A NEW APPROACH TO MENOPAUSE HORMONE THERAPY

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This presentation is intended for NZ Healthcare Professionals Only. Please discuss your menopause treatment options with your own Healthcare Professional.
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Designing a New Approach to Menopause Therapy

- Estrogens have widespread and diverse pharmacologic effects in different tissues, some are desired and others undesired
- Progestins were added to protect against hyperplasia that may occur with estrogen therapy alone in women with an intact uterus
- Progestins have complex and multiple pharmacologic effects
- Does an alternative pairing exist to offer estrogens’ efficacy with endometrial protection?
- Pharmaceutical researchers thought the answer could be found in the tissue-specific aspects of estrogen receptors and how they are activated or not activated
- The pairing of estrogens and a selective estrogen receptor modulator (SERM) was envisioned

Komm BS, et al. Pharmaceuticals 2012;5:899-924. Figure: NIH center for Molecular Modeling and Biometrics.

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The Ideal Menopause Therapy Requires a Balance of Effects in a Tissue-Dependent Manner

<table>
<thead>
<tr>
<th>Positive Effects</th>
<th>Without Negative Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central nervous system</strong></td>
<td><strong>Uterus</strong></td>
</tr>
<tr>
<td>– ↓ Vasomotor effects</td>
<td>– Neutral endometrial stimulation</td>
</tr>
<tr>
<td><strong>Skeleton</strong></td>
<td>– Neutral effect on breakthrough bleeding</td>
</tr>
<tr>
<td>– Stabilization of bone loss</td>
<td><strong>Breast</strong></td>
</tr>
<tr>
<td>– ↑ BMD</td>
<td>– Neutral preclinical effect at ERs of breast</td>
</tr>
<tr>
<td><strong>Vagina</strong></td>
<td>– No increase in breast density</td>
</tr>
<tr>
<td>– ↓ Dryness, irritation, or dyspareunia</td>
<td>– No increase in breast pain</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td></td>
<td>– No increase in risk of cardiovascular disease</td>
</tr>
</tbody>
</table>


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Achieving Balance Requires Tissue Specific Effects on the Estrogen Receptors

- Estrogens and SERMs have unique chemical structures and each bind to estrogen receptors α and β, which vary in proportion from tissue to tissue\(^1\)
- Once bound to the estrogen receptor, the complex undergoes change in shape; affecting the interaction of other proteins with the receptor (e.g., those that regulate gene expression), and may impact associated physiologic responses\(^1\)
- These responses vary according to the tissue type and ER-binding compound, leading to an agonist or antagonist effect\(^2\)
- Tailoring their effects by combining them at a specific ratio produces a composite series of agonist and antagonist responses; with effects specific to each target tissue\(^1,3\)


A Composite Effect That Is Agonist in Some Tissues, Antagonist in Others
In preclinical studies of TSECs in ovariectomized rats, only CE / BZA was statistically similar to control vehicle when administered at the minimum effective dose to reduce CE-stimulated uterine net weight and ductal tree invasion. Variation observed between SERMs, between estrogens and between TSECs.

**Endometrium**

Uterine wet weight after 14 days' treatment

**Breast**

Ductal tree invasion into the fat pad after 14 days' treatment

Groups labeled with the same letter are statistically similar (P>0.05).

V (vehicle), E2 (5 µg/kg), CE (3 mg/kg), bazedoxifene (BZA; 2 mg/kg), raloxifene (RAL; 10 mg/kg), and lasofoxifene (LAS; 2 mg/kg) alone and in combination with CE (3 mg/kg).

BZA Inhibits Endometrial Cell Proliferation Caused by CE

- In the uterus, BZA acts selectively as an estrogen antagonist to help provide protection from endometrial hyperplasia associated with estrogen-alone treatment.¹
- There are many estrogen receptors in the cell nucleus.² BZA competes with CE for binding to estrogen receptors.¹,³,⁴
- When BZA binds to an estrogen receptor, it causes a different conformational change to the receptor, which results in inhibition of the estrogen receptor.³,⁴

- The composite effect of 0.45 mg CE with 20 mg BZA in Duavive resulted in low rates of endometrial hyperplasia¹

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Duavive Provides a Novel Mechanism of Action

- Conjugated estrogens (CE) are composed of multiple estrogens and have been used for over 70 years to treat certain menopausal symptoms\(^1\)
- BZA was specifically selected as the SERM in Duavive because of its unique pharmacologic profile and mechanism of action, as demonstrated by preclinical studies that looked at a number of different SERMs\(^3,4\)

