

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **BAVENCIO™**

Avelumab for injection

Solution for Intravenous Infusion, 20 mg/mL

Professed Standard

Antineoplastic

BAVENCIO, indicated for the treatment of metastatic Merkel cell carcinoma (MCC) in previously treated adults, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for BAVENCIO please refer to Health Canada's [Notice of Compliance with conditions - drug products](#) web site.

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Date of Initial Approval:
December 18, 2017

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Submission Control No: 204052

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**This product has been authorized under the
Notice of Compliance with Conditions (NOC/c)
for one or all of its indicated uses.**

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NOC/c

BAVENCIO (avelumab for injection) is indicated for the treatment of metastatic Merkel cell carcinoma (MCC) in previously treated adults.

Marketing authorization with conditions was based on tumour response and durability of response. An improvement in survival or disease-related symptoms has not yet been established (see section 12 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of BAVENCIO in pediatric patients have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Overall differences in safety or efficacy between elderly patients (65 years and older) and younger patients (less than 65 years) have not been evaluated.

NOC/c

2 CONTRAINDICATIONS

BAVENCIO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see section 5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

NOC/c

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

BAVENCIO must be administered as an intravenous infusion (IV) under the supervision of a qualified healthcare professional. Do not administer as an IV push or bolus.

In order to improve the traceability of medicinal products, the trade name, BAVENCIO, and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

3.2 Recommended Dose and Dosage Adjustment

Dosage

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

Premedication and Monitoring

Premedicate patients 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.

Duration of Treatment

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.

Treatment modifications

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

Table 1 summarizes guidelines for treatment modifications. Detailed guidelines for the management of immune-mediated adverse drug reactions are described in section 6 WARNINGS AND PRECAUTIONS.

Table 1 – Recommended Dose Modification of BAVENCIO for Treatment-related Adverse Drug Reactions

Treatment-related Adverse Reaction	Severity*	Treatment Modification
Pneumonitis	Grade 2	Withhold**
	Grade 3 or Grade 4 or recurrent Grade 2	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN (Grade 2)	Withhold**
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN (Grade 3 or 4)	Permanently discontinue
Colitis	Grade 2 or Grade 3	Withhold**
	Grade 4 or recurrent Grade 3	Permanently discontinue
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, hyperglycemia)	Grade 3 or Grade 4	Withhold**

Treatment-related Adverse Reaction	Severity*	Treatment Modification
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN (Grade 2 or 3)	Withhold**
	Serum creatinine more than 6 times ULN (Grade 4)	Permanently discontinue
Other immune-mediated adverse reactions (including myocarditis, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome)	For any of the following: Grade 2 or Grade 3 clinical signs or symptoms of an immune-mediated adverse reaction not described above	Withhold**
	Life threatening	Permanently discontinue
Infusion reactions	Grade 1 or Grade 2	Interrupt or slow the rate of infusion
	Grade 3 or Grade 4	Permanently discontinue

*Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.03).

**Until adverse reactions recover to Grade 0-1 and/or after corticosteroid taper.

BAVENCIO should be permanently discontinued for any of the following immune-mediated adverse reactions (imARs):

- Grade 4 reactions except for endocrinopathies that are controlled with replacement hormones
- Requirement of prednisone \geq 10 mg/day or equivalent for more than 12 weeks
- Persistent Grade 2 or 3 imARs lasting \geq 12 weeks
- Reoccurrence of imARs at \geq Grade 3

3.3 Administration

BAVENCIO has to be diluted with either 0.9% or 0.45% sodium chloride solution prior to infusion.

BAVENCIO is administered over 60 minutes as an intravenous infusion using a sterile, non-pyrogenic, low-protein binding 0.2 micrometer in-line or add-on filter.

BAVENCIO infusion must not be administered as an intravenous push or bolus injection.

3.4 Reconstitution

Use aseptic technique for the preparation of the solution for infusion.

