE recommends that an individualised approach at all stages of diagnosis, investigation and management of menopause is adopted, and that people should have the right to be involved in discussions and make informed decisions about their care. NICE recommends that menopausal women are given information about hormonal, non-hormonal and non-pharmaceutical treatments for menopausal symptoms (NICE guideline on [menopause: diagnosis and monitoring](#)).

[Full text of introduction and current guidance.](#)

Product overview

Bazedoxifene is a selective oestrogen receptor modulator. The addition of bazedoxifene, acting as an oestrogen receptor antagonist in the uterus, reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women ([conjugated oestrogens and bazedoxifene summary of product characteristics](#)).

Conjugated oestrogens and bazedoxifene modified release tablets ([Duavive](#), Merck Sharp and Dohme limited) are licensed for treating 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.

The experience of treating women older than 65 years is limited ([conjugated oestrogens and bazedoxifene summary of product characteristics](#)).

Conjugated oestrogens and bazedoxifene are available as a modified release tablet containing 0.45 mg of conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene. The recommended dose is 1 tablet taken once per day.

For the treatment of postmenopausal symptoms, conjugated oestrogens and bazedoxifene 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 ([conjugated oestrogens and bazedoxifene summary of product characteristics](#)).

Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets cost £15.00 for a pack of 28 tablets excluding VAT ([MIMS](#), December 2016).

[Full text of product overview](#).

Evidence review

- The effect of conjugated oestrogens and bazedoxifene on vasomotor symptoms was investigated in the SMART 2 trial ([Pinkerton et al. 2009](#) and [Utian et al. 2009](#)). This was a 12-week, phase III, randomised, placebo-controlled, [double-blind](#) RCT in 332 postmenopausal women with an intact uterus (mean age of 53 years) who were experiencing moderate to severe hot flushes. It found that conjugated oestrogens and bazedoxifene 0.45 mg/20 mg reduced the average daily number of moderate and severe hot flushes by 7.5, from 10.3 at baseline to 2.8 at week 12. In the placebo group, moderate and severe hot flushes were reduced by 5.1, from 10.5 at baseline to 5.4 at week 12. The difference between the groups was statistically significant ($p < 0.001$). The mean daily severity score of hot flushes (calculated by adding the number of mild, moderate and severe hot flushes multiplied by 1, 2 or 3 respectively, and dividing by the total number of hot flushes for that day) reduced from 2.30 at baseline in both groups, to 1.09 in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and to 2.04 in the placebo group. The difference between the groups was statistically

significant ($p < 0.001$). Other primary outcomes included change from baseline in average daily number of moderate and severe hot flushes and mean daily severity of hot flushes at week 4. The difference between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg and the placebo group was statistically significant for both of these outcomes ($p < 0.001$).

- The effect of conjugated oestrogens and bazedoxifene on vulvar or vaginal atrophy was investigated in the SMART 3 trial ([Kagan et al. 2010](#) and [Bachman et al. 2010](#)). This was a 12-week, phase III, randomised, placebo-controlled, double-blind RCT in 664 postmenopausal women with an intact uterus (mean age 56 years) who were experiencing vulvar or vaginal atrophy. At week 12, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater increases in vaginal superficial cells, and decreases in parabasal cells (surrogate markers suggesting an improvement in the condition) from baseline compared with women in the placebo group. However the decrease in vaginal pH and change in the severity of the most bothersome vulvar or vaginal symptom was not statistically significantly different between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and the placebo group.
- Quality of life and treatment satisfaction were investigated as secondary outcomes in the SMART 2 and 3 trials. In both trials, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater improvements at week 12 in vasomotor function score and total score measured using the [menopause-specific quality of life](#) questionnaire (MENQOL; a self-administered questionnaire with scores from 1 to 8 for each of 4 domains: vasomotor, psychosocial, physical and sexual. Scores are averaged across the 4 domains with higher scores indicating more bothersome symptoms) compared with the placebo group. In the SMART 3 trial, statistically significant improvements in sexual function were also seen. There was no statistically significant difference between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg and placebo groups for the physical or psychosocial function domains of the MENQOL for either trial. In both trials, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group reported statistically significantly greater overall satisfaction with treatment on the [menopause symptoms-treatment satisfaction questionnaire](#) (MS-TSQ; an 8-item questionnaire which assesses women's satisfaction with treatment for symptoms associated with menopause) compared with women in the placebo group.
- Sleep was measured as a secondary outcome in the SMART 2 trial. Women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater improvements compared with the placebo group in time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II (a measure of overall sleep problems) but not for other domains on the [medical outcomes study \(MOS\) sleep scale](#) (a self-administered

questionnaire with scores for 7 sleep domains and 2 measures of sleep quantity). The SMART 5 trial (Pinkerton et al. 2014a and Pinkerton et al. 2014b) was a 1-year, phase III, randomised, placebo and active-controlled, double-blind RCT (n=1,886) with safety (incidence of endometrial hyperplasia at 12 months) as a primary outcome. The trial included a sleep substudy which enrolled 459 women from the trial with bothersome hot flushes or night sweats, and certain sleep difficulties. The study found that after 3 months of treatment there was no statistically significant difference between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and the placebo group in the sleep disturbance subscale of the MOS sleep scale (primary outcome).

- In the SMART 2 trial, the most common adverse events experienced by women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group were headache (15.7%), infection (7.9%), pain (7.9%) and arthralgia (7.9%). There was no statistically significant difference between the combined conjugated oestrogens and bazedoxifene groups and placebo group in the proportion of women who experienced any treatment-emergent adverse event (p=0.215).
- In the SMART 3 trial, the most common adverse events experienced by women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group were headache (18.7%), pain (11.4%) and back pain (9.6%). There was no statistically significant difference between the combined conjugated oestrogens and bazedoxifene group and placebo group in the proportion of women who experienced any treatment-emergent adverse event (p=0.16). There was a statistically significantly higher incidence of vaginitis in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with placebo (1.8% compared with 1%, p<0.05).
- In the SMART 5 trial, at 12 months there was 1 case (0.3%) of endometrial hyperplasia in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group, 1 case (0.28%) in the placebo group and no cases in the conjugated oestrogens and medroxyprogesterone acetate group. Cumulative amenorrhoea rates were reported to be high and similar to placebo in the bazedoxifene and conjugated oestrogens group. In the conjugated oestrogens and medroxyprogesterone acetate group, cumulative amenorrhoea rates were statistically significantly lower compared with other groups at all time points (p<0.001). There was no difference between the treatment groups in the proportion of women who experienced any treatment-emergent adverse event. However more women in the conjugated oestrogens and medroxyprogesterone group (14.1%) discontinued treatment because of adverse events compared with the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg (7.6%) and placebo (7.0%) groups. The most common adverse events experienced by women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group were nasopharyngitis (18.0%), headache (13.3%), back pain (9.7%) and pain in extremity (8.1%).

