Authorization with Conditions of DARZALEX™ (daratumumab) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.

June 29, 2016

Dear Health Care Professional(s),

Janssen Inc. is pleased to announce that Health Canada has issued a Notice of Compliance with Conditions under the Notice of Compliance with Conditions (NOC/c) policy for DARZALEX™ (daratumumab) concentrate for solution for infusion for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for DARZALEX™ to reflect the promising nature of the clinical data of DARZALEX™ in patients with this serious disease, and the need for further follow-up to verify the clinical benefit. DARZALEX™ possesses an acceptable safety profile based on the benefit/risk assessment.

Authorization with conditions for DARZALEX™ was primarily based on the results obtained from study MMY2002, a phase 2, open-label, 2-part, single arm study of daratumumab 16 mg/kg in 106 patients with multiple myeloma who had received at least 3 prior lines of therapy including a PI and an IMiD or whose disease was refractory to both a PI and an IMiD. The primary endpoint was overall response rate (ORR) assessed by an independent review. After a median duration of follow-up of 9.3 months, the ORR was 29.2% (95% confidence interval: 20.8, 38.9), and included a stringent complete response rate of 2.8% and a very good partial response rate of 9.4%. The median duration of response (DOR) was 7.4 months (95% confidence interval: 5.5, not estimable).

As part of its conditions, Janssen Inc. has undertaken to provide Health Canada with reports based on preplanned interim analyses as well as final reports for the following confirmatory studies:

- Study MMY3003, a phase 3 study of lenalidomide and dexamethasone with or without daratumumab in patients with previously-treated multiple myeloma.
- Study MMY3004: a phase 3 study of bortezomib and dexamethasone with or without daratumumab in patients with previously-treated multiple myeloma.
- A subgroup analysis of Overall Response Rate (ORR) by ISS staging for both confirmatory studies MMY3003 and MMY3004. The results will be submitted to Health Canada in the study reports of the confirmatory studies MMY3003 and MMY3004.

Indications and Clinical Use:
DARZALEX™ (daratumumab) has been issued market authorization with conditions for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.

Patients should be advised about the conditional market authorization for this indication.

Action and Clinical Pharmacology:
Daratumumab is an IgG1κ human monoclonal antibody (mAb) that targets the CD38 protein expressed at a high level on the surface of cells in a variety of hematological malignancies, including multiple myeloma tumor cells. CD38 protein has multiple functions such as receptor mediated adhesion, signaling and enzymatic activity. Daratumumab has been shown to inhibit the *in vivo* growth of CD38-expressing tumor cells.

Serious Warnings and Precautions:

- *Infusion-related reactions (IRRs)*: DARZALEX™ can cause severe IRRs. Patients should be monitored for symptoms of IRRs. Pre-medicate patients with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with DARZALEX™. For the prevention of delayed IRRs, administer oral corticosteroid to all patients the first and second day after each infusion. Post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should also be considered for patients with a history of obstructive pulmonary disorder to manage respiratory complications should they occur. Immediately interrupt DARZALEX™ infusion for IRRs of any grade/severity. Management of IRRs may require reduction in the rate of infusion, or treatment discontinuation of DARZALEX™. Permanently discontinue DARZALEX™ in the event of life-threatening (Grade 4) IRRs.

- *Interference with Indirect Antiglobulin Test (Indirect Coombs Test*: Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) resulting in interference with the indirect Coombs test which may result in a false positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs may mask detection of

antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rhesus (Rh) blood type are not impacted. Patient's blood should be typed and screened prior to starting DARZALEX™. In the event of a planned transfusion, blood transfusion centers should be notified of this interference with indirect antiglobulin serological testing. Please consult the "DRUG INTERACTIONS" section of the DARZALEX™ Product Monograph for further details.

- *Interference with determination of Complete Response*: Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and disease progression in some patients with IgG kappa myeloma protein. Please consult the "DRUG INTERACTIONS" section of the DARZALEX™ Product Monograph for further details.

Adverse Reactions:
The data described below reflect exposure to DARZALEX™ in three pooled open label clinical studies that included 156 patients with relapsed and refractory multiple myeloma treated with DARZALEX™ at 16 mg/kg. The median duration of DARZALEX™ treatment was 3.3 months (range: 0.03 to 20.04 months).

