

FDA Drug Safety Communication

This information is an update to the FDA Drug Safety Communication: [FDA investigating risk of severe hypocalcemia in patients on dialysis receiving osteoporosis medicine Prolia \(denosumab\) issued on November 22, 2022.](#)

FDA adds *Boxed Warning* for increased risk of severe hypocalcemia in patients with advanced chronic kidney disease taking osteoporosis medicine Prolia (denosumab)
Patients on dialysis or with mineral and bone disorder at highest risk

01-19-2024 FDA Drug Safety Communication

What safety concern is FDA announcing?

Based on a completed U.S. Food and Drug Administration (FDA) review of available information, we have concluded that the osteoporosis medicine Prolia (denosumab) increases the risk of severe hypocalcemia, very low blood calcium levels, in patients with advanced chronic kidney disease (CKD), particularly patients on dialysis. Severe hypocalcemia appears to be more common in patients with CKD who also have a condition known as mineral and bone disorder (CKD-MBD). In patients with advanced CKD taking Prolia, severe hypocalcemia resulted in serious harm, including hospitalization, life-threatening events, and death. As a result, we are revising the Prolia prescribing information to include a new *Boxed Warning*, FDA's most prominent warning, communicating this increased risk.

Severe hypocalcemia can be asymptomatic or may present with symptoms that include confusion; seizures; irregular heart rhythm; fainting; face twitching; uncontrolled muscle spasms; or weakness, tingling, or numbness in parts of the body.

What is FDA doing?

We are adding a *Boxed Warning* to the Prolia [prescribing information](#) about the significant risk of developing severe hypocalcemia in patients with advanced CKD. This warning and new labeling contains information to help reduce this risk, including appropriate patient selection for Prolia treatment, increased monitoring of blood calcium levels, and other strategies. We are also adding this updated information to the patient [Medication Guide](#) and the Prolia Risk Evaluation and Mitigation Strategy ([REMS](#)), a drug safety program required by FDA to help ensure that Prolia's benefits outweigh its risks.

What is Prolia and how can it help me?

Prolia is a prescription medicine approved in 2010 to treat postmenopausal women with osteoporosis at high risk for bone fracture. Prolia was later approved to increase bone mass in men with osteoporosis; to treat men with high risk for fracture receiving androgen deprivation therapy for prostate cancer; to treat women at high risk for fracture receiving aromatase inhibitor therapy for breast cancer; and, to treat men and women with glucocorticoid-induced osteoporosis. Prolia works by blocking a protein called RANK (receptor activator of nuclear factor kappa beta) and helps prevent bone cells called osteoclasts from breaking down bone in

the body. A health care professional administers Prolia by subcutaneous, under the skin, injection once every 6 months.

What should patients and caregivers do?

For patients considering Prolia for osteoporosis treatment, talk to your health care professional about your kidney function and the risk of severe hypocalcemia. Whether Prolia treatment is appropriate for patients with advanced CKD should be determined by a health care professional with expertise in the diagnosis and management of CKD-MBD, including renal osteodystrophy.

For patients already taking Prolia for osteoporosis, maintain adequate calcium and vitamin D intake while receiving this medicine. Since your health care professional administers Prolia by subcutaneous injection every 6 months, you should discuss with them if you are at increased risk, and if so, whether continuing this treatment is best for you. If discontinuation of Prolia treatment is recommended, your health care professional may advise other measures to monitor for and minimize the risk of rebound fractures.

For patients with advanced kidney disease, especially those on dialysis treated with Prolia, frequent monitoring of calcium in the blood, especially for the first 2 to 10 weeks after each Prolia injection, is recommended. Talk to your health care professional about specific instructions for the dose and type of calcium and vitamin D supplements that may be needed.

Do not stop taking Prolia without talking with your health care professional as your risk of bone fracture, including in the spine, is increased after stopping, skipping, or delaying Prolia. Tell your health care professional if you develop symptoms suggestive of hypocalcemia such as confusion; seizures; irregular heart rhythm; fainting; face twitching; uncontrolled muscle spasms; or weakness, tingling, or numbness in parts of the body.

What should health care professionals do?

It is important that the appropriateness of Prolia treatment in patients with advanced CKD be determined by a health care professional with expertise in the diagnosis and management of CKD-MBD including renal osteodystrophy, a complication that weakens bone. Treating bone disease in patients with advanced and dialysis-dependent CKD is challenging because of the difficulty in diagnosing and confirming the underlying altered bone metabolism responsible for the low bone mass and increased fracture risk, and the complex benefit-risk considerations of approved osteoporosis treatments in this population.

Before prescribing Prolia, health care professionals should assess their patients' kidney function. For patients with advanced CKD, particularly those on dialysis, health care professionals should consider the risk of severe hypocalcemia with Prolia in the context of other available treatments for osteoporosis. If Prolia is still being considered for these patients, for initial or continued use, check their calcium blood levels and assess them for evidence of CKD-MBD.

