

FDA Panel Backs Approval of Biologic for SLE

BY ELIZABETH MEHCATIE

FROM A MEETING OF THE FDA'S
ARTHRITIS DRUGS ADVISORY COMMITTEE

ADELPHI, MD. – Belimumab should be approved for reducing disease activity in adults with active autoantibody-positive systemic lupus erythematosus who are on standard treatment, a Food and Drug Administration advisory panel recommended in a 13-2 vote.

If approved, belimumab will be the first new treatment for systemic lupus erythematosus (SLE) in more than 50 years.

Currently, the only approved treatments for lupus are corticosteroids and hydroxychloroquine, approved in the 1950s, and aspirin.

At a Nov. 16 meeting of the FDA's Arthritis Drugs Advisory Committee, panelists strongly recommended that the

drug's label stipulate the treatment was not evaluated in patients with active lupus nephritis or central nervous system manifestations of the disease.

Several panelists supporting approval pointed out that treatment effects were mild but agreed that the efficacy data supported approval.

Belimumab, a monoclonal antibody manufactured by Human Genome Sciences Inc., inhibits the biological ac-

tivity of B-lymphocyte stimulator (BLyS), a cytokine that is elevated in patients with SLE and other autoimmune diseases.

The proposed dose is 10 mg/kg administered in an intravenous infusion at 2-week intervals for the first three doses and at 4 week intervals thereafter.

That treatment regimen was compared with a 1-mg/kg dose and placebo in two phase III randomized, placebo-controlled international studies of more than 1,600 patients (mean age 36-40 years) with active autoantibody-positive SLE.

The study participants were on standard immunosuppressive treatments. Most had musculoskeletal and mucocutaneous manifestations of SLE at baseline; those with kidney or CNS disease were excluded.

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proportion of patients on the 10-mg/kg dose met the primary end point – a combination of measures that indicated a reduction in disease activity – compared with those on placebo.

In one study, conducted primarily in Latin America and Asia, 58% of those on the 10-mg/kg dose met the primary end point, compared with 51% of those on the 1-mg/kg dose and 44% of those on placebo.

In the second study, conducted in North America and Western Europe, 43% of those on the 10-mg/kg dose met the primary end point, compared with 41% in the low-dose group and 34% in the placebo group.

There were more deaths, serious infections, and neurologic and psychiatric adverse events (including two suicides) among belimumab-treated patients in the phase III and earlier studies, although the numbers of these events was low.

Panelists were not overly concerned with these data, and agreed in a 14-1 vote that the safety profile of belimumab supported its approval. They strongly recommended that long-term safety should be followed in studies of a large number of patients.

The panel was concerned that in the trial that enrolled North American patients treatment was not effective in black patients and agreed with the company's plans to prospectively study responses in this population in postmarketing studies.

The FDA usually follows the recommendations of its advisory panels, members of which have been cleared of conflicts related to the meeting topic. If belimumab is approved, HGS plans to market it as Benlysta. ■

Brief Summary: Consult package insert for complete Prescribing Information.

INDICATIONS AND USAGE:

Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture. Prolia 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, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures (*See Clinical Studies [14.1] in Full Prescribing Information*).

DOSAGE AND ADMINISTRATION: Recommended Dosage. Prolia should be administered by a healthcare professional. The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily (*See Warnings and Precautions*).

If a dose of Prolia is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.

CONTRAINDICATIONS: Hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia (*See Warnings and Precautions*).

WARNINGS AND PRECAUTIONS: Hypocalcemia and Mineral Metabolism. Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g., history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium and mineral levels [phosphorus and magnesium] is highly recommended. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation. Adequately supplement all patients with calcium and vitamin D (*See Dosage and Administration, Contraindications, Adverse Reactions, and Patient Counseling Information [17.1] in Full Prescribing Information*).

Serious Infections. In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group (*See Adverse Reactions*). Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in Prolia-treated subjects. The incidence of opportunistic infections was balanced between placebo and Prolia 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. Consider the benefit-risk profile in such patients before treating with Prolia. In patients who develop serious infections while on Prolia, prescribers should assess the need for continued Prolia therapy.

Dermatologic Adverse Reactions. In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group. Most of these events were not specific to the injection site (*See Adverse Reactions*). Consider discontinuing Prolia if severe symptoms develop.