In the Uterus

<table>
<thead>
<tr>
<th>CE are agonists</th>
<th>BZA is an antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Receptor activity is turned on</td>
<td>Estrogen Receptor activity is dimmed</td>
</tr>
</tbody>
</table>


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In clinical studies, Duavive demonstrated <1% incidence of endometrial hyperplasia or malignancy\(^1\)

- The FDA guidance for assessing agents to treat postmenopausal symptoms in women with a uterus recommends a hyperplasia rate \(\leq 1\%\)\(^2\)
- A 17% reduction in bazedoxifene exposure was predicted in women with BMI >27 kg/m\(^2\) based on a pharmacokinetic model using data from four Phase 1 studies. A reduction of bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia\(^1\)
- Progestins should not be added\(^1\)

\(\text{BMI}=\text{body mass index.}\)


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PHASE THREE STUDIES: IS DUAVIVE EFFECTIVE?
DUAVIVE Has an Extensively Characterized Clinical Profile from the Global SMART Clinical Development Program

Clinical Studies Conducted Worldwide in Over 7,500 Women¹–⁵,α
Studies Assessed Both CE 0.45/BZA 20 mg (DUAVIVE 0.45 mg) and CE 0.625/BZA 20 mg (DUAVIVE 0.625 mg)

SMART 1, N=3,397
24 months
Menopausal symptoms and endometrial protection vs. placebo

SMART 2, N=318
3 months
VMS vs. placebo

SMART 3, N=652
3 months
VVA vs. placebo

SMART 4, N=1,061
Supportive safety study
12 months, 1 year extension
Endometrial protection and BMD vs. placebo

SMART 5, N=1,843
12 months
BMD, endometrial protection and breast density vs. placebo

α Includes additional pilot dose finding study 403.

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MENOPAUSE SYMPTOMS
Study 3: Treatment of Moderate to Severe VMS

- 12-week randomized, double-blind, placebo-controlled study
- Inclusion criteria
  - Women with an intact uterus
  - Postmenopausal as defined by at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with a serum FSH level >40 mIU/mL
  - Minimum of 7 moderate to severe hot flushes per day or at least 50 per week at screening

Postmenopausal women with a uterus
Age 42–64 yr (avg. 53 yr)
(N=318*)

Duavive (CE 0.45/BZA 20) (n=127)

Placebo (n=63)

Primary End Points
Change from baseline to Weeks 4 and 12 in:
- Average daily number of moderate to severe hot flushes
- Average daily severity score of hot flushes

* This study included a different dose of CE / BZA. The schematic shown here depicts only the patients who received Duavive or placebo.
Reduction in the Observed Average Daily Number of Moderate to Severe Hot Flushes

- **Duavive** (n=122)
- **Placebo** (n=63)

**Observed Average Daily Number of Hot Flushes**

- **% change from baseline to week 12**
  - 74% for Duavive
  - 51% for placebo

- **Average daily number of hot flushes from baseline to week 12**
  - 10.3 to 2.8 for Duavive
  - 10.5 to 5.4 for placebo

Primary analysis at weeks 4 and 12; prespecified secondary end points at all other weeks


*Based on mathematical means; not statistically analyzed.

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Significant Reduction vs. Placebo in Average Daily Severity Score of Hot Flushes

Reduction in Average Daily Severity Score of Hot Flushes – Primary End Point

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAVEE (n=122)</td>
<td>-0.6*</td>
<td>-0.9*</td>
</tr>
<tr>
<td>Placebo (n=63)</td>
<td>-0.1</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

Adjusted Mean Change from Baseline†

* P<.001 vs. placebo.
† Based on data analysis using ANCOVA model: Change from baseline = Treatment + Baseline + Site.


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Reduction in the Observed Average Daily Severity Score of Hot Flushes

Observed Average Daily Severity Score of Hot Flushes*

% change from baseline to week 12*
- 39% for Duavive
- 14% for placebo

Average daily severity score of hot flushes from baseline to week 12*
- 2.3 to 1.4 for Duavive
- 2.3 to 1.9 for Placebo

Primary analysis at weeks 4 and 12; prespecified secondary end points at all other weeks

* Based on mathematical means; not statistically analyzed.