Infusion-related reactions were the most frequently observed treatment-emergent adverse events [TEAEs] and occurred in 48% of patients treated at 16 mg/kg. IRRs include, but are not limited to the following adverse reaction terms: nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnea, nausea, bronchospasm, hypertension and hypoxia. Severe IRRs include bronchospasm, hypertension, dyspnea and hypoxia. Other frequently reported (≥20%) adverse events included fatigue, pyrexia, upper respiratory tract infection, nausea, back pain, cough, anemia, neutropenia and thrombocytopenia. Grade 3 or 4 TEAEs were reported for 56% of patients. The most commonly reported Grade 3 or 4 TEAEs (≥10%) were anemia (17%, all Grade 3), thrombocytopenia (8.3% Grade 3, 5.8% Grade 4), and neutropenia (9.6% Grade 3, 2.6% Grade 4). The most common (≥ 2%) serious TEAEs were pneumonia (6%), general physical health deterioration, hypercalcemia and pyrexia (each at 3%), cross-match incompatible and herpes zoster (each at 2%). Four percent of patients discontinued DARZALEX™ treatment due to an adverse event. Adverse events leading to treatment delay were observed in 24 (15.4%) of patients, and the most frequent adverse event was infections, reported in 13 (8.3%) patients.

Ninety-two patients (59%) had infections. The majority of the infections were respiratory tract infections (including upper respiratory tract infections and pneumonia) (47.4%). Grade 3/4 infections were reported in 16 patients (10.3%). Pneumonia was the most common Grade 3/4 infection (5.8%). Opportunistic infections were observed in 17 patients (10.9%).

Systemic anti-viral medications were used in 73% of patients. Herpes zoster was reported in 3% of patients.

Four deaths due to TEAEs (pneumonia [n=2], cardio-respiratory arrest [n=1], and general physical health deterioration [n=1]) occurred within 30 days of the last dose of DARZALEX™.

Drug Interactions:
No formal drug interaction studies have been conducted with daratumumab.

Special Populations:

Please consult the "WARNINGS AND PRECAUTIONS" section of the DARZALEX™ Product Monograph for further details.

Dosage and Administration:
DARZALEX™ should be administered by intravenous infusion, after dilution, by a healthcare professional with appropriate medical support to manage infusion-related reactions if they occur. Pre- and post-infusion medications should be administered to manage infusion-related reactions. Please consult the "DOSAGE AND ADMINISTRATION" section of the DARZALEX™ Product Monograph for further details.

The recommended dose of DARZALEX™ is 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule:

Schedule	**Weeks**
Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

Prophylaxis for Herpes Zoster Virus Reactivation:
Anti-viral prophylaxis should be considered for prevention of herpes zoster virus reactivation.

For the complete prescribing information and information available for patients/caregivers, please consult the DARZALEX™ Product Monograph. The Product Monograph is available at www.janssen.com/canada or by request by contacting Janssen Inc. Medical Information at 1-800-567-3331 or 1-800-387-8781.

Access to DARZALEX™:
Janssen Inc. has created a Patient Support Program which offers services to patients and physicians, including patient health information and navigation of drug reimbursement options. For more information please email dashboard@bioadvancemail.ca

Should you have medical enquiries regarding DARZALEX™, please contact our Medical Information Department at 1-800-567-3331 or 1-800-387-8781.

Sincerely,

Cathy Lau, Ph.D.
Vice President, Regulatory Affairs and Quality Management

Janssen Inc.
19 Green Belt Drive
Toronto, ON
M3C 1L9
Medical Information: 1-800-567-3331 or 1-800-387-8781
www.janssen.com/canada

Reporting Suspected Side Effects
Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
HEALTH CANADA
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9
Telephone: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789
Email: CanadaVigilance@hc-sc.gc.ca

The Adverse Reaction Reporting Form and the Adverse Reaction Guidelines can be found on the Health Canada website or in The Canadian Compendium of Pharmaceuticals and Specialties.

For other inquiries related to this communication, please contact Health Canada at:
Biologics and Genetic Therapies Directorate
E-mail: bgtd_ora@hc-sc.gc.ca
Telephone: 613-957-1722
Facsimile: 613-946-9520