BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DUAVEE® (conjugated estrogens-bazedoxifene) oral Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Duavee (conjugated estrogens-bazedoxifene) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Request is for a woman 18 to 75 years of age with an intact uterus

2. Individual has a confirmed diagnosis of **ONE** of the following in a woman with a uterus:
   a. Treatment of moderate to severe vasomotor symptoms (e.g., hot flashes, night sweats) associated with menopause in an individual having a minimum average of 7 moderate to severe vasomotor symptoms per day

   b. Prevention of postmenopausal osteoporosis

3. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following:
    a. For treatment of moderate to severe vasomotor symptoms associated with menopause **BOTH** of the following:
        i. **TWO** trials of a low-dose estrogen product (vaginal, oral or transdermal) containing conjugated estrogen or estradiol (e.g., vaginal ring, vaginal insert, or vaginal cream) (see Definitions section)
        ii. **ONE** trial of low dose paroxetine **or** low dose citalopram or low dose escitalopram
    b. For prevention of postmenopausal osteoporosis is **ONE** of the following: (see Definitions section)
        i. **TWO** trials of a bisphosphonate (e.g., alendronate, IV zoledronic acid, etc.)
        ii. Trial of a denosumab product

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. There are **NO** FDA-label contraindications such as:
    a. Undiagnosed abnormal uterine bleeding
    b. Known, suspected, or past history of breast cancer
    c. Known or suspected estrogen-dependent neoplasia
    d. Active or past history of venous thrombosis or pulmonary embolism
    e. Active or past history of arterial thromboembolic disease (such as stroke, myocardial infarction)
    f. Hypersensitivity (angioedema, anaphylaxis) to estrogens, bazedoxifene, or any ingredients
    g. Known hepatic impairment or disease
    h. Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders
    i. Woman who is pregnant

6. Will not be used in an individual with renal impairment

7. Will not be used in a premenopausal woman

8. Individual is not using additional progestins, estrogens, or estrogen agonist/antagonists

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Duavee (conjugated estrogens-bazedoxifene) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual has documentation of positive clinical response to therapy defined as **ONE** of the following:
    a. Achieved and maintains at least a 50% reduction in frequency and severity of vasomotor symptoms
    b. Reduction in the risk of osteoporosis is defined as **ONE** of the following:
        i. Increase in lumbar spine bone mineral density
        ii. Increase in total hip bone mineral density

2. Individual has been adherent with the medication

3. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Contraindications as listed in the criteria for initial therapy
    b. Cardiovascular disorders, including venous thromboembolism, pulmonary embolism, stroke, and retinal vascular thrombosis
    c. Malignant neoplasms, including endometrial cancer, breast cancer, and ovarian cancer
    d. Gallbladder disease
    e. Cholestatic jaundice
    f. Sudden vision loss (partial or complete) or sudden proptosis, diplopia, or migraine
    g. Papilledema or retinal vascular lesions
    h. Severe hypertriglyceridemia
    i. Pancreatitis

5. Will not be used in an individual with renal impairment

6. Will not be used in a premenopausal woman

7. Individual is not using additional progestins, estrogens, or estrogen agonist/antagonists

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of Non-Cancer Medications**

    2. **Off-Label Use of Cancer Medications**

Description:

Duavee (conjugated estrogens-bazedoxifene) is a combination conjugated estrogens with an estrogen agonist/antagonist indicated in women with a uterus for treatment of moderate to severe symptoms associated with menopause and it is indicated in women with a uterus for the prevention of postmenopausal osteoporosis. 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.

Menopausal symptoms include hot flushes and night sweats but may also include other symptoms such as sleep disturbance, joint aches, irritability, mood changes, and genitourinary problems. Numerous studies have been conducted that show the efficacy of hormonal replacement therapy in controlling menopausal symptoms. Estrogen-containing products are the most effective FDA-approved therapies for treatment of moderate to severe vasomotor symptoms (such as hot flashes and night sweats) associated with menopause and for treatment of

moderate to severe symptoms of vulvar and vaginal atrophy (such as dryness, itching, and burning) associated with menopause. Estrogen alone may be prescribed for women who have undergone a hysterectomy. In women with an intact uterus, a progestational agent should be added to the estrogen to protect the endometrium from the risk of unopposed estrogen causing development of hyperplasia and endometrial cancer.

For women who cannot use estrogen for control of severe vasomotor symptoms, non-estrogen containing medications have been used. Other agents that have been shown to be effective in the management of menopausal symptoms include other selective serotonin receptor inhibitors such as citalopram, escitalopram, fluoxetine, and paroxetine and venlafaxine, a selective serotonin norepinephrine reuptake inhibitor.

