

## Denosumab (Prolia) for Treatment of Postmenopausal Osteoporosis

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STEPS new drug reviews cover Safety, Tolerability, Effectiveness, Price, and Simplicity. Each independent review is provided by authors who have no financial association with the drug manufacturer.

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Denosumab (Prolia) is a subcutaneously administered human monoclonal antibody that decreases bone resorption by inhibiting the formation and activity of osteoclasts. Specifically, its antiresorptive activity results from inhibiting receptor activator of nuclear factor- $\kappa$  B ligand (RANKL), a protein needed for osteoclast formation and activity. It is licensed for the treatment of postmenopausal osteoporosis in women with high fracture risk, those in whom alternative osteoporosis agents have not been effective, or those who cannot tolerate other agents.<sup>1</sup>

Drug	Dosage	Dose form	Cost of one year of therapy*
Denosumab (Prolia)	60 mg subcutaneously every six months	Prefilled syringe and single-use vial containing 60 mg of denosumab per 1 mL	\$1,980

\*—Average wholesale cost, based on Micromedex.

### SAFETY

Data on the long-term safety of denosumab are limited; the largest clinical trial enrolled approximately 7,800 women and followed them for three years.<sup>2</sup> The most serious safety issue is the risk of hypocalcemia, which occurs in about 2 percent of women who receive Prolia.<sup>1</sup> The risk is higher in patients with renal impairment. Denosumab is contraindicated in patients with preexisting hypocalcemia. Serious infections were more common in treated patients (4.1 versus 3.4 percent of those who received placebo),<sup>2</sup> and the risk of infection may be increased in immunocompromised patients. Rates of opportunistic infections are similar between treated and untreated patients.<sup>1,2</sup> Patients should seek prompt medical attention if they develop symptoms of infection. As with bisphosphonates, denosumab use has been associated with osteonecrosis of the jaw. The long-term complications from suppressing bone remodeling with denosumab are unknown; atypical fractures and

delayed fracture healing have been reported in patients receiving bisphosphonates. Denosumab is a U.S. Food and Drug Administration pregnancy category C drug.<sup>1</sup>

### TOLERABILITY

Back pain, extremity pain, hypercholesterolemia, musculoskeletal pain, and cystitis occur in more than 5 percent of women receiving Prolia, and are more common than with placebo.<sup>1</sup> In clinical trials, dropout rates because of adverse effects were similar between treated patients and those receiving placebo.<sup>2</sup>

### EFFECTIVENESS

Compared with weekly administration of alendronate (Fosamax), denosumab significantly increases bone mineral density in postmenopausal women with low bone mass.<sup>3</sup> Among postmenopausal women who had received alendronate for at least six months, those switched to denosumab significantly increased bone mineral density at one year versus those who continued receiving alendronate.<sup>4</sup>

The risk of hip fracture was slightly decreased in high-risk postmenopausal women after three years of denosumab therapy, compared with those receiving calcium and vitamin D replacement therapy (400 to 800 IU of vitamin D; 0.7 versus 1.1 percent;  $P = .04$ ).<sup>2</sup> The average age of participants was 72 years, and the average dual energy x-ray absorptiometry score was  $-2.5$  to  $-4$  at the lumbar spine or total hip; about one in four of the women had at least one pre-existing vertebral fracture. Treatment was more effective at decreasing the likelihood of other nonvertebral fractures (6.5 versus 8 percent) and new radiographic vertebral fractures (2.3 versus 7.2 percent), although clinically apparent vertebral fractures were decreased to a lesser extent (0.8 versus 2.6 percent).<sup>2</sup>

Denosumab has not been directly compared with oral or intravenous bisphosphonates or with therapeutic doses of calcium and vitamin D for fracture prevention. It has also not been studied in combination with other osteoporosis agents.

#### PRICE

Prolia costs \$1,980 for one year of therapy, plus physician's or nurse's fees for administration as well as monitoring of calcium, phosphorus, and magnesium levels. Overall, Prolia is more expensive than oral or intravenous bisphosphonates.

#### SIMPLICITY

The recommended dosage of Prolia is 60 mg administered subcutaneously every six months. No dosage adjustments are necessary

in patients with renal or hepatic impairment. Patients receiving Prolia should also take at least 1,000 mg of calcium and 400 IU of vitamin D daily. Denosumab must be stored in the refrigerator and allowed to come to room temperature before injection. The manufacturer recommends administration by a health care professional.<sup>1</sup> Calcium, phosphorus, and magnesium levels should be monitored in women receiving Prolia.

#### Bottom Line

Prolia is an expensive method of preventing osteoporotic hip fractures, and is associated with significant adverse effects. Safer, less expensive options exist for preventing fracture in high-risk women.

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