Treatment with Prolia in patients with advanced CKD, including those on dialysis, and particularly patients with diagnosed CKD-MBD should involve a health care provider with expertise in the diagnosis and management of CKD-MBD. Proper management of CKD-MBD,

correction of hypocalcemia, and supplementation with calcium and activated vitamin D prior to Prolia treatment is expected to decrease the risk of developing severe hypocalcemia and any associated complications. Following Prolia administration, close monitoring of blood calcium levels and prompt management of hypocalcemia is essential to prevent complications such as seizures or arrhythmias. Advise patients to promptly report symptoms that could be consistent with hypocalcemia.

What did FDA find?

The FDA completed an evaluation to assess the risk of developing severe hypocalcemia with Prolia in patients with advanced CKD, including patients on dialysis. The evaluation primarily consisted of studies from the Centers for Medicare & Medicaid Services (CMS). The results showed a significant increase in the risk of developing severe hypocalcemia with Prolia treatment compared to another class of osteoporosis medicines called bisphosphonates. The highest risk was seen in patients with advanced CKD, including dialysis-dependent patients, and those with CKD-MBD. Patients typically developed severe hypocalcemia 2 to 10 weeks following each Prolia injection, with the greatest risk occurring during Weeks 2 to 5.

We also reviewed 25 cases submitted to FDA* from July 2010 through May 2021, describing patients with CKD, some of whom were on dialysis, who experienced complications of severe hypocalcemia after starting Prolia treatment including arrhythmias and other signs or symptoms associated with severe hypocalcemia such as confusion, seizures, face twitching, and muscle spasms or weakness.

*The cases were reported to the [FDA Adverse Event Report System \(FAERS\) database](#).

What is my risk?

All medicines have side effects even when used correctly as prescribed. It is important to know that people respond differently to medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. If you have advanced kidney disease, your risk of developing severe hypocalcemia when taking Prolia is increased. Your health care professionals know you best, so talk to them if you have questions or concerns about the risks of taking Prolia.

How do I report side effects from Prolia?

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving Prolia and other medicines to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of this page.

How can I get new safety information on medicines I’m prescribing or taking?

You can sign up for [email alerts](#) about Drug Safety Communications on medicines or medical specialties of interest to you.

Facts about Prolia (denosumab)

- Prolia is a monoclonal antibody initially developed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture or who are refractory to or cannot tolerate other therapies.
- Prolia works by blocking a protein called RANK (receptor activator of nuclear factor kappa beta) and helps prevent bone cells called osteoclasts from breaking down bone in the body.
- Prolia may lower the calcium levels in your blood.
- Prolia is administered as a subcutaneous injection under the skin by a health care professional once every 6 months.
- Common side effects of Prolia include back pain, muscle pain, and pain in the arms or legs.
- In 2022, an estimated 2.2 million Prolia pre-filled syringes were sold by the manufacturer to U.S. health care settings.¹

Additional Information for Patients and Caregivers

- FDA is adding a *Boxed Warning*, our most prominent warning, stating the osteoporosis medicine Prolia increases the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including patients on dialysis, and that this risk is further increased in the presence of chronic kidney disease-mineral and bone disorder (CKD-MBD). We are also adding this updated information to the patient [Medication Guide](#).
- Patients should talk to their health care provider about their kidney function and the risk of severe hypocalcemia prior to starting Prolia.
- Patients should maintain adequate [calcium](#) and vitamin D intake while receiving Prolia. Talk to your health care professional about specific instructions for the dose and type of calcium and vitamin D supplements that may be needed while taking Prolia.
- Do not stop taking Prolia without talking with your health care professional as your risk of broken bones, including in the spine, is increased after stopping, skipping, or delaying Prolia. Since your health care professional administers Prolia by injection every 6 months, patients with advanced CKD who are currently receiving Prolia treatment should ask your health professional whether it is best for you to continue with this medicine or to discontinue it. If discontinuation of Prolia treatment is recommended, your health care professional may advise other measures to monitor for and minimize the risk of rebound fractures.
- The risk for developing severe hypocalcemia has been mainly reported to occur 2 to 10 weeks following each Prolia injection, but it may happen earlier or later.
- Tell your health care professional if you develop the following symptoms of hypocalcemia:
 - Confusion
 - Seizures
 - Irregular heart rhythm
 - Fainting
 - Face twitching
 - Uncontrolled muscle spasms
 - Weakness, tingling, or numbness in parts of the body

- Read the patient [Medication Guide](#) every time you receive your injection of Prolia because there may be new or important additional information about this medicine. The Medication Guide explains the important things you need to know about Prolia. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch for when you are taking Prolia.
- To help FDA track safety issues with medicines, report side effects from Prolia or other medicines to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines and medical specialties of interest to you.

