Formulary Drug Reviews

Conjugated Estrogens and Bazedoxifene

Dennis J. Cada, PharmD, FASHP, FASCP (Editor)*; and Danial E. Baker, PharmD, FASHP, FASCP†

Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary*, *Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The March 2014 monograph topics are umeclidinium and vilanterol inhalation powder, sucroferric oxyhydroxide, luliconazole, edoxaban, and secukinumab. The DUE/MUE is on fentanyl transdermal system.

Generic Name:	Conjugated Estrogens and Bazedoxifene
Proprietary Name:	Duavee (Pfizer)
Approval Rating:	4: New Combination
Therapeutic Class:	Estrogens/Selective Estrogen Receptor Modulators
Similar Drugs:	Conjugated Estrogens, Raloxifene
Sound- or Look-Alike Names:	Duet, Duexis

INDICATIONS

The US Food and Drug Administration (FDA)-approved indications for the combination of conjugated estrogens and bazedoxifene include the treatment of moderate to severe vasomotor symptoms

associated with menopause in women with a uterus and the prevention of postmenopausal osteoporosis in women with a uterus. The duration of therapy for both indications is the shortest duration consistent with treatment goals and risks for the individual woman.¹ There are no other FDA-approved combination products that contain an estrogen and a selective estrogen receptor modulator (SERM).

Conjugated estrogens are approved for treatment of moderate to severe vasomotor symptoms due to menopause; treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause; treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease; treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only); and prevention of postmenopausal osteoporosis.² Bazedoxifene is not approved as a single agent ingredient; however, there are studies supporting its potential use as monotherapy in the prevention and treatment of osteoporosis in postmenopausal women.³⁻¹⁵ Raloxifene, another SERM, is approved

*Founder and Contributing Editor, *The Formulary*; †Director, Drug Information Center, and Professor of Pharmacy Practice, College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, Washington 99210-1495. The authors indicate no relationships that could be perceived as a conflict of interest.

for the treatment and prevention of osteoporosis in postmenopausal women, reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer.¹⁶

CLINICAL PHARMACOLOGY

Conjugated estrogens and bazedoxifene work together by binding to and activating estrogen receptors (ER) alpha and beta, which vary in proportion from tissue to tissue. Conjugated estrogens are a collection of estrogens and are agonists of ER-alpha and ER-beta. Bazedoxifene is an estrogen agonist/antagonist that functions as an agonist in some estrogen-sensitive tissues and as an antagonist in others (eg, uterus). The primary function of bazedoxifene in this product formulation is to oppose the effects of the estrogens on the uterus and decrease the risk of endometrial hyperplasia.¹

Clinical effects observed in animal models include prevention of ovariectomy-associated body weight increases,¹⁷ protection against ovariectomy-associated bone loss,¹⁸⁻²⁰ increased bone mineral density,^{21,22} and increased bone compressive strength.^{21,22} Bazedoxifene did not alter uterine weight¹⁷ or reduce serum cholesterol levels.^{17,20}

Bazedoxifene did not stimulate proliferation of MCF-7 breast cancer cells in an assay system, but did inhibit 17 β -estradiol-induced proliferation.²¹

In animal models, bazedoxifene had less effect on ovarian weight in immature and mature animals than did raloxifene, lasofoxifene, or ethinyl estradiol. Bazedoxifene was more effective at antagonizing the stimulatory effect of ethinyl estradiol on the uterus compared with raloxifene or lasofoxifene. Bazedoxifene did not increase luminal epithelial cell height, whereas raloxifene and lasofoxifene produced 2- and 5-fold increases in luminal epithelial cell height, respectively.²³ Coadministration of bazedoxifene with raloxifene reduced the raloxifene-stimulated hypertrophy of endometrial luminal epithelial cells and myometrial cells.²¹

PHARMACOKINETICS

Conjugated estrogens are well absorbed from the gastrointestinal (GI) tract and reach peak plasma concentrations (C_{max}) at 6.5 hours (based on estrone component). The C_{max} after administration of conjugated estrogens 0.45 mg for 10 days was 2.6 ng/mL, and the steady-state area under the curve (AUC) was 35 ng•h/mL.¹

