DUAVIVE: NEW PARADIGM\textsuperscript{1} of Menopausal treatment, TSEC\textsuperscript{†}

A novel pairing of conjugated estrogens (CE) with the selective estrogen receptor modulator (SERM) bazedoxifene (BZA)\textsuperscript{1}

+ Significant reduction in the frequency and severity of moderate to severe hot flushes\textsuperscript{2}
+ BZA helps protect the uterine lining as an alternative to a progestin\textsuperscript{1,7}
+ Effects on breast density similar to placebo at 1 year\textsuperscript{3}
+ Increase in bone mass compared to placebo at 2 years\textsuperscript{4}
+ Low incidence of endometrial hyperplasia at 1 year\textsuperscript{5}
+ An improved QOL in symptomatic postmenopausal women\textsuperscript{6}

\textsuperscript{†}TSEC: Tissue-selective estrogen complex
**DUAVIVE provides a novel mechanism of action**¹

The first and only therapy to pair CEs with SERM*, BZA, instead of a progestin¹

**CEs turn on estrogen receptors...**¹

+ Vasomotor symptoms are related to estrogen decline in postmenopausal women¹,⁷

+ The CEs in DUAVIVE help address this decline by binding to and activating estrogen receptors, which vary in proportion from tissue to tissue¹,⁷

**CEs provide significant relief of moderate to severe hot flushes due to menopause and help increase bone mineral density compared to placebo¹,⁴,⁷**

* Selective estrogen receptor modulator, an estrogen agonist/antagonist
DUAVIVE provides a novel mechanism of action\textsuperscript{1}

The first and only therapy to pair CE\textsuperscript{s} with SERM\textsuperscript{*}, BZA, instead of a progestin\textsuperscript{1}

BZA dims estrogen activity in select estrogen-sensitive tissues (e.g., the uterus)\textsuperscript{1,7}

$+$ DUAVIVE uses BZA instead of a progestin to help protect the uterine lining from endometrial hyperplasia associated with estrogen-alone treatment\textsuperscript{5,7}
$-$ <1\% incidence of endometrial hyperplasia or malignancy\textsuperscript{5}

$+$ BZA was specifically selected for DUAVIVE because of its unique pharmacologic profile, as demonstrated by preclinical studies that looked at a number of different SERMs\textsuperscript{8}

\textsuperscript{*} Selective estrogen receptor modulator, an estrogen agonist/antagonist
DUAVIVE demonstrated significant reductions in the frequency of vasomotor symptoms (VMS)\textsuperscript{2,7}

In the treatment of vasomotor symptoms (VMS), DUAVIVE significantly reduced the number of moderate to severe hot flushes at 12 weeks\textsuperscript{2}

### Mean Change from Baseline in Average Daily Frequency of Hot Flushes: Week 12

**Reduction in the mean number of moderate to severe hot flushes:**
- from \(~10\) per day to \(~3\) per day\textsuperscript{2}

**DUAVIVE delivered early and lasting results\textsuperscript{2}**

+ With DUAVIVE, reduction in the number of moderate to severe hot flushes was seen as early as week 4 and maintained through week 12 (\(p<0.001\) in both DUAVIVE treatment groups vs placebo)\textsuperscript{2}

Adapted from Pinkerton, JV et al. Menopause 2009
DUAVIVE demonstrated significant reductions in the severity of vasomotor symptoms (VMS)\textsuperscript{2,7}

Significant reduction versus placebo in the average daily severity of hot flushes\textsuperscript{2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{graph.png}
\caption{Adjusted Mean Change from Baseline in Average Daily Frequency and Severity of Hot Flushes}
\end{figure}

Adapted from Pinkerton, JV et al. Menopause 2009
With DUAVIVE: Effects on breast density similar to placebo³

In SMART-5 study, at 12 months, changes in mammographic breast density were similar to placebo³

Mean percentage change in breast density from baseline at year 1

- Placebo (n=182)
- DUAVIVE (n=186)
- BZA 20mg (n=98)
- CE 0.45mg / MPA 1.5mg (n=68)

Adapted from Pinkerton JV et al. Obstet Gynecol 2013

Note: The incidence of breast cancer has not been studied as a primary endpoint in any clinical trials of DUAVIVE
BREAST CANCER

The effect of treatment with DUAVIVE on the risk of breast cancer is unknown

+ All women should receive yearly breast examinations by an HCP and perform monthly breast self-examinations

+ Mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results

+ Known, suspected, or past history of breast cancer is contraindicated

+ DUAVIVE is contraindicated in women with known, suspected, or past history of breast cancer

+ The overall evidence suggests a possible increased risk of breast cancer in women taking estrogen-only therapy that is dependent on the duration of therapy

+ The Women’s Health Initiative (WHI) trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only therapy

+ Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of estrogen-progestin combinations. The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment
Effects on the ENDOMETRIUM

In 2 studies of 12 and 24 months in duration, <1% incidence of endometrial hyperplasia or malignancy observed\textsuperscript{5,11}

<table>
<thead>
<tr>
<th>DUAVIVE study</th>
<th>Month</th>
<th>% (n/N)\textsuperscript{*}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>0.00% (0/336)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.68% (2/293)</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0.30% (1/335)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Efficacy Evaluable population, which included patients who had taken at least 1 dose of DUAVIVE, had baseline and postbaseline endometrial biopsies, or had been diagnosed with hyperplasia\textsuperscript{7}
In a clinical study, on average, WOMEN ON DUAVIVE GAINED BONE MASS while women on placebo lost bone mass\(^4,12\)

DUAVIVE significantly increased lumbar spine bone mineral density (BMD) vs placebo at 24 months\(^4\)

**Lumbar Spine BMD Results at 24 Months\(^4,12\)**

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Placebo (n=99)</th>
<th>DUAVIVE (n=101)</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 Years Postmenopausal (Substudy II)</td>
<td>-1.9%</td>
<td>+1.72%*</td>
<td>3.62%</td>
</tr>
<tr>
<td>&gt;5 Years Postmenopausal (Substudy I)</td>
<td>-1.47%</td>
<td>+1.64%*</td>
<td>3.11%</td>
</tr>
</tbody>
</table>

*P<.001 vs placebo

Adjusted mean changes and P-values based on an ANCOVA model with treatment and region (US or non-US) as factors and baseline BMD value and years since menopause as covariates using the Modified Intention to Treat Population with Last Observation Carried Forward. Substudy excludes those subject with missing source documentation

Adapted from Lindsay Fertility and Sterility 2009 and Data on File
In a clinical study, on average, **WOMEN ON DUAVIVE GAINED BONE MASS** while women on placebo lost bone mass\(^4,12\).

**DUAVIVE significantly increased total hip BMD vs placebo at 24 months\(^4,12\)**

1-5 Years Postmenopausal (Substudy II)\(^4,12\)

\[
\begin{align*}
\text{% mean change from baseline} & \quad \\
\text{DUAVIVE (n=102)} & \quad +0.55\%^* \\
\text{Placebo (n=99)} & \quad -1.42\%
\end{align*}
\]

>5 Years Postmenopausal (Substudy I)\(^4,12\)

\[
\begin{align*}
\text{% mean change from baseline} & \quad \\
\text{DUAVIVE (n=160)} & \quad +1.07\%^* \\
\text{Placebo (n=158)} & \quad -0.65\%
\end{align*}
\]

\(^*P<.001\) vs placebo

Adjusted mean changes and P-values based on an ANCOVA model with treatment and region (US or non-US) as factors and baseline BMD value and years since menopause as covariates using the Modified Intention to Treat Population with Last Observation Carried Forward. Substudy excludes those subject with missing source documentation.

Adapted from Lindsay Fertility and Sterility 2009 and Data on File
With DUAVIVE: Lower incidence of uterine bleeding* vs CE/MPA\textsuperscript{9,10}

* secondary endpoint, p < 0.001 vs. DUAVIVE and placebo

Reduced incidence of breakthrough bleeding compared to CE/MPA\textsuperscript{9}

+ High and similar cumulative rates of amenorrhoea at year 1 among women treated with either DUAVIVE or placebo\textsuperscript{9}

Breakthrough bleeding is a common event in postmenopausal women with a uterus receiving menopausal hormone therapy (MHT) and has frequently been shown to be a reason a woman does not initiate MHT or discontinues her therapy\textsuperscript{10}

Breakthrough bleeding and spotting may occur during treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated. The investigation may include endometrial biopsy to exclude endometrial malignancy\textsuperscript{7}

\textsuperscript{7} Adapted from Mirkin S et al. Climacteric 2013

\textsuperscript{9} Rates of cumulative amenorrhoea over 1 year.
CE = conjugated estrogens
MPA = medroxyprogesterone acetate
In clinical studies, women taking DUAVIVE experienced significant improvements in sleep adequacy, sleep disturbance and reductions in time to fall asleep†

Responders (defined as ≥ 75% reduction from baseline in daily number of hot flushes) were analysed for improvements in sleep disturbance, sleep adequacy, sleep quantity, somnolence, sleep problems, shortness of breath, and snoring†

†Defined by Medical Outcomes Study (MOS) Sleep Questionnaire.
Coronary Artery Disease (CAD)

The effect of treatment with DUAVIVE on the risk of CAD is unknown.

DUAVIVE is contraindicated in women with active or past history of arterial thromboembolic disease (e.g. myocardial infarction, stroke).

