FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

Duavive®

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 0.45 mg of conjugated estrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene.

Excipients with known effect:
Each modified-release tablet contains sucrose, lactose and maltitol liquid.

For the full list of excipients, *see Description (9)* in this leaflet.

PHARMACEUTICAL FORM

Modified-release tablet.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, AND PROBABLE DEMENTIA

- **Women taking DUAVIVE® should not take additional estrogens *[see Warnings and Precautions (4.1)]***
- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. DUAVIVE® has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (4.3)]***
- **Estrogen therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (4.2, 4.4)]***
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (4.2)]***
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older during 5.2 years of treatment with daily conjugated estrogens (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (4.4)]***

In the absence of comparable data, these risks should be assumed to be similar for other doses of conjugated estrogens and other dosage forms of estrogens.

Estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

DUAVIVE® is indicated in women with a uterus for:

1.1 Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause

1.2 Prevention of Postmenopausal Osteoporosis

1.3 Important 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.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause

The recommended dosage is one DUAVIVE® tablet daily.

2.2 Prevention of Postmenopausal Osteoporosis

The recommended dosage is one DUAVIVE® tablet daily.

2.3 General Dosing Information

Take DUAVIVE® once daily, without regard to meals. Tablets should be swallowed whole.

2.4 Recommendations for Calcium and Vitamin D Supplementation

Women taking DUAVIVE® for prevention of postmenopausal osteoporosis should add supplemental calcium and/or vitamin D to their diet if daily intake is inadequate.

2.5 Administration Instructions for Missed Doses

If a dose of DUAVIVE® is missed, instruct patients to take it as soon as remembered unless it is almost time for the next scheduled dose. They should not take two doses at the same time.

2.6 Use in Patients with Renal Impairment

The pharmacokinetics of DUAVIVE® have not been evaluated in patients with renal impairment. Use in patients with renal impairment is not recommended *[see Use in Specific Populations (7.6) and Clinical Pharmacology (10.2]*.

2.7 Use in the Elderly

DUAVIVE® has not been studied in women over 75 years of age. Use in women over 75 years of age is not recommended.

3 CONTRAINDICATIONS

DUAVIVE® is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal uterine bleeding
- Known, suspected, or past history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active deep venous thrombosis, pulmonary embolism, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction) or history of these conditions
- Hypersensitivity (for example, anaphylaxis, angioedema) to estrogens, bazedoxifene, or any ingredients listed in section 9.
- Known hepatic impairment or disease
- Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders
- Pregnancy, As DUAVIVE® may cause fetal harm *[see pregnancy (7.1)]*.

4 WARNINGS AND PRECAUTIONS

4.1 Drugs Containing Progestins, Estrogens or Estrogen Agonist/Antagonists

DUAVIVE® contains conjugated estrogens and bazedoxifene, an estrogen agonist/antagonist. Women taking DUAVIVE® should not take progestins, additional estrogens or additional estrogen agonist/antagonists.

4.2 Cardiovascular Disorders

Estrogen agonist/antagonists (including bazedoxifene, a component of DUAVIVE®) and estrogens individually are known to increase the risk of VTE.

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should any of these occur or be suspected, DUAVIVE® should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or VTE (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily conjugated estrogens (CE) (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (12.5)]*.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving conjugated estrogens (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

Should a stroke occur or be suspected, DUAVIVE® should be discontinued immediately *[see Contraindications (3)]*.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction, silent myocardial infarction, or CHD death) was reported in women receiving estrogen-alone compared to placebo *[see Clinical Studies (12.5)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE [DVT and pulmonary embolism (PE)] was increased for women receiving daily conjugated estrogens (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years *[see Clinical Studies (12.5)]*.

If feasible, DUAVIVE® should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Because immobilization increases the risk for venous thromboembolic events independent of therapy, DUAVIVE® should be discontinued prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest) and DUAVIVE® therapy should be resumed only after the patient is fully ambulatory. In addition, women taking DUAVIVE® should be advised to move about periodically during travel involving prolonged immobilization.

4.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more of treatment. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

DUAVIVE® contains an estrogen agonist/antagonist. This component reduces the risk of endometrial hyperplasia that can occur with the conjugated estrogens component. Endometrial hyperplasia may be a precursor to endometrial cancer. Women taking DUAVIVE® should not take additional estrogens as this may increase the risk of endometrial hyperplasia.

Clinical surveillance of all women taking DUAVIVE® is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Breast Cancer

The most important randomized clinical study providing information about breast cancer in estrogen-alone users is the WHI substudy of daily conjugated estrogens (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily conjugated estrogen (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80).

The use of estrogen-alone has been reported to result in an increase in abnormal mammograms requiring further evaluation. The effect of treatment with DUAVIVE® on the risk of breast cancer is unknown.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

The effect of treatment with DUAVIVE® on the risk of ovarian cancer is unknown.

4.4 Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years *[see Use in Specific Populations (7.5) and Clinical Studies (12.6)]*.

4.5 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

4.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, DUAVIVE® should be permanently discontinued.

4.7 Elevated Blood Pressure

In a small number of case reports in women receiving estrogens, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical study, a generalized effect of estrogens on blood pressure was not seen.

