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Medication Policy Manual | **Policy No:** dru487

Topic: Rayaldee®, calcifediol extended-release | **Date of Origin:** February 17, 2017

Committee Approval Date: October 13, 2017 | **Next Review Date:** October 2018

Effective Date: October 13, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Calcifediol ER (Rayaldee) is an oral, extended-release vitamin D analog indicated for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and who have low levels of vitamin D.

Policy/Criteria

I. Most contracts require prior authorization approval of calcifediol ER (Rayaldee) prior to coverage. Calcifediol ER (Rayaldee) may be considered medically necessary when criteria A, B, C, D, and E below are met.

A. A diagnosis of secondary hyperparathyroidism (SHPT) in stage 3 or 4 chronic kidney disease (CKD) is established by or in consultation with a specialist in nephrology or endocrinology.

AND

B. The patient is <u>not</u> on dialysis.

AND

C. Serum total 25-hydroxyvitamin D level is < 30 ng/mL within the past 3 months.

AND

D. Serum calcium level is < 9.8 mg/dL within the past 3 months.

AND

E. At least two alternative vitamin D analogs (see *Appendix 1*) have been ineffective, not tolerated, or contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers calcifediol ER (Rayaldee) to be a self-administered medication.

B. When prior authorization is approved, calcifediol ER (Rayaldee) may be authorized in the following quantities:

1. **Initial authorization:** Up to #30 calcifediol ER (Rayaldee) 30-mcg capsules per 30 days.
2. **Continued authorization:** Up to #60 of calcifediol ER (Rayaldee) 30-mcg capsules per 30 days may be authorized if intact parathyroid hormone (iPTH) is above the treatment goal after 3 months of therapy, serum calcium < 9.8 mg/dL, phosphorus < 5.5 mg/dL, and 25-hydroxyvitamin D < 100 ng/mL.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Calcifediol ER (Rayaldee) is considered investigational when used for all other conditions.

Position Statement

Summary

- Calcifediol ER (Rayaldee) is an oral, extended-release vitamin D analog approved for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels < 30 ng/mL. [1]
- SHPT 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.
- Clinical practice guidelines for SHPT differ in their recommendations regarding the important of calcium, phosphorous, and PTH levels. KDOQI guidelinesrecommend that patients be on a phosphate-restricted diet, then add pharmacological therapies (phosphate binders, vitamin D analogs, and calcimimetics) as indicated based on stage of CKD and serum concentrations of phosphorus, calcium, and PTH. The updated KDIGO guidelines recognize that there are no clinical trials demonstrating clinically meaningful benefit from targeting PTH levels in non-dialysis patients, and recommend against routine use of vitamin D analogues in this population. [2-4]
- Calcifediol ER (Rayaldee) has been shown to reduce intact parathyroid hormone (iPTH) levels and increase vitamin D levels. However, it has not been shown to improve clinical outcomes (e.g. decreased morbidity or mortality, prevent metabolic bone disorder, or improve quality of life). [1,5,6]
- There is not sufficient evidence to establish that calcifediol ER (Rayaldee) is more effective or safer than other less costly, generic vitamin D analogs used for SHPT. Other vitamin D analogs are available via oral or intravenous administration. Cholecalciferol is available over-the-counter as oral tablets or capsules.
- Calcifediol ER (Rayaldee) has not been studied in patients on dialysis.
- Calcifediol ER is dosed at 30 mcg orally once daily at bedtime. Serum calcium should be below 9.8 mg/dL before initiating treatment. If iPTH levels are still above treatment goals after 3 months of therapy, the dose can be increased to 60 mcg once daily. [1]
- Serum calcium, phosphorus, vitamin D, and iPTH levels should be routinely monitored.

Clinical Efficacy

- Two double-blinded, placebo-controlled randomized trials evaluated patients receiving either calcifediol ER (Rayaldee) or placebo. [5,6]
    * The primary outcome was the number of patients achieving a reduction in serum iPTH that was 30 percent or greater from baseline after 26 weeks of treatment. Significantly more patients in the calcifediol ER (Rayaldee) arm achieved this goal relative to placebo.
    * The secondary outcome was the number of patients who had achieved normal serum levels of 25-hydroxyvitamin D defined as ≥ 30 ng/mL. Significantly more patients in the calcifediol ER (Rayaldee) arm achieved this goal relative to placebo.