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Significant Improvements in Length and Quality of Sleep

- Significant improvements in sleep parameters demonstrated among responders with either dose of DUAVIVE at Week 12 compared with placebo in SMART 2 (P<0.05)\(^1\)
  - Significant improvements in time to fall asleep, sleep disturbance, and sleep adequacy also demonstrated against placebo for both doses at Month 12 in SMART 5 substudy (P<0.05)\(^2\)

Mean Change from Baseline in Sleep Parameters at 12 Weeks Post Treatment in SMART 2\(^1*\)

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**Increase in Sleep Adequacy**

- DUAVIVE 0.45 mg: 10.5
- DUAVIVE 0.625 mg: 6
- Placebo: 0

**Reduction in Sleep Disturbance**

- DUAVIVE 0.45 mg: -12.4
- DUAVIVE 0.625 mg: -14.8
- Placebo: -5.8

* DUAVIVE 0.45 mg (n=127); DUAVIVE 0.625 mg (n=128); placebo (n=63); Responders were women with at least 75% reduction from baseline in mean daily number of moderate-to-severe hot flashes. Sleep parameters were evaluated using the 12-item Medical Outcomes Study (MOS) sleep scale. The items, scored on a 6-point scale (1, all the time; 6, none of the time), create six sleep subscales: sleep adequacy, sleep disturbance, sleep quantity, daytime somnolence, snoring, and waking with shortness of breath or headache. Mean time taken to fall asleep is also measured by the questionnaire.

Changes in most bothersome vaginal symptom at baseline and after 12 weeks of Duavive

MBS include:
- Itch
- Dryness
- Dyspareunia

Kagan et al., *Menopause* 17(2);2010

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Significant Improvements In Quality of Life for Women with Menopause

Percentage of subjects reporting overall satisfaction as “extremely satisfied” or “satisfied” in SMART 2

Adjusted mean reduction from baseline in total MENQoL score at Month 12 in SMART 5


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Duavive use is associated with higher rates of amenorrhoea and lower rates of bleeding than CE/medroxyprogesterone acetate in 2 clinical trials.
FIG. 1. Adjusted mean change from baseline in (A) body weight and (B) body mass index (BMI) over time. Error bars represent 95% confidence intervals. BZA, bazedoxifene; CE, conjugated estrogens.

*P=0.015 vs placebo.
*A

*P=0.014 vs placebo.

B

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BONE LOSS
Duavive Efficacy for the Prevention of Postmenopausal Bone Loss

- 24-month, randomized, double-blind, placebo- and active-controlled study
- Primary end point: Endometrial hyperplasia at 1 year
- Secondary: BMD change of lumbar spine and total hip at 24 months

Postmenopausal women with a uterus
Age 40–75 yr (avg. 56 yr)
(N=3,397*)

BMD Analysis – Substudy I
(>5 years LMP)

BMD Analysis – Substudy II
(1 to 5 years LMP)

Duavive
(CE 0.45 / BZA 20)
(n=155)

Placebo
(n=151)

Duavive
(CE 0.45 / BZA 20)
(n=95)

Placebo
(n=95)

Change from baseline in:
- Lumbar Spine BMD (Primary – BMD Substudies)
- Total Hip BMD (Secondary – BMD Substudies)

* This study included different doses of CE / BZA and a comparator. The schematic shown here depicts only the patients who received the approved dose of Duavive or placebo.

LMP=last menstrual period.

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Duavive Significantly Increased Lumbar Spine BMD vs. Placebo at 24 Months

<table>
<thead>
<tr>
<th></th>
<th>&gt;5 Years Postmenopausal</th>
<th>1–5 Years Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAVIVE (n=160)</td>
<td>1.64*</td>
<td>1.72*</td>
</tr>
<tr>
<td>Placebo (n=159)</td>
<td>-1.47</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

% Mean Change from Baseline: 3.11% / 3.62%

Treatment Difference:
- DUAVIVE (n=160)
- Placebo (n=159)

* P<0.001 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. Study 1 excluded those subjects with missing source documentation.

Adapted from Lindsay Fertility and Sterility 2009 and Data on File.

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Duavive Significantly Increased Total Hip BMD vs. Placebo at 24 Months

Total Hip BMD Results at 24 Months

<table>
<thead>
<tr>
<th>Region</th>
<th>DUAVIVE (n=96)</th>
<th>Placebo (n=95)</th>
<th>DUAVIVE (n=155)</th>
<th>Placebo (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 Years Postmenopausal</td>
<td>1.07*</td>
<td>-0.65</td>
<td>0.55*</td>
<td>-1.42</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td>1.73%</td>
<td></td>
<td>1.96%</td>
<td></td>
</tr>
<tr>
<td>1–5 Years Postmenopausal</td>
<td></td>
<td></td>
<td></td>
<td>-1.42</td>
</tr>
</tbody>
</table>

* P<0.001 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. Study 1 excluded those subjects with missing source documentation.

