Health Canada Endorsed Updated Renal Safety Information on Zometa* (Zoledronic Acid) and Aclasta* (Zoledronic Acid)

NOVARTIS

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Subject: **Update Letter on Renal Safety for Zoledronic Acid**

- ***For ZOMETA* (in patients with bone metastases from solid tumors and osteolytic lesions of multiple myeloma or patients with tumor-induced hypercalcemia)***
  - New reduced dosing schedule of Zometa* for patients with mild to moderate renal impairment (baseline creatinine clearance 30 mL/min to 60 mL/min) in patients with bone metastases from solid tumors and osteolytic lesions of multiple myeloma.
  - New reduced dose of Zometa* for retreatment in patients with tumor-induced hypercalcemia.

- ***For ACLASTA* (in patients with Paget's disease of bone)***
  - Newly approved labeling for renal dysfunction.

Dear Health Care Professional,

In close collaboration with Health Canada's Therapeutic Products Directorate, we are informing you of the following changes made to the Zometa* (zoledronic acid 4 mg intravenous infusion) Product Monograph/prescribing information and the new Product Monograph of Aclasta* (zoledronic acid for injection – 5 mg single-dose intravenous infusion).

ZOMETA* (zoledronic acid)

Zometa* (zoledronic acid for injection) is indicated for the treatment of patients with bone metastases from solid tumors or osteolytic lesions of multiple myeloma and for the treatment of tumor-induced hypercalcemia following adequate saline rehydration. The changes to the Zometa* Product Monograph are designed to enhance renal safety of Zometa* in patients with tumor-induced hypercalcemia requiring retreatment and in patients with advanced cancer

whose baseline creatinine clearance is between 30 to 60 mL/min. The use of Zometa* is not recommended in patients with severe renal impairment. The use of the 8 mg dose of Zometa* for the retreatment of tumor-induced hypercalcemia is no longer recommended.

- **RENAL**

The important changes to the Product Monograph that impact clinical management include the following:

WARNINGS

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa* (zoledronic acid) should not exceed 4 mg and the duration of the infusion should be no less than 15 minutes.

Bisphosphonates, including Zometa* have been associated with reports of renal dysfunction. **Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zometa* or other bisphosphonates, or using an infusion time shorter than currently recommended (the 4-mg dose is given as a single-dose intravenous infusion over not less than 15 minutes in not less than 100 mL diluent). Concomitant use of potentially nephrotoxic drugs (i.e. ASA, NSAIDS, diuretics, ACE inhibitors etc.) may also increase the potential for renal impairment. Renal function should be monitored appropriately during therapy with Zometa***. Increases in serum creatinine may occur in some patients with chronic administration of Zometa* at recommended doses. Patients with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with Zometa* outweighs the possible risk.

DOSAGE AND ADMINISTRATION

Tumor-Induced Hypercalcemia (TIH)

The recommended dose of Zometa* (zoledronic acid for injection) in hypercalcemia (albumin-corrected serum calcium $\geq$ 3.0 mmol/L (12 mg/dL)) is 4 mg. The 4-mg dose is given as a single-dose intravenous infusion over no less than 15 minutes following standard rehydration procedures.

Patients who show complete or partial response initially may be retreated with Zometa* 4 mg if serum calcium does not return to normal or does not remain normal after initial treatment. However, retreatment with Zometa* 4 mg in TIH patients has not been assessed for efficacy and safety in prospective studies. Possible deterioration in renal function must be assessed prior to each re-administration.

Bone Metastases of Solid Tumors and Osteolytic Lesions of Multiple Myeloma

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 based on pharmacokinetic data in

order to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. However, the efficacy and safety of adjusted dosing has not been prospectively assessed in clinical trials. Creatinine clearance (CrCl) is calculated using Cockcroft-Gault formula[†].

$$^{\dagger}CrCl\ (mL/min) = \frac{1.2\ [140 - age\ (years)] \times [total\ body\ weight\ (kg)]}{serum\ creatinine\ (\mu mol/L)}$$

{multiply equation by 0.85 for females}

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 the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine (< 123 µmol/L or < 1.4 mg/dL), an increase of 44 µmol/L or 0.5 mg/dL
- For patients with abnormal baseline creatinine (> 123 µmol/L or > 1.4 mg/dL), an increase of 88 µmol/L or 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.

RECONSTITUTION AND DILUTION

Zometa* Lyophilized Powder and Zometa* Concentrate

Reduced Doses for Patients with Baseline CrCl $\leq$ 60 mL/min: Withdraw an appropriate volume of the reconstituted solution (4 mg/ 5 mL) or Zometa* concentrate (5 mL) 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 reconstituted solution or withdrawn concentrate must be further 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.

The currently approved Product Monograph for Zometa* as yet does not include these new dosing recommendations for mild to moderate renal impairment, however Novartis has taken necessary steps to inform Health Canada of this information, and is therefore in the process of updating the Product Monograph.

ACLASTA* (zoledronic acid)

Health Canada recently granted approval to Aclasta* (zoledronic acid) 5 mg/100 mL solution for intravenous infusion. Aclasta* is indicated as a single-dose intravenous infusion for the treatment of Paget's disease of bone in men and women.

It is important to note that there are important differentiating features between the use of Zometa* for prevention of skeletal related events in patients with cancer metastatic to bone and the use of Aclasta* for the treatment of Paget's disease of bone. These important differentiating features include the patient population being treated, prevalent co-morbidities, cumulative annual dose and dosing interval.

WARNINGS AND PRECAUTIONS

- **RENAL**
  Class-labeling

Renal dysfunction:
Renal dysfunction has been reported following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration, etc).

Rationale:

While the revised product labeling for Zometa will state that the 4 mg unit dose should not be exceeded, this recommendation applies only to patients with cancer who, for all the reasons stated above, are at greater risk for renal deterioration than patients without cancer. The Aclasta* 5 mg unit dose has not been associated with significant renal deterioration in patients with Paget's disease.*

This new class-labeling information is included in the approved Aclasta* Product Monograph.

Healthcare professionals should continue to report all serious adverse events suspected to be associated with the use of Zometa* or Aclasta* to Novartis Pharmaceuticals Canada Inc. or to Health Canada as follows:

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, (QC) H9S 1A9
Phone:1-800-363-8883

Any suspected adverse reaction can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

For other inquiries, please refer to contact information:
Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS)
BMORS_enquiries@hc-sc.gc.ca
Tel: (613) 941-3171
Fax: (613) 941-1365

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

Your professional commitment in this regard has an important role in protecting the well being of your patients by contributing to early signal detection and informed drug use.

Should you have any questions or require additional information regarding the use of Aclasta* (zoledronic acid – 5 mg) and Zometa* (zoledronic acid – 4 mg) please contact Novartis Pharmaceuticals Canada Inc., at 1-800-363-8883 from 8:30 AM to 4:30 PM Monday to Friday Eastern Standard Time.

Novartis Pharmaceuticals Canada Inc.

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[Pr]Zometa* is a registered trademark and [Pr]Aclasta* is a trademark.