CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-080

SUMMARY REVIEW

DIVISION DIRECTOR'S MEMO

NDA	22-080
Drug Product	Reclast® (zoledronic acid) injection
Indication	Treatment of Postmenopausal Osteoporosis
Clinical Reviewers	William Lubas, M.D., Ph.D. Theresa Kehoe, M.D.

This Type 6 NDA proposes a new indication for the use of zoledronic acid in the treatment of postmenopausal osteoporosis (PMO). The recommended dosing is 5 mg iv infused over no less than 15 minutes once yearly. This indication will be marketed under the tradename, Reclast®.

Zoledronic acid is approved under the tradename, Zometa®, for the treatment of hypercalcemia of malignancy, treatment of patients with multiple myeloma, and patients with bone metastases from solid tumors. The usual recommended dose for these indications is 4 mg iv infused over no less than 15 minutes. Reduced dosing is recommended for patients with renal impairment (see prescribing information for Zometa®). Retreatment for hypercalcemia of malignancy is dependent upon biochemical response but should be considered only after 7 days have elapsed since last treatment. Zoledronic acid is also approved for the treatment of Paget's disease under the tradename, Reclast®. The recommended dosing for Paget's is 5 mg iv infused over no less than 15 minutes. Repeat dosing is based on clinical response, as assessed by clinical symptoms and/or serum alkaline phosphatase levels.

Thorough reviews have been completed by several disciplines with all secondary sign-off recommending approval of Reclast® for the treatment of PMO. The reader is referred to these other reviews for a thorough discussion of the drug substance, product and manufacturing (CMC/microbiology), the pharmacokinetics and pharmodynamics supporting dose selection (Clinical Pharmacology), nonclinical pharmacology and toxicology studies, and the clinical efficacy and safety studies (medical and biostastistics). My memo will only highlight issues that required more extensive evaluation, labeling negotiations, or commitments/agreements from the company prior to approval.

Efficacy

Efficacy was based on the 3-year fracture study, Study 2301, which enrolled 7,736 women with postmenopausal osteoporosis as defined by a femoral neck bone mineral density T-score below -2.5 or a femoral neck BMD T-score below – 1.5 with radiologic evidence of prevalent vertebral fractures. Drs. Lubas and Kehoe from the medical discipline and Dr. Liu from biostatistics have described the trial design, patient population, endpoints, conduct and findings in their reviews. A unique feature of this trial was the stratification of patients into two different groups based on concomitant use of osteoporosis medications. Stratum I referred to women for whom usual care involved taking calcium and vitamin D only but NO additional concomitant osteoporosis medications. Stratum II referred to women for whom usual care involved taking calcium and vitamin D plus additional osteoporosis therapies, either starting or continuing from randomization. This design partly reflects the changing landscape of treatment for postmenopausal osteoporosis and the difficulties of conducting placebo-controlled trials of large and long enough duration to evaluate fracture risk reduction.

Data from the two strata were considered together and separately in the primary efficacy analyses. The risk of experiencing a new morphometric vertebral fracture was evaluated from Stratum I whereas time-to-first hip fracture combined data from both Strata. For morphometric vertebral fractures at Year 3, the proportion of patients treated with zoledronic acid who experienced at least 1 new fracture was 3.8% compared to 12.8% in the placebo-treated group (See Table 4 below from Dr. Liu's review). Both the absolute risk reduction and relative risk reductions significantly favored zoledronic acid. Significant risk reductions were observed at Year 1 and 2 evaluations.

Table 4 – Results for Proportion of Patients with New Morphometric Vertebral Fractures (mITT, Stratum I)

	Zoledronic acid	Placebo	p-value	Relative Risk	95% CI
Year 1	42 / 2814 (1.5%)	106 / 2847 (3.7%)	<0.0001	0.40	(0.28, 0.57)
Year 2	63 / 2814 (2.2%)	218 / 2847 (7.7%)	<0.0001	0.29	(0.22, 0.39)
Year 3	87 / 2260 (3.8%)	300 / 2352 (12.8%)	<0.0001	0.30	(0.24, 0.38)

231 and 192 subjects in the zoledronic acid and placebo groups, respectively, did not have any post-baseline radiographic vertebral fractures and thus were excluded from the mITT population.

Although this endpoint employed only data from patients not receiving other anti-osteoporosis therapies (Stratum 1), it is interesting to note that analysis of Stratum II at Year 3 (spinal x-rays were only obtained at this time point for this stratum) also revealed a significant risk reduction (ARR of 4.9% and RRR of 56%). While somewhat attenuated, patients receiving other anti-osteoporosis therapies (excluding bisphosphonates) incurred additional benefit with zoledronic acid therapy.

