Health Canada Endorsed Important Safety Information on XGEVA® (denosumab)

May 28, 2012

Dear Healthcare Professional:

Subject: XGEVA® (denosumab) – Risk of severe symptomatic hypocalcemia, including fatal cases

Amgen Canada Inc., in consultation with Health Canada, would like to inform you of new important safety information related to hypocalcemia associated with XGEVA treatment.

XGEVA is indicated in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours for reducing the risk of developing skeletal-related events (SREs). XGEVA is not indicated in patients with multiple myeloma. XGEVA is administered as a single 120 mg subcutaneous injection given once every 4 weeks.

- Post-marketing cases of severe symptomatic hypocalcemia have occurred at an estimated rate of 1 - 2%, including some cases which were fatal.
  - Signs and symptoms of these cases included altered mental status, tetany, seizures and QTc prolongation, which were temporally associated with XGEVA use, when serum calcium levels were decreased. Patients treated with XGEVA should be informed of these symptoms and the need to seek immediate medical attention if they occur.
- During clinical trials, severe hypocalcemia (corrected serum calcium < 7 mg/dL or < 1.75 mmol /L) occurred in 3.1% of patients receiving treatment with XGEVA.
- Serum calcium levels should be monitored and corrected before and during the treatment with XGEVA as necessary.

Important information for healthcare professionals

- The risk of severe symptomatic hypocalcemia among patients receiving XGEVA may be minimized by the following:
  - Correcting pre-existing hypocalcemia prior to initiating XGEVA therapy
  - Supplementing patients with calcium and vitamin D, unless hypercalcemia is present
  - Monitoring calcium levels as necessary while patients are receiving XGEVA
  - Identifying risk factors for hypocalcemia in patients receiving XGEVA. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at a greater risk of developing hypocalcemia in the absence of calcium supplementation.
  - If hypocalcemia occurs while receiving XGEVA, additional short-term calcium supplementation may be necessary
- If severe symptomatic hypocalcemia occurs, the benefit of continuing the treatment in these patients should be reassessed.

The XGEVA Product Monograph is being updated to include new safety information on severe symptomatic hypocalcemia, which can sometimes be fatal.

A copy of this letter is available on the Health Canada website (www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php). This information is also available at www.amgen.ca.

Further Information

For more information regarding XGEVA, refer to the XGEVA Product Monograph, which can be found at www.amgen.ca or www.xgeva.ca.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of severe symptomatic hypocalcemia or other serious or unexpected adverse reactions in patients receiving XGEVA (denosumab) should be reported to Amgen Canada Inc. or Health Canada at the following addresses:

Amgen Canada Inc.
6775 Financial Drive, Suite 100
Mississauga, Ontario L5N 0A4
Safety Tel: 1-866-512-6436 or Fax: 1-888-264-3655
Safety e-mail: safetycanada@amgen.com

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties*.

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate (MHPD)
E-mail: MHPD_DPSC@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

Clive Ward-Able, MD
Executive Medical Director
AMGEN Canada Inc.