European Commission Approves Expanded Indication For Amgen's XGEVA® (denosumab) For The Prevention Of Skeletal-Related Events In Patients With Multiple Myeloma

April 3, 2018

This Approval was Based on the Largest International Trial Ever Conducted for the Prevention of Skeletal-Related Events in Multiple Myeloma Patients

THOUSAND OAKS, Calif., April 2, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the European Commission (EC) has approved an expanded indication for XGEVA® (denosumab) for the prevention of skeletal-related events in adults with advanced malignancies involving bone. The indication now covers patients with bone metastases from solid tumors and those with multiple myeloma. The approval is based on data from the Phase 3 '482 study, the largest international trial ever conducted for the prevention of skeletal-related events in multiple myeloma patients.

"Many patients with multiple myeloma have bone lesions at diagnosis, which can result in serious and devastating complications, including broken bones, the need for surgery or radiation to the bone and spinal cord compression," said David M. Reese, M.D., senior vice president of Translational Sciences and Oncology at Amgen. "Until now, treatment options for the prevention of bone complications were limited to bisphosphonates, which unlike XGEVA, are cleared by the kidneys and can be associated with increased renal toxicity. We are pleased with the expanded indication for XGEVA in Europe, underscoring our dedication to advancing care for patients with multiple myeloma."

In the Phase 3 '482 study, XGEVA successfully met the primary endpoint, demonstrating non-inferiority to zoledronic acid in delaying the time to first on-study skeletal-related event in patients with multiple myeloma (HR=0.98, 95 percent CI: 0.85-1.14). The median time to first on-study skeletal-related event was 22.8 months for XGEVA and 24.0 months for zoledronic acid. The safety profile was consistent with known adverse events of XGEVA.

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, cells which break down bone – thereby inhibiting osteoclast-mediated bone destruction. On Jan. 5, 2018, the U.S. Food and Drug Administration approved the supplemental Biologics License Application for XGEVA to expand the currently approved indication for the prevention of skeletal-related events in patients with bone metastases from solid tumors to include patients with multiple myeloma. Additional regulatory applications for XGEVA for the prevention of skeletal-related events in patients with multiple myeloma are underway and have been submitted to health authorities worldwide.

Approval from the EC grants a centralized marketing authorization with unified labeling in the 28 countries that are members of the European Union (EU). Norway, Iceland and Liechtenstein, as members of the European Economic Area, will take corresponding decisions on the basis of the decision of the EC.

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 and bone disease. 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 at baseline) and subcutaneous placebo every four weeks, plus investigators' choice first-line antimyeloma therapy. Skeletal surveys using conventional radiography were obtained every 12 to 24 weeks per protocol. 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 versus zoledronic acid with respect to time to first on-study skeletal-related event and first-and-subsequent on-study skeletal-related event and evaluation of overall survival. Progression-free survival was a prespecified, exploratory endpoint and was not powered for statistical significance. The secondary endpoints, delaying time to first skeletal-related event and delaying time to first-and-subsequent skeletal-related events, did not demonstrate superiority. Overall survival was comparable between XGEVA and zoledronic acid, with a hazard ratio of 0.90 (95 percent CI: 0.70, 1.16). Median progression-free survival was 46.1 months (95 percent CI: 34.3 months, not estimable [NE], n=219) for XGEVA and 35.4 months (95 percent CI: 30.2 months, NE, n=260) for zoledronic acid.

The safety and tolerability of XGEVA were also compared with zoledronic acid. The safety profile was consistent with known adverse events of XGEVA. The most common adverse reactions (greater than or equal to 10 percent) were diarrhea, musculoskeletal pain, hypocalcaemia and dyspnea.

About Multiple Myeloma and Bone Complications

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 as well as renal failure, which are both part of diagnosis (CRAB criteria).[3] 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.[4] Preventing bone complications is a critical aspect of caring for patients with multiple myeloma, because these events can result in significant morbidity.[5] Current treatment options to prevent bone complications are limited to bisphosphonates, including zoledronic acid, which are cleared through the kidneys.[6] Approximately 60 percent of all multiple myeloma patients have or will develop renal impairment over the course of the disease.[7]

About XGEVA® (denosumab)

XGEVA targets the RANKL pathway to prevent the formation, function and survival of osteoclasts, which break down bone. In the EU, XGEVA is indicated for the prevention of skeletal-related events in adults with advanced malignancies involving bone. XGEVA is also indicated in the EU for 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.