Osteonecrosis of the Jaw. Osteonecrosis of the jaw (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 (*See Adverse Reactions*). A routine oral exam should be performed by the prescriber prior to initiation of Prolia treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with Prolia. 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 Prolia 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 Prolia therapy should be considered based on individual benefit-risk assessment.

Suppression of Bone Turnover. In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry (*See Clinical Pharmacology [12.2] and Clinical Studies [14.1] in Full Prescribing Information*). The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

ADVERSE REACTIONS: The following serious adverse reactions are discussed below and also elsewhere in the labeling:

- Hypocalcemia (*See Warnings and Precautions*)
- Serious Infections (*See Warnings and Precautions*)
- Dermatologic Adverse Reactions (*See Warnings and Precautions*)
- Osteonecrosis of the Jaw (*See Warnings and Precautions*)

The most common adverse reactions reported with Prolia are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions leading to discontinuation of Prolia are breast cancer, back pain, and constipation. The Prolia Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please see www.proliasafety.com or call 1-800-772-6436 for more information about this program.



Clinical Trials Experience. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Treatment of postmenopausal women with osteoporosis

The safety of Prolia in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day. The incidence of all-cause mortality was 2.3% (n = 90) in the placebo group and 1.8% (n = 70) in the Prolia group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and Prolia groups, respectively. Adverse reactions reported in ≥ 2% of postmenopausal women with osteoporosis and more frequently in the Prolia-treated women than in the placebo-treated women are listed in the table below.

Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-treated Patients

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 [3.3]	107 [2.8]
CARDIAC DISORDERS		
Angina pectoris	101 [2.6]	87 [2.2]
Atrial fibrillation	79 [2.0]	77 [2.0]
EAR AND LABYRINTH DISORDERS		
Vertigo	195 [5.0]	187 [4.8]
GASTROINTESTINAL DISORDERS		
Abdominal pain upper	129 [3.3]	111 [2.9]
Flatulence	84 [2.2]	53 [1.4]
Gastroesophageal reflux disease	80 [2.1]	66 [1.7]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema peripheral	189 [4.9]	155 [4.0]
Asthenia	90 [2.3]	73 [1.9]
INFECTIONS AND INFESTATIONS		
Cystitis	228 [5.9]	225 [5.8]
Upper respiratory tract infection	190 [4.9]	167 [4.3]
Pneumonia	152 [3.9]	150 [3.9]
Pharyngitis	91 [2.3]	78 [2.0]
Herpes zoster	79 [2.0]	72 [1.9]
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia	280 [7.2]	236 [6.1]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1347 [34.7]	1340 [34.6]
Pain in extremity	453 [11.7]	430 [11.1]
Musculoskeletal pain	297 [7.6]	291 [7.5]
Bone pain	142 [3.7]	117 [3.0]
Myalgia	114 [2.9]	94 [2.4]
Spinal osteoarthritis	82 [2.1]	64 [1.7]
NERVOUS SYSTEM DISORDERS		
Sciatica	178 [4.6]	149 [3.8]
PSYCHIATRIC DISORDERS		
Insomnia	126 [3.2]	122 [3.1]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	96 [2.5]	79 [2.0]
Pruritus	87 [2.2]	82 [2.1]

Hypocalcemia. Decreases in serum calcium levels to less than 8.5 mg/dL were reported in 0.4% women in the placebo group and 1.7% women in the Prolia group at the month 1 visit. The nadir in serum calcium level occurs at approximately day 10 after Prolia dosing in subjects with normal renal function.

In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 patients with varying degrees of renal function, serum calcium levels < 7.5 mg/dL or symptomatic hypocalcemia were observed in 5 subjects. These included no subjects in the normal renal function group, 10% of subjects in the CrCL 50 to 80 mL/min group, 29% of subjects in the CrCL < 30 mL/min group, and 29% of subjects in the hemodialysis group. These subjects did not receive calcium and vitamin D supplementation. In a study of 4550 postmenopausal women with osteoporosis, the mean change from baseline in serum calcium level 10 days after Prolia dosing was -5.5% in subjects with creatinine clearance < 30 mL/min vs. -3.1% in subjects with CrCL ≥ 30 mL/min.