Adapted from Lindsay Fertility and Sterility 2009 and Data on File.

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Duavive Efficacy for the Prevention of Postmenopausal Bone Loss

- 12-month, double-blind, randomized, placebo- and active-controlled study
- Primary end point: endometrial hyperplasia at 1 year
- Secondary: BMD changes at 1 year

Postmenopausal women with a uterus
Less than 5 years since LMP  
(N=590*)

BMD Analysis

Duavive  
(CE 0.45/BZA 20)  
(n=119)

Placebo  
(n=139)

BMD Analysis

Change from baseline in:
- Lumbar Spine BMD (Primary – BMD Substudy)
- Total Hip BMD (Secondary – BMD Substudy)

* This study included a different dose of CE / BZA and comparators. The schematic shown here depicts only the patients who received the approved dose of Duavive or placebo.

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Duavive Significantly Increased Lumbar Spine and Total Hip BMD vs. Placebo at 12 Months

% Mean Change from Baseline

Lumbar Spine

- **0.24***
- **1.51%**
- **Treatment Difference**
- **-1.28**

**DUAVIVE (n=119)**

**Placebo (n=139)**

Total Hip

- **0.5***
- **1.21%**
- **Treatment Difference**
- **-0.72**

*P<0.001 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.

Data on file.

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## Effects on the Breast and Endometrium

Breast tolerability profile similar to placebo following up to 2 years of treatment with DUAVIVE\textsuperscript{1-3}

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of breast cancer incidence up to 2 years (per 1,000 woman-years)</th>
<th>Incidence of reported breast pain/tenderness up to 12 weeks</th>
<th>Incidence of abnormal mammogram at month 12</th>
<th>Mean change in breast density at month 12 (SMART 5)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.45 mg (n=1,585)</td>
<td>0.625 mg (n=1,583)</td>
<td>Placebo (n=1,241)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer incidence up to 2 years (per 1,000 woman-years)</td>
<td>1.00 (CI 0.00–3.21)</td>
<td>0.00 (CI 0.00–1.54)</td>
<td>1.40 (CI 0.00–4.17)</td>
<td></td>
</tr>
<tr>
<td>Incidence of reported breast pain/tenderness up to 12 weeks</td>
<td>9.8–11.5%</td>
<td>9.8–10.2%</td>
<td>8.1–11.2%</td>
<td></td>
</tr>
<tr>
<td>Incidence of abnormal mammogram at month 12</td>
<td>2.58%</td>
<td>2.60%</td>
<td>3.16%</td>
<td></td>
</tr>
<tr>
<td>Mean change in breast density at month 12 (SMART 5)*</td>
<td>-0.38%</td>
<td>-0.44%</td>
<td>-0.32%</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of endometrial hyperplasia occurred in <1% of women following up to 2 years of treatment with DUAVIVE\textsuperscript{1,3}

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence at month 12 (n/N)</th>
<th>Incidence at month 24 (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.45 mg</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>SMART 1</td>
<td>0.00% (0/336)</td>
<td>0.32% (1/314)</td>
</tr>
<tr>
<td>SMART 5</td>
<td>0.30% (1/335)</td>
<td>0.27% (1/368)</td>
</tr>
</tbody>
</table>

*\textsuperscript{n= 186, n=191 and n=182 for DUAVIVE 0.45 mg, 0.625 mg and placebo respectively.}


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**EFFECTS ON THE BREAST**

![Graph showing the effects on the breast](image)

**Figure 3.** Cumulative rates of breast tenderness at 4-week cycles for 12 weeks of CE/BZA treatment in SMART-5 (mITT population) based on daily diaries.71
Breast Cancer

- CE/baxedoxifene increases the degradation of ERα in breast and endometrial tissue.
- BZA blocks the in vitro effects of both estradiol and CE on cell growth and gene expression in MCF-7 cells.
- BZA completely blocks CE- or E₂-stimulated ductal and terminal end bud growth of immature murine mammary glands and the growth of experimental breast cancers.
Effects of bazedoxifene on the breast 7 year RCT follow up

(c) Incidence, %

- BZA 20 + 40/20 mg (n=3758)
- PBO (n=1885)

Breast Carcinoma: 0.6, 0.6
Breast Cyst: 0.6, 0.8
Fibrocystic Breast Disease: 0.5, 0.8
Breast Pain: 3.0, 2.8
Breast Neoplasm: 1.0, 1.2

Archer et al., Menopause 16: 2009

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

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

Studies have mostly reported a smaller risk of having breast cancer diagnosed in women using estrogen alone than that found in users of estrogen-progestin combinations.
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.
- Duavive is contraindicated in women with known, suspected or past history of breast cancer.

