BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
ORIGINAL EFFECTIVE DATE:	**3/15/2018**
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RAYALDEE® (calcifediol) extended-release oral capsule

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.

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.**

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Criteria:

- **Criteria for initial therapy:** Rayaldee (calcifediol) extended release is considered ***medically necessary*** and will be approved when **ALL** of 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. A confirmed diagnosis of secondary hyperparathyroidism defined as persistently elevated or progressively rising serum intact PTH that is above the upper limit of normal for the assay used

  4. Individual has Stage 3 or 4 chronic kidney disease

  5. Individual has failed, or intolerant to, or has a contraindication such that the individual is unable to use **ALL** the following preferred step therapy agents:
     a. Calcitrol (generic for Rocaltrol)
     b. Doxercalciferol (generic for Hectorol)
     c. Paricalcitol (generic for Zemplar)

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

  7. Individual does not have Stage 5 chronic kidney disease or end-stage renal disease on dialysis

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Rayaldee (calcifediol) extended release is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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 and not worsened while on therapy
     a. Response is defined as:
        i. Serum total 25-hydroxyvitamin D level is between 30-100 ng/mL
        ii. Intact parathyroid hormone (PTH) level is within the desired therapeutic range
        iii. Serum calcium (corrected for low albumin) is within the normal range
        iv. Serum phosphorus is < 5.5 mg/dL

  3. Individual has been adherent with the medication

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4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Severe hypercalcemia
        ii. Hypercalciuria
        iii. Hyperphosphatemia
        iv. Serum 25-hydroxyvitamin D is consistently above 100 ng/mL
        v. Intact parathyroid hormone (PTH) is persistently abnormally low

5. There are no significant interacting drugs

Renewal duration: 12 months

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.

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Definitions:

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 (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. 12-2019, at DailyMed http://dailymed.nlm.nih.gov accessed January 26, 2021.

Quarles LD, Berkoben M. Management of secondary hyperparathyroidism in adult nondialysis patients with chronic kidney disease. In: UpToDate, Goldfarb S, Motwani S (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on January 26, 2021.

Quarles LD, Berkoben M. Management of secondary hyperparathyroidism in adult dialysis patients. In: UpToDate, Goldfarb S, Motwani S (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on January 26, 2021.