- Visually inspect vial for particulate matter and discoloration. BAVENCIO is a clear, colourless to slightly yellow solution. Discard vial if the solution is cloudy, discoloured, or contains particulate matter.
- Take an infusion bag of appropriate size (250 mL preferable) containing either 0.9% or 0.45% sodium chloride solution. Withdraw the required volume of BAVENCIO from the vial(s) and transfer it to the infusion bag. Discard any partially used or empty vials.
- Mix the diluted solution by gently inverting the infusion bag in order to avoid foaming or

- excessive shearing of the solution.
- Inspect the solution to ensure it is clear, colourless, and free of visible particles. Use the diluted solution immediately once prepared.
- Do not co-administer other drugs through the same intravenous line.
- Administer the infusion as described above.
- After the administration of BAVENCIO, flush the line with either 0.9% or 0.45% sodium chloride solution.
- BAVENCIO does not contain a preservative. If BAVENCIO is not infused immediately, the diluted solution can be stored up to 8 hours at room temperature or up to 24 hours in the refrigerator at 2°C to 8°C. If refrigerated, allow the diluted solution to come to room temperature prior to administration. This storage time includes the storage of the infusion solution in the infusion bag, and the duration of infusion.

BAVENCIO is compatible with either 0.9% or 0.45% sodium chloride solution and must not be mixed with other products.

BAVENCIO is compatible with polyethylene, polypropylene, and ethylene vinyl acetate infusion bags, glass bottles, polyvinyl chloride infusion sets and in line filters with polyethersulfone membranes with pore sizes of 0.2 micrometer.

3.5 Missed Dose

If a planned dose of BAVENCIO is missed, it should be administered as soon as feasible or continue at the next planned dose.

4 OVERDOSAGE

There are limited experiences with overdose with BAVENCIO in clinical studies. Treatment is directed to the management of symptoms.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution for infusion / 20 mg/mL	D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, Water for Injection

BAVENCIO is a sterile, clear, colourless to slightly yellow solution.

BAVENCIO is supplied as a single-use vial. One vial of 10 mL contains 200 mg of avelumab.

6 WARNINGS AND PRECAUTIONS

General

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.

Driving and Operating Machinery

BAVENCIO has no or negligible influence on the ability to drive and use machines. Fatigue has been reported following administration of BAVENCIO (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

Immune-mediated Adverse Drug Reactions (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions)

The immune-mediated adverse drug reactions described below in more detail reflect the exposure to BAVENCIO in a total of 1738 patients in Study EMR100070-001 (Study 001) (N=1650) and Study EMR100070-003 (Study 003) (N=88) with a median duration of treatment of 12 weeks in Study 001 and 17 weeks in Study 003 at the time of data cut-off.

Immune-mediated pneumonitis

Immune-mediated pneumonitis including fatal outcomes has been reported in patients receiving BAVENCIO (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

Patients should be monitored for signs and symptoms of immune-mediated pneumonitis and causes other than immune-mediated pneumonitis should be ruled out. Suspected pneumonitis should be confirmed with radiographic imaging.

Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 - 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper of at least 1 month duration which should be initiated upon improvement).

BAVENCIO should be withheld for Grade 2 immune-mediated pneumonitis until resolution to Grade 1 or less, and permanently discontinued for Grade ≥ 3 pneumonitis or recurrent Grade 2 immune-mediated pneumonitis (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Immune-mediated hepatitis

Immune-mediated hepatitis including fatal outcomes has been reported in patients receiving BAVENCIO (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

Patients should be monitored for changes in liver function and symptoms of immune-mediated hepatitis. Causes other than immune-mediated hepatitis should be ruled out. Corticosteroids should be administered (initial dose 1 - 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper of at least 1 month duration which should be initiated upon improvement).

BAVENCIO should be withheld for Grade 2 immune-mediated hepatitis until resolution to Grade 1 or less, and permanently discontinued for Grade ≥ 3 immune-mediated hepatitis (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Immune-mediated colitis

Immune-mediated colitis has been reported in patients receiving BAVENCIO (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

Patients should be monitored for signs and symptoms of colitis and causes other than immune-mediated colitis should be ruled out. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 - 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper of at least 1 month duration which should be initiated upon improvement).

BAVENCIO should be withheld for Grade 2 or Grade 3 immune-mediated colitis until resolution to Grade 1 or less, and permanently discontinued for Grade 4 immune-mediated colitis or recurrent Grade 3 immune-mediated colitis (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Immune-mediated endocrinopathies

Immune-mediated thyroid disorders, immune-mediated adrenal insufficiency and type 1 diabetes mellitus occurred in patients receiving BAVENCIO (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

Patients should be monitored for clinical signs and symptoms of endocrinopathies.

Thyroid disorders (Hypothyroidism/Hyperthyroidism)

Thyroid disorders can occur at any time during treatment. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Manage hypothyroidism with replacement therapy and hyperthyroidism with anti-thyroid drug as needed.