- Oestrogen therapy can increase the risk of endometrial hyperplasia and carcinoma, breast cancer, ovarian cancer, venous thromboembolism, and ischaemic stroke. For more information on this and cautions and contraindications see the [summary of product characteristics for conjugated oestrogens and bazedoxifene modified release tablets](#).
- The RCTs discussed in this evidence summary were all double-blind trials, enrolling between 332 and 1,886 women. The SMART 2 trial found that at week 12, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg statistically significantly reduced the average daily number of moderate and severe hot flushes from baseline compared with placebo. However no active control group was included in this study. This makes it difficult to determine how conjugated oestrogens and bazedoxifene compare to established treatments for vasomotor symptoms such as conjugated oestrogens and progestogen. The SMART 3 trial investigated the effect of conjugated oestrogens and bazedoxifene 0.45 mg/20 mg on vulvar or vaginal atrophy. First-line recommended treatment for urogenital atrophy is vaginal (rather than oral) oestrogen. In the SMART 5 trial, 4 women who had an endometrial thickness of at least 4 mm did not have an endometrial biopsy and 8 did not have a biopsy or transvaginal ultrasound carried out meaning endometrial hyperplasia could not be determined. The [European Medicines Agency \(EMA\)](#) highlight that even a very low number of additional cases of hyperplasia would change the outcome of the study ([EPAR for conjugated oestrogens and bazedoxifene](#)). The EPAR for conjugated oestrogens and bazedoxifene states that because the number of women exposed, lack of data in older women, and duration of treatment, the available safety data do not allow for assessment of whether the incidence of rare but important adverse events such as cardiovascular or cerebrovascular events, venous thromboembolism or cancer (including breast or ovarian cancer) is increased in women taking conjugated oestrogens and bazedoxifene compared with placebo, or historical data for conjugated oestrogens and medroxyprogesterone.

[Full text of evidence review.](#)

Context

The NICE guideline on [menopause: diagnosis and monitoring](#) recommends that women should be offered HRT for vasomotor symptoms of the menopause after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. For women with a uterus, the choice of preparation should be an oestrogen and progestogen.

For women with an intact uterus, unscheduled vaginal bleeding is a common adverse effect of HRT within the first 3 months of treatment. The NICE guideline on menopause recommends that bleeding should be reported at the 3-month review appointment, or promptly if it occurs after the

first 3 months. The NICE clinical knowledge summary on [menopause](#) recommends that unexplained bleeding should always be investigated before changing treatment, to exclude serious gynaecological pathology, such as endometrial cancer. If serious gynaecological pathology has been excluded, altering the progestogen part of the regimen may improve bleeding problems.

Progestogen-related adverse effects other than bleeding can also occur. The NICE clinical knowledge summary on [menopause](#) recommends that women who experience progestogen-related adverse effects other than bleeding should be encouraged to persist with treatment for 3 months as adverse effects may resolve. For persistent or troublesome symptoms altering the progestogen part of the regimen can also be tried. Changing to continuous combined therapy or tibolone often reduces non-bleeding progestogenic adverse effects with established use. However, this option is only suitable for postmenopausal women.

Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets may offer an alternative treatment option for women with an intact uterus for whom treatment with a progestin-containing treatment is not suitable.

[Full text of context.](#)

Estimated impact for the NHS

Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets have been shown in an RCT to reduce the average daily number of moderate and severe hot flushes in the short term. However comparisons were against placebo and so it is not possible to determine from the available evidence the effectiveness of conjugated oestrogens and bazedoxifene compared with other treatments for vasomotor symptoms such as progestogen-based HRT. Although in another RCT conjugated oestrogens and bazedoxifene 0.45 mg/20 mg had some beneficial effects on vulvar or vaginal atrophy compared with the placebo, first-line recommended treatment for urogenital atrophy is vaginal (rather than oral) oestrogen.

The limited number of women exposed, lack of data in older women, and limited duration of treatment, means that the available safety data do not allow for assessment of whether the incidence of rare but important adverse events such as cardiovascular or cerebrovascular events, venous thromboembolism or cancer (including breast or ovarian cancer) is increased in women taking conjugated oestrogens and bazedoxifene compared with placebo, or historical data for conjugated oestrogens and medroxyprogesterone.

Conjugated oestrogens and bazedoxifene modified release tablets may present an alternative treatment option for oestrogen deficiency symptoms in postmenopausal women for whom treatment with a progestin-containing therapy is not suitable. However, local decision makers will need to take safety (in particular the limited data on rare adverse events), efficacy, patient factors and cost into account when considering the likely place in therapy of conjugated oestrogens and bazedoxifene modified release tablets.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Menopause is a biological stage in a woman's life when she enters the end of her reproductive phase and is marked by the cessation of menstruation. A woman is defined as postmenopausal from 1 year after her last period. The changes associated with menopause and the perimenopause (the years leading up to the menopause) occur when ovarian function diminishes and ceases. This includes the cessation of both egg (oocyte) maturation and sex hormone (principally oestrogens and progesterone) secretion (NICE full guideline on [menopause: diagnosis and management](#)).

Many women experience a range of symptoms during the menopause and perimenopause and these symptoms are often short lived and lessen or disappear over time. The most common include vasomotor symptoms (for example hot flushes and sweats), effects on mood (for example low mood) and urogenital symptoms (for example vaginal dryness). Of women responding to a postal survey carried out in Scotland ([Duffy et al. 2012](#)) about symptoms experienced in the previous month, 47% reported hot flushes, 46% reported night sweats and 26% reported vaginal dryness (NICE full guideline on [menopause: diagnosis and management](#)).

NICE recommends that an individualised approach at all stages of diagnosis, investigation and management of menopause is adopted, and that people should have the right to be involved in discussions and make informed decisions about their care. NICE recommends that menopausal women are given information about hormonal, non-hormonal and non-pharmaceutical treatments for menopausal symptoms (NICE guideline on [menopause: diagnosis and monitoring](#)).