4.8 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, treatment with estrogens may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of DUAVIVE® if pancreatitis occurs.

4.9 Hepatic Impairment and Past History of Cholestatic Jaundice

DUAVIVE® has not been studied in women with impaired liver function or past history of cholestatic jaundice.

Estrogens may be poorly metabolized in women with impaired liver function.

On average, women with hepatic impairment treated with bazedoxifene alone showed a 4.3-fold increase in overall exposures compared with controls *[see Use in Specific Populations (7.7) and Clinical Pharmacology (10.2)]*.

For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised; and in the case of recurrence, DUAVIVE® should be discontinued. Use of DUAVIVE® in patients with hepatic impairment is contraindicated *[see Contraindications (3)]*.

4.10 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

4.11 Fluid Retention

Estrogens may cause some degree of fluid retention. Because of this, patients who have conditions that might be influenced by this factor, such as cardiac dysfunction or renal impairment, warrant careful observation when estrogens are prescribed. Use of DUAVIVE® in patients with renal impairment is not recommended *[see Use in Specific Populations (7.6)]*.

4.12 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

4.13 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

4.14 Exacerbation of Other Conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

4.15 Premenopausal Women

There is no indication for premenopausal use of DUAVIVE®. The efficacy and safety of DUAVIVE® in premenopausal women have not been established, and its use is not recommended. Additionally, there is concern regarding inadvertent drug exposure in pregnancy in women of reproductive potential who become pregnant, due to risk of fetal harm *[see Use in Specific Populations (7.1)]*.

4.16 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

4.17 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay), or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

4.18 Important information regarding some of the ingredients of the medicine

DUAVIVE® contains lactose, sucrose, glucose (in polydextrose and maltitol liquid) and sorbitol (in polydextrose). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

5 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiovascular Disorders *[see Warnings and Precautions (4.2)]*
- Malignant Neoplasms *[see Warnings and Precautions (4.3)]*
- Gallbladder Disease *[see Warnings and Precautions (4.5)]*
- Hypertriglyceridemia *[see Warnings and Precautions (4.8)]*

5.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of conjugated estrogens/bazedoxifene was evaluated in four Phase 3 clinical trials ranging from 12 weeks to 24 months in duration and enrolling 6,210 postmenopausal women age 40 to 75 years (mean age 55 years). A total of 1,224 patients were treated with DUAVIVE® and 1,069 patients received placebo. Women enrolled in Studies 1 and 2 received calcium (600-1200 mg) and vitamin D (200-400 IU) daily, while women in Studies 3 and 4 received no calcium and vitamin D supplementation as part of the protocol.

The incidence of all-cause mortality was 0.0% in the DUAVIVE® group and 0.2% in the placebo group. The incidence of serious adverse reactions was 3.5% in the DUAVIVE® group and 4.8% in the placebo group. The percentage of patients who withdrew from treatment due to adverse reactions was 7.5% in the DUAVIVE® group and 10.0% in the placebo group. The most common adverse reactions leading to discontinuation were hot flush, abdominal pain upper, and nausea.

The most commonly observed adverse reactions (incidence ≥ 5%) more frequently reported in women treated with DUAVIVE® than placebo are presented in Table 1.

Table 1: Adverse Reactions (Incidence ≥ 5%) More Common in the DUAVIVE® Treatment Group in Placebo-controlled Trials

	DUAVIVE® (N=1224) n (%)	Placebo (N=1069) n (%)
Gastrointestinal disorders		
Nausea	100 (8)	58 (5)
Diarrhea	96 (8)	57 (5)

Dyspepsia	84 (7)	59 (6)
Abdominal pain upper	81 (7)	58 (5)
Musculoskeletal and connective tissue disorders		
Muscle spasms	110 (9)	63 (6)
Neck pain	62 (5)	46 (4)
Nervous system disorders		
Dizziness	65 (5)	37 (3)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	80 (7)	61 (6)

Venous thromboembolism: In the clinical studies with DUAVIVE®, the reporting rates for venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) were low in all treatment groups. Adverse reactions of venous thromboembolism were reported in 0.0% of patients treated with DUAVIVE® and 0.1% of patients treated with placebo. Due to the low rate of events in both groups, it is not possible to conclude that the risk of venous thromboembolism with DUAVIVE® is different from that seen with other estrogen therapies *[see Warnings and Precautions (4.2)]*.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

6 DRUG INTERACTIONS

6.1 Cytochrome P450 (CYP)

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Concomitant administration of itraconazole, a strong CYP3A4 inhibitor, with DUAVIVE®, resulted in increases in bazedoxifene exposure (40%) and, to a lesser extent, conjugated estrogens exposure (9% for baseline-adjusted total estrone, 5% for total equilin), compared to DUAVIVE® alone *[see Pharmacokinetics (10.2)]*. Inducers of CYP3A4, such as St. John's Wort (Hypericum perforatum) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of some estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile.

Bazedoxifene does not induce or inhibit the activities of major CYP isoenzymes. *In vitro* data suggest that bazedoxifene is unlikely to interact with co-administered drugs via CYP-mediated metabolism.

