



PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/17/16
LAST REVIEW DATE: 11/16/17
LAST CRITERIA REVISION DATE: 11/16/17
ARCHIVE DATE:

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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

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.

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. **Incomplete forms or forms without the chart notes will be returned.**

**PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS**

**ORIGINAL EFFECTIVE DATE: 11/17/16
LAST REVIEW DATE: 11/16/17
LAST CRITERIA REVISION DATE: 11/16/17
ARCHIVE DATE:**

DUAVEE® (conjugated estrogens-bazedoxifene) oral tablet (cont.)

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.

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, 17 α -dihydroequilin, 17 α -estradiol, and 17 β -dihydroequilin.

DUAVEE® (conjugated estrogens-bazedoxifene) oral tablet (cont.)

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.

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

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/17/16
LAST REVIEW DATE: 11/16/17
LAST CRITERIA REVISION DATE: 11/16/17
ARCHIVE DATE:

DUAVEE® (conjugated estrogens-bazedoxifene) oral tablet (cont.)

Fragility fracture:

A fracture occurring spontaneously or after a minor trauma

Duavee (conjugated estrogens-bazedoxifene)

Medication class:

Estrogen derivative and a selective estrogen receptor modulator (SERM)

FDA-approved indication(s):

- Prevention of postmenopausal osteoporosis in women with a uterus
- Treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus

Recommended Dose:

- One tablet daily

Maximum dosage

- One tablet daily

Available Dosage Forms:

- 0.45 mg conjugated estrogens / 20 mg bazedoxifene tablets

Limitations of use:

- Duavee (conjugated estrogens-bazedoxifene) should be used for the shortest duration consistent with treatment goals and risks for the individual woman

Warnings and Precautions:

- Use for the shortest duration consistent with treatment goals and risks for the individual woman
- Should not be used in a woman without a uterus
- Should not be used with another estrogen containing product
- Should not be used with another progestin containing product
- Should not be used with another selective estrogen receptor modulator such as Ospheña (ospemifene), Evista (raloxifene) and its generic
- It has not been studied in women 75 years of age or older and is not recommended in this population
- It has not been studied in women with renal impairment and is not recommended in this population
- Women taking Duavee for prevention of postmenopausal osteoporosis should add supplemental calcium and/or vitamin D to their diet if daily intake is inadequate
- It has not been studied in women with impaired liver function or past history of cholestatic jaundice
- Use in a patient with renal impairment is not recommended
- The safety and efficacy of Duavee have not been established for use in premenopausal woman and use is not recommended
- Discontinue if a stroke occurs
- Discontinue if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine
- Permanently discontinue if there is papilledema or retinal vascular lesions
- Discontinue if pancreatitis occurs

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/17/16
LAST REVIEW DATE: 11/16/17
LAST CRITERIA REVISION DATE: 11/16/17
ARCHIVE DATE:

DUAVEE® (conjugated estrogens-bazedoxifene) oral tablet (cont.)

- Duavee must not be used in a woman who is pregnant or may become pregnant
 - Woman who is breast feeding an infant or child should stop breast feeding
 - Absolute bioavailability of bazedoxifene is 6%, uridine diphosphate glucuronosyltransferase (UGT) inducers such as carbamazepine, phenobarbital, phenytoin, or rifampin may reduce bazedoxifene levels
-

