AUTHORIZATION WITH CONDITIONS FOR BAVENCIO™

March 2, 2018

Dear Health Care Professional(s):

EMD Serono and Pfizer Canada Inc. are 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 BAVENCIO™ (avelumab for injection), 20 mg/mL solution for intravenous infusion, for the treatment of metastatic Merkel Cell Carcinoma (MCC) in previously treated adults.

Health Canada has issued a marketing authorization with conditions for BAVENCIO to reflect the promising nature of the clinical data of BAVENCIO in patients with this serious disease and the need for further follow-up to verify the clinical benefit.

Health Canada considers that the benefit-risk profile of BAVENCIO is favourable for the treatment of metastatic Merkel cell carcinoma in previously treated adults. As part of its condition, EMD Serono has undertaken to provide Health Canada with the final study report for the confirmatory Study EMR100070-003 Part B entitled "A Phase II, open-label, multi-center trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with metastatic MCC" (NCT02155647).

Authorization with conditions for BAVENCIO was based on the efficacy results obtained from the open-label, single-arm, multi-center Study EMR1000070-003 Part A in 88 patients with histologically confirmed metastatic MCC whose disease had progressed after at least one chemotherapy treatment for distant metastatic disease. Patients received BAVENCIO at a dose of 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Tumour response assessments were performed every 6 weeks.

The primary efficacy analysis was confirmed best overall response (BOR) per RECIST v1.1 by independent committee review. The key secondary efficacy analysis was duration of response (DOR).

The objective response rate (ORR) was 33.0% (95% confidence interval [CI]: 23.3, 43.8), consisting of 10 complete responses and 19 partial responses in patients treated

with BAVENCIO. Of 29 patients with objective responses, duration of response ranged from 2.8 to an ongoing response at 23.3 months. Durable response (defined as response ≥ 6 months) was achieved in 25 patients (28.4%). A total of 21 patients remained in response at their last tumor assessment. Among these, 13 patients had a duration of response lasting at least 12 months.

Indications and Clinical Use
BAVENCIO is indicated for the treatment of metastatic Merkel Cell Carcinoma (MCC) in previously treated adults.

An improvement in survival or disease-related symptoms has not yet been established.

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

Action and Clinical Pharmacology
Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumour T-cell responses. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

As a fully human IgG1, avelumab retains FCγ receptor binding and has shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*.

Warnings and Precautions:
Immune-mediated adverse reactions occurred in patients receiving BAVENCIO. The following immune-mediated adverse reactions have been reported in patients receiving BAVENCIO: pneumonitis, hepatitis, colitis, endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus), nephritis and renal dysfunction. Other immune-mediated adverse reactions including myocarditis, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis and Guillain-Barré syndrome have also occurred in patients treated with BAVENCIO. Infusion reactions, which might be severe, occurred in patients receiving BAVENCIO.

Please refer to the BAVENCIO Product Monograph for a complete list and details on the management of immune-mediated adverse reactions and infusion reactions. Treatment with BAVENCIO should be initiated and supervised by a physician experienced in the treatment of cancer.

Adverse Reactions
The safety of BAVENCIO at doses of 10 mg/kg intravenously every two weeks has been evaluated in a total of 1738 patients, in Study 001, a phase I, single arm, multi-center study in patients with other solid tumours (N = 1650) and in Study 003, a single arm, multi-center study with patients with metastatic MCC (N = 88).

In 88 patients with metastatic MCC, the most common adverse reactions (≥ 20%) were

fatigue, musculoskeletal pain, diarrhea, nausea, infusion reaction, rash, peripheral edema and decreased appetite. The most common Grade ≥ 3 adverse reactions (≥ 3%) were anemia, hypertension, increased alanine aminotransferase (ALT) and increased lipase. None of the 88 patients treated with BAVENCIO experienced an adverse reaction which led to death. Serious adverse reactions that occurred in more than one patient were anemia, abdominal pain, and asthenia.

Drug Interactions
No interaction studies have been conducted with BAVENCIO in humans.

Avelumab is primarily metabolized through catabolic pathways. Therefore, it is not expected that BAVENCIO will have drug-drug interactions with other medicinal products.

Dosage and Administration
The recommended dose of BAVENCIO is 10 mg/kg body weight administered intravenously over 60 minutes every 2 weeks.

Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions of BAVENCIO. Premedication should be administered for subsequent BAVENCIO doses based upon clinical judgment and presence/severity of prior infusion reactions.

It is recommended that patients are treated with BAVENCIO until loss of clinical benefit or unmanageable toxicity. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.

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 BAVENCIO Product Monograph at www.emdserono.ca or www.pfizer.ca.

Should you have medical enquiries regarding BAVENCIO, please contact EMD Serono Medical Information via email at Medinfo-Canada@emdserono.com or Pfizer Medical Information at 1-800-463-6001, 9AM-5PM EST, Monday – Friday or visit www.pfizermedinfo.ca.

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Health Canada
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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:
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