Health Canada posts safety alerts, public health advisories, press releases and other notices from industry as a service to health professionals, consumers, and other interested parties. Although Health Canada authorizes therapeutic products, Health Canada does not endorse either the product or the company. Any questions regarding product information should be discussed with your health professional.

This is duplicated text of a letter from **Bristol-Myers Squibb Canada**.
Contact the company for a copy of any references, attachments or enclosures.

Bristol-Myers Squibb Canada

AUTHORIZATION WITH CONDITIONS OF *OPDIVO®*

April, 29th, 2016

Dear Health Care Professional(s),

Bristol-Myers Squibb Canada 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 OPDIVO® (as nivolumab) 40 mg/4 ml (10mg/mL) vial or 100 mg/10 ml (10mg/mL) vial for intravenous infusion for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for OPDIVO® to reflect the promising nature of the clinical data of OPDIVO® in this patient population with this serious disease and the need to further follow-up to verify the clinical benefit. OPDIVO® is of high quality and possesses an acceptable safety profile based on the benefit/risk assessment. As part of its conditions under Health Canada's NOC/c policy, Bristol-Myers Squibb Canada has undertaken to provide Health Canada with the final clinical study report for study CA209-037: A Randomized, Open-Label Phase 3 Trial of BMS-936558 (Nivolumab) versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy.

Authorization with conditions for OPDIVO® was based on the efficacy and safety results obtained from a phase III, open-label, randomized study to evaluate the safety and efficacy of nivolumab 3 mg/kg administered every 2 weeks as a single agent for the treatment of advanced (unresectable or metastatic) melanoma. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. Treatment was continued until disease progression (or discontinuation of study therapy in patients receiving nivolumab beyond progression), discontinuation due to toxicity, or other reasons.

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO® and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by an independent review and duration of response (DOR).

The ORR was 31.7 % (95% confidence interval [CI]: 23.5, 40.8), consisting of 4 complete responses and 34 partial responses in OPDIVO® -treated patients. The median DOR among IRRC-assessed responders was not reached for the nivolumab group (range: 1.4+ to 10.0+ months).

There were objective responses in patients with and without BRAF V600 mutation-positive melanoma.

Indication and Clinical Use:

OPDIVO® is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF 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.

Other Uses of OPDIVO®:

OPDIVO® has been issued market authorization without conditions for the treatment of:

- unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults;
- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO®.
- adult patients with advanced or metastatic renal cell carcinoma who have received prior anti-angiogenic therapy.

Action and Clinical Pharmacology:

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligand occurs in some tumours and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Serious Warnings and Precautions:

- Immune-mediated adverse reactions occurred in patients receiving OPDIVO®. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of OPDIVO®, administration of corticosteroids and/or other immunosuppressive medications. The following immune-mediated adverse reactions have been reported in patients receiving OPDIVO®: pneumonitis; diarrhea; colitis; hepatitis; nephritis; endocrinopathies (including hypophysitis, type 1 diabetes mellitus, thyroid disorders, adrenal insufficiency); and uveitis Other immune-related adverse reactions include pancreatitis, demyelination, Guillain-Barré syndrome, myasthenic syndrome, and

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encephalitis. Please refer to the OPDIVO® Product Monograph for a complete list and further details on these immune-mediated adverse reactions.

- Severe infusion-related reactions, and serious skin reactions such as toxic epidermal necrolysis (TEN) have also been reported.
- OPDIVO® 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 OPDIVO® Product Monograph.

Adverse Reactions:

The most common adverse reactions (any severity, frequency of 15% or greater) were fatigue, nausea, diarrhea, pruritus and rash.

The information related to the use of OPDIVO® in special population including pregnancy, lactating women, hepatic impairment, renal impairment and other pre-existing autoimmune diseases are provided in the OPDIVO® Product Monograph.

Drug-Drug Interactions:

No formal drug-drug interaction studies have been conducted with OPDIVO (nivolumab). Nivolumab is considered to have low potential to affect pharmacokinetics of other drugs based on the lack of effect on cytokine in peripheral circulation. Please refer to the OPDIVO® Product Monograph for information related to the use of OPDIVO® with other systemic immunosuppressants.

Dosage and Administration:

The recommended dose of OPDIVO® is 3 mg/kg administered intravenously over 60 minutes every 2 weeks. Continue treatment as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

For the complete prescribing information and information available for the patients/caregivers please consult the OPDIVO® Product Monograph. The Product Monograph can be found at: http://www.bmscanada.ca or by requested by contacting Bristol-Myers Squibb Canada at 1-866-463-6267.

Should you have medical enquiries regarding OPDIVO®, please contact our Medical Information Department at 1-866-463-6267.

original signed by

Babak Abbaszadeh
Vice-President Medical

Bristol-Myers Squibb Canada

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Saint-Laurent (Quebec)
H4S 0A4

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php#a1) and the Adverse Reaction Guidelines (http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2011-guidance-directrice_reporting-notification/index-eng.php) can be found on the Health Canada website or in The Canadian Compendium of Pharmaceuticals and Specialties (https://www.pharmacists.ca/products-services/compendium-of-pharmaceuticals-and-specialties/).

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Gastroenterology Infection and Viral Diseases
E-mail: BGIVD_enquiries@hc-sc.gc.ca
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