In the U.S., XGEVA is indicated for:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- 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.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

EU Important Safety Information

∇ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Calcium and Vitamin D supplementation
Supplementation with calcium and vitamin D is required in all patients unless hypercalcemia is present.

Hypocalcemia
Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. Hypocalcemia can occur at any time during therapy with XGEVA®. Monitoring of calcium levels should be conducted (i) prior to the initial dose of XGEVA®, (ii) within two weeks after the initial dose, (iii) if suspected symptoms of hypocalcemia occur. Additional monitoring of calcium level should be considered during therapy in patients with risk factors for hypocalcemia, or if otherwise indicated based on the clinical condition of the patient.

Patients should be encouraged to report symptoms indicative of hypocalcemia. If hypocalcemia occurs while receiving XGEVA®, additional calcium supplementation and additional monitoring may be necessary.

In the post marketing setting, severe symptomatic hypocalcemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy, but can occur later.

Renal impairment
Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcemia. The risk of developing hypocalcemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels is especially important in these patients.

Osteonecrosis of the jaw (ONJ)
ONJ has been reported commonly in patients receiving XGEVA®.

The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with XGEVA®.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- cancer, co-morbid conditions (e.g. anemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, pre-existing dental disease, invasive dental procedures (e.g. tooth extractions).

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with XGEVA®. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to XGEVA® administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of XGEVA® treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur
Atypical femoral fractures have been reported in patients receiving XGEVA. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of XGEVA therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. During XGEVA treatment,

patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

Patients with growing skeletons

XGEVA® is not recommended in patients with growing skeletons. Clinically significant hypercalcemia has been reported in XGEVA®-treated patients with growing skeletons weeks to months following treatment discontinuation.

Others

Patients being treated with XGEVA® should not be treated concomitantly with other denosumab containing medicinal products (for osteoporosis indications).

Patients being treated with XGEVA® should not be treated concomitantly with bisphosphonates.

Malignancy in Giant Cell Tumour of Bone or progression to metastatic disease is an infrequent event and a known risk in patients with Giant Cell Tumour of Bone. Patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis. Available clinical data does not suggest an increased risk of malignancy in GCTB patients treated with XGEVA®.

Warnings for excipients

XGEVA® contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use XGEVA®.

This medicinal product contains less than 1 mmol sodium (23 mg) per 120 mg, i.e. essentially 'sodium-free'.

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 cancer, 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.

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation
Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures. When XGEVA® treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

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 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.

For multiple myeloma patients receiving XGEVA®, the most common adverse reactions were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. The most common serious adverse reaction was pneumonia. The most common adverse reaction resulting in discontinuation of XGEVA® was osteonecrosis of the jaw.

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 current reports on 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, including our devices, 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. 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, including in Puerto Rico, 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. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data security. 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. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

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 or the EMA 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.

CONTACT: Amgen, Thousand Oaks
Kristen Davis, 805-447-3008 (Media)
Kristen Neese, 805-313-8267 (Media)
Arvind Sood, 805-447-1060 (Investors)

Amgen, Europe
Emma Gilbert, +41 413692542

References:

1. Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence in 2012. http://globocan.iarc.fr/Pages /fact_sheets_population.aspx. Accessed March 26, 2018.
2. Multiple Myeloma Research Foundation. What is Multiple Myeloma? https://www.themmrf.org/multiple-myeloma/what-is-multiple-myeloma/. Accessed March 26, 2018.
3. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538-e548.
4. Kristinsson SY, Minter AR, Korde N, et al. Bone disease in multiple myeloma and precursor disease: novel diagnostic approaches and implications on clinical management. *Expert Rev Mol Diagn*. 2011;11(6): 593–603.
5. Drake MT. Bone disease in multiple myeloma. *Oncology (Williston Park)*. 2009;23(14 Suppl 5):28-32.
6. 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.
7. Bhowmik D, et al. Prevalence Of Renal Impairment In Patients With Multiple Myeloma: Analysis Of Real-World Database. *Journal of the International Society for Pharmacoeconomic and Outcomes Research*. 2016;9(3):A141.

View original content with multimedia:http://www.prnewswire.com/news-releases/european-commission-approves-expanded-indication-for-amgens-xgeva-denosumab-for-the-prevention-of-skeletal-related-events-in-patients-with-multiple-myeloma-300623000.html

SOURCE Amgen