The NICE guideline on menopause: diagnosis and monitoring recommends that women should be offered HRT for vasomotor symptoms of the menopause after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. The choice of preparation should be an oestrogen and progestogen for women with a uterus, or oestrogen alone for women without a uterus. Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and clonidine are not recommended for routine first-line treatment for vasomotor symptoms alone. For psychological symptoms, NICE recommends considering HRT to alleviate low mood, or cognitive behavioural therapy (CBT) to alleviate low mood or anxiety that can arise as a result of the menopause. There is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression.

For women with urogenital atrophy, NICE recommends offering vaginal oestrogen (including to those who are on systemic HRT) and continuing this for as long as needed to relieve symptoms.

NICE recommends that people who are receiving treatment for short-term menopausal symptoms should have their treatment reviewed at 3 months to assess efficacy and tolerability. Treatment should then be reviewed at least annually, or sooner if there are clinical reasons why an early review is needed, such as treatment ineffectiveness, side effects or adverse events.

Product overview

Drug action

Conjugated oestrogens substitute for the loss of oestrogen production in menopausal women and alleviate menopausal symptoms. As oestrogens promote the growth of the endometrium, when used alone (without progestogen) oestrogens increase the risk of endometrial hyperplasia and cancer. Bazedoxifene is a selective oestrogen receptor modulator. The addition of bazedoxifene, acting as an oestrogen receptor antagonist in the uterus, reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women ([conjugated oestrogens and bazedoxifene summary of product characteristics](#)).

Licensed therapeutic indication

Conjugated oestrogens and bazedoxifene modified release tablets ([Duavive](#), Merck Sharp and Dohme limited) were launched in the UK in July 2016. They are licensed for treating 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.

The experience of treating women older than 65 years is limited ([conjugated oestrogens and bazedoxifene summary of product characteristics](#)).

Course and cost

Conjugated oestrogens and bazedoxifene are available as a modified release tablet containing 0.45 mg of conjugated oestrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene. The recommended dose is 1 tablet taken once per day.

For the treatment of postmenopausal symptoms, conjugated oestrogens and bazedoxifene 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 ([conjugated oestrogens and bazedoxifene summary of product characteristics](#)).

Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets cost £15.00 for a pack of 28 tablets excluding VAT ([MIMS](#), December 2016).

Evidence review

Five phase III, [randomised controlled trials](#) (RCTs) were submitted to support the licence application for conjugated oestrogens and bazedoxifene tablets. These were the [SMART 1](#), [SMART 2](#), [SMART 3](#), [SMART 4](#) and [SMART 5](#) trials. The [best available evidence](#) that supports the licensed indication of treatment of oestrogen deficiency symptoms in postmenopausal women with an intact uterus (the SMART 2, SMART 3 and SMART 5 trials) has been selected to be discussed in detail in this evidence summary.

The SMART 1 trial included a relevant primary outcome of incidence of endometrial hyperplasia. However, in the [European Public Assessment Report \(EPAR\) for conjugated oestrogens and bazedoxifene tablets](#), the [European Medicines Agency \(EMA\)](#) highlighted flaws in this trial and concluded that it could not be used to demonstrate the endometrial safety of conjugated oestrogens and bazedoxifene tablets. The SMART 4 trial included incidence of endometrial hyperplasia as a co-primary endpoint (along with bone mineral density outcomes). However, in the EPAR for conjugated oestrogens and bazedoxifene, the EMA highlighted that this study used a tablet that was not bioequivalent to the product to be marketed because of reduced bioavailability. For these reasons, the SMART 1 and 4 trials will not be discussed in detail in this evidence summary.

In the original submission to the EMA, the marketing authorisation holder for conjugated oestrogens and bazedoxifene tablets applied for a licence for the indications 'treatment of oestrogen deficiency symptoms in postmenopausal women' and 'treatment of osteoporosis in postmenopausal women at increased risk of fracture'. Two strengths of conjugated oestrogens were included in the original application, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg and conjugated oestrogens and bazedoxifene 0.625 mg/20 mg. During the application, the marketing authorisation holder withdrew the indication for treatment of osteoporosis in postmenopausal women and the higher strength tablet. The studies included in this evidence summary investigated both strengths of conjugated oestrogens and bazedoxifene.

SMART 2 (Pinkerton et al. 2009 and Utian et al. 2009)

- Design: 12-week, phase III, randomised, placebo-controlled, double-blind RCT completed at 43 sites in the US.
- Population: 332 postmenopausal women (approximately 85% of women were of white ethnicity) with an intact uterus aged 40 to 65 years (mean age 53 years). Women were enrolled if they had at least 12 months of spontaneous amenorrhoea or 6 months amenorrhoea with a serum follicle-stimulating hormone level greater than 40 mIU/ml. Participants had to have sought treatment for hot flushes and experienced at least 7 moderate to severe hot flushes per day, or 50 per week at screening. Participants had to have a body mass index (BMI) of 34 kg/m² or less (mean 26.2 kg/m²). Exclusion criteria included participants with endometrial hyperplasia, oestrogen-dependant hyperplasia, undiagnosed vaginal bleeding, chronic renal or hepatic disease, thromboembolic disorders, cerebrovascular disease, cardiovascular disease, uncontrolled hypertension, neuro-ocular disorders, gallbladder disease, active endocrine disease, malignancy or treatment for malignancy in the previous 5 years, and history of breast cancer, gynaecological cancer or melanoma. In addition participants with a known alcohol or drug misuse problem, and heavy smokers (more than 15 cigarettes per day) were excluded. Transvaginal ultrasound was completed at screening. Women in whom endometrial thickness could not be measured, or those with endometrial thickness of greater than 4 mm, focal endometrial abnormality, or complex or simple ovarian cysts (depending on the size) were excluded. Participants could not have used oral oestrogen, progestin, androgen or selective oestrogen receptor modulator-containing drugs, transdermal hormone products, intrauterine progestins in the 8 weeks before screening, vaginal hormone products within 4 weeks before screening, or progestin implants or injectables, or oestrogen pellets or injectables within 6 months of screening.
- Intervention and comparison: participants were randomised to receive conjugated oestrogens and bazedoxifene modified release tablets 0.45 mg/20 mg (n=133), 0.625 mg/20 mg (n=133)

or placebo (n=66) once daily for 12 weeks. Allocation to treatment was concealed. Participants were not permitted to use any medications, remedies or supplements to treat vasomotor symptoms during the trial.