- One double-blinded, placebo-controlled randomized trial reported a dose-dependent mean reduction in serum intact parathyroid hormone (iPTH) with calcifediol extended-release (Rayaldee) compared to a mean increase with placebo. [7]
- Reducing iPTH levels and normalizing 25-hydroxyvitamin D levels are surrogate endpoints with unknown correlation to clinical outcomes (e.g. improved morbidity, mortality, or quality of life).
- Due to a lack of head-to-head trials and differences in study design, there is insufficient evidence to differentiate calcifediol ER (Rayaldee) from other vitamin D analogs.
- The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) recommend that calcitriol and vitamin D analogs not be routinely used in adult patients with CKD Stages 3a-5 who are not on dialysis. The use of calcitriol and vitamin D analogs should be reserved for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism. [8]

Safety [1]

- There is no reliable evidence to conclude that calcifediol ER (Rayaldee) is safer than other vitamin D analogs used for SHPT.
- Adverse events (AEs) associated with calcifediol ER (Rayaldee) are generally manageable. The most common AEs (≥ 3% and more frequent than placebo) reported were anemia, nasopharyngitis, increased serum creatinine, dyspnea, congestive heart failure, and constipation.
- Calcifediol ER (Rayaldee) had slightly higher rates of congestive heart failure compared to placebo; however, the FDA did not require any post-marketing surveillance.
- AEs most commonly associated with vitamin D analogs include hypercalcemia and hypercalciuria. Vitamin D overdose can be associated with constipation, poor appetite, nausea, vomiting, dehydration, fatigue, and muscle weakness.
- Calcifediol ER (Rayaldee) has not been studied in patients on dialysis. The safety of calcifediol ER (Rayaldee) in this population is unknown.
- Serum calcium, phosphorus, 25-hydroxyvitamin D, and iPTH levels should be monitored 3 months after starting therapy or if changing the dose.

Dosing [1]

- The recommended initial dose of calcifediol ER (Rayaldee) is 30 mcg orally once daily at bedtime. Serum calcium should be below 9.8 mg/dL before initiating treatment.
- If iPTH is still above the treatment goal after 3 of starting therapy, the dose should be increased to calcifediol ER (Rayaldee) 60 mcg once daily. Serum calcium should be below 9.8 mg/dL, phosphorus below 5.5 mg/dL and 25-hydroxyvitamin D below 100 ng/mL before increasing the dose.
- Calcifediol ER (Rayaldee) should be stopped if iPTH is persistently abnormally low, serum calcium is consistently above the normal range or serum 25-hydroxyvitamin D is consistently above 100 ng/mL.

Appendix 1: Alternative Vitamin D Analogs
calcitriol (capsules, IV solution, oral solution)
cholecalciferol (over-the-counter: tablets, capsules)
doxercalciferol (capsules, IV solution)
ergocalciferol capsules
paricalcitol (capsules, IV solution)

Cross References
N/A

Codes	Number	Description
ICD-10	N25.81	Secondary hyperparathyroidism of renal origin
ICD-10	E55.9	Vitamin D deficiency, unspecified

References

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2. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009:S1-130. PMID: 19644521
3. KDIGO 2016 Clinical Practice Guideline Update on the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MPD: Public Review Draft. 2016.
4. Inker, LA, Astor, BC, Fox, CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2014 May;63(5):713-35. PMID: 24647050
5. Sprague, SM, Crawford, PW, Melnick, JZ, et al. Use of Extended-Release Calcifediol to Treat Secondary Hyperparathyroidism in Stages 3 and 4 Chronic Kidney Disease. *Am J Nephrol*. 2016;44:316-25. PMID: 27676085
6. Extension Study of CTAP101-CL-3001 or CTAP101-CL-3002. [cited 09/29/16]; Available from: https://clinicaltrials.gov/ct2/show/NCT02282813
7. Sprague, SM, Silva, AL, Al-Saghir, F, et al. Modified-release calcifediol effectively controls secondary hyperparathyroidism associated with vitamin D insufficiency in chronic kidney disease. *Am J Nephrol*. 2014;40:535-45. PMID: 25572630
8. Ketteler, M, Block, GA, Evenepoel, P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney international*. 2017 Jul;92(1):26-36. PMID: 28646995

Revision History

Revision Date	Revision Summary
10/13/2017	No changes to coverage criteria with this annual update.
02/17/2017	New policy (effective 2/17/17)