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. Individual is 18 to 74 years of age
 2. A confirmed diagnosis of **ONE** of the following:
 - Treatment of moderate to severe vasomotor symptoms associated with menopause
 - 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 or intolerance to preferred step therapy agents:
 - For treatment of moderate to severe vasomotor symptoms associated with menopause use of **two** preferred estrogen products (With a progestin if have an intact uterus or without progestin if the woman has had a hysterectomy):
 - Preferred estrogen, oral tabs
 1. Conjugated estrogen (such as Premarin)
 2. Estradiol (such as Estrace)
 3. Estropipate
 - Preferred estrogen, transdermal
 1. Estradiol transdermal (such as Menostar, Minivelle, Climara, Vivelle-Dot)
 - Esterified Estrogen-Progestin, oral tabs (such as Prempro, Premphase, Mimvey)
 - Preferred progestins, if needed:
 1. Medroxyprogesterone acetate
 2. Micronized progesterone
 - For prevention of postmenopausal osteoporosis use of a **1 bisphosphonate** and **1 preferred SERM** :
 - Preferred bisphosphonates, oral tabs:
 1. Alendronate
 2. Ibandronate
 3. Risedronate
 - Preferred selective estrogen receptor modulator (SERM), oral tabs:
 1. Evista (raloxifene)
 2. Raloxifene HCl
 4. There are **NO** contraindications
 - Contraindications include:
 - Undiagnosed abnormal uterine bleeding
 - Known, suspected, or past history of breast cancer

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/17/16
LAST REVIEW DATE: 11/16/17
LAST CRITERIA REVISION DATE: 11/16/17
ARCHIVE DATE:

DUAVEE® (conjugated estrogens-bazedoxifene) oral tablet (cont.)

- 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

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. 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 indication for use is one that requires a longer duration than the usual and the provider assesses need for continuation of therapy at least yearly
 - Prevention of postmenopausal osteoporosis:
 - Continues to be at high risk for fracture, bone loss is still evident
 - Other alternatives as listed in the criteria for initial therapy section cannot be used
 - Moderate to severe vasomotor symptoms associated with menopause
 - Any previous attempts at discontinuation have failed as seen by recurrence of symptoms
 - Other alternatives as listed in the criteria for initial therapy section cannot be used
 3. Individual has been adherent with the medication
 4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
 - Contraindications as listed in the criteria for initial therapy
 5. There are no significant interacting drugs

Renewal duration: 12 months

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/17/16
LAST REVIEW DATE: 11/16/17
LAST CRITERIA REVISION DATE: 11/16/17
ARCHIVE DATE:

DUAVEE® (conjugated estrogens-basedoxifene) oral tablet (cont.)

Resources:

Duavee. Package Insert. Revised by manufacturer 9/2015. Accessed 9/16/16.

Watts NB, Bilezikian JP, Camacho PM, et al.: American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Osteoporosis. *Endocrine Pract* 2010, 16 (Sup 3 Nov/Dec):1-37

UpToDate: Preparations for menopausal hormone therapy. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/preparations-for-menopausal-hormone-therapy?source=search_result&search=vasomotor%20symptoms%20menopause&selectedTitle=4~150#H595401618

UpToDate: Treatment of menopausal symptoms with hormone therapy. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/treatment-of-menopausal-symptoms-with-hormone-therapy?source=search_result&search=vasomotor%20symptoms%20menopause&selectedTitle=2~150

UpToDate: Menopausal hot flashes. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/menopausal-hot-flashes?source=search_result&search=vasomotor%20symptoms%20menopause&selectedTitle=1~150

UpToDate: Overview of the management of osteoporosis in postmenopausal women. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/overview-of-the-management-of-osteoporosis-in-postmenopausal-women?source=search_result&search=postmenopausal%20osteoporosis&selectedTitle=1~150

UpToDate: The use of bisphosphonates in postmenopausal women with osteoporosis. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/the-use-of-bisphosphonates-in-postmenopausal-women-with-osteoporosis?source=search_result&search=postmenopausal%20osteoporosis&selectedTitle=3~150

UpToDate: Postmenopausal hormone therapy in the prevention and treatment of osteoporosis. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/postmenopausal-hormone-therapy-in-the-prevention-and-treatment-of-osteoporosis?source=search_result&search=postmenopausal%20osteoporosis&selectedTitle=4~150

UpToDate: Selective estrogen receptor modulators for the prevention and treatment of osteoporosis. Current through Sep 2017. https://www.uptodate-com.mwu.idm.oclc.org/contents/selective-estrogen-receptor-modulators-for-prevention-and-treatment-of-osteoporosis?source=search_result&search=prevention%20of%20postmenopausal%20osteoporosis&selectedTitle=9~150

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: _____ Date: _____

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.