6.2 Uridine Diphosphate Glucuronosyltransferase (UGT)

Bazedoxifene undergoes metabolism by UGT enzymes in the intestinal tract and liver. The metabolism of bazedoxifene may be increased by concomitant use of substances known to

induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin. A reduction in bazedoxifene exposure may be associated with an increase risk of endometrial hyperplasia. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

6.3 Atorvastatin

Concomitant administration of bazedoxifene (40 mg daily) and atorvastatin (20 mg, single-dose) to healthy postmenopausal women did not affect the pharmacokinetics of bazedoxifene, atorvastatin or its active metabolites.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

DUAVIVE® is contraindicated for use in pregnant women and is not indicated for use in females of reproductive potential *[see Contraindications (3), Warnings and Precautions (4.15)]*.

Conjugated Estrogens (CE)

There are no data with the use of conjugated estrogens in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital and non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives before conception or during early pregnancy.

Bazedoxifene

There are no available data on bazedoxifene use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Animal studies have shown that oral bazedoxifene administered during the period of organogenesis to pregnant rats or rabbits at 0.3 and 2 times, respectively, the exposure at the maximum recommended dose, can cause fetal harm *[see Data]*. Based on mechanism of action, bazedoxifene may block the important functions that estrogen has during all stages of pregnancy *[see Clinical Pharmacology (10.1)]*.

Data

Animal data

Bazedoxifene
Administration of bazedoxifene to rats at maternally toxic dosages ≥1 mg/kg/day (≥ 0.3 times the human area under the curve (AUC) at the 20 mg dose) resulted in reduced numbers of live fetuses and/or reductions in fetal body weights. No fetal developmental anomalies were observed. In studies conducted with pregnant rabbits treated with bazedoxifene, abortion and an increased incidence of heart (ventricular septal defect) and skeletal system (ossification delays,

misshapen or misaligned bones, primarily of the spine and skull) anomalies in the fetuses were present at maternally toxic dosages of ≥ 0.5 mg/kg/day (≥ 2 times the human AUC at the 20 mg dose).

7.2 Lactation

Risk Summary

DUAVIVE® is not indicated for use in females of reproductive potential *[see Warnings and Precautions (4.15)]*.

Conjugated Estrogens

Estrogens are present in human milk and can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established.

Bazedoxifene

There are no data on the presence of bazedoxifene in either human or animal breast milk, the effect on the breastfed infant, or the effects on milk production. Based on mechanism of action, bazedoxifene may block the important functions that estrogen has in mammary tissue during lactation *[see Clinical Pharmacology (10.1)]*.**7.3 Females and Males of Reproductive Potential**

Infertility

Bazedoxifene

Based on animal data, bazedoxifene administration may adversely affect female fertility. However, clinical fertility studies with bazedoxifene have not been conducted *[see Nonclinical Toxicology (11.1)]*.

7.4 Pediatric Use

DUAVIVE® is not indicated for use in children *[see Indications and Usage (1)]*.

7.5 Geriatric Use

DUAVIVE® is not recommended for use in women greater than 75 years of age *[see Dosage and Administration (2.7) and Clinical Pharmacology 10.2)]*.

Of the total number of women in phase 3 clinical studies who received DUAVIVE®, 4.60% (n=224) were 65 years and over. DUAVIVE® was not studied in women aged 75 and over. No overall differences in safety or effectiveness were observed between women 65-74

years of age and younger women, and other reported clinical experience has not identified differences in responses between the elderly and younger women, but greater sensitivity of some older women cannot be ruled out.

An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative using daily conjugated estrogens (0.625 mg) *[see Clinical Studies (12.6)]*.

7.6 Renal Impairment

DUAVIVE® is not recommended for use in patients with renal impairment *[see Dosage and Administration (2.6) and Clinical Pharmacology (10.2)]*.

The pharmacokinetics, safety, and efficacy of DUAVIVE® have not been evaluated in women with renal impairment.

7.7 Hepatic Impairment

DUAVIVE® is contraindicated in patients with hepatic impairment *[see Contraindications (3) and Clinical Pharmacology (10.2)]*.

The pharmacokinetics, safety, and efficacy of DUAVIVE® have not been evaluated in women with hepatic impairment. In a pharmacokinetics study of bazedoxifene 20 mg alone, the C_{max} and AUC of bazedoxifene increased 67% and 143%, respectively, in women with mild hepatic impairment (Child Pugh Class A), compared to healthy women. The C_{max} and AUC of bazedoxifene increased 32% and 109%, respectively, in women with moderate hepatic impairment (Child Pugh Class B). The C_{max} and AUC of bazedoxifene increased 20% and 268%, respectively, in women with severe hepatic impairment (Child Pugh Class C).

No pharmacokinetic studies with conjugated estrogens were conducted in women with hepatic impairment.

7.8 Body Mass Index (BMI)

Following DUAVIVE® administration, the systemic exposures of conjugated estrogens and bazedoxifene were lower in obese subjects, compared to non-obese subjects *[see Pharmacokinetics (10.2)]*.