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received estrogen-only therapy. Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

Estrogen therapy should not be used for the prevention of cardiovascular disease.
Venous thromboembolism (VTE*)

In clinical trials of up to 2 years duration in postmenopausal women with DUAVIVE, cases of VTE have been reported. SERMs (including BZD) and estrogens individually increase the risk of VTE. Hormone therapy is associated with a 1.3-3 fold risk of developing VTE. The occurrence of such an event is more likely in the first year of MHT than later.

Patients with known thrombophilic states have an increased risk of VTE and hormone therapy may add to this risk. DUAVIVE is contraindicated in these patients. If VTE develops after initiating therapy, or is suspected, DUAVIVE should be discontinued immediately.

Women should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

*VTE=deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis
SERM=selective estrogen receptor modulator
BZD=bazedoxifene
MHT=menopausal hormone therapy.
Stroke

The effect of treatment with DUAVIVE on the risk of stroke is unknown\(^7\)

DUAVIVE is contraindicated in women with active or past history of arterial thromboembolic disease (e.g. myocardial infarction, stroke)

Estrogen-only therapy is associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use hormone therapy will increase with age

The effect of DUAVIVE on the risk of stroke is unknown

Estrogen therapy should not be used for the prevention of cardiovascular disease
More women expressed satisfaction with DUAVIVE vs placebo\textsuperscript{5}

The percentages of subjects reporting satisfaction (“extremely satisfied” or “satisfied”) with the ability to control hot flushes during the day and night: the effects on sleep quality, mood or emotions, interest in sex, and ability to concentrate; and tolerability for DUAVIVE vs placebo is presented\textsuperscript{6}

MS-TSQ = Menopause Symptoms Treatment Satisfaction Questionnaire

Adapted from Utian WH. et al Maturitas 2009
Prescribe DUAVIVE (0.45 mg/20 mg) for the treatment of estrogen deficiency symptoms in post menopausal women with a uterus for whom progestin-containing therapy is inappropriate⁷

+ DUAVIVE pairs two active ingredients in a single once-daily tablet⁷
+ Can be taken with or without food⁷
+ Tablets must be swallowed whole⁷
+ May be taken with calcium and/or vitamin D⁴
+ Use DUAVIVE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary
References


2. Pinkerton JV, Utian WH, Constantine GD, Oliver S, Pickar HJ. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomised, controlled trial. Menopause. 2009; 16(6):1116-1124


7. Duavive Data Sheet


12. Data on file
Use Duavive for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

**DUAVIVE®**
Conjugated Estrogens/Bazedoxifene
0.45 mg/20 mg Modified-Release Tablets

**INDICATIONS**
Treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since the last menses) for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 years is limited.

**CONTRAINDICATIONS**
- Hypersensitivity to conjugated estrogens, bazedoxifene or excipients;
- Known, suspected or history of breast cancer, estrogen-dependent malignant tumours; undiagnosed genital bleeding; untreated endometrial hyperplasia;
- Active or history of VTE, arterial thromboembolic disease; thrombophilic disorders; impaired liver function; porphyria;
- Not to be taken by women of childbearing potential. See Data Sheet for details.

**PRECAUTIONS**
- Not to be given with concomitant progestins, additional estrogens or other SERMs.
- Full medical examination before initiation and follow up, especially of breast health; conditions requiring supervision: leiomyoma or endometriosis, risk factors for thromboembolic disorders or estrogen-dependent tumours, hypertension, coronary artery disease and stroke, liver disorders (liver function), diabetes mellitus, cholelithiasis, migraine, systemic lupus erythematosus, endometrial hyperplasia history, epilepsy, asthma, otosclerosis; risk of endometrial hyperplasia and carcinoma; risk of VTE; cholecystitis reported; monitor patients with hypertriglyceridaemia; may cause fluid retention; estrogens increase thyroid binding globulin; use in pregnancy Category D; minor influence on ability to drive and use machines. See Data Sheet for details.

**ADVERSE EFFECTS**
- Abdominal pain; vulvovaginal candidiasis; constipation; diarrhoea; nausea; muscle spasms; blood triglycerides increased; VTE; breast tenderness; hot flushes. See Data Sheet for details.

**DOSAGE AND ADMINISTRATION**
Recommended: CE 0.45 mg/bazedoxifene 20 mg taken as a single oral tablet, once daily.

Use DUAVIVE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

**MEDICINES CLASSIFICATION**
Prescription Medicine; DUAVIVE is an unfunded medicine – a prescription charge will apply. Before prescribing, review Data Sheet available from Medsafe (www.medsafe.govt.nz) or Pfizer New Zealand Limited (www.pfizer.co.nz) or call 0800 736 363.

Pfizer New Zealand Limited, Level 1, Suite 1.4, Building B, 8 Nugent St, Grafton, Auckland 1023.

**DUAVIVE** is a Registered Trademark. © Pfizer 2017.