PHARMACY COVERAGE GUIDELINE

RAYALDEE® (calcifediol) extended-release oral capsule 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:** Rayaldee (calcifediol) extended release and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist or Endocrinologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of secondary hyperparathyroidism in an individual with stage 3 or 4 chronic kidney disease (CKD) and has a serum total 25-hydroxyvitamin D levels less than 30 ng/mL

4. Individual does not have Stage 2 or Stage 5 CKD or end-stage renal disease on dialysis

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Serum phosphorus, albumin, 25-hydroxyvitamin D, and intact parathyroid hormone (PTH)
    b. Corrected serum calcium is < 9.8 mg/dL before initiation
    c. Serum total 25-hydroxyvitamin D levels are between 10-30 ng/mL

6. **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)

7. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following:
    a. Calcitriol (brand Rocaltrol or generic)
    b. Doxercalciferol (generic)
    c. Paricalcitol (brand Zemplar or generic)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Rayaldee (calcifediol) extended release and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist or Endocrinologist

2. Individual's condition has responded while on therapy with response defined as the following:
    a. Serum total 25-hydroxyvitamin D level is between 30-100 ng/mL
    b. Intact parathyroid hormone (PTH) level is within the desired therapeutic range
    c. Serum calcium (corrected for low albumin) is within the normal range
    d. Serum phosphorus is less 5.5 mg/dL

3. Individual has been adherent with the medication

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. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Severe hypercalcemia
    b. Hypercalciuria
    c. Hyperphosphatemia
    d. Serum 25-hydroxyvitamin D is consistently above 100 ng/mL
    e. Intact parathyroid hormone (PTH) is persistently abnormally low

6. Individual does not have Stage 2 or Stage 5 CKD or end-stage renal disease on dialysis

PHARMACY COVERAGE GUIDELINE

RAYALDEE® (calcifediol) extended-release oral capsule Generic Equivalent (if available)

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:

Rayaldee (calcifediol ER) is a vitamin D3 analog indicated for the treatment of secondary hyperparathyroidism in adult patients with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. It is not indicated for the treatment of secondary hyperparathyroidism in patients with stage 5 CKD or in patients with end-stage renal disease on dialysis.

Calcifediol is also known as calcidiol, 25-hydroxycholecalciferol or 25-hydroxyvitamin D3. Calcifediol is a prohormone of the active form of vitamin D3, calcitriol (or 1, 25-dihydroxyvitamin D3). Calcifediol is converted to calcitriol by cytochrome P450 27B1 (CYP27B1) (also called 1-alpha hydroxylase) primarily in the kidney. Calcitriol binds to the vitamin D receptor in target tissues and activates vitamin D responsive pathways that result in increased intestinal absorption of calcium and phosphorus and reduced parathyroid hormone synthesis.

Secondary hyperparathyroidism is a complication of CKD that can result in considerable morbidity and mortality, including severe bone disease. It is associated with elevated levels of parathyroid hormone (PTH) and phosphorus, and decreased levels of calcium and vitamin D.

Rayaldee (calcifediol ER) has been shown to reduce intact parathyroid hormone (iPTH) levels and increase vitamin D levels.

The major factors responsible for stimulating parathyroid gland function in renal failure are hypocalcemia, diminished 1,25-dihydroxyvitamin D3 levels, and hyperphosphatemia. If physiologic abnormalities are uncorrected, renal bone disease will develop. This disorder can result in weakness, fractures, bone and muscle pain, and avascular necrosis, which most commonly occurs in those undergoing dialysis.

The management of secondary hyperparathyroidism in dialysis patients principally involves the administration of some combination of phosphate binders (either calcium- or non-calcium-containing binders), calcitriol or synthetic vitamin D analogs and a calcimimetic (cinacalcet, etelcalcetide).

Serum calcium, albumin, phosphate, 25-hydroxyvitamin D (25(OH)D), and intact PTH (iPTH) levels are measured initially and then on an ongoing basis.

PHARMACY COVERAGE GUIDELINE

RAYALDEE® (calcifediol) extended-release oral capsule Generic Equivalent (if available)

Definitions:

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

Serum calcium correction for albumin:

Corrected calcium = serum calcium + 0.8 (4 – serum albumin)
Ex. Calcium 9.9 mg/dl; albumin 3.2 gm/dl
Corrected calcium = 9.9 + 0.8 (4 – 3.2)
Corrected calcium = 10.54 (or 10.5 mg/dl)

Stages of CKD:

Stage	GFR (mL/min/1.73 m^2)	
1	≥ 90	Normal kidney or high
2	60-89	Mildly reduced kidney function
3 A	45-59	Mild to moderately reduced kidney function
3 B	30-44	Moderate to severely reduced kidney function
4	15-29	Severely reduced kidney function
5	< 15 or on dialysis	End stage kidney failure (sometimes called established renal failure)
In the absence of evidence of kidney damage, neither Stage 1 nor Stage 2 fulfill the criteria for CKD		

Resources:

Rayaldee (calcifediol) extended-release capsule product information, revised by OPKO Pharmaceuticals, LLC. 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 26, 2024.

Quarles LD, Kendrick J. Management of secondary hyperparathyroidism in adult nondialysis patients with chronic kidney disease. In: UpToDate, Berns JS, Taylor EN (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through December 2024. Topic last updated October 01, 2024. Accessed January 08, 2025.

Quarles LD, Kendrick J. Management of secondary hyperparathyroidism in adult dialysis patients. In: UpToDate, Berns JS, Taylor EN (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through December 2024. Topic last updated July 15, 2024. Accessed January 08, 2025.

Quarles LD, Kendrick J. Management of hyperphosphatemia in adults with chronic kidney disease. In: UpToDate, Berns JS, Taylor EN (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through December 2024. Topic last updated September 27, 2024. Accessed January 08, 2025.