Novartis Pharmaceuticals Corporation
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NOVARTIS ONCOLOGY

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Dear Doctor:

Novartis is fully committed to assuring timely dissemination of safety information about its products to the healthcare community. In close collaboration with the US Food and Drug Administration, we are informing you of changes made to the Zometa® (zoledronic acid) Injection prescribing information. These changes are designed to enhance renal safety of Zometa in patients with advanced cancer whose baseline creatinine clearance is 60 ml/min or lower.

This letter will highlight the changes (noted in ***bold italic***) that impact the clinical management of patients with renal impairment. The following information is being added under **Dosage and Administration** and **Warnings** sections:

Dosage and Administration

Multiple Myeloma and Metastatic Bone Lesions From Solid Tumors
The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors ***for patients with creatinine clearance >60 mL/min***, is 4 mg infused over ***no less than*** 15 minutes every three **to** four weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are listed in the following table. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance renal function of 75 mL/min. Creatinine clearance (CrCl) is calculated using Cockcroft-Gault formula.

Baseline Creatinine Clearance (ml/min)	***Zometa Recommended Dose ****
> 60	***4.0 mg***
50 - 60	***3.5 mg***
40 - 49	***3.3 mg***
30 - 39	***3.0 mg***

****Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl=75mL/min)***

During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. ***Zometa should be re-initiated at the same dose as that prior to treatment interruption.***

Preparation of Solution
4 mg dose
Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Reduced doses for patients with baseline CLcr ≤ 60 mL/min: Withdraw an appropriate volume of the 5 mL - Zometa concentrate as needed:

4.4 mL for 3.5 mg dose
4.1 mL for 3.3 mg dose
3.8 mL for 3.0 mg dose

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Warnings

• ***Pre-existing renal insufficiency and multiple cycles of Zometa and other bisphosphonates are risk factors for subsequent renal deterioration with Zometa. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs should be identified and managed if possible*.**

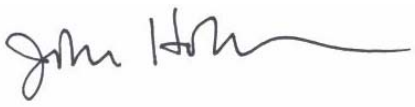
Healthcare professionals should report all serious adverse events suspected to be associated with the use of Zometa to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover NJ 07936 or by phone (888-NOW NOVARTIS or 888 669 6682) or the internet at http://www.us.zometa.com/utils/contact/hcp/emailh.jsp or http://www.us.zometa.com/hcp/tools/medicalinquiry.jsp

Alternatively this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile 1-800-FDA-0178, by mail using the Form 3500 at http://www.fda.gov/medwatch/index.html.

A revised package insert is included with this letter.

Please contact Novartis Oncology Medical Services at 1-888-669-6682 if you have further questions.

Sincerely,



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