



PHARMACY COVERAGE GUIDELINES  
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/17/2016  
LAST REVIEW DATE: 11/18/2021  
LAST CRITERIA REVISION DATE: 11/18/2021  
ARCHIVE DATE:

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## DUAVEE® (conjugated estrogens-bazedoxifene) oral

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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com). **Incomplete forms or forms without the chart notes will be returned.**

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### Criteria:

- **Criteria for initial therapy:** Duavee (conjugated estrogens-bazedoxifene) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
1. A woman 18 to 74 years of age with an intact uterus
  2. A confirmed diagnosis of **ONE** of the following:
    - a. Moderate to severe vasomotor symptoms associated with menopause
    - b. Prevention of postmenopausal osteoporosis in a woman with or without an osteoporotic fracture or in a woman at high risk for an osteoporotic fracture
  3. Individual has failure, contraindication per FDA label or intolerance to the following:
    - a. For treatment of moderate to severe vasomotor symptoms associated with menopause use of **TWO** of the following (Note: a woman with an intact uterus should use estrogen product with a progestin; a progestin is not needed if the woman has had a hysterectomy):
      - i. Oral estrogen tabs:
        1. Conjugated estrogen (such as Premarin)
        2. Estradiol (such as Estrace)
        3. Estropipate
      - ii. Transdermal estrogen:
        1. Estradiol transdermal (such as Minivelle, Climara, Vivelle-Dot)
      - iii. Esterified Estrogen-Progestin, oral tabs (such as Prempro, Premphase, Mimvey)
      - iv. Progestins, if needed:
        1. Medroxyprogesterone acetate
        2. Micronized progesterone
    - b. For prevention of postmenopausal osteoporosis use of a **1 bisphosphonate** and **1** selective estrogen receptor modulator (**SERM**):
      - i. Oral bisphosphonate tabs:
        1. Alendronate
        2. Ibandronate
        3. Risedronate
      - ii. Oral SERM tabs:
        1. Evista (raloxifene)
        2. Raloxifene HCl
  4. 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 thromboembolism or pulmonary embolism
    - e. Active or past history of arterial thromboembolism (such as stroke, myocardial infarction)
    - f. Hypersensitivity (angioedema, anaphylaxis) to estrogens, bazedoxifene, or any ingredients



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- 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
5. Will not be used in an individual with renal impairment
6. Will not be used in an individual with normal ovarian function
7. There are no significant interacting drugs

**Initial approval duration:** 12 months

➤ **Criteria for continuation of coverage (renewal request):** Duavee (conjugated estrogens-bazedoxifene) is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:

1. Individual's response while on therapy is **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
    - iii. No evidence of bone fracture(s)
2. Individual has been adherent with the medication
3. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
  - a. Contraindications as listed in the criteria for initial therapy
  - b. Significant adverse effect such as:
    - i. Cardiovascular disorders, including venous thromboembolism, pulmonary embolism, stroke, and retinal vascular thrombosis
    - ii. Malignant neoplasms, including endometrial cancer, breast cancer, and ovarian cancer
    - iii. Gallbladder disease
    - iv. Cholestatic jaundice
    - v. Vision loss
    - vi. Severe hypertriglyceridemia
4. There are no significant interacting drugs

**Renewal duration:** 12 months

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- 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 a Non-cancer Medications**
  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**
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### 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 flashes 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.

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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)  $\alpha$  and  $\beta$ , which vary in proportion from tissue to tissue. Conjugated estrogens are composed of multiple estrogens and are agonists of ER-  $\alpha$  and  $\beta$ . 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,  $17\alpha$ -dihydroequilin,  $17\alpha$ -estradiol, and  $17\beta$ -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:**

#### **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](http://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)

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- 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 $\geq 3\%$ or a 10-year probability of any major osteoporosis related fracture of $\geq 20\%$ 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-Y gastric bypass)
- GI intolerance to oral bisphosphonates
- Inability to follow the dosing requirements of oral bisphosphonates, including an inability to sit upright for 30 to 60 minutes and/or to swallow a pill

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### Resources:

Duavee (conjugated estrogens-bazedoxifene) product information, revised U.S. Pharmaceuticals. 12-2019. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed September 10, 2021.

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