A single dose of DUAVIVE® (conjugated estrogens 0.45 mg/bazedoxifene 20 mg) was administered to 12 obese BMI ≥ 30 [mean (SD) = 32.7 (2.7) kg/m^2] and 12 non-obese BMI < 30 [mean (SD) 25.3 (2.6) kg/m^2] postmenopausal women. In obese subjects, systemic exposures of total estrone, total equilin, and bazedoxifene were 2%, 32%, and 13% lower, respectively, compared to non-obese subjects.

A greater reduction in bazedoxifene exposure compared to conjugated estrogens may be associated with decreased protection from endometrial hyperplasia. Monitor and evaluate women

with postmenopausal or unexplained genital bleeding for possible endometrial hyperplasia or malignancy *[see Warnings and Precautions (4.3)]*.

8 OVERDOSAGE

In case of overdosage, there is no specific antidote, and the treatment should be symptomatic.

Symptoms of overdosage of estrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur.

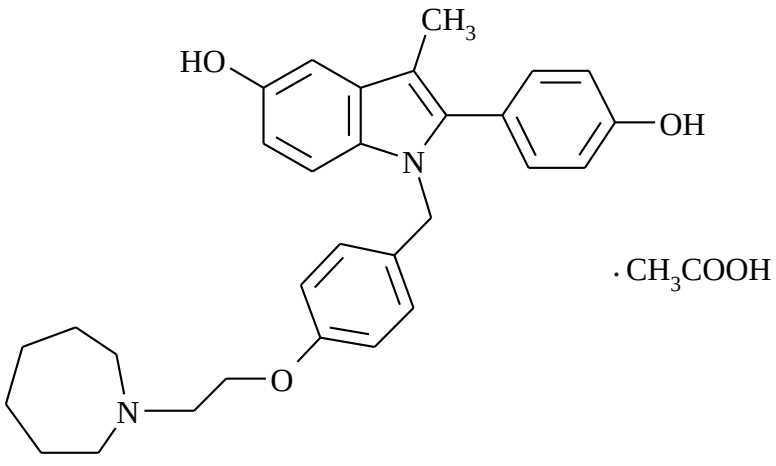
9 DESCRIPTION

DUAVIVE® (conjugated estrogens/bazedoxifene), contains conjugated estrogens with bazedoxifene, an estrogen agonist/antagonist.

Conjugated estrogens are purified from pregnant mares' urine and consist of the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. Conjugated estrogens are a mixture of sodium estrone sulfate and sodium equilin sulfate, and also contain as concomitant components, sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin.

Bazedoxifene is supplied as the acetate salt (bazedoxifene acetate) and has the chemical name 1*H*-Indol-5-ol, 1-[[4-[2-(hexahydro-1*H*-azepin-1-yl) ethoxy]phenyl]methyl]-2-(4-hydroxyphenyl)-3-methyl-, monoacetate. The empirical formula is $C_{30}H_{34}N_2O_3 \bullet C_2H_4O_2$, and the molecular weight is 530.65.

Bazedoxifene acetate is a white to tan powder. The aqueous solubility of bazedoxifene is pH-dependent. Solubility is higher at lower pH. The solubility of bazedoxifene acetate in unbuffered sterile water was measured to be 923 micrograms/mL at pH 5.4. The following represents the chemical structure of bazedoxifene acetate:



DUAVIVE® is available for oral administration as modified-release tablets containing 0.45 mg of conjugated estrogens and bazedoxifene acetate equivalent to 20 mg bazedoxifene. Each modified-release tablet of DUAVIVE® contains the following inactive ingredients: sucrose, hypromellose, lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, calcium phosphate tribasic, macrogol 400, ascorbic acid, sucrose palmitic acid ester, magnesium stearate, titanium dioxide (E171), red iron oxide (E172), hydroxyethylcellulose, povidone (E1201), polydextrose, maltitol liquid, poloxamer 188, black iron oxide (E172), isopropyl alcohol and propylene glycol (E1520).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

DUAVIVE® pairs conjugated estrogens with bazedoxifene. Conjugated estrogens and bazedoxifene function by binding to and activating estrogen receptors (ER) α and β, which vary in proportion from tissue to tissue. Conjugated estrogens are composed of multiple estrogens and are agonists of ER- α and β. Bazedoxifene is an estrogen agonist/antagonist that acts as an agonist in some estrogen-sensitive tissues and an antagonist in others (e.g., uterus). The pairing of conjugated estrogens with bazedoxifene produces a composite effect that is specific to each target tissue. The bazedoxifene component reduces the risk of endometrial hyperplasia that can occur with the conjugated estrogens component.

Pharmacodynamic studies have not been conducted with DUAVIVE®.

10.2 Pharmacokinetics

Absorption

Following administration of multiple doses of conjugated estrogens 0.45 mg/bazedoxifene 20 mg to healthy women who were naturally postmenopausal or who had undergone bilateral oophorectomy, the mean steady state pharmacokinetic parameters at Day 10 for conjugated estrogens (baseline adjusted for total estrone) and bazedoxifene are summarized in Table 2.