Bazedoxifene is poorly absorbed from the GI tract and reaches its C_{max} at 2.5 hours. Bazedoxifene's absolute bioavailability is approximately 6%. It demonstrates linear pharmacokinetics after single-dose administration of 0.5 to 120 mg and multiple-dose administration of 1 to 80 mg. The C_{max} after administration of bazedoxifene 20 mg for 10 days was 6.9 ng/mL, and the steady-state AUC was 71 ng•h/mL.¹ Serum half-life is 32.8 hours.²⁴

Administration with a high-fat/high-calorie meal caused no change in bazedoxifene's C_{max} , but it increased the AUC by 25%. No information was provided on how food affected the absorption of conjugated estrogens.¹

Distribution information is available on the individual product ingredients, but it was not determined after administration of the combination formulation. Individual administration of conjugated estrogens results in a wide distribution throughout the body similar to endogenous estrogens. These estrogens generally circulate in the blood bound to sex hormone-binding globulin and albumin. The volume of distribution for bazedoxifene is 14.7 L/kg; bazedoxifene is highly bound (98% to 99%) to plasma protein, but not sex hormone-binding globulin.¹

The estrogens are metabolized by dynamic equilibrium of metabolic interconversion and sulfate conjugation; 17 β -estradiol is converted reversibly to estrone, and both 17 β -estradiol and estrone are converted to estriol. Portions of all of these estrogens exist as sulfate conjugates that serve as a circulating reservoir for the formation of more active estrogens. However, one route of elimination of estrogens does involve the cytochrome P450 (CYP-450) 3A4 metabolic pathway. The elimination half-life of estrone is 17 hours. Excretion occurs in the kidney for 17 β -estradiol, estrone, estriol, and glucuronide and sulfate conjugates of these estrogens.¹

Bazedoxifene is extensively metabolized, with the glucuronidation being the major metabolic pathway.^{1,24,25} Bazedoxifene undergoes little or no CYP-450-mediated metabolism.^{1,24} Also, bazedoxifene is metabolized by uridine diphosphate glucuronosyltransferase (UGT) in the intestinal tract and liver. The elimination half-life of bazedoxifene is 30 hours. Excretion involved elimination in the feces (85%) and less than 1% in urine. Bazedoxifene is thought to undergo enterohepatic recycling from the gut back to the systemic circulation, which may be a potential source for drug interactions.¹

Pharmacokinetics studies have not been conducted in pediatric patients or in patients with renal or hepatic impairment.¹

COMPARATIVE EFFICACY

Indication: Treatment of Moderate to Severe Vasomotor Symptoms Associated With Menopause in Women With a Uterus

Studies

Drug: Conjugated Estrogens/Bazedoxifene vs Placebo

Reference: Pinkerton JV, 2009 (SMART-2)²⁶⁻²⁸

Study Design: Phase 3, randomized, double-blind, multicenter, placebo-controlled study

Study Funding: Wyeth Research

Patients: 332 healthy postmenopausal women with an intact uterus seeking treatment for hot flashes at 42 sites in the United States. Women were 40 to 65 years of age with a body mass index (BMI) of 34 kg/m² or less. The frequency of hot flashes had to be a minimum of 7 moderate to severe hot flashes per day or 50 per week.

Intervention: Patients were randomized to 12 weeks of treatment with conjugated estrogens 0.45 mg plus bazedoxifene 20 mg, conjugated estrogens 0.625 mg plus bazedoxifene 20 mg, or placebo. No oral drugs containing estrogen, progestin, androgen, or SERMs; transdermal hormone products; or intrauterine progestins could have been used within 8 weeks. Vaginal hormone products had to be avoided for at least 4 weeks, and progestin implants/injectables or estrogen pellets/injectables had to be avoided for at least 6 months prior to screening. During the study, the patient could not use any investigational drug; estrogen-, progestin-, androgen-, or SERM-containing drugs other than the study drug; or any medications, remedies, and supplements intended for the treatment of vasomotor symptoms.

