

Royaldee[®] (calcifediol)

Policy # 00551

Original Effective Date: 04/19/2017

Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Royaldee^{®‡} (calcifediol) to be **eligible for coverage**** when the patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for Royaldee (calcifediol) will be considered when ALL of the following criteria are met:

Initial:

- Patient has a diagnosis of secondary hyperparathyroidism; AND
- Patient is 18 years of age or older; AND
- Patient has stage 3 or 4 chronic kidney disease; AND
- Patient is NOT on dialysis; AND
- Patient's serum total 25-hydroxyvitamin D level is less than 30 ng/mL; AND
- Patient has tried and failed at least TWO generic products for the requested condition (e.g. calcitriol or vitamin D analogs such as doxercalciferol, paricalcitol)
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

Continuation:

- Patient has received an initial approval for the requested medication; AND
- Patient continues to benefit from therapy with the requested medication as attested to by the prescriber.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Royaldee (calcifediol) when the patient has NOT tried and failed at least TWO generic products for the requested condition (e.g. calcitriol or vitamin D analogs such as doxercalciferol, paricalcitol) to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of Royaldee when the patient has not demonstrated a beneficial response to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Royaldee (calcifediol) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****) to be **investigational.***

Policy Guidelines

Stages of Chronic Kidney Disease (CKD)		
Stage	GFR mL/min per 1.73m ²	Terms
Stage 1	≥ 90	eGFR 90 or higher and kidney damage (e.g. uACR 30 or higher) for 3 months or more
Stage 2	60 - 89	eGFR 60-89 and kidney damage (e.g. uACR 30 or higher) for 3 months or more
Stage 3a	45 - 59	Mild to moderate loss of kidney function (eGFR 45-59 for 3 months or more)
Stage 3b	30 - 44	Moderate to severe loss of kidney function (eGFR 30-44 for 3 months or more)

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Stage 4	15 - 29	Severe loss of kidney function (eGFR 15-29 for 3 months or more)
Stage 5	< 15	Kidney failure (eGFR less than 15 for 3 months or more) or patient is on dialysis

*eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio

Background/Overview

Royaldee is approved for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. Other therapies for this condition include calcitriol or vitamin D analogs, such as doxercalciferol capsules and injection (Hectorol®[†]) and paricalcitol capsules and injection (Zemplar®[‡]). Each of these products has a different mechanism of action. Royaldee is an analog of a naturally occurring prohormone of calcitriol and innate negative feedback pathways prevent excessive conversions of Royaldee to calcitriol. Due to the slow rise in calcitriol, it has been proposed that Royaldee may result in lower rates of adverse events. However, there are no comparative data with Royaldee and the other vitamin D analogs to prove whether or not the rates of adverse events differ. There is also no comparative data to prove that Royaldee provides any clinical advantage as compared to the other options for treatment of secondary hyperparathyroidism. To note, other vitamin D analogs are approved for use in patients on dialysis, while Royaldee is not recommended in that patient population.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Royaldee is approved for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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Royaldee was evaluated in two identical, multicenter, randomized, double-blind, placebo controlled trials in patients with secondary hyperparathyroidism with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D level between 10 ng/mL and 30 ng/mL. The primary endpoint for these trials was at least a 30% reduction in plasma intact parathyroid hormone levels from baseline to the end of the trial. In the first study, 33% of patients receiving Royaldee achieved the primary endpoint compared with 8% of patients receiving placebo (P < 0.001). In the second study, 34% of patients receiving Royaldee achieved the primary endpoint compared with 7% of patients receiving placebo (p < 0.001).

The patient selection criteria presented in this policy takes into consideration the FDA approved indication of this drug as well as other therapeutic alternatives that currently exist for this condition. There have been no direct, head to head comparisons of Royaldee to calcitriol or other vitamin D analogs to prove that Royaldee has any clinical superiority over the existing products.

References

1. Royaldee [package insert]. Opko Pharmaceuticals, LLC. Miami, Florida. Updated June 2016.
2. Royaldee Drug Evaluation. Express Scripts. Updated August 2016.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024;105(4S):S117-S314. doi:10.1016/j.kint.2023.10.018

Policy History

Original Effective Date: 04/19/2017

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04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Implementation Committee approval. New policy
04/05/2018	Medical Policy Committee review
04/18/2018	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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04/06/2023 Medical Policy Committee review
04/12/2023 Medical Policy Implementation Committee approval. No change to coverage.
04/04/2024 Medical Policy Committee review
04/10/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2025 Medical Policy Committee review
04/09/2025 Medical Policy Implementation Committee approval. Added continuation criteria allowing continued coverage for patients who have previously received approval and are continuing to benefit from the requested medication. Added Policy Guidelines section with chart depicting CKD classifications to aid in medical policy review.

Next Scheduled Review Date: 04/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.