AUTHORIZATION WITH CONDITIONS OF KEYTRUDA®
for use in the treatment of patients with:
Metastatic Non-Small Cell Lung Carcinoma (NSCLC) whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving KEYTRUDA®.

April 1, 2016

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 mg/vial of powder for solution for infusion for the treatment of patients with metastatic Non-Small Cell Lung Carcinoma (NSCLC) whose tumours express PD-L1 (as determined by a validated test, refer to Dosage and Administration Section in Product Monograph) and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving KEYTRUDA®.

Health Canada has issued this marketing authorization with conditions 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. As part of its conditions Merck Canada Inc. has undertaken to provide Health Canada with the following confirmatory study:

- The final report of the confirmatory study (KEYNOTE-010) entitled "A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer". An exploratory analysis by KRAS status should be performed.

Authorization with conditions for KEYTRUDA® was based on the results of a multicentre, open-label, single-arm, multi-cohort study KEYNOTE 001. The efficacy of KEYTRUDA® was investigated in a dose-comparative subgroup of 280 patients with NSCLC. The safety database
was based on all NSCLC patients who received at least one dose of KEYTRUDA® (n=550). Key eligibility criteria was metastatic NSCLC that was PD-L1 positive using a clinical trial immunohistochemistry assay, with progression of disease on or following at least one prior treatment with platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations had disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA®. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Patients were randomized to receive 10 mg/kg of KEYTRUDA® every 2 or 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 9 weeks.

The primary efficacy outcome measure was objective response rate ORR (according to RECIST 1.1 as assessed by blinded independent central review). The key secondary endpoint was duration of response.

The prevalence of patients with a PD-L1 expression Tumour Proportion Score (TPS) greater than or equal to 50% among screened patients with NSCLC as ascertained retrospectively by the companion diagnostic PD-L1 IHC 22C3 pharmDx™ kit was 26%. Among the randomized patients with tumour samples evaluable for PD-L1 expression, 61 had TPS greater than or equal to 50%. This subgroup accounts for 22% of the 280 patients in the cohort. Within this subgroup, the ORR was 41% (95% confidence interval, 29 - 54). The median response duration was not reached (range 2.1+-9.2+ months).

**Indication and Clinical Use:**

KEYTRUDA® is indicated for the treatment of patients with metastatic Non-Small Cell Lung Carcinoma (NSCLC) whose tumours express PD-L1 (as determined by a validated test, refer to Dosage and Administration Section of the Product Monograph) and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving KEYTRUDA®. An improvement in survival or disease-related symptoms has not yet been established.

KEYTRUDA® has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

**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 reactivates anti-tumour immunity.

**Serious Warnings and Precautions:**

Immune-mediated adverse reactions occurred in patients receiving KEYTRUDA®. The following immune-mediated adverse events have been reported in patients receiving KEYTRUDA®: pneumonitis, colitis, endocrinopathies, severe skin reactions (i.e. rash, rash maculo-papular, dermatitis exfoliative, erythema multiforme and toxic skin eruption), vasculitis, autoimmune hemolytic anemia, serum sickness and myasthenic syndrome. Hepatitis, nephritis, uveitis, type I diabetes mellitus, pancreatitis, bullous pemphigoid and Guillain-Barre syndrome have also occurred in patients treated with KEYTRUDA®. Please refer to the KEYTRUDA® Product Monograph for a complete list and further details on these immune-mediated adverse events. Monitor patients for sign and symptoms of immune-mediated adverse reactions. Administer corticosteroids, withhold or permanently discontinue KEYTRUDA® based on the severity of the reactions. For further details, please consult the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the KEYTRUDA® Product Monograph.

Severe or life-threatening infusion-related reactions have also been reported. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA® with close monitoring; premedication with antipyretic and antihistamine may be considered. For severe or life-threatening infusion reactions, stop infusion and permanently discontinue KEYTRUDA®.

**Adverse Reactions:**

In KEYNOTE-001, the most common adverse events (AEs) (≥15%) reported in NSCLC patients receiving KEYTRUDA® were fatigue, decreased appetite, dyspnea, rash, cough, nausea, diarrhea, arthralgia, and constipation. A total of 45.5% of the patients had Grade ≥ 3 AEs, and 41.5% experienced serious AEs (SAEs). The most common SAEs were pleural effusion, dyspnea, pneumonitis, pneumonia, pulmonary embolism and pyrexia. Seventy-nine patients (14.4%) discontinued the study drug due to an AE, and pneumonitis was the most frequent cause of drug discontinuation. Infusion reactions occurred in 19 patients (3.5%).

A total of 19 patients receiving KEYTRUDA® died due to an AE. Of these, 16 patients (4.5%) had an ECOG status of 1, and 3 patients (1.6%) had an ECOG status of 0. The causes of death were respiratory failure (5 patients), pulmonary embolism (3 patients), sepsis (2 patients), cardio-respiratory arrest, pneumonia, intestinal perforation, pneumothorax, interstitial lung disease, septic shock and diffuse alveolar damage (1 patient each). The causes of death for 2 patients were unknown.

Treatment-related SAEs reported up to 90 days after the last dose occurred in 8% of patients receiving KEYTRUDA®. Of these treatment-related SAEs, pneumonitis (n=14), colitis (n=3), and nausea (n=3) occurred in more than two patients out of 550.
**Drug interaction:**

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA®. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA® should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA®. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA® to treat immune-mediated adverse reactions.

**Dosage and Administration:**

Patients should be selected for treatment of metastatic NSCLC with KEYTRUDA® based on the presence of positive PD-L1 expression defined as a Tumour Proportion Score (TPS) ≥ 50%, PD-L1 expression with TPS ≥ 50% should be determined by an experienced laboratory using a validated test. Please refer to the KEYTRUDA® Product Monograph for details on PD-L1 selection for NSCLC patients.

The recommended dose of KEYTRUDA® is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA® until disease progression or unacceptable toxicity. Atypical responses (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 the patients/caregivers please consult the KEYTRUDA® Product Monograph. The Product Monograph is available at: www.merck.ca or can be 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

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Reporting Suspected Side Effects
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Health Canada
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
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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
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For other inquiries related to this communication, please contact Health Canada at:
Biologics and Genetic Therapies Directorate
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