- **Outcomes:** the primary outcomes for the trial 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. The severity of hot flushes was assessed using a scoring system ranging from 0 to 3. The daily severity score was calculated by adding the number of mild, moderate and severe hot flushes multiplied by 1, 2 or 3 respectively, and dividing by the total number of hot flushes for that day. All data were self-recorded by the participants on daily diary card. Secondary outcomes included the number of participants that had at least a 50% or 75% reduction in the number of hot flushes (moderate and severe, or mild, moderate and severe) from baseline; time to reach a 50% reduction in hot flushes from baseline for at least 3 consecutive days; the medical outcomes study (MOS) sleep scale (a self-administered questionnaire with scores for 7 sleep domains and 2 measures of sleep quantity); the menopause-specific quality of life questionnaire (MENQOL; a self-administered questionnaire with scores from 1 to 8 for each of 4 domains: vasomotor, psychosocial, physical and sexual. Scores are averaged across the 4 domains with higher scores indicating more bothersome symptoms); and the menopause symptoms-treatment satisfaction questionnaire (MS-TSQ; an 8-item questionnaire which assesses women's satisfaction with treatment for symptoms associated with menopause). Safety outcomes included adverse events, clinical laboratory findings, transvaginal ultrasound screening, and endometrial histology. Efficacy results for the primary outcomes were analysed in the modified intention-to-treat population which included all people who took at least 1 dose of study medication, recorded at least 5 days of data in the baseline week, and had at least 5 days of data for at least 1 on-therapy week. The safety population included all people who took at least 1 dose of study medication.

Table 1 Summary of SMART 2 (Pinkerton et al. 2009 and Utian et al. 2009)

	CO/BZA 0.45/20 mg	CO/BZA 0.625/ 20 mg ^a	Placebo	Analysis
Randomised	n=133	n=133	n=66	
Efficacy	n=122	n=125	n=63	

Primary outcome: change from baseline in average daily number of moderate and severe hot flushes at week 4 ^b	-5.90 (10.30 hot flushes at baseline compared with 4.40 at week 4)	-6.60 (10.50 hot flushes at baseline compared with 3.90 at week 4)	-2.84 (10.50 hot flushes at baseline compared with 7.66 at week 4)	p<0.001 for both strengths of CO/BZA compared with placebo
Primary outcome: change from baseline in average daily number of moderate and severe hot flushes at week 12	-7.50 (10.30 hot flushes at baseline compared with 2.80 at week 12)	-8.10 (10.50 hot flushes at baseline compared with 2.40 at week 12)	-5.10 (10.50 hot flushes at baseline compared with 5.40 at week 12)	p<0.001 for both strengths of CO/BZA compared with placebo
Primary outcome: mean change from baseline in daily severity score of hot flushes at week 4 ^{b,c}	-0.58 (2.30 at baseline compared with 1.72 at week 4)	-0.64 (2.30 at baseline compared with 1.66 at week 4)	-0.09 (2.30 at baseline compared with 2.21 at week 4)	p<0.001 for both strengths of CO/BZA compared with placebo
Primary outcome: mean change from baseline in daily severity score of hot flushes at week 12 ^{b,c}	-0.87 (2.30 at baseline compared with 1.43 at week 12)	-1.21 (2.30 at baseline compared with 1.09 at week 12)	-0.26 (2.30 at baseline compared with 2.04 at week 12)	p<0.001 for both strengths of CO/BZA compared with placebo
Selected secondary outcomes:				
Secondary outcome 1: proportion of people with at least a 75% reduction in moderate and severe hot flushes at week 12	61%	73%	27%	p<0.001 for both strengths of CO/BZA compared with placebo
Secondary outcome 2: mean change from baseline in total MENQOL score at week 12	-1.6	-1.9	-1.0	p<0.001 for both strengths of CO/BZA compared with placebo

Secondary outcome 3: percentage of participants reporting overall satisfaction with treatment on the MS-TSQ at week 12	73.5%	78.2%	44.4%	p<0.001 for both strengths of CO/BZA compared with placebo
Safety	n=127	n=128	n=63	
Participants experiencing any treatment emergent adverse event	60.6% (77/127)	67.2% (86/128)	73.0% (46/63)	No statistically significant difference between the CO/BZA and placebo groups (p=0.215)

^a During the licensing application to the EMA, the marketing authorisation holder for conjugated oestrogens and bazedoxifene withdrew the higher strength (0.65 mg/20 mg) product. Therefore this higher strength product does not have a licence and is not available in the UK.

^b Data provided by Merck Sharp and Dohme limited.

^c The severity of hot flushes was assessed using a scoring system ranging from 0 to 3. The daily severity score was calculated by adding the number of mild, moderate and severe hot flushes multiplied by 1, 2 or 3 respectively, and dividing by the total number of hot flushes for that day. The average daily score for each week was calculated by adding the daily severity scores for each week and dividing by the number of days with data.

Abbreviations: CO/BZA, conjugated oestrogens and bazedoxifene; MENQOL, menopause-specific quality of life questionnaire; MS-TSQ, menopause symptoms-treatment satisfaction questionnaire.

SMART 3 (Kagan et al. 2010 and Bachman et al. 2010)

- Design: 12-week, phase III, randomised, placebo-controlled, double-blind RCT completed at 66 sites in the US.
- Participants: 664 postmenopausal women (approximately 92% of women were of white ethnicity) with an intact uterus aged 40 to 65 years (mean age 56 years). At screening, all women had to have a vaginal cytological smear showing 5% or less superficial cells and vaginal pH greater than 5. They also had to identify on a symptom questionnaire, at least 1 moderate

to severe vulvar or vaginal symptom that was most bothering them out of vaginal dryness, itching or irritation, or pain with intercourse. Pain with intercourse and vaginal dryness were the most frequently reported most bothersome symptoms at baseline. All other inclusion and exclusion criteria were the same as for the SMART 2 trial.

- **Intervention and comparison:** participants were randomised to receive conjugated oestrogens and bazedoxifene modified release tablets 0.45 mg/20 mg (n=225), 0.625 mg/20 mg (n=221), bazedoxifene 20 mg tablets (n=110), or placebo (n=108) once daily for 12 weeks. Allocation to treatment was concealed. Participants were not permitted to use any medications, remedies or supplements to treat vulvar or vaginal atrophy during the trial.
- **Outcomes:** the co-primary endpoints were the proportion of vaginal superficial cells, the proportion of parabasal cells, vaginal pH, and severity of the most bothersome vulvar or vaginal symptom at week 12. Secondary outcomes included individual vulvar or vaginal symptoms, the MENQOL questionnaire, and the MS-TSQ. Safety outcomes included adverse events, clinical laboratory findings, transvaginal ultrasound screening, and endometrial histology. Efficacy results were analysed in the modified intention-to-treat population which included all people who took at least 1 dose of study medication, had a baseline value, and had at least 1 on-therapy value for the parameter being analysed. The safety population included all people who took at least 1 dose of study medication.

