CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125320

OFFICE DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: June 1, 2010

TO: BLA 125320
PROLIA (denosumab) Injection, 60 mg/mL
Amgen, Inc.

FROM: Julie Beitz, M.D. Julie Beitz 6/1/10
Director, Office of Drug Evaluation III

RE: Approval Action

Denosumab is a fully human IgG2 monoclonal antibody that targets receptor activator of nuclear factor kappa B ligand (RANKL), a member of the tumor necrosis factor superfamily of cytokines. RANKL promotes osteoclast formation, differentiation and activation, as well as B cell and T cell differentiation and dendritic cell maturation. Blockade of RANKL is believed to result in decreased bone resorption, and increased bone mass and strength in both cortical and trabecular bone.

This memo documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP's) recommendation for approval of Prolia (denosumab), administered by subcutaneous injection every 6 months, for the treatment of postmenopausal women with osteoporosis at high risk of fracture. Discussions regarding the product label, REMS, and postmarketing requirements and commitments have concluded satisfactorily.

REGULATORY HISTORY

BLA 125320 was received on December 19, 2008 and granted a standard review. Given that the BLA contained data regarding four distinct indications, it was administratively split as follows: BLAs 125320 and 125331 supporting the treatment and prevention of postmenopausal osteoporosis, respectively, and BLAs 125332 and 125333 supporting the treatment and prevention of bone loss in patients undergoing hormone ablation for breast and prostate cancer, respectively. The Division of Reproductive and Urologic Products

reviewed the postmenopausal osteoporosis indications while the Division of Biologic Oncology Products reviewed the oncology indications.[1]

All four proposed indications were discussed before the Reproductive Health Drugs Advisory Committee (RHDAC) on August 13, 2009. Although denosumab has been shown to be effective in reducing the risk of fracture in subjects with postmenopausal osteoporosis, several potentially serious risks were reported more frequently with denosumab use including serious infections, serious dermatologic adverse events, and the potential for oversuppression of bone turnover and resulting sequelae (e.g., atypical fractures, osteonecrosis of the jaw, and delayed fracture healing).

Considering all the available data, the RHDAC unanimously (15 to 0) recommended approval of denosumab for the treatment of postmenopausal osteoporosis; however, many Committee members advised that the indicated population should be limited to those subjects with a high risk of fracture given the concerns regarding the potential long-term risks of denosumab treatment.

Twelve Committee members also advised that denosumab have a risk evaluation and mitigation strategy or REMS if it is approved. Committee members recommended the implementation of a Medication Guide and a communication plan to advise denosumab users and healthcare providers, respectively, of the risks associated with denosumab. Some members also suggested that a registry was warranted to better monitor safety outcomes in denosumab users prospectively.

DRUP staff and I were in general agreement with the recommendations of the RHDAC. On October 2, 2009, the applicant was notified that a REMS would be required for denosumab if it is approved. The elements of the REMS would be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. Amgen submitted a proposed REMS on October 8, 2009.

On October 16, 2009, a complete response letter was issued for BLA 125320 requesting that the applicant submit adequate information demonstrating the feasibility of, and the methodologies to be used, in a required postmarketing observational study in administrative claims databases designed to assess the long-term risks of denosumab. In addition, FDA would need to review the designs of a long-term, targeted surveillance study in subjects with postmenopausal osteoporosis receiving denosumab, and of a proposed pregnancy exposure registry study. Review of the REMS and labeling negotiations were deferred to the next cycle. On January 25, 2010, the applicant submitted a complete response to the October 2009 action letter.

EFFICACY

The efficacy of denosumab 60 mg relative to placebo for the treatment of postmenopausal osteoporosis was assessed in a single randomized, placebo-controlled trial. Study 20030216 was a 3-year clinical trial that randomized 7808 women to receive subcutaneous injections of either denosumab (N = 3906) or placebo (N = 3906) once

[1] See my previous review dated October 16, 2009 for additional details regarding BLAs 125320 and 125331.

every six months. Enrolled subjects were women aged 60-91 years (mean age 72) with a mean BMD T-score of -2.8 at the lumbar spine. Nearly a quarter of enrolled subjects had a vertebral fracture at baseline. Treatment with denosumab resulted in a 68% reduction in the risk of new radiologically-diagnosed vertebral fractures at year 3 compared to placebo (95% CI: 59, 74; $p < 0.0001$). Denosumab reduced the risk of new vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD or history of fracture, or prior use of osteoporosis medications.

