DUAVEE® (conjugated estrogens-bazedoxifene) oral tablet

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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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. 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.

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:

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

Drug related events:
Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be
documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

**Precertification:**
Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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).
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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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Duavee (conjugated estrogens-bazedoxifene) requires completion of the specific request form in its entirety. 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. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) for an initial request for Duavee (conjugated estrogens-bazedoxifene) is considered medically necessary when ALL of the following criteria are met:

1. Individual is 18 to 74 years of age

2. Medical record documentation of a confirmed diagnosis of ONE of the following:
   - Treatment of moderate to severe vasomotor symptoms associated with menopause
   - Prevention of postmenopausal osteoporosis with ONE of the following:
     - T-score of -2.5 or worse (e.g., -3.0, -3.5)
     - T-score at the lumbar spine, total hip or femoral neck between -1.0 and -2.5 at high 10-year risk of fracture using the US-adapted FRAX tool available at www.shef.ac.uk/FRAX (≥ 3% for hip fracture or ≥ 20% for a major osteoporosis-related fracture)
     - Presence or history of osteoporotic fracture

3. Medical record documentation that the individual is unable to use ALL of the following due to a failed response, significant adverse drug event or contraindication:
   - For treatment of moderate to severe vasomotor symptoms associated with menopause:
     - Estrogen, oral tabs
       - Conjugated estrogen (such as Premarin)
       - Estradiol (such as Estrace)
       - Estropipate
     - Estrogen, transdermal
       - Estradiol transdermal (such as Menostar, Minivelle, Climara, Vivelle-Dot)
     - Esterified Estrogen-Progestin, oral tabs (such as Prempro, Premphase, Mimvey)
   - For prevention of postmenopausal osteoporosis:
     - Biphosphonate
       - Alendronate
       - Ibandronate
       - Risedronate
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- Selective estrogen receptor modulator, oral tabs
  - Evista (raloxifene)
  - Raloxifene HCl
- Estrogen, oral tabs
  - Conjugated estrogen (such as Premarin)
  - Estradiol (such as Estrace)
  - Estropipate
- Estrogen, transdermal
  - Estradiol transdermal (such as Menostar, Minivelle, Climara, Vivelle-Dot)
- Esterified Estrogen-Progesterin, oral tabs (such as Prempro, Premphase, Mimvey)

4. Absence of ALL of the following contraindications:
   - 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 or pulmonary embolism
   - Active or past history of arterial thromboembolism (such as stroke, myocardial infarction)
   - Hypersensitivity (angioedema, anaphylaxis) to estrogens, bazedoxifene, or any ingredients
   - Known hepatic impairment or disease
   - Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders
   - Woman who is pregnant
   - Woman of child bearing potential who may become pregnant, unless uses adequate contraception
   - Woman breast feeding an infant or child

5. Absence of ALL of the following exclusions:
   - Simultaneous use with another estrogen containing product
   - Simultaneous use with another progestin containing product
   - History of cholestatic jaundice
   - Woman without a uterus
   - Woman with renal impairment
   - Woman 75 years of age or older
   - Premenopausal woman

➢ Continuation of coverage for Duavee for members already approved by BCBSAZ, is considered medically necessary with documentation of ALL of the following:

1. The individual has benefited from therapy but remains at risk for development of ONE of the following:
   - Moderate to severe vasomotor symptoms associated with menopause
   - Osteoporotic fracture

2. The condition has not progressed or worsened on therapy

3. The individual has not developed any contraindications or other exclusions to its continued use
Duavee (conjugated estrogens-bazedoxifene) for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

Resources:


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Duavee is a combination of conjugated estrogens with an estrogen agonist/antagonist indicated for treatment of the following conditions in women with a uterus:</td>
<td>Take one tablet orally once daily</td>
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<tr>
<td>• Treatment of moderate to severe vasomotor symptoms associated with menopause</td>
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<tr>
<td>• Prevention of postmenopausal osteoporosis</td>
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<tr>
<td>Limitation of Use: Duavee should be used for the shortest duration consistent with treatment goals and risks for the individual woman</td>
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