Table 2 Summary of SMART 3 ([Kagan et al. 2010](#) and [Bachman et al. 2010](#))

	CO/BZA 0.45/ 20 mg	CO/BZA 0.625/ 20 mg ^a	Placebo	Analysis
Randomised	n=225	n=221	n=108	
Efficacy	n=210	n=209	n=98	
Primary outcome: mean increase from baseline in the proportion of vaginal superficial cells at week 12 ^b	4.41%	5.80%	2.50%	p<0.01 for both strengths of CO/BZA compared with placebo

Primary outcome: mean decrease from baseline in the proportion of vaginal parabasal cells at week 12 ^b	21.30%	24.00%	3.07%	p<0.001 for both strengths of CO/BZA compared with placebo
Efficacy	n=217	n=213	n=101	
Primary outcome: mean decrease from baseline in vaginal pH at week 12 ^b	-0.25	-0.50	-0.09	p<0.001 for CO/BZA 0.625/ 20 mg compared with placebo. No statistically significant difference between CO/BZA 0.45/ 20 mg and placebo (p<0.116)
Efficacy^c	n=201	n=195	n=93	
Primary outcome: severity of the most bothersome vulvar or vaginal symptom at week 12 ^b	None: 42/ 201 (20.90%) Mild: 64/ 201 (31.48%) Moderate: 50/201 (24.88%) Severe: 33/201 (16.42%) n/a: 12/ 201 (5.97%) ^d	None: 48/ 195 (24.62%) Mild: 58/195 (29.74%) Moderate: 42/195 (21.54%) Severe: 35/ 195 (17.95%) n/a: 12/195 (6.15%) ^d	None: 16/ 93 (17.20%) Mild: 26/ 93 (27.96%) Moderate: 30/93 (32.36%) Severe: 19/93 (20.43%) n/a: 2/93 (2.15%) ^d	p=0.024 for CO/BZA 0.625/ 20 mg compared with placebo. No statistically significant difference between CO/BZA 0.45/ 20 mg and placebo
Secondary outcome 1: adjusted mean change from baseline in total MENQOL score at week 12	-1.09	-1.18	-0.67	P≤0.001 for both strengths of CO/BZA compared with placebo

Secondary outcome 2: percentage of participants reporting overall satisfaction with treatment on the MS-TSQ at week 12	62.6%	69.4%	47.4%	P<0.05 for CO/BZA 0.45/20 mg compared with placebo; p<0.001 for CO/BZA 0.625/20 mg compared with placebo
Safety	n=219	n=218	n=105	
Participants experiencing any treatment emergent adverse event	74.9% (164/219)	80.3% (175/218)	71.4% (75/105)	There was no statistically significant difference between the groups (p=0.16)

^a During the licensing application to the EMA, the marketing authorisation holder for conjugated oestrogens and bazedoxifene withdrew the higher strength (0.65 mg/20 mg) product. Therefore this higher strength product does not have a licence and is not available in the UK.

^b Data provided by Merck Sharp and Dohme limited.

^c Analysed in the modified intention-to-treat population using last observation carried forward and observed cases.

^d People with an n/a on-therapy value for pain with intercourse were excluded from the statistical analyses.

Abbreviations: CO/BZA, conjugated oestrogens and bazedoxifene; MENQOL, menopause-specific quality of life questionnaire; MS-TSQ, menopause symptoms-treatment satisfaction questionnaire.

SMART 5 ([Pinkerton et al. 2014a](#) and [Pinkerton et al. 2014b](#))

- Design: 1-year, phase III, randomised, placebo and active-controlled, double-blind RCT completed at 166 sites internationally.
- Participants: 1,886 postmenopausal women (approximately 90% of women were of white ethnicity) with an intact uterus aged 40 to 65 years (mean age 54 years) who were seeking treatment for menopausal symptoms. Participants had to have a BMI of 34 kg/m² or less (mean 26.1 kg/m²) and endometrial biopsy results with no clinically abnormal findings on histological interpretation obtained from sufficient tissue. The trial included an osteoporosis substudy (which will not be discussed further because the licensed indication does not include

treatment of osteoporosis in postmenopausal women at increased risk of fracture), a breast density substudy and sleep substudy.

- Intervention and comparison: participants were randomised and received conjugated oestrogens and bazedoxifene modified release tablets 0.45 mg/20 mg (n=445), 0.625 mg/20 mg (n=474), bazedoxifene 20 mg (n=231), conjugated oestrogens and medroxyprogesterone acetate tablets 0.45 mg/1.5 mg (n=220) or placebo (n=474) once daily for 1 year. A total of 43 participants who were randomised did not take any study medication. Allocation to treatment was concealed. All women received daily calcium and vitamin D supplements.
- Outcomes: the primary endpoint for the main study was the incidence of endometrial hyperplasia at 12 months. Secondary endpoints included cumulative amenorrhoea, breast tenderness, changes from baseline in breast density (breast density substudy), and sleep parameters (sleep substudy). Safety was assessed by physical examinations, endometrial biopsies, cervical cytology samples, transvaginal ultrasounds, mammograms, vital signs, electrocardiograms, and clinical laboratory findings. Adverse events were recorded. Incidence of endometrial hyperplasia was assessed in the pre-specified efficacy population which included all randomised women who received at least 1 dose of study drug, did not have endometrial hyperplasia at baseline, had endometrial biopsies at screening and month 12 or a diagnosis of endometrial hyperplasia before month 12, and had no major protocol violations. Safety analyses were carried out in all women who took at least 1 dose of study medication.

Clinical effectiveness

Vasomotor symptoms

In the SMART 2 trial, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg reduced the average daily number of moderate and severe hot flushes by 7.5, from 10.3 at baseline to 2.8 at week 12. In the placebo group, moderate and severe hot flushes were reduced by 5.1, from 10.5 at baseline to 5.4 at week 12. The difference between the groups was statistically significant ($p < 0.001$). The mean daily severity score of hot flushes reduced from 2.30 at baseline in both groups, to 1.09 in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and to 2.04 in the placebo group. The difference between the groups was statistically significant ($p < 0.001$). Other primary outcomes included change from baseline in average daily number of moderate and severe hot flushes, and mean daily severity score of hot flushes at week 4. The difference between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and the placebo group was statistically significant for both of these outcomes ($p < 0.001$).