Reductions in the incidence of hip and non-vertebral fractures were also seen with denosumab treatment. At year 3, the relative risk reduction in hip fractures was 40% ($p = 0.04$) and 20% in non-vertebral fractures ($p = 0.01$). Treatment also increased BMD at all sites at year 3 relative to placebo. Increases of 8.8% at the lumbar spine, 6.4% at the total hip, 5.2% at the femoral neck, and 8.3% at the trochanter were noted.

Approximately 45% of enrolled subjects were considered to be at high risk of fracture (defined as having 2 of the following: age > 70, prevalent fracture at baseline, or baseline BMD T-score of ≤ 3.0). Treatment with denosumab in these subjects resulted in a 65% reduction in the risk of new vertebral fracture ($p < 0.0001$). In addition, a significant reduction in the risk of hip fracture (but not non-vertebral fracture) was demonstrated with denosumab treatment.

SAFETY

The safety of denosumab 60 mg relative to placebo in the treatment of postmenopausal osteoporosis was also assessed in Study 20030216. The following is a summary of some of the major clinical safety findings.[2]

Deaths. All-cause mortality was 1.8% and 2.3% in denosumab-treated and placebo-treated subjects, respectively. The most common causes of death (neoplasms, cardiac disorders, and nervous system disorders) would be expected given the age of the enrolled population.

Serious Adverse Events. Rates of serious adverse events were similar in denosumab- and placebo-treated subjects (25% and 24%, respectively). The most common serious adverse events reported were cardiac disorders, musculoskeletal disorders, neoplasms, and infections.

Serious Infections. RANKL is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as denosumab may increase the risk of infection. In phase 1 trials, two relatively healthy subjects were hospitalized with pneumonia following treatment with denosumab.

The incidence of infections resulting in death was 0.2% in both treatment groups, but the incidence of non-fatal serious infections was 4.0% in denosumab-treated subjects as compared to 3.3% in placebo-treated subjects. The numeric imbalance in the incidence

[2] Limited information is available from denosumab-treated subjects who are enrolled in an ongoing, 7-year, open-label extension phase of Study 20030216. To date, no new safety concerns have been identified in subjects treated with denosumab for postmenopausal osteoporosis for > 3 years.

of serious infections was accounted for by events of cellulitis, erysipelas, diverticulitis, ear and urinary tract infections. Three subjects receiving denosumab developed endocarditis; no cases of endocarditis were reported on placebo. Opportunistic infections were rare and were balanced between treatment groups.

New Malignancies. Denosumab cannot be tested in a traditional 2-year rodent study to evaluate carcinogenic potential; while the applicant did evaluate a knock-in human RANKL transgenic mouse model and a surrogate rodent antibody, this was not considered an appropriate model for carcinogenicity testing.

New malignancies were reported in 4.8% of denosumab-treated subjects as compared to 4.3% of placebo-treated subjects. There were imbalances in the numbers of new malignancies in denosumab-treated subjects as compared to placebo-treated subjects involving breast, gastrointestinal, and reproductive tract cancer. Breast cancer was listed as the most common adverse event that led to study discontinuation in densumab-treated subjects with postmenopausal osteoporosis. The significance of these findings in a 3-year trial is unclear due to the long latency for the development of new malignancies.

Serious Dermatologic Adverse Events. Serious skin and soft tissue conditions, excluding infections, were reported more frequently in denosumab-treated subjects as compared to placebo-treated subjects (10.8% vs. 8.2%). These conditions included bullous conditions, photosensitivity, pruritis, skin rashes, dermatitis and eczema.

Pancreatitis. There were 8 serious reports of pancreatitis on denosumab as compared to one serious report and 3 non-serious reports on placebo. Many of these subjects had a prior history of pancreatitis. One of the denosumab-treated subjects with pancreatitis died.

Immunogenicity. The presence of binding antibodies to denosumab was evaluated in over 8000 subjects who received denosumab for up to five years. Positive results were found in less than 1% of subjects. There was no apparent correlation between positive binding antibody tests and altered pharmacokinetic profile, toxicity profile, or clinical response. None of the subjects tested positive for neutralizing antibodies.