Table 2: Mean ± SD Steady-State Pharmacokinetic Parameters (n=24)

	C_{max} (ng/mL)	**T_{max} (hr)**	**AUCss (ng·hr/mL)**
Baseline-Adjusted Total Estrone	2.6 ± 0.8	6.5 ± 1.6	35 ± 12
Bazedoxifene	6.9 ± 3.9	2.5 ± 2.1	71 ± 34

Results from monotherapy studies with conjugated estrogens or bazedoxifene components of DUAVIVE®, are noted below:

Conjugated estrogens are soluble in water and are well-absorbed from the gastrointestinal tract after release from the drug formulation.

Bazedoxifene exhibits a linear increase in plasma concentrations for single doses from 0.5 mg up to 120 mg and multiple daily doses from 1 mg to 80 mg. The absolute bioavailability of bazedoxifene is approximately 6%.

Food Effect

In a single-dose, crossover study in 23 postmenopausal women given conjugated estrogens 0.625 mg/bazedoxifene 20 mg with a high fat/high calorie meal, food increased $AUC_{0\text{-}inf}$ of bazedoxifene by 25%. The C_{max} of bazedoxifene was unchanged.

Distribution

The distribution of conjugated estrogens and bazedoxifene after administration of DUAVIVE® has not been studied.

Results from monotherapy studies with conjugated estrogens or bazedoxifene, components of DUAVIVE®, are noted below:

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Following intravenous (IV) administration of a 3 mg dose of bazedoxifene, the volume of distribution is 14.7 ± 3.9 L/kg. Bazedoxifene is highly bound (98%-99%) to plasma proteins *in vitro,* but does not bind to SHBG.

Metabolism

The metabolic disposition of conjugated estrogens and bazedoxifene, after administration of DUAVIVE®, has not been studied.

Results from monotherapy studies with conjugated estrogens or bazedoxifene, components of DUAVIVE®, are noted below:

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. 17-β estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. In postmenopausal women, a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

The metabolic disposition of bazedoxifene has been determined following oral administration of 20 mg of radiolabeled bazedoxifene. Bazedoxifene is extensively metabolized in women. Glucuronidation is the major metabolic pathway. Little or no cytochrome P450-mediated metabolism is evident. Bazedoxifene-5-glucuronide is the major circulating metabolite.

The concentrations of this glucuronide are approximately 10-fold higher than those of unchanged drug in plasma.

Excretion

After administration of a single dose of conjugated estrogens/bazedoxifene, baseline-adjusted total estrone (representing conjugated estrogens) is eliminated with a half-life of approximately 17 hours. Bazedoxifene is eliminated with a half-life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration.

Results from monotherapy studies with conjugated estrogens or bazedoxifene, components of DUAVIVE®, are noted below:

The conjugated estrogens components, 17β-estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

The clearance of bazedoxifene is 0.4 ± 0.1 L/h/kg based on intravenous administration. The major route of excretion after oral administration of 20 mg of radiolabeled bazedoxifene is via biliary excretion, followed by elimination in the feces (~85%), with < 1% of the radioactive dose eliminated in the urine. Based on these results, it is expected that bazedoxifene undergoes entero-hepatic recycling from the gut back to the systemic circulation, therefore, some drugs may potentially interfere with bazedoxifene recycling process in the gut by various mechanisms resulting in a decrease in its systemic exposure.

Use in Specific Populations

Pediatric
The pharmacokinetics of conjugated estrogens/bazedoxifene tablets have not been evaluated in a pediatric population *[see Use in Specific Populations (7.4)]*.

Geriatric
The effect of age on the pharmacokinetics of conjugated estrogens/bazedoxifene tablets have not been evaluated *[see Use in Specific Populations (7.5)]*.

No pharmacokinetic studies with conjugated estrogens were conducted in specific populations, including women over 75 years of age.

The pharmacokinetics of a 20 mg single-dose of bazedoxifene, were evaluated in postmenopausal women. On average, compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC, and women ≥ 75 years of age (n=8) showed a 2.6-fold increase in AUC.

Renal Impairment
The pharmacokinetics of conjugated estrogens/bazedoxifene tablets have not been evaluated in women with renal impairment *[see Dosage and Administration (2.6) and Use in Specific Populations 7.6)]*.

Hepatic Impairment
The pharmacokinetics of conjugated estrogens/bazedoxifene tablets have not been evaluated in women with hepatic impairment *[see Contraindications (3), Warnings and Precautions (4.5), and Use in Specific Populations (7.7)]*.

No pharmacokinetic studies with conjugated estrogens were conducted in specific populations, including women with hepatic impairment.

A single dose of bazedoxifene 20 mg was given to fasted, healthy (N=18) and hepatically impaired postmenopausal women. In six mild hepatic impairment patients (Child Pugh Class A), C_{max} and AUC of bazedoxifene increased 67% and 143%, respectively, compared to healthy subjects. In six moderate hepatic impairment patients (Child Pugh Class B), C_{max} and AUC of bazedoxifene increased 32% and 109%, respectively, compared to healthy subjects. In six severe hepatic impairment patients (Child Pugh Class C), C_{max} and AUC of bazedoxifene increased 20% and 268%, respectively, compared to healthy subjects. Half-life was prolonged from 32 to 50 hrs in patients with severe hepatic impairment, compared to healthy subjects.