HCP=health care professional.

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CARDIOVASCULAR SAFETY
LIPID PROFILE

Skouby et al., Menopause 22(6) 2014

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<table>
<thead>
<tr>
<th></th>
<th>Duavive (CE0.45/BZA 20mg) n = 1585</th>
<th>Placebo n = 1241</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any venous thromboembolism</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Rate/1000 woman years</td>
<td>0.3 (0.0-2.0)</td>
<td>0.6 (0.0-2.9)</td>
</tr>
<tr>
<td>Relative risk vs placebo</td>
<td>0.9 (0.2-4.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

Komm et al., *Climacteric* 18(4) 2015

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Venous Thromboembolism (VTE)

- Hormone therapy is associated with a 1.3-3 fold risk of developing VTE. The occurrence of such an events is more common in the first year of MHT than later.
- SERMS (including BZA) and estrogens individually increase the risk of VTE.
- Minimal effects on coagulation factors in SMART trials. More neutral than conventional MHT.
- 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 a 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

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Data Sheet
Stroke and CAD

The effect of treatment with stroke and CAD is unknown

Stroke

- Estrogen only therapy is associated with an up to 1.5-fold increase in risk of ischaemic stroke. This risk is not seen in women under 60 unless there are other risk factors for stroke.
- Duavive is contraindicated with active or past history of thromboembolic disease (e.g. myocardial infarction, stroke)

CAD

- The Cochrane Collaboration (2015) has demonstrated a reduction in CAD in women using MHT in their 50s or within 10 years of LMP
- Verified randomised controlled data found no increased risk of CAD in healthy women using estrogen-only or estrogen-progestin therapy.
- Duavive is contraindicated in women with active or past history of arterial thromboembolic disease/CAD

- Stevenson J. Post Reprod Health 2016 22(2)
- Boardman et al., 2015. Cochrane Library

CAD=coronary artery disease; MI=myocardial infarction.

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Women’s Health Initiative and CAD

### Primary end points

#### Coronary heart disease

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>CEE + MPA (n=8506)</th>
<th>Placebo (n=8102)</th>
<th>Difference/10,000 PY</th>
<th>HR (95% CI)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>38 (0.23)</td>
<td>27 (0.17)</td>
<td>5</td>
<td>1.34 (0.82-2.19)</td>
<td>.81</td>
</tr>
<tr>
<td>60-69</td>
<td>79 (0.37)</td>
<td>73 (0.37)</td>
<td>0</td>
<td>1.01 (0.73-1.39)</td>
<td>.08</td>
</tr>
<tr>
<td>70-79</td>
<td>79 (0.82)</td>
<td>59 (0.63)</td>
<td>19</td>
<td>1.31 (0.93-1.84)</td>
<td>.99</td>
</tr>
</tbody>
</table>

#### Coronary heart disease

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>CEE + MPA (n=5310)</th>
<th>Placebo (n=5429)</th>
<th>Difference/10,000 PY</th>
<th>HR (95% CI)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>21 (0.17)</td>
<td>35 (0.28)</td>
<td>-11</td>
<td>0.60 (0.35-1.04)</td>
<td>.08</td>
</tr>
<tr>
<td>60-69</td>
<td>100 (0.61)</td>
<td>108 (0.63)</td>
<td>-3</td>
<td>0.95 (0.72-1.24)</td>
<td>.12</td>
</tr>
<tr>
<td>70-79</td>
<td>83 (0.97)</td>
<td>79 (0.90)</td>
<td>7</td>
<td>1.09 (0.80-1.49)</td>
<td>.12</td>
</tr>
</tbody>
</table>

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Manson et al., *JAMA* 2013;310(13)

A: Intervention phase. B: Cumulative 13yr f/up
ADVERSE EVENTS
Adverse Reactions in Placebo-Controlled Trials