Results:

Primary Endpoint(s):

- Change from baseline in the average daily number of moderate and severe hot flashes at week 4 was decreased in both doses of conjugated estrogens/bazedoxifene compared with placebo ($P < .001$).
- Change from baseline in the average daily number of moderate and severe hot flashes at week 12.

- Conjugated estrogens 0.45 mg/bazedoxifene 20 mg decreased by 74% (10.3 at baseline compared with 2.8 at week 12) versus 51% (10.5 at baseline compared with 5.4 at week 12) with placebo at week 12 ($P < .001$).
- Conjugated estrogens 0.625 mg/bazedoxifene 20 mg decreased by 80% versus 51% (10.5 at baseline compared with 5.4 at week 12) with placebo at week 12 ($P < .001$).
- Change from baseline in the average severity of hot flashes was better than placebo with both doses of conjugated estrogens plus bazedoxifene at weeks 4 and 12 ($P < .001$).

Secondary Endpoint(s):

- A 50% reduction in number of hot flashes (moderate and severe) was achieved by 83% of the women taking conjugated estrogen 0.45 mg/bazedoxifene 20 mg, 86% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and 52% with placebo ($P < .001$) at week 12.
- A 75% reduction in number of hot flashes (moderate and severe) was achieved by 61% of the women taking conjugated estrogen 0.45 mg/bazedoxifene 20 mg, 73% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and 27% with placebo ($P < .001$). More patients treated with the higher dose conjugated estrogen plus bazedoxifene achieved a 75% reduction in number of hot flashes than the lower dose group at week 12.
- A 75% reduction in number of hot flashes (mild, moderate, and severe) was achieved by about 50% of the women taking conjugated estrogen 0.45 mg/bazedoxifene 20 mg, 65% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and 22% with placebo ($P < .001$) at week 12.
- A 50% reduction in number of hot flashes (mild, moderate, and severe) was achieved by 77% of the women taking conjugated estrogen 0.45 mg/bazedoxifene 20 mg, 81% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and 48% with placebo ($P < .001$) at week 12.
- Median time to 50% reduction in number of hot flashes for at least 3 consecutive days was 15 days with conjugated estrogens 0.45 mg/bazedoxifene 20 mg, 14 days with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and 30 days with placebo ($P \leq .001$).
- Conjugated estrogens/bazedoxifene therapy was associated with improvements in sleep parameters, sleep quality, effects on mood/emotions,

tolerability, quality of life scores, and overall satisfaction with treatment compared with placebo.

Comments: Efficacy was evaluated using a modified intent-to-treat cohort defined as a patient who took at least 1 dose of study medication, recorded at least 5 days of data during the baseline week, and had at least 5 days of data for at least 1 on-therapy week with missing data handled using a last observation carried forward approach. The difference between the reduction in number of hot flashes versus placebo became significant by week 3 with conjugated estrogens 0.45 mg/bazedoxifene 20 mg ($P = .008$) and week 2 with conjugated estrogens 0.625 mg/bazedoxifene 20 mg ($P = .007$). The severity of the hot flashes was better than placebo in both treatment groups as early as week 3, and the higher dose of conjugated estrogen was better than the lower dose from week 6 ($P = .011$) to week 12 ($P = .002$).

Limitations: Short-term study that lasted only 12 weeks. This provides enough time to show efficacy in the treatment of menopausal symptoms, but not to evaluate the long-term safety of this drug combination.

Drug: Conjugated Estrogens/Bazedoxifene vs Bazedoxifene vs Placebo

Reference: Kagan R, et al, 2007 (SMART-3)^{29,30}

Study Design: Phase 3, randomized, double-blind, multicenter, placebo-controlled and active comparator study

Study Funding: Wyeth Research

Patients: 664 healthy postmenopausal women with an intact uterus were enrolled from 66 sites in the United States. Women were 40 to 65 years of age with a BMI of 34 kg/m² or less. Treatment with oral drugs containing estrogen, progestin, androgen, or SERMs; transdermal hormone products; or intrauterine progestins were allowed within 8 weeks of screening. Vaginal hormone product use was allowed within 4 weeks, progestin implants/injectables or estrogen pellets/injectables within 6 months, intrauterine devices within 12 weeks, or an investigational drug within 60 days. The average age of the patients was 56 years old, more than 90% were White, average BMI was 25.3 kg/m², average time from last menstrual period was 7.4 years, and all had natural menopause. Efficacy was evaluated using the modified

intent-to-treatment cohort with last observation carried forward while on therapy method used for missing data. The study was completed by 92% of the enrollees.

