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**AUTHORIZATION WITH CONDITIONS OF KEYTRUDA™
for the treatment of patients with unresectable or metastatic melanoma and disease
progression following ipilimumab therapy and, if BRAF V600 mutation positive, following
a BRAF or MEK inhibitor**

May 8, 2015

Dear Health Care Professional(s):

Merck Canada 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 KEYTRUDA™ (pembrolizumab), 50 milligram/vial of powder for solution for infusion, for the treatment of patients with unresectable or metastatic melanoma and disease progression, following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

Health Canada has issued this marketing authorization with conditions under the NOC/c policy for KEYTRUDA™ based on the promising nature of the clinical findings in this category of patients that received KEYTRUDA™ in a Phase I clinical trial. At this time, Health Canada has determined that the benefits outweigh the risks of treatment with KEYTRUDA™ with this serious disease. However additional studies are required to verify the clinical benefit.

Authorization with conditions for KEYTRUDA™ was based on the efficacy and safety results of a Phase I, multicenter, uncontrolled, open-label, dose-comparative trial (KEYNOTE-001, Part B2). Key eligibility criteria were: advanced melanoma not amenable to local therapy with curative intent; refractory to ipilimumab, defined as confirmed progression following at least 2 doses of ipilimumab and within 6 months of the last dose of ipilimumab; progression on the most recent prior treatment regimen; measurable disease; and if BRAF V600 mutation-positive, received a BRAF or MEK inhibitor. Patients were randomized to receive 2 milligram/kilogram (n = 89) or 10 milligram/kilogram (n = 84) of KEYTRUDA™ every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumour status was performed every 12 weeks.

The primary efficacy outcome measure was overall response rate (ORR) as assessed by an independent review. The secondary efficacy outcome measure was response duration. The ORR was 24% [95% confidence interval (CI): 15, 34] in the 2 milligram/kilogram arm, consisting of 1 complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.2 months after initial response.

Indication and Clinical Use

KEYTRUDA™ has been issued market authorization with conditions for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor. An improvement in survival or disease-related symptoms has not yet been established.

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

Action and Clinical Pharmacology

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumour cells to inhibit active T-cell immune surveillance. KEYTRUDA™ is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA™ reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and thereby also reactivates anti-tumour immunity.

Serious Warnings and Precautions

- Immune-mediated adverse reactions occurred in patients receiving KEYTRUDA™. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA™, administration of corticosteroids and/or supportive care. The following immune-mediated adverse events have been reported in patients receiving KEYTRUDA™: pneumonitis; colitis; hepatitis; nephritis; endocrinopathies (including hypophysitis, type 1 diabetes mellitus, thyroid disorders); uveitis; myositis; and severe skin reactions. Please refer to the KEYTRUDA™ Product Monograph for a complete list and further details on these immune-mediated adverse events.
- Severe infusion-related reactions have also been reported.
- Therefore, KEYTRUDA™ should only be prescribed by and under the supervision of a qualified physician experienced in the use of anticancer agents. For further details see the KEYTRUDA™ Product Monograph.

Adverse Reactions

Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA™ at a dose of 2 milligram/kilogram every 3 weeks. Of these treatment-related SAEs, those occurring in more than one patient (out of 162)

were: hypophysitis (n = 2) and colitis (n = 2). The most common treatment-related adverse reactions (reported in >10% of patients) included arthralgia, diarrhea, fatigue, nausea, pruritus and rash.

Dosage and Administration

The recommended dose of KEYTRUDA™ is 2 milligram/kilogram administered intravenously over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA™ until disease progression or unacceptable toxicity. Atypical responses [that is (i.e.), an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage] have been observed. Clinically stable patients with initial evidence of disease progression should remain on treatment until disease progression is confirmed.

Recommended Dose and Dosage Adjustment

Immune-mediated adverse reactions occurred in patients receiving KEYTRUDA™. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA™, administration of corticosteroids and/or supportive care. Please consult the Product Monograph for detailed instructions on Dosage Adjustment.

For complete prescribing information and information available for patients/caregivers please consult the KEYTRUDA™ Product Monograph. The Product Monograph is available at: www.merck.ca or requested by contacting Merck Canada Inc. at 1-800-567-2594.

Should you have medical enquiries regarding KEYTRUDA™, please contact our Medical Information Centre at 1-800-567-2594.

original signed by

Mauricio Ede, M.D.

Executive Director, Medical Affairs

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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 Facsimile: 613-957-0335

To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Facsimile: 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 (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) or in *The Canadian Compendium of Pharmaceuticals and Specialties* (<https://www.pharmacists.ca/index.cfm/products-services/compendium-of-pharmaceuticals-and-specialties/>).

For other inquiries related to this communication, please contact Health Canada at:

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