

March 09, 2011

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence to Support the Use of Zometa in Patients with Multiple Myeloma Based on its Clinical Anti-cancer Activity

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Date of request: March 09, 2011
NCCN Panel: Multiple Myeloma

To Whom It May Concern:

As the NCCN Multiple Myeloma Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma, v.1.2011 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with Zometa (zoledronic acid). This information is highlighted below:

- Data to support zoledronic acid's clinical anti-cancer activity in patients with multiple myeloma

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Zometa Clinical Anti-cancer Activity in Patients with Multiple Myeloma

This request is for the Panel to consider the addition of zoledronic acid for patients with multiple myeloma in conjunction with standard induction chemotherapy in section "Myeloma Therapy, page 13" of the Multiple Myeloma Guidelines and the associated "NCCN Drugs and Biologics Compendium™" due to its clinical anti-cancer activity. Previously, clodronate reported clinical anti-cancer activity in multiple myeloma and metastatic prostate cancer.⁽¹⁻²⁾ Another study in patients with previously untreated multiple myeloma demonstrated that zoledronic acid plus chemotherapy resulted in a significant delay in event-free survival ($P < .01$) and overall survival (OS) ($P < .01$) compared with patients who received standard chemotherapy alone.⁽³⁾ More recently, a large phase III trial conducted by Morgan and colleagues examined the efficacy and safety of zoledronic acid versus the active comparator clodronate in patients with multiple myeloma. A total of 1970 patients were enrolled in the study. However, 1960 patients were eligible for the intent to treat analysis. Patients received treatment for a median of 350 days before disease progression, with a median follow up of 3.7 years. The primary endpoints of the trial were OS, progression-free survival (PFS), and overall response rate (ORR). Secondary endpoints included skeletal-related events (SREs) and safety. Zoledronic acid therapy significantly reduced the risk of death by 16% compared to clodronate ($P = .0118$), and extended median overall survival by 5.5 months ($P = .04$). PFS was also significantly improved by 12% with zoledronic acid compared to clodronate ($P = .0179$), and increased median PFS by 2.0 months ($P = .07$). Rates of complete, very good partial, or partial response did not differ significantly between the zoledronic acid and clodronate groups. Both zoledronic acid and clodronate were generally well tolerated with no significant difference in the development of acute renal failure or treatment-related serious adverse events. The overall incidence of osteonecrosis of the jaw (ONJ) was 4% [35/983] for zoledronic acid and <1% [3/979] for clodronate.⁽⁴⁾

Specific changes recommended for the Guidelines & Compendium

Please add the use of zoledronic acid for patients with multiple myeloma for its clinical anti-cancer activity.

FDA Status

Zometa (zoledronic acid) is FDA approved for patients with multiple myeloma and documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

Rationale for recommended change

In patients with multiple myeloma with and without bone lesions, a randomized phase III trial demonstrated that the anti-cancer effects of zoledronic acid resulted in an improved overall survival.⁽⁴⁾

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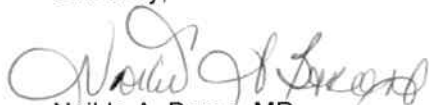
Literature support

1. Dearnaley DP, Mason MD, Parmar MK, et al. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *Lancet Oncol.* 2009 Sep;10(9):872-6. DOI:10.1016/S1470-2045(09)70201-3.
2. McCloskey EV, Dunn JA, Kanis JA, et al. Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *Br J Haematol.* 2001 Jun;113(4):1035-43.
3. Avilés A, Nambo MJ, Neri N, et al. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Med Oncol.* 2007;24(2):227-30.
4. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet.* 2010. 376:1989-1999.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Multiple Myeloma Panel. If you have any questions or require additional information, please do not hesitate to contact me at 862-778-5494 or via e-mail at neilda.baron@novartis.com. Thank you for your time and consideration.

Sincerely,



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Enclosures: Copies of referenced primary literature