Intervention: Computer randomization to treatment with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, conjugated estrogens 0.45 mg/bazedoxifene 20 mg, bazedoxifene 20 mg, or placebo orally once daily for 12 weeks. The bazedoxifene was included as an active comparator, but was not intended for statistical comparison with the conjugated estrogens/bazedoxifene therapy. Tablets were over-encapsulated to match the placebo capsules. Other medications (eg, investigational drugs; estrogen-, progestin-, androgen-, or SERM-containing medications other than the study drug; medications, remedies, and supplements intended to treat vulvar/vaginal atrophy) were not allowed.

Results:

Primary Endpoint(s):

- Proportion of vaginal superficial cells increased with both doses of conjugated estrogens/bazedoxifene compared with placebo ($P < .01$) and with bazedoxifene versus placebo ($P < .001$). Mean change from baseline was about 6% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, about 4.2% with conjugated estrogens 0.45 mg/bazedoxifene 20 mg, about 1% with bazedoxifene 20 mg, and about 2.2% with placebo.
- Proportion of parabasal cells decreased with both doses of conjugated estrogens/bazedoxifene compared with placebo ($P < .001$) and with bazedoxifene versus placebo ($P < .001$). Mean change from baseline was about -22% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg, about -18% with conjugated estrogens 0.45 mg/bazedoxifene 20 mg, about +10% with bazedoxifene 20 mg, and about -2% with placebo.
- Vaginal pH decreased with both doses of conjugated estrogens/bazedoxifene, but it was only less than placebo in the higher dose group ($P < .01$) and was unchanged in the bazedoxifene and placebo groups.
- Severity of most bothersome vulvar/vaginal symptom was improved over placebo in the higher dosed conjugated estrogens/bazedoxifene group ($P = .048$) and was not significant in the lower dose conjugated estrogens/bazedoxifene group.

Secondary Endpoint(s):

- The average responder rate (women who had vaginal superficial cells greater than 5%, vaginal pH less than 5, and/or improvement in the most bothersome vulvar/vaginal symptom by at least 1 category from baseline) was 81% with conjugated estrogens 0.625 mg/bazedoxifene 20 mg ($P = .005$ vs placebo), 78% with conjugated estrogens 0.45 mg/bazedoxifene 20 mg ($P = .027$ vs placebo), 58% with bazedoxifene 20 mg ($P < .001$ vs placebo), and 66% with placebo.
- Improvement in sexual function, vaginal lubrication, and treatment satisfaction questionnaires occurred with both conjugated estrogens/bazedoxifene groups, but no change was observed in the overall total Arizona Sexual Experiences Scale score.

Comments: Standard study duration for this type of study. Endpoints included vaginal symptoms associated with menopause, not vasomotor symptoms.

Limitations: Short-term study (12 weeks) in a mainly White postmenopausal female population.

Indication: Prevention of Postmenopausal Osteoporosis in Women With a Uterus

Studies

Drug: Conjugated Estrogens/Bazedoxifene vs Raloxifene vs Placebo

Reference: Lindsay R, et al, 2009 (SMART-1)³¹⁻³⁵

Study Design: Phase 3, randomized, double-blind, multicenter, placebo-controlled and active comparator study

Study Funding: Wyeth Research

Patients: 3,397 healthy postmenopausal women with intact uterus were enrolled from 94 sites in the United States, Europe, and Brazil and took at least one dose of study medication. Women were 40 to 75 years of age with a BMI of 32.2 kg/m² or less and no evidence of endometrial hyperplasia. Treatment with oral drugs containing estrogen, progestin, androgen, or SERMs; transdermal hormone products; or intrauterine progestins were allowed within 8 weeks of screening. Vaginal hormone products were allowed within 4 weeks, progestin implants/injectables or estrogen pellets/injectables within 6 months, intrauterine devices within 12 weeks, or an investigational drug within

