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IN BRIEF

Severe Hypocalcemia with Denosumab (*Prolia*) in Chronic Kidney Disease

The FDA is requiring a boxed warning in the label of denosumab (*Prolia* – Amgen)¹, a monoclonal antibody that inhibits osteoclasts, about an increased risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD; eGFR <30 mL/min/1.73 m²), particularly those on dialysis.² FDA-approved indications for *Prolia* are listed in Table 1.

Denosumab is also available as *Xgeva* for prevention of skeletal-related events or treatment of hypercalcemia in patients with malignancies. The warning has not been added to the *Xgeva* label.

An FDA analysis of studies from the Centers for Medicare & Medicaid Services found that use of *Prolia* in patients with advanced CKD was associated with a significant increase in the risk of developing severe hypocalcemia, compared to use of bisphosphonates. In 2804 dialysis-dependent patients treated for osteoporosis, the incidence of severe hypocalcemia was 41.1% with denosumab, compared to 2.0% with oral bisphosphonates. *Prolia* is given subcutaneously once every 6 months. Severe hypocalcemia, which generally occurred 2-10 weeks after each injection of the drug, can lead to muscle spasms, seizures, cardiac arrhythmias, and death.^{2,3}

Table 1. FDA-Approved Indications for Denosumab (*Prolia*)

- ▶ Treatment of postmenopausal women with osteoporosis at high risk for fracture
- ▶ Increase bone mass in men with osteoporosis at high risk for fracture
- ▶ Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture
- ▶ Increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- ▶ Increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

In patients with advanced CKD, pre-existing hypocalcemia should be corrected before starting *Prolia* and serum calcium levels should be monitored weekly for the first month of treatment with the drug and monthly thereafter. Adequate calcium and vitamin D supplementation can decrease the risk of hypocalcemia. ■

1. Drugs for postmenopausal osteoporosis. *Med Lett Drugs Ther* 2020; 62:105.
2. FDA Drug Safety Communication. FDA adds boxed warning for increased risk of severe hypocalcemia in patients with advanced chronic kidney disease taking osteoporosis medicine *Prolia* (denosumab). January 19, 2024. Available at: <https://bit.ly/3l7zGjb>. Accessed February 14, 2024.
3. ST Bird et al. Severe hypocalcemia with denosumab among older female dialysis-dependent patients. *JAMA* 2024; 331:491.

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