Hypocalcemia. Hypocalcemia is a known class effect of antiresorptive drugs. In subjects with normal renal function, denosumab-induced hypocalcemia was transient, occurring in the first month after dosing (nadir at day 10) with spontaneous resolution and without any serious sequelae. In subjects who are predisposed to hypocalcemia and disturbances of mineral metabolism, or who have severe renal impairment (creatinine clearance < 30 mL/min) and/or are receiving dialysis, close monitoring of calcium, phosphorus and magnesium levels should be performed. All individuals receiving denosumab should be adequately supplemented with calcium and vitamin D. Pre-existing hypocalcemia should be corrected prior to initiating denosumab treatment.

Bone Histomorphometry. Parameters of bone resorption and formation are expected to decrease with denosumab therapy. Iliac crest bone biopsies were performed in 92 subjects in three trials (including 53 and 62 specimens from denosumab-treated and placebo-treated subjects, respectively). Absence of double tetracycline labeling in bone

biopsy specimens (suggestive of suppressed bone turnover and formation) was observed in 21% of denosumab-treated subjects at month 12, in 35% of subjects at month 24, and in 38% of subjects at month 36. Absence of labeling was not observed in any placebo-treated subject tested.

While there is little evidence for lasting suppressive effects on bone turnover after denosumab treatment is discontinued, the degree of suppression of bone turnover suggested by the available data remains a concern, especially with chronic denosumab use. In the clinical trial experience in postmenopausal osteoporosis, similar numbers of subjects developed complications related to fracture healing (21 on denosumab and 25 on placebo). Of hip or femur fractures sustained on treatment, only one was reported as subtrochanteric (i.e., atypical) in a subject receiving > 3 years of denosumab (on the extension phase of Study 20030216). The long-term effects of denosumab on bone turnover and the potential for complications of oversuppression will be the subject of required postmarketing studies (see below).

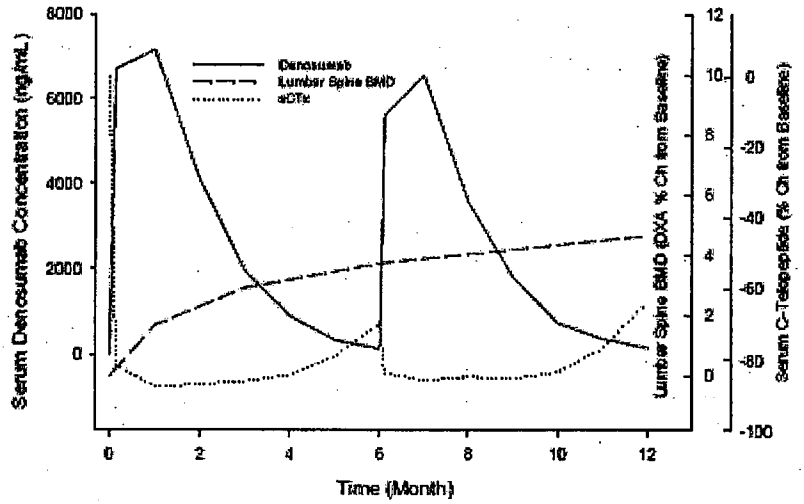
Osteonecrosis of the Jaw. Osteonecrosis of the jaw (ONJ) has been associated with long-term (> 3 years) bisphosphonate use and IV bisphosphonate use. An adjudicated case of ONJ has been identified in a subject treated with denosumab for postmenopausal osteoporosis; additional cases have been positively adjudicated in patients with multiple myeloma and other cancers who received higher doses of denosumab for prevention of bone metastases. A dental examination with appropriate preventive dentistry should be considered prior to starting treatment with denosumab in individuals at risk for developing ONJ, including those who have invasive dental procedures, poor oral hygiene, periodontal or other pre-existing dental disease, coagulopathy, anemia, infection or cancer.