Vaginal atrophy

In the SMART 3 trial, at week 12, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater increases in vaginal superficial cells ($p < 0.01$), and decreases in parabasal cells ($p < 0.001$) from baseline compared with women in the placebo group. These are surrogate markers suggesting an improvement in the condition. However the decrease in vaginal pH and change in the severity of the most bothersome vulvar or vaginal symptom was not statistically significantly different between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and the placebo group.

Quality of life and treatment satisfaction

Secondary endpoints in the SMART 2 and SMART 3 trials included the MENQOL and MS-TSQ questionnaires. In the SMART 2 trial, at week 12 women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater improvements from baseline in vasomotor function score (-3.3 points compared with -1.6) and total score (-1.6 points compared with -1.0) on the MENQOL compared with women in the placebo group ($p < 0.001$ for both). Changes in psychosocial function, physical function and sexual function were not statistically significantly different between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and placebo group. In the SMART 3 trial, compared with the placebo group, at week 12, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater improvements from baseline on the MENQOL questionnaire in vasomotor function (-1.33 points compared with -0.51), sexual function (-1.95 points compared with -1.24) and total score (-1.09 points compared with -0.67) from baseline ($p \leq 0.001$ for all). The changes in physical function and psychosocial function were not statistically significantly different between conjugated oestrogens and bazedoxifene 0.45 mg/20 mg and the placebo groups. [Lewis et al. 2005](#) report that a reduction of greater than 1 point in MENQOL scores is considered to be clinically significant.

In both the SMART 2 and 3 trials, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group reported statistically significantly greater overall satisfaction with treatment on the MS-TSQ compared with women in the placebo group ($p < 0.05$).

Sleep

In the SMART 2 trial sleep was a secondary endpoint measured using the MOS sleep scale. At week 12, women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group had statistically significantly greater improvements ($p < 0.001$) from baseline in certain domains of the MOS sleep scale compared with women in the placebo group: time to fall asleep (-18.06 points compared with -2.54 points), sleep adequacy (16.53 points compared with 1.07 points), sleep disturbance (-19.95

compared with -5.90 points), and sleep problem indices I and II (a measure of overall sleep problems).

Most endpoints in the SMART 5 trial relate to safety and are discussed below. Sleep parameters were included as secondary efficacy outcomes as part of a sleep substudy (reported by [Pinkerton et al. \[2014b\]](#)). To be eligible for the sleep substudy women had to have bothersome hot flushes or night sweats, wake during sleep time and have difficulties falling asleep, and believe that they often did not get the amount of sleep they needed. The substudy enrolled 459 women from the SMART 5 population. The sample size of the substudy provided sufficient power to compare one primary endpoint (sleep disturbance) at 1 time point (3 months). The study found that after 3 months of treatment there was no statistically significant difference between the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with the placebo group in the sleep disturbance subscale of the MOS sleep scale. A statistically significant improvement from baseline in time to fall asleep in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with the placebo group was found but there was no statistically significant difference between these groups for any other sleep domains on the MOS sleep scale. Although an active comparator was included in this study (conjugated oestrogens and medroxyprogesterone acetate), only comparisons with placebo were reported for efficacy outcomes. Direct comparisons between conjugated oestrogens and bazedoxifene and conjugated oestrogens and medroxyprogesterone acetate were not reported.

Safety and tolerability

The summary of product characteristics for conjugated oestrogens and bazedoxifene modified release tablets ([Duavive](#), Merck Sharp and Dohme limited) states that very common adverse events affecting 10 in 100 or more people include abdominal pain. Common adverse events affecting 1 in 100 or more people include vulvovaginal candidiasis, constipation, diarrhoea, nausea, muscle spasms, and increased blood triglycerides. Conjugated oestrogens and bazedoxifene tablets have not been evaluated in people with renal or hepatic impairment and so use in these populations is not recommended. Experience of using conjugated oestrogens and bazedoxifene in women aged over 65 years is limited. Contraindications to using conjugated oestrogens and bazedoxifene include women with known, suspected, or past history of breast cancer; known, past or suspected oestrogen-dependent malignant tumours (for example, endometrial cancer); undiagnosed genital bleeding; untreated endometrial hyperplasia; active or past history of venous thromboembolism; known thrombophilic disorders; and active or past history of myocardial infarction or stroke.

The effect of HRT on risks such as venous thromboembolism, cardiovascular disease, stroke, type 2 diabetes, breast cancer, dementia, and benefits such as reduced risk of fragility fracture and effect

on muscle mass and strength are discussed in detail in the NICE guideline on [menopause: diagnosis and management](#). NICE did not discuss ovarian cancer risk in women taking HRT. However, evidence from a meta-analysis of 52 epidemiological studies found that HRT use may be associated with a small increased risk of ovarian cancer, even with less than 5 years of use starting at around 50 years of age. The evidence showed that the risk is greatest in current users of HRT, falls after cessation of HRT, and varies by tumour type (NICE clinical knowledge summary: [menopause](#)). For more information on these risks with conjugated oestrogens and bazedoxifene modified release tablets, see the [summary of product characteristics](#).

In the SMART 2 trial, there was no statistically significant difference between the combined conjugated oestrogens and bazedoxifene groups and placebo group in the proportion of women who experienced any treatment-emergent adverse event ($p=0.215$). The most common adverse events experienced by women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group were headache (15.7%), infection (7.9%), pain (7.9%) and arthralgia (7.9%). A total of 5/127 (4%) people in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group discontinued treatment due to adverse events compared with 6/63 (10%) in the placebo group.

In the SMART 3 trial, the authors report that there was no statistically significant difference between the treatment groups in the proportion of women who experienced any treatment-emergent adverse event ($p=0.16$). The most common adverse events experienced by women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group were headache (18.7%), pain (11.4%) and back pain (9.6%). The incidence of gynaecological treatment-emergent adverse events such as breast pain, endometrial disorder, ovarian cysts, and vaginal bleeding was not significantly different in women taking conjugated oestrogens and bazedoxifene compared with women taking placebo. However there was a statistically significantly higher incidence of vaginitis in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with placebo (1.8% compared with 1%, $p<0.05$). A total of 7/219 (3%) people in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group discontinued treatment due to adverse events compared with 7/105 (7%) in the placebo group. The difference between the groups was not statistically significant ($p=0.290$).

