Important Drug Safety Notice

TO ALL PARTICIPATING PHARMACIES

Circular Letter MC24-005-CG
February 8, 2024

FDA announced that, based on a completed FDA review of available information, FDA has 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. FDA is adding a Boxed Warning to the Prolia prescribing information about the significant risk of developing severe hypocalcemia in patients with advanced CKD. The FDA is 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.

RECOMMENDATIONS

Patients

- 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.

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- 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.

Health Care Professionals

- 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.

    1. Expect patients to visit your pharmacy asking for information on this safety issue and prepare your pharmacy staff on how to handle the situation.

MC-Rx Pharmacy Services Department

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FDA U.S. FOOD & DRUG ADMINISTRATION

Prolia (denosumab): Drug Safety Communication - FDA Adds Boxed Warning for Increased Risk of Severe Hypocalcemia in Patients with Advanced Chronic Kidney Disease

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[Posted 01/19/2024]

AUDIENCE: Patient, Health Professional, Endocrinology, Nephrology, Pharmacy

ISSUE: Based on a completed FDA review of available information, FDA has 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, the FDA is 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.

FDA is 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. The FDA is 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.

BACKGROUND:

- 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 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.

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- 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, and it 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.

RECOMMENDATIONS:

Patients

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- 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.

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- 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.

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