CLINICAL PHARMACOLOGY

In a trial of healthy volunteers, the mean C_{max} following a single subcutaneous dose of denosumab 60 mg was attained at 10 days (range 3-21 days). After C_{max}, serum concentrations declined over a period of 4-5 months with a mean half-life of 25.4 days (SD = 8.5 days). No accumulation or change in denosumab pharmacokinetics with time was observed upon multiple dosing of 60 mg subcutaneously administered once every 6 months.

Following subcutaneous administration of denosumab 60 mg, the C_{max} for denosumab coincides with a rapid, dramatic, and sustained reduction in the bone resorption marker, serum type 1 C-telopeptide (sCTX1). At the end of each dosing interval, sCTX1 reductions become attenuated as serum denosumab concentrations decline, reflecting the reversibility of denosumab effects on bone remodeling. Upon re-dosing, the degree of inhibition of sCTX1 is similar. There is no adverse effect on lumbar spine BMD (see figure below).

Figure 1: Mean Serum Denosumab Concentration and Mean Percent Change From Baseline for Serum CTX1 and Lumbar Spine BMD Following Two 60-mg Q6M Doses of Denosumab to Postmenopausal Women with Low BMD (Study 20010223)



No drug-drug interaction trials have been conducted with denosumab. However, it cannot be definitively concluded that denosumab has no effect on CYP450 regulation, expression or activity. The applicant will be required to conduct a postmarketing drug-drug interaction trial with a CYP3A4 substrate in postmenopausal subjects with osteoporosis to assess the potential for denosumab to interact with a frequently co-prescribed medication such as midazolam.

PEDIATRIC CONSIDERATIONS

Denosumab is not recommended for use in pediatric patients. Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit tooth eruption.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application because the required studies are impossible or highly impracticable because the indication for this product (postmenopausal osteoporosis) does not occur in the pediatric population.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

As described in our letter dated October 2, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for PROLIA (denosumab) to ensure that the benefits of the drug outweigh the risk of serious infections, dermatologic adverse events, and oversuppression of bone turnover associated with its use. We have determined that the REMS for this product must include a Medication Guide, a communication plan, and a timetable for submission

of assessments of the REMS. The applicant's proposed REMS submitted on June 1, 2010 has been found acceptable.

A communication plan to support implementation of the REMS will be directed to healthcare providers who treat osteoporosis, including endocrinologists, rheumatologists, gynecologists and primary care physicians. The communication plan will consist of a Dear Healthcare Provider Letter that will be sent by mass mailing or electronic mailing within 60 days of approval of the REMS and/or in conjunction with the launch of Prolia (denosumab), whichever is sooner. The letter will also be distributed to professional societies annually for up to 3 years after approval. New prescribers, who were not previously sent the letter, will be sent a letter for up to 2 years after approval of the REMS or product launch.

REMS assessments will be required at 18 months, 3 years, and 7 years from the date of approval of the REMS.

POSTMARKETING REQUIREMENTS UNDER 505(o)

As described in our letters dated October 2, 2009, and October 16, 2009, in accordance with section 505(o)(3) of the FDCA, we have determined that the applicant is required to conduct the following postmarketing studies of Prolia (denosumab) to assess signals of the serious risks of serious infection including skin infection, dermatologic adverse events, and oversuppression of bone turnover:

1. A retrospective cohort study using multiple existing observational databases to collect data from a 5-year period prior to the availability of denosumab. The study should identify women with postmenopausal osteoporosis and determine the occurrence of serious infection including skin infection, dermatologic adverse events, and oversuppression of bone turnover in each database in order to assess the background rates of those adverse events. The data obtained in this study will be used to inform the implementation of postmarketing requirement #2.

2. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and oversuppression of bone turnover in postmenopausal women administered Prolia (denosumab).

3. A long-term surveillance study in postmenopausal women administered Prolia (denosumab) to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and oversuppression of bone turnover.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of drug interactions of Prolia (denosumab) with CYP3A4 substrates. Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct:

4. An *in vivo* drug-drug interaction clinical trial with a CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interactions of Prolia (denosumab) with CYP3A4 substrates.

Our October 16, 2009 complete response letter also stated that the applicant would be required to conduct a long-term pregnancy exposure registry study in denosumab users who become pregnant on the drug. We have determined that this study would not be feasible because the drug does not have an indication for use in women of childbearing potential. Therefore, this study is not currently required.

TRADENAME REVIEW

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "Prolia" is acceptable.