In the SMART 5 trial, the primary outcome was the incidence in endometrial hyperplasia at 12 months. At 12 months there was 1 case (0.3%) of endometrial hyperplasia in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group, 1 case (0.28%) in the placebo group and no cases in the conjugated oestrogens and medroxyprogesterone acetate group. The upper limit of the 95% confidence intervals were less than 2% for all groups which is in line with recommendations in the Committee for Medicinal Products for Human Use (CHMP) [guideline on clinical investigation of medicinal products for HRT of oestrogen deficiency symptoms in postmenopausal women](#).

Cumulative amenorrhoea rates were reported to be high and similar to placebo in the bazedoxifene and conjugated oestrogens group. [Pinkerton et al. \(2014a\)](#) report that cumulative amenorrhoea rates were statistically significantly lower in the conjugated oestrogens and medroxyprogesterone acetate group compared with other groups at all time points ($p < 0.001$). There was no statistically significant difference between the placebo and the bazedoxifene and conjugated oestrogens groups in the proportion of women reporting more than 1 day of breast tenderness during 4-week cycles over 12 months. The incidence of breast pain was statistically significantly higher at all time points in the conjugated oestrogens and medroxyprogesterone acetate group compared with the placebo ($p < 0.001$) and other active treatment groups ($p < 0.01$).

In the SMART 5 trial, the authors report that there was no difference between the treatment groups in the proportion of women who experienced any treatment-emergent adverse event. However more women in the conjugated oestrogens and medroxyprogesterone group (14.1%) discontinued treatment because of adverse events compared with the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg (7.6%) and placebo (7.0%) groups. The most common adverse events experienced by women in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group were nasopharyngitis (18.0%), headache (13.3%), back pain (9.7%) and pain in extremity (8.1%).

There were no differences between the groups in the incidence of selected cardiovascular or cerebrovascular adverse events. There was 1 deep vein thrombosis reported in the conjugated oestrogens and medroxyprogesterone group but no cases of venous thromboembolism in any of the other groups. Two cases of breast cancer occurred in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group, 1 case each in the conjugated oestrogens and medroxyprogesterone and placebo groups, and no cases in the conjugated oestrogens and bazedoxifene 0.625 mg/20 mg group. The incidence of vaginal bleeding-related adverse events was 7% in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group which was similar to the placebo group (8.4%). The incidence of bleeding in the conjugated oestrogens and medroxyprogesterone group was statistically significantly higher (22.3%, $p < 0.001$).

Evidence strengths and limitations

The RCTs discussed in this evidence summary were all double-blind trials, enrolling between 339 and 1,886 women.

The SMART 2 trial investigated the effect of conjugated oestrogens and bazedoxifene on vasomotor symptoms. The [CHMP guideline on clinical investigation of medicinal products for HRT of oestrogen deficiency symptoms in postmenopausal women](#) states that the most important oestrogen deficiency symptoms in postmenopausal women are vasomotor symptoms and that the

proposed primary endpoint for efficacy trials is the frequency of moderate to severe hot flushes. Therefore the primary outcome of the SMART 2 trial (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) seems appropriate. The trial found that at week 12, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg statistically significantly reduced the average daily number of moderate and severe hot flushes from baseline compared with placebo. However no conjugated oestrogens and progestogen control group was included in this study. The EPAR for conjugated oestrogens and bazedoxifene states that according to the results of a phase II study, bazedoxifene reduces the effectiveness of conjugated oestrogens for the treatment of vasomotor symptoms. Therefore by not including an active control group, it is not possible to determine the extent that bazedoxifene reduces the effectiveness of conjugated oestrogens, or how conjugated oestrogens and bazedoxifene compares to established treatments for vasomotor symptoms such as conjugated oestrogens and progestogen.

The EPAR also highlighted flaws with regards to the reporting of adverse events in the SMART 2 trial. The EPAR states that relatedness of adverse events to study medication was incorrectly assessed by investigators and was clearly shifted to 'not related'. The EPAR concluded that the validity of adverse event reporting in the trial was not demonstrated but that the assessment of efficacy in relation to vasomotor symptoms was considered valid.

The SMART 3 trial found that in women with vulvar or vaginal atrophy, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg had a statistically significantly greater effect on increases in vaginal superficial cells, and decreases in parabasal cells compared with the placebo. However, the decrease in vaginal pH and change in the severity of the most bothersome vulvar or vaginal symptom was not statistically significantly different between these 2 groups. First-line recommended treatment for urogenital atrophy is vaginal (rather than oral) oestrogen.

The SMART 1 trial was not included in detail in this evidence summary because of flaws in the trial discussed in the EPAR for conjugated oestrogens and bazedoxifene, meaning it could not be used to demonstrate endometrial safety. Nevertheless, the EPAR highlighted that 2 cases of endometrial hyperplasia were detected in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group during the second year of treatment. The EPAR considered this to be a potential safety signal.

In the SMART 5 study, 1 (0.3%) case of endometrial hyperplasia occurred in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group and the upper limit of the 95% confidence interval was below 2% in line with EMA guidance (see the [safety section](#) for more information). However in the EPAR for conjugated oestrogens and bazedoxifene, the EMA discusses concerns with the findings from this study. For various reasons, 4 women who had an endometrial thickness

of at least 4 mm did not have a biopsy and 8 did not have a biopsy or transvaginal ultrasound carried out meaning endometrial hyperplasia could not be determined. They highlight that even a very low number of additional cases of hyperplasia would change the outcome of the study. Nevertheless, the EMA state that this amount of missing data is not unusual for a study of such size and summarise that endometrial safety was sufficiently demonstrated for conjugated oestrogens and bazedoxifene 0.45 mg/20 mg.

The SMART 5 study found no differences between the study groups in the incidence of selected cardiovascular or cerebrovascular adverse events and no cases of venous thromboembolism occurred in the bazedoxifene and conjugated oestrogens groups. There were 2 cases of breast cancer in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group. However, the EPAR for conjugated oestrogens and bazedoxifene states that because the number of women exposed, lack of data in older women, and duration of treatment, the available safety data do not allow for assessment of whether the incidence of these rare but important adverse events is increased in women taking conjugated oestrogens and bazedoxifene compared with placebo, or historical data for conjugated oestrogens and medroxyprogesterone.