BAVENCIO should be withheld for Grade ≥ 3 thyroid disorders until resolution to Grade 1 or less (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Adrenal insufficiency

Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. Corticosteroids should be administered (1 - 2 mg/kg/day prednisone IV or oral equivalent) for Grade ≥ 3 adrenal insufficiency, followed by a taper until a dose less than or equal to 10 mg/day has been reached.

BAVENCIO should be withheld for Grade ≥ 3 symptomatic adrenal insufficiency until resolution to Grade 1 or less (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Type 1 diabetes mellitus

BAVENCIO can cause type 1 diabetes mellitus, including diabetic ketoacidosis (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

Patients should be monitored for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin for type 1 diabetes mellitus. BAVENCIO should be withheld and anti-hyperglycemics or insulin in patients with \geq Grade 3 hyperglycemia should be administered. Resume treatment with BAVENCIO when metabolic control is achieved on insulin replacement or anti-hyperglycemics (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Immune-mediated nephritis and renal dysfunction

BAVENCIO can cause immune-mediated nephritis.

Patients should be monitored for elevated serum creatinine prior to and periodically during treatment. Corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) should be administered for Grade \geq 2 nephritis.

BAVENCIO should be withheld for Grade 2 or Grade 3 nephritis until resolution to Grade 1 or less and permanently discontinued for Grade 4 nephritis (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Other immune-mediated adverse drug reactions

BAVENCIO can result in severe and fatal immune-mediated adverse reactions (see section 7 Adverse Reactions). As observed with other immune-checkpoint inhibitors, immune-mediated reactions may involve any organ system. Most immune-mediated reactions initially manifest during treatment; however, immune-mediated adverse reactions can occur after discontinuation.

Other clinically important immune-mediated adverse reactions were reported in less than 1% of patients: myocarditis including with fatal outcome, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, and Guillain-Barré syndrome.

The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: immune-mediated skin disorders (bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN)), pancreatitis, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis and encephalitis.

Infusion reactions

Infusion reactions, which might be severe, occurred in patients receiving BAVENCIO.

Patients should be monitored for signs and symptoms of infusion reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria.

For Grade 1 infusion reactions, the infusion rate has to be slowed by 50% for the current infusion. For patients with Grade 2 infusion reactions, the infusion should be temporarily discontinued until Grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate. For Grade \geq 3 infusion reactions, stop infusion and permanently discontinue BAVENCIO (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Patients have to 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 (see section 3.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Fertility

Studies to evaluate the effect of BAVENCIO on fertility have not been conducted. The effect of BAVENCIO on male and female fertility is unknown.

In 1 month and 3 month repeat dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs.

Embryo-fetal toxicity

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the Programmed Death-1/Programmed Death Ligand-1 (PD-1/PD-L1) signalling pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise women of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

6.1 Special Populations

6.1.1 Pregnant Women

There are no or limited data from the use of avelumab in pregnant women.

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman and may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Animal reproduction studies have not been conducted with avelumab to evaluate its effect on reproduction and fetal development.

In animal models, the PD-1/PD-L1 signalling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.

Human IgG1 immunoglobulins are known to cross the placenta. Therefore, avelumab has the potential to be transmitted from the mother to the developing fetus.

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. Therefore, potential risks of administering BAVENCIO during pregnancy include increased rates of abortion or stillbirth.

BAVENCIO is not recommended during pregnancy or in women with child-bearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Advise women of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

6.1.2 Breast-feeding

It is unknown whether avelumab is excreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or discontinue BAVENCIO, taking into account the benefit of breast-feeding for the child and the benefit of BAVENCIO therapy for the mother.

Breast-feeding women should be advised not to breastfeed during treatment and for 1 month after the last dose due to the potential for serious adverse reactions in breastfed infants.

6.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of BAVENCIO in pediatric patients have not been established.

6.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Overall differences in safety or efficacy between elderly patients (65 years and older) and younger patients (less than 65 years) have not been evaluated.

NOC/c 7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

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).