Body Mass Index

In a clinical study, a single dose of DUAVIVE® (conjugated estrogens 0.45 mg/bazedoxifene 20 mg) was administered to 12 obese [mean (SD) BMI = 32.7 (2.7) kg/m^2] and 12 non-obese [mean (SD) BMI = 25.3 (2.6) kg/m^2] postmenopausal women. In obese subjects, systemic exposure (AUC_{0-72}) of total estrone was 2% lower and systemic exposures (AUC_{0-inf}) of total equilin and bazedoxifene were 32% and 13% lower, respectively, compared to non-obese subjects.

Drug Interactions

Effect of Co-Administered Drugs on the Pharmacokinetics of Conjugated Estrogens/Bazedoxifene

In a drug-drug interaction study, itraconazole 200 mg, a strong CYP3A4 inhibitor, was administered with breakfast to 24 postmenopausal women for 4 days, followed by a fifth dose of itraconazole 200 mg with breakfast and DUAVIVE® on Day 5 (3 hours after itraconazole). Itraconazole 200 mg was continued for 2 additional days after the co-administration of itraconazole 200 mg and DUAVIVE®. Following co-administration of DUAVIVE® and itraconazole, baseline-adjusted total estrone C_{max} and AUC_{0-72} increased 9% and 9%, respectively, total equilin C_{max} and AUC_{0-72} increased 11% and 5%, respectively, and bazedoxifene C_{max} and AUC_{0-inf} increased 11% and 40%, respectively, compared to subjects treated with DUAVIVE® alone.

Effect of Co-Administered Drugs on the Pharmacokinetics of Bazedoxifene

Conjugated Estrogens

Conjugated estrogens 0.625 mg were administered alone for 6 consecutive days prior to the co-administration of a single dose of 20 mg bazedoxifene and conjugated estrogens 0.625 mg in thirty postmenopausal women. Conjugated estrogens 0.625 mg were continued for 2 additional days after the co-administration of bazedoxifene and conjugated estrogens. The C_{max} of bazedoxifene increased by 3% and AUC of bazedoxifene decreased by 6%.

Ibuprofen
A single dose of ibuprofen 600 mg was given with a bazedoxifene 20 mg capsule in twelve postmenopausal women after an overnight fast. Co-administration of ibuprofen and bazedoxifene increased C_{max} and AUC of bazedoxifene by 18% and 7%, respectively.

Atorvastatin
Atorvastatin 20 mg was given once with bazedoxifene 40 mg in thirty postmenopausal women. Co-administration of atorvastatin and bazedoxifene decreased C_{max} of bazedoxifene by 3% and increased AUC of bazedoxifene by 6%.

Azithromycin
Azithromycin 500 mg was given once daily for 8 consecutive days in thirty postmenopausal women. Azithromycin 500 mg and a bazedoxifene 40 mg tablet were co-administered on Day 9. Azithromycin 250 mg administration once daily continued on Days 10 to 13. Co-administration of azithromycin and bazedoxifene increased C_{max} of bazedoxifene by 6% and decreased AUC of bazedoxifene by 15%.

Aluminum and Magnesium Hydroxide
A single dose of 460 mg aluminum hydroxide and 400 mg magnesium hydroxide was given with a bazedoxifene 40 mg tablet in thirty postmenopausal women after an overnight fast. Co-administration of aluminum/magnesium hydroxide and bazedoxifene decreased C_{max} of bazedoxifene by 8% and increased AUC of bazedoxifene by 7%.

Effect of Bazedoxifene on the Pharmacokinetics of Co-Administered Drugs

Conjugated Estrogens
Bazedoxifene 20 mg was administered alone for 8 consecutive days prior to co-administration of a single dose of conjugated estrogens 0.625 mg and bazedoxifene 20 mg in twenty-six postmenopausal women. Bazedoxifene 20 mg was continued for 2 additional days after co-administration of bazedoxifene and conjugated estrogens. The C_{max} and AUC of unconjugated estrone increased by 11% and 3%, respectively. The C_{max} and AUC of unconjugated equilin increased by 17% and 14%, respectively.

Ibuprofen
A single dose of bazedoxifene 20 mg capsule was given with a single dose of ibuprofen 600 mg in twelve fasted, postmenopausal women. Co-administration of bazedoxifene and ibuprofen increased the C_{max} of ibuprofen by 6%. The AUC of ibuprofen was unchanged.

Atorvastatin

Bazedoxifene 40 mg was given for 8 consecutive days prior to co-administration of bazedoxifene 40 mg and atorvastatin 20 mg. Co-administration of bazedoxifene and atorvastatin decreased C_{max} of atorvastatin by 14%. The AUC of atorvastatin was unchanged. The C_{max} and AUC of 2-OH atorvastatin were decreased by 18% and 8%, respectively.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies with conjugated estrogens/bazedoxifene have not been conducted.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

In 6-month oral gavage carcinogenicity studies of bazedoxifene in transgenic Tg.RasH2 mice, there was a drug-related increased incidence of benign, ovarian granulosa-cell tumors in female mice given 150 or 500 mg/kg/day. In a two-year dietary carcinogenicity study of bazedoxifene in rats (administered at 0.003%, 0.01%, 0.03%, or 0.1%) a drug-related marked increased incidence of benign, ovarian granulosa-cell tumors was observed in female rats at concentrations of 0.03% and 0.1%. Systemic exposure (AUC) of bazedoxifene in these groups was 3 and 8 times that observed in postmenopausal women administered 20 mg/day. In male rats, drug-related renal tumors (adenomas and carcinomas), in the presence of renal toxicity, were observed at all doses tested, which corresponded to exposure ratios of 0.06 to 5 times the clinical AUC at a dose of 20 mg.

Mutagenesis

Mutagenicity studies with conjugated estrogens/bazedoxifene have not been conducted.

Bazedoxifene was not genotoxic or mutagenic in a battery of tests, including *in vitro* bacterial reverse mutation assay, *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, and *in vivo* mouse micronucleus assay.

Impairment of Fertility

Impairment of fertility studies with conjugated estrogens/bazedoxifene have not been conducted.

Female rats were administered daily dosages of 0.3 to 30 mg/kg bazedoxifene (0.03 to 10 times human AUC at the 20 mg dose) prior to and during mating with untreated males. Estrous cycles and fertility were adversely affected in all bazedoxifene-treated female groups.

11.2 Animal Toxicology and/or Pharmacology

In a 12-month study in ovariectomized rats, co-administration of conjugated estrogens (2.5 mg/kg/day) and bazedoxifene (0.1, 0.3, or 1 mg/kg/day) prevented the loss of bone mass at the spine, femur, and tibia with concomitant maintenance of biomechanical strength parameters.

12 CLINICAL STUDIES

12.1 Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause in Women with a Uterus

The safety and efficacy of DUAVIVE® as a treatment for moderate to severe vasomotor symptoms associated with menopause was established in a 12-week randomized, double-blind, placebo-controlled study (Study 3). Study 3 enrolled a total of 318 women, age 42-64 (mean age of 53 years), who had at least 7 moderate to severe hot flushes per day or at least 50 per week at baseline. The mean number of years since menopause was 4.5 years with all women undergoing natural menopause. A total of 127 women were assigned to DUAVIVE® and 63 women were assigned to placebo.

In Study 3, DUAVIVE® significantly reduced the number and severity of moderate to severe hot flushes, as measured by the daily severity score, compared with placebo at Weeks 4 and 12. The change from baseline in the number and severity of moderate to severe hot flushes observed and the difference from placebo in Study 3 are shown in Table 3.

Table 3: Adjusted Mean Change from Baseline in the Average Daily Frequency and Severity of Hot Flushes (Study 3)

	Frequency		Severity	
	DUAVIVE®	**Placebo**	**DUAVIVE®**	**Placebo**
N	122	63	122	63
Baseline	10.3	10.5	2.3	2.3
Week 4				
Mean Change[1]	-5.9	-2.8	-0.6	-0.1
Treatment Difference[2]	-3.1 (-4.4, -1.7)*	--	-0.5 (-0.7, -0.3)*	--
Week 12				
Mean Change[1]	-7.6	-4.9	-0.9	-0.3
Treatment Difference[2]	-2.7 (-3.8, -1.6)*	--	-0.6 (-0.9, -0.4)*	--

*$p<0.001$
[1] Change from baseline using ANCOVA model
[2] Based on raw data analysis using ANCOVA model: Difference= Treatment + Baseline + Site

12.2 Prevention of Postmenopausal Osteoporosis in Women with a Uterus

The safety and efficacy of DUAVIVE® for the prevention of postmenopausal osteoporosis was demonstrated in Study 1 and Study 2.

Study 1 was a 24-month, double-blind, randomized, placebo- and active-controlled study evaluating the safety and efficacy of multiple combinations of conjugated estrogen/bazedoxifene (including conjugated estrogens 0.45 mg/bazedoxifene 20 mg) compared to placebo. The primary endpoint of the study was the incidence of endometrial hyperplasia at Year 1. Bone mineral density change at the lumbar spine at Year 2 was the key secondary endpoint, assessed in two subsets of patients (Substudy I and Substudy II). Patients enrolled into Substudy I had to be more than 5 years postmenopausal, have a lumbar spine or total hip T-score of -1 to -2.5, and have at least one additional risk factor for osteoporosis (e.g., Caucasian race, family history of osteoporosis, early menopause, thin/small frame, inactive lifestyle, tobacco abuse). Those enrolled into Substudy II had to be 1-5 years postmenopausal with at least one additional risk factor for osteoporosis. A total of 3,397 women age 40-75 (mean age of 56 years) were enrolled in the overall study. Substudy I enrolled a total of 1,454 women (182 women receiving DUAVIVE®) with mean baseline T-scores of -1.43 and -1.52 in the DUAVIVE® and placebo groups, respectively. Substudy II enrolled a total of 861 women (with 111 women receiving DUAVIVE®) with mean baseline T-scores of -0.81 and -0.94 in the DUAVIVE® and placebo groups, respectively. Women also took calcium (600-1200 mg) and vitamin D (200-400 IU) daily.

In these substudies, treatment with DUAVIVE® significantly increased lumbar spine bone mineral density (BMD) at 24 months compared to placebo in both groups of postmenopausal women (Table 4).