Additional Information for Health Care Professionals

- FDA is adding a *Boxed Warning* stating the osteoporosis medicine Prolia increases the risk of severe hypocalcemia in patients with advanced CKD, including on dialysis, and that this risk is further increased in the presence of CKD-MBD.
- We are also adding this updated information to the patient [Medication Guide](#) and the Prolia Risk Evaluation and Mitigation Strategy ([REMS](#)).
- Our analysis found that most of the severe hypocalcemia events occur 2 to 10 weeks following Prolia injection, with the greatest risk for hypocalcemia occurring during Weeks 2 to 5.
- Inform patients about the risk of severe hypocalcemia when prescribing Prolia.
- Explain the signs and symptoms of severe hypocalcemia to patients and tell them to seek medical attention if they experience symptoms including confusion; seizures; irregular heart rhythm; face twitching; uncontrolled muscle spasms; or weakness, tingling, or numbness in parts of the body.
- Steps to help reduce the risk of severe hypocalcemia include the following:
 - Involving a health care professional with expertise in the diagnosis and management of CKD-MBD, such as a nephrologist, when determining the appropriateness of initiating and continuing Prolia in patients with advanced CKD.
 - Considering whether Prolia’s benefits are expected to outweigh the risks in patients with advanced CKD based on patient selection and risk factors for hypocalcemia: assess kidney function, identify evidence of CKD-MBD, and check blood calcium levels.
 - Managing CKD-MBD, correcting hypocalcemia, and supplementing with calcium and activated vitamin D prior to and during Prolia treatment may decrease the risk of severe hypocalcemia and any associated complications.
 - Following Prolia administration, close monitoring of serum calcium levels and prompt management of severe hypocalcemia is critical to reduce the risk of complications such as seizures and arrhythmias.
- Encourage patients to read the [Medication Guide](#) they receive with their injection because there may be new or important additional information about Prolia.

- To help FDA track safety issues with medicines, report side effects from Prolia or other medicines to the FDA MedWatch program using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines and medical specialties of interest to you.

Data Summary

FDA conducted two studies to evaluate the risk for severe hypocalcemia with Prolia using CMS data, in addition to assessing cases reported to FDA through FAERS.*

The first study evaluated the incidence and risk of severe hypocalcemia in female dialysis-dependent U.S. Medicare patients treated for osteoporosis with Prolia or oral bisphosphonates. Severe hypocalcemia was defined as total albumin-corrected serum calcium below 7.5 mg/dL (1.87 mmol/L) or a primary hospital or emergency department hypocalcemia diagnosis (emergent care). The study population included 1,523 dialysis-dependent women treated with Prolia and 1,281 dialysis-dependent women treated with oral bisphosphonates. A markedly increased incidence of severe hypocalcemia was identified in dialysis-dependent patients treated with Prolia compared to oral bisphosphonates, with a 12-week weighted cumulative incidence of severe hypocalcemia of 41.1 percent with denosumab versus 2.0 percent with oral bisphosphonates. The greatest hypocalcemia risk occurred during Weeks 2 to 5.

The second study evaluated the risk of severe hypocalcemia requiring emergent treatment among female U.S. Medicare patients receiving Prolia, intravenous bisphosphonates, or oral bisphosphonates, with stratification by stage of chronic kidney disease (CKD) and presence of chronic kidney disease-mineral and bone disorder (CKD-MBD). Severe hypocalcemia requiring emergent treatment was defined as a primary discharge diagnosis of hypocalcemia after hospital or emergency department admission. The study population included 495,269 women treated with Prolia, 899,331 women treated with oral bisphosphonates, and 212,430 women treated with intravenous bisphosphonates. Severe hypocalcemia requiring emergent treatment was observed in 242 women treated with denosumab (218.9/100,000 person-years), 57 women treated with intravenous bisphosphonates (52.1/100,000 person-years), and 20 women treated with oral bisphosphonates (19.4/100,000 person-years), from weighted cohorts. Worsening CKD stage was associated with progressive increases in the rate of Prolia-induced severe hypocalcemia. CKD-MBD was a significant factor in the impact of advanced CKD on the risk for Prolia-induced severe hypocalcemia. The increased risk for severe hypocalcemia with Prolia peaked at Week 2 post-administration and remained elevated compared to oral bisphosphonates through Week 10. In the 30 days following onset of severe hypocalcemia with Prolia, 21 (8.7 percent) patients with this outcome developed seizures or cardiac arrhythmias and 8 (3.3 percent) patients died.

FDA also reviewed U.S. cases received in the FAERS database from July 2010 through May 2021, involving 77 patients who experienced severe symptomatic hypocalcemia after receiving Prolia. When reported, the median age of the patients was 68 years (range: 21-93 years). Of the 77 patients, about a third (n=25) of patients had CKD, some of whom were on dialysis, with or without other potential risk factors for the development of hypocalcemia; however, it is possible

other patients had CKD that was undiagnosed or not reported. The manifestations of severe symptomatic hypocalcemia in the patients with CKD included, but were not limited to, confusion; seizures; irregular heart rhythm; face twitching; uncontrolled muscle spasms; or weakness, tingling, or numbness in parts of the body. Some of the patients with CKD had recurrent hypocalcemia despite treatment with intravenous and oral calcium and vitamin D.

Reference

1. IQVIA. National Sales Perspective™ database. Data extracted January 2024.
<https://www.iqvia.com/insights/the-iqvia-institute/available-iqvia-data>.

Related Information

- [Hypocalcemia](#)
- [Osteoporosis](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)