60 days. In substudy 1 ($n = 1,454$), the average age of the patients was 58 years, 78% were White and 20% were Black, average BMI was 26 kg/m², and average time from last menstrual period was 11 years. In substudy 2 ($n = 861$), the average age of the patients was 52 years, 80% were White and 12.5% were Black, average BMI was 26 kg/m², and average time from last menstrual period was 3 years. The primary efficacy endpoint was evaluated using the modified intent-to-treat cohort with last observation carried forward while on therapy method used for missing data.

Intervention: Computer randomization to treatment with 1 of 8 treatment regimens: conjugated estrogens 0.625 mg/bazedoxifene 10 mg, conjugated estrogens 0.625 mg/bazedoxifene 20 mg, conjugated estrogens 0.625 mg/bazedoxifene 40 mg, conjugated estrogens 0.45 mg/bazedoxifene 10 mg, conjugated estrogens 0.45 mg/bazedoxifene 20 mg, conjugated estrogens 0.45 mg/bazedoxifene 40 mg, raloxifene 60 mg, or placebo orally once daily for 2 years. Supplemental calcium and vitamin D (*Caltrate 600*), determined based on estimated daily calcium intake at the time of randomization, were used to maintain a target calcium intake of 1,000 to 1,600 mg. The raloxifene was included as an active comparator. Tablets were over-encapsulated to match the placebo capsules. Other medications that could affect bone or calcium metabolism (eg, glucocorticoids, calcitonin, anabolic steroids, parathyroid hormone, fluoride, bisphosphonates, daily nonsteroidal anti-inflammatory drugs, regular use of laxatives, diuretics, antihypertensive agents containing diuretics, thyroid replacement agents, anti-thyroid medications) were not allowed.

Results:**Primary Endpoint(s):**

- Endometrial hyperplasia at 12 months was less than 1% with all doses of conjugated estrogens/bazedoxifene, except the conjugated estrogens 0.625 mg/bazedoxifene 10 mg, with a pre-defined acceptable limit of 2% or less.
- Mean percent change in baseline bone mineral density (BMD) of lumbar spine by dual-energy x-ray absorptiometry at 12 months:
 - Substudy 1: Mean annual percent change with conjugated estrogens/bazedoxifene produced +0.51% to +1.59%, raloxifene produced +0.79%, and placebo produced -1.08%. A greatest change occurred with conjugated

estrogens (0.625 or 0.45 mg)/bazedoxifene 10 mg than with raloxifene ($P < .05$).

- Substudy 2: Mean annual percent change with conjugated estrogens/bazedoxifene produced +0.55% to +1.60%, raloxifene produced -0.07%, and placebo produced -1.41%. A greater change occurred with conjugated estrogens 0.625 mg/bazedoxifene 10 mg ($P < .001$), conjugated estrogens 0.45 mg/bazedoxifene 10 mg ($P < .01$), and conjugated estrogens 0.45 mg/bazedoxifene 20 mg ($P < .01$).

Secondary Endpoint(s):

