April 24, 2006

Dear Health Professional(s),

Janssen-Ortho Inc. is pleased to announce that Health Canada has granted a Notice of Compliance with Conditions (NOC/c) for VELCADE* (bortezomib mannitol boronic ester) for Injection for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for stem cell transplantation. This marketing authorization reflects the promising nature of the clinical evidence in patients with this serious disease and the need for additional data to verify the clinical benefit.

VELCADE was first approved under Health Canada’s NOC/c policy on January 27, 2005 for the treatment of multiple myeloma patients who have relapsed following front-line therapy and are refractory to their most recent therapy.

The new second-line approval is based on the results of a Phase III, international, randomized, open-label study comparing VELCADE against high-dose dexamethasone in 669 randomized patients with relapsed multiple myeloma who had received 1 to 3 prior therapies. Patients considered to be refractory to prior high-dose dexamethasone were excluded, as were those with baseline ≥ Grade 2 peripheral neuropathy or platelet counts < 50 x 10⁹/L. The primary endpoint was time to progression. Secondary endpoints included overall survival, one-year survival and response rate.

VELCADE significantly improved time to progression (TTP) compared to dexamethasone. Median TTP was 189 days (6.2 months) for VELCADE and 106 days (3.5 months) for dexamethasone (p < 0.0001). In addition, VELCADE significantly improved overall and one-year survival compared to dexamethasone. The likelihood of survival at one year was 80% on VELCADE and 66% on dexamethasone (p = 0.0005). VELCADE significantly improved overall response rate (CR+PR) (38% vs. 18%) and CR rate (6% vs. <1%) compared to dexamethasone (p < 0.0001).

Indications and Clinical Use

VELCADE is indicated for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for stem cell transplantation.

Effectiveness and safety have not been established in children and adolescents.
**Pharmacology**

Bortezomib is a selective, reversible proteasome inhibitor.

**Warnings**

The following is a summary list of warnings and precautions based on the integrated safety database from one Phase III and two Phase II studies that include 897 patients with multiple myeloma:

- Peripheral neuropathy (predominantly sensory with cases of sensorimotor neuropathy) which is dose-related and cumulative. Complete resolution to baseline has been documented in 14% of patients with severe symptoms with limited follow-up data available.
- Autonomic neuropathy (postural hypotension, diarrhea, constipation with ileus and pyrexia)
- Seizures
- Orthostatic hypotension and syncope
- Congestive heart failure (acute development or exacerbation)
- Hematological toxicities, mostly thrombocytopenia which is dose-related and cyclical with cases of intracerebral and internal hemorrhage
- Gastrointestinal events (nausea, diarrhea, constipation, ileus and vomiting)
- Hepatic insufficiency (patient population not studied but bortezomib metabolized by hepatic enzymes)
- Renal insufficiency (patient population not studied)
- Tumour lysis syndrome
- Pregnancy
- Lactation
- Protein accumulation such as amyloidosis (impact of proteasome inhibition unknown)
- Dose preparation: careful attention to ensure the recommended dose is not exceeded (fatalities have been reported after accidental administration of at least twice the recommended dose)

**Drug Interactions**

No formal drug interaction studies have been conducted with VELCADE.

Hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics.

**Adverse Events**

In the Phase III study, the most commonly reported adverse events in the VELCADE-treated patients were: asthenic conditions (61%), diarrhea (58%), nausea (57%), constipation (42%), peripheral neuropathy (36%), vomiting, pyrexia, thrombocytopenia (each 35%), anorexia and decreased appetite (34%), anemia and headache (each 26%), dyspnea (25%), myalgia, muscle cramps, spasms and stiffness (24%), rash (24%), and cough and paresthesia (each 21%).

In VELCADE-treated patients, the most commonly reported serious adverse events included pyrexia (6%), diarrhea (5%), dyspnea and pneumonia (4%), and vomiting (3%). The most commonly reported drug-related event leading to discontinuation was peripheral neuropathy (8%).

In this study, four deaths were considered to be related to VELCADE treatment: one case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered to be dexamethasone-related: two cases of sepsis, one case of bacterial meningitis, and one case of sudden death at home.

**Dosage and Administration**

The recommended starting dose of bortezomib is 1.3 mg/m² body surface area administered as a 3 to 5 second bolus intravenous injection twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). This 3-week period is considered a treatment cycle. For extended therapy beyond 8 cycles, VELCADE may be administered on a maintenance schedule of once weekly for 4 weeks.
(Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of VELCADE.

For tolerability reasons, dose reduction to 1.0 mg/m² has been found effective. VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or any Grade 4 hematological toxicities, excluding neuropathy. Once the symptoms of the toxicity have resolved, VELCADE treatment may be re-initiated at a 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELCADE must be considered unless the benefit of treatment clearly outweighs the risk.

The Product Monograph is available to physicians and pharmacists upon request.

A Fact Sheet on the use of VELCADE in the treatment of multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for stem cell transplantation is available to consumers on the Health Canada website.

Should you have medical enquiries regarding VELCADE for the treatment of multiple myeloma, please contact our Medical Information Department at 1-800-567-3331. Reporting of adverse events can be emailed to dsscan@joica.jnj.com

Original Signed by

Catherine Lau, Ph.D.
Vice President
Regulatory and Quality

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**Any suspected adverse drug reactions can also be reported to:**

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Product Safety Division
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in The Canadian Compendium of Pharmaceuticals and Specialities, or on the Health Canada web site, along with the ADR Guidelines at: