FDA Accepts Supplemental Biologics License Application For Prolia® (Denosumab) In Glucocorticoid-Induced Osteoporosis

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Glucocorticoid-Induced Osteoporosis is the Most Common Form of Secondary Osteoporosis

THOUSAND OAKS, Calif., Oct. 9, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the supplemental Biologics License Application (sBLA) for Prolia® (denosumab) for the treatment of patients with glucocorticoid-induced osteoporosis (GIOP). The sBLA, which was submitted on July 28, 2017, is based on a Phase 3 study evaluating Prolia compared with risedronate in patients receiving glucocorticoid treatment. The FDA has set a Prescription Drug User Fee Act (PDUFA) action date of May 28, 2018.

Glucocorticoid medications, which are used to treat many inflammatory conditions, can cause significant side effects, including bone loss. GIOP is the most common form of secondary osteoporosis[1], and it is estimated that one percent of the U.S. population is treated long-term with glucocorticoid medications.[2] Within the first three months of beginning glucocorticoid treatment, fracture risk increases by up to 75 percent, with bone mineral density (BMD) continuing to decline significantly in the months that follow.[3]

"We believe that Prolia can address a critical treatment need for patients with glucocorticoid-induced osteoporosis, which is the most common drug-induced form of the disease," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "We will continue to work closely with the FDA as they review our application and look forward to expanding Prolia's benefits to patients with this serious condition that is often underestimated and untreated."

The sBLA is supported by a Phase 3 randomized, double-blind, double-dummy, active-controlled study evaluating the safety and efficacy of Prolia compared with risedronate in patients receiving glucocorticoid treatment.[4] The study included two patient groups: those receiving continuing glucocorticoid therapy and those newly initiating glucocorticoid therapy. The study met the primary endpoint (percent change from baseline in lumbar spine BMD at 12 months, assessing non-inferiority) and all secondary endpoints assessed at 12 months (the percent changes from baseline in lumbar spine and total hip BMD, assessing superiority). Study results showed that, in patients receiving continuing glucocorticoid therapy, Prolia treatment led to greater gains in BMD, compared with risedronate, both at the lumbar spine (4.4 percent versus 2.3 percent, respectively) and total hip (2.1 percent versus 0.6 percent, respectively). Similarly, in patients newly initiating glucocorticoid therapy, Prolia treatment led to greater increases in BMD, compared with risedronate, both at the lumbar spine (3.8 percent versus 0.8 percent, respectively) and total hip (1.7 percent versus 0.2 percent, respectively).

Adverse events and serious adverse events were similar between treatment groups and consistent with the known safety profile of Prolia. No serious adverse events were reported with a subject incidence of two percent or greater in either treatment group.

About Glucocorticoid-Induced Osteoporosis (GIOP)

GIOP is the most common form of secondary osteoporosis[1], and it is estimated that one percent of the U.S. population is treated long-term with glucocorticoid medications.[2] While the number of GIOP patients that overlap with osteoporosis patients is not clear, the most frequent chronic inflammatory diseases associated with long-term glucocorticoid use are chronic obstructive pulmonary disorder (COPD), asthma and rheumatoid arthritis.[5] The exact prevalence is not clear due to overlap with the osteoporosis population. More than 10 percent of patients who receive long-term glucocorticoid treatment are diagnosed with a clinical fracture, and 30 to 40 percent have radiographic evidence of vertebral fractures.[6,7]

About Prolia® (denosumab)

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.

Prolia 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.

Prolia 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 Prolia also reduced the incidence of vertebral fractures.

Prolia 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 (U.S.)

Contraindications

Prolia is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia. Prolia is contraindicated in women who are pregnant and may cause fetal harm. Prolia is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling and urticaria.

Same Active Ingredient

Prolia contains the same active ingredient (denosumab) found in XGEVA®. Patients receiving Prolia should not receive XGEVA®.

Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia. 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 Prolia.

Hypocalcemia
Hypocalcemia may worsen with the use of Prolia, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended within 14 days of Prolia injection. Adequately supplement all patients with calcium and vitamin D.

Osteonecrosis of the Jaw (ONJ)
ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia. An oral exam should be performed by the prescriber prior to initiation of Prolia. A dental examination with appropriate preventive dentistry is recommended prior to treatment 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 co-morbid disorders. Good oral hygiene practices should be maintained during treatment with Prolia. The risk of ONJ may increase with duration of exposure to Prolia.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia should be considered based on individual benefit-risk assessment.