Table 4: Lumbar Spine Bone Mineral Density Results at 24 Months (Study 1)

	DUAVIVE®	Placebo
Between 1 and 5 Years Postmenopausal		
N	95	95
% Mean Change	1.72	-1.90
Difference from Placebo (95% C.I.)	3.62 (2.64, 4.60)*	
More Than 5 Years Postmenopausal		
N	155	151
% Mean Change	1.64	-1.47
Difference from Placebo (95% C.I.)	3.11 (2.29, 3.93)*	—

* p-value < 0.001
** Adjusted mean changes, confidence intervals, and p-values based on an ANCOVA model with treatment and region (U.S. or non-U.S.) 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 excludes those subjects with missing source documentation.

In Study 1, treatment with DUAVIVE® also significantly increased total hip BMD. The treatment difference (or difference from placebo) in total hip BMD at 24 months was 1.96% (DUAVIVE® minus placebo) in women who had been postmenopausal between 1 and 5 years and 1.73% (DUAVIVE® minus placebo) in women who had been postmenopausal for more than 5 years.

Study 2 was a 12-month, double-blind, randomized, placebo- and active-controlled study. The primary endpoint was the incidence of endometrial hyperplasia at 12 months. The prevention of osteoporosis was assessed in a substudy that enrolled women (n=590) who were less than 5 years postmenopausal (mean 2.5 years). The mean baseline T-score in the substudy was -0.91 in the DUAVIVE® group and -0.95 in the placebo group. The mean age of women (n=135) taking DUAVIVE® was 53 years (range 46-60 years). Women also took calcium (600 mg) and vitamin D (400 IU) daily.

In Study 2, treatment with DUAVIVE® significantly increased mean lumbar spine BMD (treatment difference, 1.51%), at 12 months compared to placebo in women who had been postmenopausal between 1 and 5 years. Treatment with DUAVIVE® also increased total hip BMD. The treatment difference in total hip BMD at 12 months was 1.21%.

12.3 Effects on the Endometrium

Effects of DUAVIVE® on endometrial hyperplasia and endometrial malignancy were assessed in Study 1 and Study 2. The Efficacy Evaluable population included patients who had taken at least one dose of DUAVIVE®, had baseline and post baseline endometrial biopsies, or had been

diagnosed with hyperplasia. By endometrial biopsy, the incidence of endometrial hyperplasia or malignancy for DUAVIVE® was below 1% in both studies (see Table 5).

Table 5: Incidence of Endometrial Hyperplasia or Malignancy at Month 12 and Month 24

		STUDY 1*		STUDY 2*	
Treatment Group	**Month**	**% (n/N)**	**1 – Sided 95% UL**	**% (n/N)**	**1 – Sided 95% UL**
DUAVIVE®	12	0.00% (0/336)	0.89	0.30% (1/335)	1.41
	24	0.68% (2/294)	2.13	--	--
UL = Upper limit * = Efficacy Evaluable population					

12.4 Effects on Uterine Bleeding and Spotting

Uterine bleeding or spotting were evaluated in two clinical studies (Studies 1 and 2) by daily diary. In Study 1, cumulative amenorrhea at Year 1 was 83% in women treated with DUAVIVE® and 85% in women who received placebo. In Study 2, cumulative amenorrhea at Year 1 was 88% in women treated with DUAVIVE® and 84% in women who received placebo.

12.5 Women's Health Initiative Studies

The WHI enrolled approximately 11,000 predominantly healthy postmenopausal women to assess the risks and benefits of daily oral conjugated estrogens 0.625 mg compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of conjugated estrogens on menopausal symptoms.

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow- up of 7.1 years are presented in Table 6.

Table 6: Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310	Placebo N = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71-1.43)*	*16*	*16*
All strokes[c]	1.33 (1.15-1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19-2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[e]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.65 (0.45-0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47-0.72)	35	59
Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88-1.22)	79	75
Global Index[g]	1.02 (0.92-1.13)	206	201

a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
b Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
c Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
d Not included in "global index".
e Results are based on an average follow-up of 6.8 years.
f All deaths, except from breast or colorectal cancer, definite or probable CHD, PE, or cerebrovascular disease.
g A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures. The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving conjugated estrogens-alone compared to placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant differences in distribution of stroke subtype or severity, including fatal strokes, in women receiving conjugated estrogens-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy, stratified by age, showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].

12.6 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age, 36 percent were 70 to 74 years of age, and 19 percent were 75 years of age and older) to evaluate the effects of daily conjugated estrogens (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for conjugated estrogens-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for conjugated estrogens-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (4.4) and Use in Specific Populations (7.5)]*.

13 HOW SUPPLIED/STORAGE AND HANDLING

Blister packs containing 28 modified-release tablets. The tablets are oval, biconvex, pink coated tablet, branded with "0.45/20" in black ink on one side.

Storage

Do not store above 25ºC.

Store in the original package and protect from moisture.

Use within 60 days, after opening the blister pouch.

The expiry date of the product is indicated on the packaging materials.

14 MANUFACTURER:

Pfizer Ireland Pharmaceuticals, Newbridge, Ireland.

15 LICENSE HOLDER:

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

16 LICENSE NUMBER:

157-37-34551

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