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**NCCN Guidelines Panel:** Multiple Myeloma / Systemic Light Amyloidosis /  
Waldenström's Macroglobulinemia Panel

On behalf of Amgen Inc., I respectfully request the NCCN Multiple Myeloma / Systemic Light Amyloidosis / Waldenström's Macroglobulinemia panel members to review the enclosed data on this international, phase 3, randomized, double blind study comparing the efficacy and safety of XGEVA® (denosumab) to zoledronic acid (ZA) for the treatment of bone disease in patients with newly diagnosed multiple myeloma.

New data were recently presented at the 16<sup>th</sup> International Myeloma Workshop (IMW) on March 4, 2017. These data are from an international, phase 3, randomized double-blind study evaluating denosumab compared with ZA in newly diagnosed symptomatic myeloma patients. A total of 1718 patients were randomized 1:1 to denosumab 120mg SC Q4W or ZA 4mg (adjusted) IV Q4W along with anti-myeloma therapy. The primary endpoint was non-inferiority of denosumab to ZA with respect to time to first on-study SRE. Secondary endpoints included superiority of denosumab for time to first on-study SRE and first-and-subsequent on-study SRE, and overall survival (OS). Progression-free survival (PFS) was an exploratory endpoint. Safety was also assessed.

During the primary blinded treatment period (median follow-up 17.4 months), 43.8% of patients on denosumab and 44.6% on ZA had a first on-study SRE. The median time to first on-study SRE was similar between denosumab (22.83 months) and ZA (23.98 months). Denosumab was non-inferior to ZA ( $P = 0.01$ ) in delaying time to first on-study SRE (HR [95%CI] = 0.98 [0.85, 1.14]). Superiority was not demonstrated for time to first on-study SRE ( $P = 0.82$ ) and time to first-and-subsequent on-study SRE (rate ratio [95%CI] = 1.01 [0.89, 1.15];  $P = 0.84$ ). OS was similar between denosumab and ZA (HR [95%CI] = 0.90 [0.70, 1.16];  $P=0.41$ ), with fewer deaths in denosumab (121 [14.1%]) than in ZA (129 [15.0%]). PFS yielded a HR (95%CI) = 0.82 (0.68, 0.99); descriptive  $P = 0.036$ . The most common (>25%) Treatment-emergent adverse events (TEAEs) for denosumab (%) and ZA (%) were diarrhea (33.5, 32.4) and nausea (31.5, 30.4). The rates of serious AEs (46.0, 47.3), hypocalcemia (16.9, 12.4; serious: 0.9, 0.2), and positively adjudicated osteonecrosis of the jaw (ONJ; 4.1, 2.8) were comparable to known safety profiles. Fewer AEs potentially related to renal toxicity occurred with

denosumab (10.0, 17.1). TEAEs led to investigational product discontinuation in 12.2% of all patients (12.9 in the ZA arm vs. 11.5 in the denosumab arm).

Denosumab met the primary endpoint, demonstrating non-inferiority to ZA in delaying time to first on-study SRE in patients with newly diagnosed myeloma. The rates of AEs, including hypocalcemia and ONJ, are generally consistent with the known safety profile of denosumab. OS was similar between arms and the PFS difference, although exploratory, is promising.

**Supporting Documentation:** The following publication has been submitted. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of this publication.

1. Raje N, Terpos E, Willenbacher W, et al. An International, Randomized, Double Blind Trial Comparing Denosumab with Zoledronic Acid (ZA) for the Treatment of Bone Disease in Patients (Pts) with Newly Diagnosed Multiple Myeloma. Presented at: 16<sup>th</sup> International Myeloma Workshop (IMW); March 4, 2017; New Delhi, India.

Sincerely,

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