PONLIMSI™ (denosumab-adet) Injection, for subcutaneous use

INDICATIONS

PONLIMSI is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.

PONLIMSI is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

PONLIMSI is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

PONLIMSI is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures.

PONLIMSI is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE HYPOCALCEMIA IN PATIENTS WITH ADVANCED KIDNEY DISEASE

- **Patients with advanced chronic kidney disease (eGFR <30 mL/min/1.73 m^2), including dialysis-dependent patients, are at greater risk of severe hypocalcemia following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported.**
- **The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia in these patients.**
- **Prior to initiating PONLIMSI in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with PONLIMSI in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD.**

CONTRAINDICATIONS

PONLIMSI is contraindicated in:

- Patients with hypocalcemia: Pre-existing hypocalcemia must be corrected prior to initiating therapy with PONLIMSI.
- Pregnant women: Denosumab products may cause fetal harm when administered to a pregnant woman. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with PONLIMSI.
- Patients with hypersensitivity to denosumab products: PONLIMSI is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling, and urticaria.

WARNINGS AND PRECAUTIONS

Severe Hypocalcemia and Mineral Metabolism Changes

Denosumab products can cause severe hypocalcemia and fatal cases have been reported. Pre-existing hypocalcemia must be corrected prior to initiating therapy with PONLIMSI. Adequately supplement all patients with calcium and vitamin D. In patients without advanced chronic kidney disease who are predisposed to hypocalcemia and disturbances of mineral metabolism (e.g., history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, treatment with other calcium-lowering drugs), assess serum calcium and mineral levels (phosphorus and magnesium) 10 to 14 days after PONLIMSI injection.

Patients with Advanced Chronic Kidney Disease

Patients with advanced chronic kidney disease [i.e., eGFR <30 mL/min/1.73 m^2] including dialysis-dependent patients are at greater risk for severe hypocalcemia following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. The presence of underlying chronic kidney disease-mineral bone disorder (CKD-MBD, renal osteodystrophy) markedly increases the risk of hypocalcemia. Concomitant use of calcimimetic drugs may also worsen hypocalcemia risk.

To minimize the risk of hypocalcemia in patients with advanced chronic kidney disease, evaluate for the presence of chronic kidney disease mineral and bone disorder with intact parathyroid hormone (iPTH), serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$ vitamin D prior to decisions regarding PONLIMSI treatment. Consider also assessing bone turnover status (serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may be present. Monitor serum calcium weekly for the first month after PONLIMSI administration and monthly thereafter. Instruct all patients with advanced chronic kidney disease, including those who are dialysis-dependent, about the symptoms of hypocalcemia and the importance of maintaining serum calcium levels with adequate calcium and activated vitamin D supplementation. Treatment with PONLIMSI in these patients should be supervised by a healthcare provider who is experienced in diagnosis and management of CKD-MBD.

Drug Products with Same Active Ingredient

Patients receiving PONLIMSI should not receive other denosumab products concomitantly.

Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with denosumab products. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of PONLIMSI.

Osteonecrosis of the Jaw (ONJ)

ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving denosumab products. A routine oral exam should be performed by the prescriber prior to initiation of PONLIMSI treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with PONLIMSI in patients with risk factors for ONJ such as invasive dental procedures, diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and comorbid disorders. Good oral hygiene practices should be maintained during treatment with PONLIMSI. The risk of ONJ may increase with duration of exposure to denosumab products.

For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit-risk assessment.

Patients who are suspected of having or who develop ONJ while on PONLIMSI should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of PONLIMSI therapy should be considered based on individual benefit-risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical low energy or low trauma fractures of the shaft have been reported in patients receiving denosumab products. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with antiresorptive agents.

During PONLIMSI treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Interruption of PONLIMSI therapy should be considered, pending a benefit-risk assessment, on an individual basis.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Treatment
Following discontinuation of denosumab products, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of denosumab. Prior vertebral fracture was a predictor of multiple vertebral fractures after denosumab discontinuation. Evaluate an individual's benefit-risk before initiating treatment with PONLIMSI. If PONLIMSI treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

Serious Infections
In a clinical trial of over 7,800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in PONLIMSI than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with denosumab. Endocarditis was also reported more frequently in denosumab-treated patients. The incidence of opportunistic infections was similar between placebo and denosumab groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on PONLIMSI, prescribers should assess the need for continued PONLIMSI therapy.

Dermatologic Adverse Reactions
Epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate with denosumab products compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing PONLIMSI if severe symptoms develop.

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking denosumab products. The time to onset of symptoms varied from one day to several months after starting denosumab products. Consider discontinuing use if severe symptoms develop.

Suppression of Bone Turnover
In clinical trials in women with postmenopausal osteoporosis, treatment with denosumab resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with denosumab products are unknown. Monitor patients for these consequences.

Hypercalcemia in Pediatric Patients with Osteogenesis Imperfecta
PONLIMSI is not approved for use in pediatric patients. Hypercalcemia has been reported in pediatric patients with osteogenesis imperfecta treated with denosumab products. Some cases required hospitalization.

ADVERSE REACTIONS

The most common adverse reactions (>5% and more common than placebo) reported with denosumab products in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

The most common adverse reactions (>5% and more common than placebo) reported with denosumab products in men with osteoporosis are back pain, arthralgia, and nasopharyngitis.

The most common adverse reactions (>3% and more common than placebo) reported with denosumab products in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache.

The most common (per patient incidence ≥10%) adverse reactions reported with denosumab products in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials.

The most common adverse reactions leading to discontinuation of denosumab products in patients with postmenopausal osteoporosis are back pain and constipation.

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please click here for full Prescribing Information for PONLIMSI, including BOXED WARNINGS.

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