Serious Infections. Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as Prolia may increase the risk of infection. In the clinical study of 7808 postmenopausal women with osteoporosis, the incidence of infections resulting in death was 0.2% in both placebo and Prolia treatment groups. However, the incidence of nonfatal serious infections was 3.3% in the placebo group and 4.0% in the Prolia group. Hospitalizations due to serious infections in the abdomen [0.7% placebo vs. 0.9% Prolia], urinary tract [0.5% placebo vs. 0.7% Prolia], and ear [0.0% placebo vs. 0.1% Prolia] were reported. Endocarditis was reported in no placebo patients and 3 patients receiving Prolia. Skin infections, including erysipelas and cellulitis, leading to hospitalization were reported more frequently in patients treated with Prolia (< 0.1% placebo vs. 0.4% Prolia). There was no imbalance in the reporting of opportunistic infections.

Dermatologic Reactions. A significantly higher number of patients treated with Prolia developed epidermal and dermal adverse events (such as dermatitis, eczema, and rashes), with these events reported in 8.2% of placebo and 10.8% of Prolia group (p < 0.0001). Most of these events were not specific to the injection site (*See Warnings and Precautions*).

Osteonecrosis of the Jaw. ONJ has been reported in the osteoporosis clinical trial program in patients treated with Prolia (*See Warnings and Precautions*).

Pancreatitis. Pancreatitis was reported in 4 patients [0.1%] in the placebo and 8 patients [0.2%] in the Prolia groups. Of these reports, one subject in the placebo group and all 8 subjects in the Prolia group had serious events including one death in the Prolia group. Several patients had a prior history of pancreatitis. The time from product administration to event occurrence was variable.

New Malignancies. The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia groups. New malignancies related to breast [0.7% placebo vs. 0.9% Prolia], reproductive [0.2% placebo vs. 0.5% Prolia], and gastrointestinal systems [0.6% placebo vs. 0.9% Prolia] were reported. A causal relationship to drug exposure has not been established.

Immunogenicity. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% [55 out of 8113] of patients treated with Prolia for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biological assay. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS: No drug-drug interaction studies have been conducted with Prolia.

USE IN SPECIFIC POPULATIONS:

Pregnancy. Pregnancy Category C. There are no adequate and well-controlled studies of Prolia in pregnant women. In genetically engineered mice in which RANK ligand (RANKL) was turned off by gene removal [a "knockout mouse"], absence of RANKL [the target of denosumab] caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice also showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (*See Use in Nursing Mothers*). Prolia is approved only for use in postmenopausal women. Prolia should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who become pregnant during Prolia treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll. In an embryofetal developmental study, cynomolgus monkeys received subcutaneous denosumab weekly during organogenesis at doses up to 13-fold higher than the recommended human dose of 60 mg administered once every 6 months based on body weight (mg/kg). No evidence of maternal toxicity or fetal harm was observed. However, this study only assessed fetal toxicity during a period equivalent to the first trimester and fetal lymph nodes were not examined. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Potential adverse developmental effects resulting from exposures during the second and third trimesters have not been assessed in animals (*See Nonclinical Toxicology [13.2] in Full Prescribing Information*).

Nursing Mothers. It is not known whether Prolia is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Prolia, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Maternal exposure to Prolia during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (*See Nonclinical Toxicology [13.2] in Full Prescribing Information*).

Pediatric Use. Prolia is not recommended in pediatric patients. The safety and effectiveness of Prolia in pediatric patients have not been established. Treatment with Prolia may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL [the target of Prolia therapy] with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates dosed with denosumab at 10 and 50 times (10 and 50 mg/kg dose) higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg), had abnormal growth plates (*See Nonclinical Toxicology [13.2] in Full Prescribing Information*).

Geriatric Use. Of the total number of patients in clinical studies of Prolia, 9943 patients (76%) were ≥ 65 years old, while 3576 (27%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment. No dose adjustment is necessary in patients with renal impairment. In clinical studies, patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis were at greater risk of developing hypocalcemia. Consider the benefit-risk profile when administering Prolia to patients with severe renal impairment or receiving dialysis. Clinical monitoring of calcium and mineral levels [phosphorus and magnesium] is highly recommended. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (*See Warnings and Precautions, Adverse Reactions, and Clinical Pharmacology [12.3] in Full Prescribing Information*).

Hepatic Impairment. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Prolia.

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