- BMD of hip sites:
 - Substudy 1: The various doses of conjugated estrogens/bazedoxifene (increased BMD) were better than placebo (decreased BMD) from baseline to months 12 and 24. The difference from raloxifene was significant for the conjugated estrogens 0.625 mg/bazedoxifene 10 mg, conjugated estrogens 0.45 mg/bazedoxifene 10 mg, and conjugated estrogens 0.625 mg/bazedoxifene 20 mg groups at 24 months ($P < .05$).
 - Substudy 2: The various doses of conjugated estrogens/bazedoxifene (increased BMD) were better than placebo (decreased BMD) from baseline to months 12 and 24. The difference from raloxifene was significant for the conjugated estrogens 0.625 mg/bazedoxifene 10 mg, conjugated estrogens 0.45 mg/bazedoxifene 10 mg, and conjugated estrogens 0.45 mg/bazedoxifene 20 mg groups at 24 months ($P < .05$).
- Lumbar spine BMD responder rates (no change or an increase in BMD from baseline) at 24 months:
 - Substudy 1: 63% to 76% with the various doses of conjugated estrogens/bazedoxifene, 59% with raloxifene, and 30% with placebo. The difference from raloxifene was significant for the conjugated estrogens 0.625 mg/bazedoxifene 10 mg and conjugated estrogens 0.45 mg/bazedoxifene 10 mg groups.
 - Substudy 2: 61% to 76% with the various doses of conjugated estrogens/bazedoxifene, 51% with raloxifene, and 31% with placebo. The difference from raloxifene was significant for all conjugated estrogens/bazedoxifene groups at month 12 ($P < .01$) and all of the conjugated estrogens/bazedoxifene groups at month 24 except for 3 groups ($P < .05$).

- Cumulative amenorrhea occurred in more than 83% of the patients treated with conjugated estrogens 0.45 mg/bazedoxifene 20 mg, conjugated estrogens 0.45 mg/bazedoxifene 40 mg, conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and conjugated estrogens 0.625 mg/bazedoxifene 40 mg during cycles 1 to 13 and in more than 93% during cycles 10 to 13 and was similar to rates observed in placebo-treated patients. The incidence of bleeding or spotting was comparable with those seen in the placebo group.
- Endometrial hyperplasia at 24 months was less than 1% with conjugated estrogens 0.45 mg/bazedoxifene 20 mg, conjugated estrogens 0.45 mg/bazedoxifene 40 mg, conjugated estrogens 0.625 mg/bazedoxifene 20 mg, and conjugated estrogens 0.625 mg/bazedoxifene 40 mg. The rate of hyperplasia was 7.14% with conjugated estrogens 0.625 mg/bazedoxifene 10 mg and 2.53% with conjugated estrogens 0.45 mg/bazedoxifene 10 mg.
- Conjugated estrogens 0.45 mg/bazedoxifene 20 mg and conjugated estrogens 0.625 mg/bazedoxifene 20 mg reduced the frequency and severity of hot flashes and improved measures of vaginal atrophy compared with placebo. The incidence of breast pain was similar to placebo, and neither dosage combination affected mammographic breast density.

Comments: This is a large multinational study in postmenopausal women that was divided into several substudies. Substudy 1 focused on women who were more than 5 years natural postmenopausal with a screening BMD T-score at lumbar spine or total hip between -1 and -2.5 (inclusive) and at least 1 additional risk factor for osteoporosis conducted at 40 study sites. Substudy 2 focused on women who were between 1 and 5 years postmenopausal with at least 1 risk factor for osteoporosis conducted at 25 study sites. These 2 substudies were conducted because the difference in bone loss between these 2 populations might be different; the greater loss in those women immediately after menopause compared with those enrolled in later years. The primary analysis of BMD for substudy 1 included 1,295 (89%) women and substudy 2 included 783 (91%) women. The change in lumbar spine BMD increased more with the higher dose of conjugated estrogen, was largest with the lowest dose of bazedoxifene (10 mg), and tended to attenuate as the dose of bazedoxifene increased.

All doses of conjugated estrogens/bazedoxifene and raloxifene produced better changes in lumbar spine BMD than placebo.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Contraindications for the use of conjugated estrogens and bazedoxifene include undiagnosed abnormal uterine bleeding; known, suspected, or past history of breast cancer; known or suspected estrogen-dependent neoplasia; active or past history of venous thromboembolism; active or past history of arterial thromboembolism; hypersensitivity (angioedema, anaphylaxis) to estrogens, bazedoxifene, or any tablet ingredient (calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, ascorbic acid, sucrose palmitic acid ester, hydroxyethylcellulose, titanium dioxide, red iron oxide, yellow iron oxide, black iron oxide, povidone, polydextrose, maltitol, poloxamer 188, propylene glycol, isopropyl alcohol); known hepatic impairment or disease; known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders; and pregnancy, women who may become pregnant, and breast-feeding women.¹