Postmenopausal osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing the individual to an increased risk of fracture. Measurement of bone density is the primary method for the pre-fracture diagnosis of osteoporosis and for monitoring treatment; it is based on obtaining a bone mineral density (BMD) that is expressed as a T-score that compares the individual's BMD with the mean value for young normal persons and expresses the difference as a standard deviation score. Treatment is recommended for postmenopausal women with a hip or spine fracture (clinical or radiographic), a T-score of -2.5 or worse at the spine, femoral neck, or total hip, and a T-score between-1 and -2.5 at high 10-year risk of fracture with use of the US-adapted Fracture Risk Assessment (FRAX) tool treatment is considered cost-effective if the 10-year risk is 3% or more for hip fracture or 20% or more for major osteoporosis-related fracture (humerus, forearm, hip, or clinical vertebral fracture). Oral agents approved by the FDA for prevention or treatment of osteoporosis include bisphosphonates (alendronate, ibandronate, and risedronate), estrogen, and raloxifene. All these drugs act by reducing bone resorption.

Duavee (conjugated estrogens-bazedoxifene) pairs conjugated estrogens with bazedoxifene an estrogen agonist/antagonist.

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. 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 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.

The use of estrogen-alone has been reported to result in an increase in abnormal mammograms requiring further evaluation. The effect of treatment with Duavee (conjugated estrogens-bazedoxifene) on the risk of breast cancer is unknown. In some epidemiological studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. The effect of treatment with Duavee (conjugated estrogens-bazedoxifene) on the risk of ovarian cancer is unknown.

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Estrogens: (not an all inclusive list)

- Oral estrogen tabs:
  - Conjugated estrogen (such as Premarin)
  - Esterified estrogen (such as Menest)
  - Estradiol (such as Estrace)
  - Estropipate
- Transdermal estrogen:
  - Estradiol transdermal (such as Alora, Climara, Vivelle-Dot)
- Vaginal estrogen:
  - Conjugated estrogen cream (such as Premarin)
  - Estradiol acetate cream (such as Estrace)
  - Estradiol acetate ring (such as Femring)
  - Estradiol tablet (such as Vagifem)
- Esterified Estrogen-Progestin, oral tabs (such as Prempro, Premphase, Mimvey)
- Estrogen-Progestin, transdermal (such as CombiPatch)

Progestins, if needed:

- Medroxyprogesterone
- Micronized progesterone

Bisphosphonates: (not an all inclusive list)

- Alendronate
- Risedronate
- Zoledronic acid

Selective estrogen receptor modulator:

- Raloxifene brand or generic
- Osphena (ospemifene)

Neurokinin 3 (NK3) receptor antagonist:

- Veozah (fezolinetant)

World Health Organization definitions for osteoporosis:

T-Scores are reported as standard deviations (SD):

Normal:	T-score of -1 or better
Osteopenia:	T-score of -1 to -2.5
Osteoporosis:	T-score of -2.5 or worse
Severe Osteoporosis:	T-score of -2.5 or worse with fragility fractures

Fracture Risk Assessment Tool (FRAX tool):

The World Health Organization developed a risk assessment tool to assist providers in evaluating osteopenic individuals. The tool uses clinically proven risk factors to determine a 10-year probability of hip fracture and a

10-year probability for a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fractures). Treatment may be considered if the 10-year risk is 3% or more for hip fracture or if the risk for other bone fracture is 20% or more.

The tool can be viewed at www.shef.ac.uk/FRAX.

Risk factors associated with the development of postmenopausal osteoporosis:

- Early menopause
- Moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women)
- Thin body build
- Caucasian or Asian race
- Family history of osteoporosis

Risk factors associated with development of fracture:

- Previous fragility fracture of spine, hip, forearm, or shoulder
- Significantly low bone mass
- Frequent falls
- Limited movement
- Medical conditions likely to cause bone loss
- Medicines that may cause bone loss, e.g., seizure medicines, blood thinners, corticosteroids, high doses of vitamins A or D

Fragility fracture:

A fracture occurring spontaneously or after a minor trauma

Guide for Pharmacologic Intervention in Postmenopausal Females & Males 50 years of age or older:

History of hip or vertebral fracture
T-score of -2.5 or worse (DVA) at the femoral neck or spine, after exclusion of secondary causes
T-score of -1 to -2.5 at the femoral neck or spine, and a 10-year probability of hip fracture of ≥ 3% or a 10-year probability of any major osteoporosis related fracture of ≥ 20% based upon the United States adapted WHO algorithm

Conditions where Oral Biphosphonate should not be used: [IV Biphosphonate can be used]

- Patients with esophageal disorders (achalasia, scleroderma involving the esophagus, esophageal strictures, varices)
- Certain types of bariatric surgery in which surgical anastomoses are present in the gastrointestinal (GI) tract (e.g., Roux-en-Ygastric bypass)
- GI intolerance to oral bisphosphonates
- Inability to follow the dosing requirements of oral bisphosphonates, including an inability to sit upright for 30 to 60minutes and/or to swallow a pill

Resources:

Duavee (conjugated estrogens-bazedoxifene) product information, revised U.S. Pharmaceuticals. 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

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