Atypical Femoral Fractures
Atypical low-energy, or low trauma fractures of the shaft have been reported in patients receiving Prolia. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents.

During Prolia 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 evaluated to rule out an incomplete femur fracture. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment
Following discontinuation of Prolia treatment, 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 Prolia. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia discontinuation. Evaluate an individual's benefit/risk before initiating treatment with Prolia. If Prolia treatment is discontinued, consider transitioning to an alternative anti-resorptive therapy.

Serious Infections
In a clinical trial (N= 7808) in women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group 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 Prolia.

Endocarditis was also reported more frequently in Prolia-treated patients. The incidence of opportunistic infections and the overall incidence of infections were 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 Prolia, prescribers should assess the need for continued Prolia therapy.

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

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking Prolia. Consider discontinuing use if severe symptoms develop.

Suppression of Bone Turnover
In clinical trials in women with postmenopausal osteoporosis, Prolia 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 are unknown. Monitor patients for these consequences, including ONJ, atypical fractures, and delayed fracture healing.

Adverse Reactions
The most common adverse reactions (>5% and more common than placebo) in women 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) in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. Pancreatitis has been reported with Prolia.

In women with postmenopausal osteoporosis, the overall incidence of new malignancies was 4.3% in the placebo group and 4.8% in the Prolia group. In men with osteoporosis, new malignancies were reported in no patients in the placebo group and 4 (3.3%) patients in the Prolia group. A causal relationship to drug exposure has not been established.

The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. Additionally, in Prolia-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed.

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

For more information, please see the Prolia Prescribing Information, and Medication Guide.

About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Amgen Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including its most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those Amgen projects. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for Amgen to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and Amgen expects similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints Amgen has selected. Amgen develops product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as Amgen may have believed at the time of entering into such relationship. Also, Amgen or others could identify safety, side effects or manufacturing problems with its products, including its devices, after they are on the market.

Amgen's results may be affected by its ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing its products and global economic conditions. In addition, sales of Amgen's products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, Amgen's research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Amgen's business may be impacted by government investigations, litigation and product liability claims. In addition, Amgen's business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If Amgen fails to meet the compliance obligations in the corporate integrity agreement between it and the U.S. government, Amgen could become subject to significant sanctions. Further, while Amgen routinely obtains patents for its products and technology, the protection offered by its patents and patent applications may be challenged, invalidated or circumvented by its competitors, or Amgen may fail to prevail in present and future intellectual property litigation. Amgen performs a substantial amount of its commercial manufacturing activities at a few key manufacturing facilities and also depends on third parties for a portion of its manufacturing activities, and limits on supply may constrain sales of certain of its current products and product candidate development. In addition, Amgen competes with other companies with respect to many of its marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for Amgen's products are supplied by sole third-party suppliers. Certain of Amgen's distributors, customers and payers have substantial purchasing leverage in their dealings with Amgen. The discovery of significant problems with a product similar to one of Amgen's products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on its business and results of operations. Amgen's efforts to acquire other companies or products and to integrate the operations of companies Amgen has acquired may not be successful. Amgen may not be able to access the capital and credit markets on terms that are favorable to it, or at all. Amgen is increasingly dependent on information technology systems, infrastructure and data security. Amgen's stock price may be volatile and may be affected by a number of events. Amgen's business performance could affect or limit the ability of the Amgen Board of Directors to declare a dividend or its ability to pay a dividend or repurchase its common stock.

The scientific information discussed in this news release relating to new indications is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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References

1. Briot K, Roux C. Glucocorticoid-induced osteoporosis. RMD Open. 2015;1:e000014.
2. Buckley L, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Rheum. 2017;69:1521-1537.
3. Weinstein RS. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. ASBMR 8th Edition. 2013.
4. Effect of Denosumab Compared With Risedronate in Glucocorticoid-treated Individuals: Results From the 12-month Primary Analysis of a Randomized, Double-blind, Active-controlled Study. Presented at the Annual American College of

Rheumatology (ACR) and Association of Rheumatology Health Professionals (ARHP) Annual Meeting in Washington, D.C., Nov.11-16, 2016.
5. Feldstein A, et al. Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. Osteoporosis Int. 2005;16:2168-2174.
6. Curtis J, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006; 55:420-6.
7. Angeli A, Guglielmi G, Dovio A, Capelli G, de Feo D, Giannini S, et al. High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. Bone. 2006;39:253-9.

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