Warnings and Precautions

Boxed Warnings

The *Duavee* label contains the required boxed warning for estrogens. These warnings include the following: use of additional estrogens is not recommended; use of unopposed estrogens in women with a uterus is associated with an increased risk of endometrial hyperplasia. All patients should be using direct or random endometrial sampling when indicated. Development of undiagnosed persistent or recurring abnormal genital bleeding in a postmenopausal woman using estrogens should be evaluated for a malignancy; estrogens should not be used to prevent cardiovascular disease or dementia; risk of stroke and deep vein thrombosis (DVT) is increased with estrogen therapy in older women; and risk of probable dementia may be increased in postmenopausal women 65 years and older treated with estrogens.

Other Warnings and Precautions

Coadministration with progestins, additional estrogens, or additional estrogen agonists/antagonists is not recommended.¹

Cardiovascular disorders, including venous thromboembolism, pulmonary thromboembolism, stroke, and retinal vascular thrombosis, may occur during treatment with estrogen agonists or estrogens. The risk of these cardiovascular complications is increased in patients treated with estrogen agonists/antagonists or estrogens. If stroke or DVT occurs or is suspected, the conjugated estrogens/bazedoxifene therapy should be discontinued immediately. Women requiring surgery that is associated with increased risk of thromboembolism should discontinue the combination therapy at least 4 to 6 weeks before the surgery, if possible. Prolonged immobilization may also increase the risk of thromboembolisms. Retinal vascular thrombosis may occur with estrogen therapy. If the patient experiences a sudden partial or complete loss of vision or develops a sudden onset of proptosis, diplopia, or migraine, therapy should be discontinued pending examination. If the problem was caused by papilledema or retinal vascular lesions, therapy with conjugated estrogens/bazedoxifene should be permanently discontinued.¹

Malignant neoplasms, including endometrial cancer, breast cancer, and ovarian cancer, may occur with estrogen therapy. The risk of endometrial cancer is increased when unopposed estrogen therapy is used in women with a uterus, especially if treatment is beyond 1 year.¹ The bazedoxifene component of *Duavee* should reduce the risk of endometrial hyperplasia associated with the use of the conjugated estrogens alone.^{1,36} Development of undiagnosed persistent or recurring abnormal genital bleeding in a postmenopausal woman using estrogens should be evaluated for malignancy. Use of estrogen only is associated with an increased risk of ovarian cancer and abnormal mammograms. The risk of ovarian cancer or breast cancer with the combination of conjugated estrogens and bazedoxifene is unknown.¹

Estrogens increase the risk of gallbladder disease. Estrogen therapy has also been associated with fluid retention; hypocalcemia; elevated blood pressure; hereditary angioedema; exacerbation of asthma, diabetes mellitus, epilepsy, migraine, or porphyria; systemic lupus erythematosus; and hepatic hemangioma.¹

Discontinue estrogen if severe hypertriglyceridemia or cholestatic jaundice occurs. Severe hypertriglyceridemia can cause pancreatitis.¹

Monitor thyroid function in women on thyroid replacement therapy. Estrogen therapy can increase thyroid-binding globulin levels and decrease the amount of circulating thyroid, requiring an adjustment in the dose of the patient's thyroid medication.¹

The risk of dementia may be increased in women older than 65 years who receive estrogen therapy. A probable increased risk of dementia was noted in this patient population in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative.¹

Women with a BMI higher than 27 kg/m² treated with conjugated estrogens/bazedoxifene may be at increased risk of developing endometrial hyperplasia.¹

The combination of conjugated estrogens/bazedoxifene is not indicated for use in premenopausal women. Safety and effectiveness in this patient population have not been evaluated.¹

The combination of conjugated estrogens/bazedoxifene is classified as Pregnancy Category X. The drug is a potential teratogen and should not be used in women who are or may become pregnant.¹

Use in breast-feeding women is not recommended. It is not known whether the drug is excreted in breast milk. Estrogen levels are detectable in the milk of women receiving conjugated estrogens. In addition, the estrogen may decrease the quantity and quality of the milk.¹

ADVERSE REACTIONS

The most commonly reported adverse reactions are muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain (see **Table 1**).¹

DRUG INTERACTIONS

No drug-drug interactions studies have been conducted with *Duavee*. However, one of the routes of elimination of estrogens is via CYP3A4 metabolism.