Over the 3-year treatment period, 1.3% of the zoledronic-treated patients experienced a new hip fracture compared to 2.3% of the placebo-treated patients. The K-M estimates were 1.5% and 2.5%, respectively, and the difference was statistically significant. Unlike vertebral fractures, significant risk reductions were not observed at Year 1 and 2 although the hazard ratios favored zoledronic acid.

Other secondary efficacy assessments supported the primary efficacy findings and support the conclusion that zoledronic acid administered once yearly as a 5 mg iv infusion significantly reduces the risk of morphometric vertebral and hip fractures in women with postmenopausal osteoporosis.

Safety

Dr. Lubas's review and Dr. Kehoe's memo thoroughly discusses the safety findings in this application. Careful consideration was given for cardiovascular safety, renal safety, and osteonecrosis of the jaw and will be discussed in my memo.

Cardiovascular Safety

As discussed in Dr. Kehoe's memo, publication of two articles in the May 2007 issue of the *New England Journal of Medicine* sparked some public interest on the bisphosphonate use and associated risks of atrial fibrillation. Dr. Lubas has carefully reviewed the finding of atrial fibrillation in this 3-year trial. The imbalance is predominantly seen with the incidence of atrial fibrillation cases that were coded as serious (1.2% in zoledronic acid vs 0.4% in placebo). His review of each case (n=48 in zoledronic group and n=17 in placebo) supports that they were serious (resulted in hospitalization) but very few were considered life-threatening. He also evaluated associated risk factors for atrial fibrillation and onset of event that might explain the difference in rates reported. A slightly higher percentage of patients in the zoledronic acid group had a history of Afib/flutter, CHF, and valvular heart disease than placebo (See Table 21 from Dr. Lubas's review) but a review of the cases with serious atrial fibrillation revealed the converse. More patients in the placebo group had baseline history that might predispose them to developing atrial fibrillation than the zoledronic acid group (See Table 22 from Dr. Lubas's review).

Adding further to the uncertainty of this finding is an absence of an imbalance in other zoledronic acid studies summarized by Dr. Lubas (Studies 2313, 2315, 0041e2, 2310, and 2047). A subset of patients in Study 2301 (559 patients) who had routine ECG assessments did not reveal an imbalance in the incidence of atrial fibrillation. I concur that the findings should be described in labeling and ongoing/future trials should continue to prospectively assess for the risk of atrial fibrillation; however, I do not believe this finding precludes the approval of this product for treatment of PMO.

In her review, Dr. Kehoe summarized a table derived from the applicant's submission which included a higher rate of deaths due to acute MI in the zoledronic acid group compared to placebo. She discusses in the paragraph preceding this table that all MI events with preferred terms of acute MI and MI that were fatal did not have a marked imbalance nor was there an imbalance in the rates of serious MI.

Renal Safety

Renal safety concerns were a result of reported cases of renal failure in cancer patients treated with Zometa. As a consequence, Novartis also conducted a renal safety study and submitted these results to the PMO NDA for Reclast. In this study a higher percentage of zoledronic-treated patients had increases in serum creatinine (0.5 mg/dL) at 9 to 11 days post-infusion than placebo (1.8% vs 0.8%). However, long-term follow-up did not reveal any difference in development of renal toxicity or impairment. Although, the label for use of zoledronic acid in cancer indications appropriately requires dose adjustments, I concur with the Drs. Lubas and Kehoe that dose adjustments are not necessary in the PMO population provided that patients have baseline CrCl $\geq$35 ml/min and serum creatinine levels are obtained prior to drug administration. Other recommendations for intermittent monitoring post-dosing based on individual risk factors have been included in labeling.

Osteonecrosis of the Jaw

This is a fairly recent adverse event associated with bisphosphonate use. Although observed at a higher rate in the oncology population, cases have also been reported in patients receiving bisphosphonates for the treatment of PMO. Notable for this application is the occurrence of the only case of ONJ reported in a clinical trial for PMO. While the applicant noted that a placebo-treated patient was also reported to have ONJ, this finding doesn't dismiss the causal association with zolendronic acid therapy. These events are too rare to determine if this finding suggests a different risk from other bisphosphonates used for PMO. As I anticipate a high degree of interest in using and prescribing a once-yearly treatment for PMO, I am requiring that the applicant commit to a 15-day expedited reporting of ONJ in the first year of marketing as a term of Reclast's approval for the treatment of PMO. Novartis has agreed to this. FDA will re-evaluate this requirement after the first year of marketing should it appear that the reporting rate (based on reasonable usage) is no greater than other bisphosphonates.

Conclusions

In conclusion, I concur with the review staff that Reclast® can be approved for the treatment of postmenopausal osteoporosis.

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/s/

Mary Parks
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MEDICAL OFFICER