FDA Accepts Amgen's Supplemental Biologics License Application To Expand Indication For XGEVA® (denosumab) To Include Multiple Myeloma Patients

June 19, 2017

FDA Sets PDUFA Target Action Date of Feb. 3, 2018

THOUSAND OAKS, Calif., June 19, 2017 /PRNewswire/ -- Amgen (NASDAQ: AMGN) today announced that the U.S. Food and Drug Administration (FDA) has accepted the XGEVA® (denosumab) supplemental Biologics License Application (sBLA) that seeks to expand the currently approved indication for the prevention of fractures and other skeletal-related events in patients with bone metastases from solid tumors to include patients with multiple myeloma. The FDA has set a Prescription Drug User Fee Act (PDUFA) action date of Feb. 3, 2018.

"Multiple myeloma patients with fractures and other bone complications have a very poor prognosis. Bisphosphonates are the only approved class of agents for the prevention of skeletal-related events in this patient population. However, these agents have several limitations, including kidney toxicity and acute phase reactions," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Based on the data we have submitted to the FDA, we look forward to potentially making XGEVA available as a novel option for patients with multiple myeloma."

XGEVA is the first fully human monoclonal antibody that binds to and neutralizes RANK ligand (RANKL) – a protein essential for the formation, function and survival of osteoclasts, which break down bone – thereby inhibiting osteoclast-mediated bone destruction. XGEVA is not cleared by the kidneys. XGEVA is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors and is the number one prescribed agent by oncologists for this indication in the U.S. In the U.S., XGEVA currently has a limitation of use noting that it is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

The sBLA, submitted on April 3, 2017, is based on the efficacy and safety data from the pivotal Phase 3 '482 study, the largest international multiple myeloma trial ever conducted, which successfully demonstrated that XGEVA is non-inferior to zoledronic acid in delaying the time to first on-study skeletal-related event in patients with multiple myeloma. The secondary endpoints of superiority in delaying time to first on-study skeletal-related event and delaying time to first-and-subsequent skeletal-related event were not met in this study. Progression-free survival was an exploratory endpoint. The hazard ratio of XGEVA versus zoledronic acid for progression-free survival was 0.82 (95 percent CI: 0.68, 0.99; descriptive *p*=0.036) and the median difference in progression-free survival between arms was 10.7 months in favor of XGEVA. Data from the '482 study are also the basis of an application for a variation to the marketing authorization submitted to the European Medicines Agency (EMA).

About '482 Study (NCT01345019)
The '482 study was an international, Phase 3, randomized, double-blind, multicenter trial of XGEVA compared with zoledronic acid in the prevention of skeletal-related events in adult patients with newly diagnosed multiple myeloma. In the study, a total of 1,718 patients (859 on each arm) were randomized to receive either subcutaneous XGEVA 120 mg and intravenous placebo every four weeks, or intravenous zoledronic acid 4 mg (adjusted for renal function) and subcutaneous placebo every four weeks.

The primary endpoint of the study was non-inferiority of XGEVA versus zoledronic acid with respect to time to first on-study skeletal-related event (pathologic fracture, radiation to bone, surgery to bone or spinal cord compression). Secondary endpoints included superiority of XGEVA over zoledronic acid with respect to time to first on-study and first-and-subsequent on-study skeletal-related event and evaluation of overall survival. The hazard ratio of overall survival was 0.90 for XGEVA as compared to zoledronic acid (95 percent CI: 0.70, 1.16). The hazard ratio of XGEVA versus zoledronic acid for progression-free survival, an exploratory endpoint, was 0.82 (95 percent CI: 0.68, 0.99; descriptive *p*=0.036). The median difference in progression-free survival between arms was 10.7 months in favor of XGEVA. The safety and tolerability of XGEVA were also compared with zoledronic acid in the study. The most common adverse events (greater than or equal to 25 percent) in both arms were diarrhea and nausea.

About Multiple Myeloma and Bone Complications (Skeletal-Related Events)
Multiple myeloma is the second most common hematologic cancer, and it develops in plasma cells located in the bone marrow microenvironment.[1,2] It is typically characterized by osteolytic bone lesions and renal impairment, which are both part of diagnosis (CRAB criteria).[3,4] Each year an estimated 114,000 new cases of multiple myeloma are diagnosed worldwide, resulting in more than 80,000 deaths per year.[1]

More than 90 percent of patients develop osteolytic lesions during the course of the disease.[3] Current treatment options for bone complications are limited to bisphosphonates, including zoledronic acid; these are cleared by the kidneys and are associated with renal toxicity which is a common complication among multiple myeloma patients.[5] The majority (approximately six out of 10) of all multiple myeloma patients have or will develop renal impairment over the course of the disease.[6] Preventing bone complications is a critical aspect of caring for patients with multiple myeloma, because these events can cause significant morbidity.[7]

About XGEVA® (denosumab)
XGEVA targets the RANKL pathway to prevent the formation, function and survival of osteoclasts, which break down bone. As a monoclonal antibody, XGEVA is not cleared by the kidneys. XGEVA is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors. In the U.S., XGEVA currently has a limitation of use noting that it is not indicated for the prevention of skeletal-related events in patients with multiple myeloma. XGEVA is also indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. XGEVA is also indicated in the U.S. for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

U.S. Important Safety Information

Hypocalcemia
Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and

vitamin D as necessary. Monitor levels more frequently when XGEVA® is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.

An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Hypersensitivity

XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient

Patients receiving XGEVA® should not take Prolia® (denosumab).

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with osseous metastasis, the incidence of ONJ was higher with longer duration of exposure.

Patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance are at a greater risk to develop ONJ. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®. Consider temporarily interrupting XGEVA® therapy if an invasive dental procedure must be performed.

Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® 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. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Hypercalcemia Following Treatment Discontinuation in Patients with Growing Skeletons

Clinically significant hypercalcemia has been reported in XGEVA® treated patients with growing skeletons, weeks to months following treatment discontinuation. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately.

Embryo-Fetal Toxicity

XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects.

Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Adverse Reactions

The most common adverse reactions in patients receiving XGEVA® with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.

The most common adverse reactions in patients receiving XGEVA® for giant cell tumor of bone were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis. The most common adverse reactions resulting in discontinuation of XGEVA® were osteonecrosis of the jaw and tooth abscess or tooth infection.

The most common adverse reactions in patients receiving XGEVA® for hypercalcemia of malignancy were nausea, dyspnea, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea.

Denosumab is also marketed as Prolia® in other indications.

Please visit www.amgen.com or www.xgeva.com for Full U.S. Prescribing Information.

About Amgen's Commitment to Oncology

Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

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.

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 our 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 we project. 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 us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop 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 we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products after they are on the market.

Our results may be affected by our 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 our products and global economic conditions. In addition, sales of our 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, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. We or others could identify safety, side effects or manufacturing problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock.

The scientific information discussed in this news release relating to new indications for our products 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. Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence in 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed April 25, 2017.
2. Multiple Myeloma Research Foundation. What is Multiple Myeloma? https://www.themmrf.org/multiple-myeloma/what-is-multiple-myeloma/. Accessed April 25, 2017.
3. Roodman GD. Pathogenesis of myeloma bone disease. *Leukemia.* 2009;23(3):435–441.
4. International Myeloma Working Group. International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma. http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/. Accessed April 25, 2017.
5. Terpos E, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. 2013;31(18):2347-57.
6. Amgen Data on File.
7. Drake MT. Bone disease in multiple myeloma. *Oncology (Williston Park)*. 2009;23(14 Suppl 5):28-32.