The studies discussed in this evidence summary included women aged 65 years or under, and around 90% of the women were of white ethnicity. This limits the applicability of the findings to women aged over 65 and women who are not of white ethnicity.

Context

Alternative treatments

The NICE guideline on [menopause: diagnosis and monitoring](#) recommends that women should be offered HRT for vasomotor symptoms of the menopause after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. For women with a uterus, the choice of preparation should be an oestrogen and progestogen.

For women with an intact uterus, unscheduled vaginal bleeding is a common adverse effect of HRT within the first 3 months of treatment. The NICE guideline on menopause recommends that bleeding should be reported at the 3-month review appointment, or promptly if it occurs after the first 3 months. The NICE clinical knowledge summary on [menopause](#) recommends that unexplained bleeding should always be investigated before changing treatment, to exclude serious gynaecological pathology, such as endometrial cancer. If serious gynaecological pathology has been excluded, altering the progestogen part of the regimen may improve bleeding problems.

Progestogen-related adverse effects other than bleeding include fluid retention, breast tenderness, headaches or migraine, mood swings, depression, acne, lower abdominal pain, and back pain. They tend to occur in a cyclical pattern during the progestogen phase of cyclical HRT. The NICE clinical knowledge summary on [menopause](#) recommends that women who experience progestogen-related adverse effects other than bleeding should be encouraged to persist with treatment for 3 months as adverse effects may resolve. For persistent or troublesome symptoms, changing the progestogen type, changing the route of progestogen delivery (such as to intrauterine progestogen), reducing the regimen of progestogen administration, changing to a product with a lower dose of progestogen, or reducing the frequency of progestogen dosing may be helpful. Many of these options are the opposite of what may be needed to better control bleeding. Changing to continuous combined therapy or tibolone often reduces non-bleeding progestogenic adverse effects with established use. However, this option is only suitable for postmenopausal women.

Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets offer an alternative treatment option for women with an intact uterus for whom treatment with a progestin-containing treatment is not suitable.

Table 3: Alternative treatment costs

Drug	Usual dosage ^a	28-day cost excluding VAT
Conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets	1 daily	£15.00 ^b
Tibolone 2.5 mg tablets	1 daily	£10.36 ^c
Conjugated oestrogens 300 microgram tablets ^d plus Mirena 52 mg T-shaped intrauterine system	1 daily Once fitted Mirena can remain in situ for up to 4 years	£2.02 ^c £88.00 per 4 years ^b
Conjugated oestrogens 625 microgram tablets ^d plus Mirena 52 mg T-shaped intrauterine system	1 daily Once fitted Mirena can remain in situ for up to 4 years	£1.34 ^c £88.00 per 4 years ^b

Estradiol 1 mg tablets ^d plus Mirena 52 mg T-shaped intrauterine system	1 daily Once fitted Mirena can remain in situ for up to 4 years	£1.69 ^c £88.00 per 4 years ^b
Estradiol 2 mg tablets ^d plus Mirena 52 mg T-shaped intrauterine system	1 daily Once fitted Mirena can remain in situ for up to 4 years	£1.69 ^c £88.00 per 4 years ^b
Estradiol ^d 50 microgram/24 hour transdermal patch plus Mirena 52 mg T-shaped intrauterine system	1 patch applied twice weekly Once fitted Mirena can remain in situ for up to 4 years	£3.88 ^{b,e} £88.00 per 4 years ^b

^a Dosages taken from the relevant [summaries of product characteristics](#).

^b Costs taken from [MIMS](#); December 2016.

^c Costs taken from the [drug tariff](#); December 2016.

^d A range of oestrogen containing products are available that may be used with Mirena intrauterine system for HRT in women with an intact uterus. The options shown are examples but the list is not exhaustive. Costs may vary depending on the oestrogen preparation chosen.

^e Costs based on Evorel patches.

Estimated impact for the NHS

Likely place in therapy

For women with an intact uterus, the first-line recommended treatment option for vasomotor symptoms associated with the menopause is HRT with an oestrogen and progestogen. However progestogen therapy can have adverse effects making it unsuitable for some women. For women who experience adverse effects of progestogens other than unscheduled vaginal bleeding, options to try to reduce these include persisting with treatment for 3 months (as adverse effects may resolve), altering the progestogen part of the regimen, or changing to continuous combined therapy or tibolone (but this is only suitable for postmenopausal women).

Conjugated oestrogens and bazedoxifene modified release tablets have been shown in an RCT to reduce the average daily number of moderate and severe hot flushes in the short term. However

comparisons were against placebo and so it is not possible to determine from the available evidence, the effectiveness of conjugated oestrogens and bazedoxifene compared with other treatments for vasomotor symptoms such as progestogen-based HRT. Although in another RCT, conjugated oestrogens and bazedoxifene 0.45 mg/20 mg had some beneficial effects on vulvar or vaginal atrophy compared with the placebo, first-line recommended treatment for urogenital atrophy is vaginal (rather than oral) oestrogen. Both RCTs found statistically significant improvements in total score and vasomotor function score measured using the MENQOL questionnaire in the conjugated oestrogens and bazedoxifene 0.45 mg/20 mg group compared with the placebo group. Additionally in the trial in women with vulvar or vaginal atrophy, improvements in sexual function score were seen.

The limited number of women exposed, lack of data in older women, and limited duration of treatment, means that the available safety data do not allow for assessment of whether the incidence of rare but important adverse events such as cardiovascular or cerebrovascular events, venous thromboembolism or cancer (including breast and ovarian cancer) is increased in women taking conjugated oestrogens and bazedoxifene compared with placebo, or historical data for conjugated oestrogens and medroxyprogesterone.

Conjugated oestrogens and bazedoxifene modified release tablets may present an alternative treatment option for oestrogen deficiency symptoms in postmenopausal women for whom treatment with a progestin-containing therapy is not suitable. However, local decision makers will need to take safety (in particular the limited data on rare adverse events), efficacy, patient factors and cost into account when considering the likely place in therapy of conjugated oestrogens and bazedoxifene modified release tablets.

Estimated usage

Merck Sharp and Dohme limited were not able to accurately predict the estimated usage of conjugated oestrogens and bazedoxifene 0.45 mg/20 mg modified release tablets.

Relevance to NICE guidance programmes

NICE has issued a guideline on [menopause: diagnosis and monitoring](#).

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Nigel Holland: No interests declared

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Fiona Nelson: No interests declared.

Nuttan Tanna: Besins Healthcare sponsorship for IMS 2016 conference, to support CPD.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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