Therefore, CYP3A4 inhibitors (eg, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, grapefruit juice) may decrease the metabolism of conjugated estrogens and increase the risk of adverse reactions, including endometrial hyperplasia. CYP3A4 inducers (eg, St. John's wort, phenobarbital, carbamazepine, rifampin) may increase the rate of metabolism and decrease the estrogens' therapeutic effect and/or changes in uterine bleeding.¹ Bazedoxifene is metabolized by UGT in the intestinal tract and liver.¹ UGT inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) may increase the metabolism of bazedoxifene and may increase the risk of endometrial hyperplasia.¹

Administration of conjugated estrogens/bazedoxifene with ibuprofen, atorvastatin, azithromycin, and aluminum and magnesium hydroxide had little effect on bazedoxifene C_{max} and AUC (see **Table 2**), and bazedoxifene had little effect on the absorption of other drugs (see **Table 3**).

DOSING

The recommended dose for both indications is 1 tablet orally once daily.¹

The safety and effectiveness of the combination of conjugated estrogens/bazedoxifene was not evaluated in women 75 years and older or in patients with renal impairment. Use of conjugated estrogens/bazedoxifene in these patient populations is not recommended.¹

PRODUCT AVAILABILITY AND STORAGE

Each *Duavee* tablet contains conjugated estrogens 0.45 mg and bazedoxifene 20 mg. The tablets are supplied in packages that contain 2 blisters of 15

Table 1. Adverse reactions more common with conjugated estrogens/bazedoxifene than placebo in placebo-controlled trials¹

Adverse reactions	Conjugated estrogens/bazedoxifene (n = 1,224)	Placebo (n = 1,069)
Muscle spasms	9%	6%
Nausea	8%	5%
Diarrhea	8%	5%
Dyspepsia	7%	6%
Abdominal pain	7%	5%
Oropharyngeal pain	7%	6%
Neck pain	5%	4%
Dizziness	5%	3%

Table 2. Effect of concurrent drug administration on bazedoxifene levels and absorption¹

Drug	Bazedoxifene	
	Change in C _{max}	Change in AUC
Ibuprofen	Increased 18%	Increased 7%
Atorvastatin	Decreased 3%	Increased 6%
Azithromycin	Increased 6%	Decreased 15%
Aluminum and magnesium hydroxide	Decreased 8%	Increased 7%

Note: AUC = steady-state area under the curve; C_{max} = peak plasma concentrations.

Table 3. Effect of bazedoxifene administration on C_{max} and absorption of other drugs¹

Drug	Change in C _{max}	Change in AUC
Conjugated estrogens		
Unconjugated estrone	Increased 11%	Increased 3%
Unconjugated equilin	Increased 17%	Increased 14%
Ibuprofen	Increased 6%	Unchanged
Atorvastatin	Decreased 14%	Unchanged

Note: AUC = steady-state area under the curve; C_{max} = peak plasma concentrations.

tablets each. The product should be stored between 20°C and 25°C (68°F and 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). The tablets should be protected from moisture and should not be removed from the blister until immediately before use. The product should be used within 60 days of opening the foil pouch.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for conjugated estrogens/bazedoxifene.

CONCLUSION

Conjugated estrogens/bazedoxifene is a combination estrogen and SERM indicated for the treatment of moderate to severe vasomotor symptoms (eg, hot flashes) associated with menopause in postmenopausal women with a uterus and for the prevention of postmenopausal osteoporosis in women with a uterus. Bazedoxifene is a replacement for the traditional progestin component of previous estrogen combination products. It appears that bazedoxifene is able to decrease the risk of endometrial changes reported with unopposed estrogen therapy, without increasing the risk of breast cancer that may occur with estrogen and estrogen/progestin therapy.

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