- Duavive was evaluated in 4 Phase 3 trials ranging from 12 weeks to 24 months in duration

### Adverse reactions (incidence ≥5%) that were more common with Duavive

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Duavive (N=1224) n (%)</th>
<th>Placebo (N=1069) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>100 (8)</td>
<td>58 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>96 (8)</td>
<td>57 (5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>84 (7)</td>
<td>59 (6)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>81 (7)</td>
<td>58 (5)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>110 (9)</td>
<td>63 (6)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>62 (5)</td>
<td>46 (4)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>65 (5)</td>
<td>37 (3)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>80 (7)</td>
<td>61 (6)</td>
</tr>
</tbody>
</table>

**Incidence of serious adverse reactions**
- 3.5% with Duavive
- 4.8% with placebo

Data on File.

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The most common adverse reactions leading to discontinuation were hot flushes (Duavive 0.7%, placebo 1.8%), upper abdominal pain (Duavive 0.5%, placebo 0.5%), and nausea (Duavive 0.5%, placebo 0.7%).

In clinical studies ranging from 12 weeks to 24 months:

Discontinuations due to adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAVEE</td>
<td>7.5%</td>
</tr>
<tr>
<td>(n=1224)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>10%</td>
</tr>
<tr>
<td>(n=1069)</td>
<td></td>
</tr>
</tbody>
</table>

Data on file.

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• DUAVIVE is the first TSEC, partnering CE with BZA in a specific ratio

• This novel MOA acts as an agonist in some estrogen-sensitive tissues and an antagonist in others (e.g., Uterus)

• The outcome of this tissue-selective activity is distinct from administering either component alone

• Thus, the TSEC provides relief from VMS and maintains BMD in postmenopausal women; while protecting uterine tissues from hyperplasia associated with estrogens alone so there is no need for progestin
Duavive Is the Only Approved Combination of CE with a SERM

- The pairing of CE and BZA produces a composite effect
- Duavive provides

**EFFICACY**

- Estrogen efficacy in treating moderate to severe hot flushes associated with menopause and preventing postmenopausal bone loss

**ENDOMETRIAL PROTECTION**

- An alternative to a progestin to help protect the uterine lining from hyperplasia that can occur with the CE component in women with a uterus

**Limitations of Use**

- 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
- When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered

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DUAVIVE’s Novel MOA Provides the Benefit of Tissue-selective Agonist and Antagonist Effects

<table>
<thead>
<tr>
<th>CE</th>
<th>BZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composed of Multiple estrogens ER-α and -β agonists</td>
<td>Estrogen agonist / antagonist Tissue-dependent agonism / antagonism</td>
</tr>
</tbody>
</table>

**CE**
- VMS
- Breast tenderness / density
- Uterine hyperplasia
- VVA
- BMD

**BZA**

**DUAVIVE (CE / BZA TSEC)**
Composite action of CE and BZA Effect specific to target tissue

Clinical Profile
- Neutral
- Less Favorable
- More Favorable


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• A CE 0.45 mg/bazedoxifene 20mg combination product (tissue selective estrogen complex) has recently been approved for the management of VMS. This is potentially a useful option in women who are intolerant to the effects of progestogens. The combination leads to reduced breast density but further data are required to confirm its impact on breast cancer incidence.

• In women with a uterus, the stimulatory effects of CE on the endometrium can be opposed by the selective estrogen receptor modulator (SERM) bazedoxifene. This combination, also known as tissue selective estrogen complex, has been shown to prevent the bone loss associated with menopause but the effect on fracture reduction has not been explored[1+]

Baber, Panay, Fenton et al., Climacteric 2016
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## DUAVIVE Indications and Usage

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAVEE is indicated for the treatment of estrogen deficiency symptoms in post menopausal women with a uterus with whom progestin therapy is inappropriate.</td>
<td>• DUAVIVE pairs two active ingredients in a single once daily tablet</td>
</tr>
<tr>
<td></td>
<td>• Tablets must be swallowed whole</td>
</tr>
<tr>
<td></td>
<td>• May be taken at the same time as calcium or vitamin D supplements, as necessary</td>
</tr>
</tbody>
</table>

Use DUAVIVE for the shortest duration consistent with treatment goals and risks for the individual women. Post menopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.
Menopause: Exploring the evidence

21st Annual Congress
Australasian Menopause Society

Sofitel Sydney Wentworth • 13 – 15 October 2017
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