The study population characteristics of the 1738 patients were median age of 64 years (range: 19 to 91 years); 52% male; 78% White, 9% Asian, 5% Black or African American, and 8% other ethnic groups; Eastern Cooperative Oncology Group (ECOG) performance score of 0 (38%), 1 (62%), or > 1 (0.4%); and the underlying malignancies were non-small cell lung cancer (20%), gastric and gastroesophageal cancer (15%), urothelial cancer (14%), ovarian cancer (13%), metastatic breast cancer (10%), head and neck cancer (9%), metastatic MCC (5%), mesothelioma, renal cell carcinoma, melanoma, adrenocortical carcinoma (3% each), colorectal cancer, castrate-resistant prostate cancer, and unknown (1% each). In this population, 24% of patients were exposed to BAVENCIO for ≥ 6 months and 7% were exposed to BAVENCIO for ≥ 12 months.

In Study 003, the median duration of exposure to BAVENCIO was 17 weeks (range: 2 weeks to 102 weeks) with a median of 7 doses (range: 1 dose to 42 doses). In this ongoing study, 39.8% of patients received BAVENCIO for more than 6 months and 13.6% for more than one year.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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.

BAVENCIO was permanently discontinued in 4 (4.5%) patients due to adverse reactions of ileus, gamma-glutamyltransferase increased, alanine aminotransferase increased, blood creatine phosphokinase increased and transaminases increased. BAVENCIO was temporarily discontinued in 21 (24%) patients for treatment-emergent adverse events, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. Abnormal laboratory values (anemia and increased ALT), gastrointestinal disorders, and infections were the common reasons for temporary discontinuation of BAVENCIO.

Table 3 summarizes the adverse reactions that occurred in at least 1% of patients receiving

BAVENCIO in Study 003.

Table 3 – All Grade Adverse Reactions in ≥ 1% of Patients with Metastatic MCC in Study 003

MedDRA System Organ Class and Preferred Term	BAVENCIO (N = 88)	
	All Grades n (%)	Grade 3-4 n (%)
Blood and lymphatic system disorder		
Anemia	13 (14.8)	9 (10.2)
Endocrine disorders		
Hypothyroidism*	4 (4.5)	1 (1.1)
Hyperthyroidism*	1 (1.1)	0
Gastrointestinal disorders		
Nausea	19 (21.6)	0
Diarrhea	20 (22.7)	0
Constipation	15 (17.0)	1 (1.1)
Vomiting	11 (12.5)	0
Abdominal pain ^a	14 (15.9)	2 (2.3)
General disorders and administration site conditions		
Fatigue ^b	44 (50.0)	2 (2.3)
Pyrexia [#]	2 (2.3)	0
Edema peripheral ^c	18 (20.5)	0
Chills [#]	2 (2.3)	0
Immune system disorders		
Drug hypersensitivity [#]	1 (1.1)	0
Hypersensitivity [#]	1 (1.1)	0
Injury, poisoning and procedural complications		
Infusion-related reaction [#]	19 (21.6)	0
Investigations		
Weight decreased	13 (14.8)	0
Aspartate aminotransferase (AST) increased*	1 (1.1)	0
Alanine aminotransferase (ALT) increased*	1 (1.1)	1 (1.1)
Transaminases increased*	1 (1.1)	1 (1.1)
Metabolism and nutrition disorders		
Decreased appetite	18 (20.5)	2 (2.3)
Musculoskeletal and connective tissue disorders		
Back pain [#]	1 (1.1)	0
Musculoskeletal pain ^d	28 (31.8)	2 (2.3)
Arthralgia	9 (10.2)	1 (1.1)
Nervous system disorders		
Dizziness	12 (13.6)	0
Headache	9 (10.2)	0
Renal and urinary disorders		
Tubulointerstitial nephritis	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders		
Cough	16 (18.2)	0
Dyspnea ^e	10 (11.4)	1 (1.1)
Skin and subcutaneous tissue disorders		
Rash ^f	19 (21.6)	0
Pruritus ^g	9 (10.2)	0
Rash maculo-papular*	1 (1.1)	0
Erythema*	1 (1.1)	0
Vascular disorders		

MedDRA System Organ Class and Preferred Term	BAVENCIO (N = 88)	
	All Grades n (%)	Grade 3-4 n (%)
Hypertension	11 (12.5)	5 (5.7)
Hypotension [#]	1 (1.1)	0

*Immune-mediated adverse drug reaction

[#]Infusion adverse reaction (IRR) based on predefined definition based on timely relationship including signs and symptoms of IRR including drug hypersensitivity, hypersensitivity, chills, pyrexia, back pain, flushing, and hypotension

^aAbdominal pain is a composite term which includes abdominal pain and abdominal pain upper

^bFatigue is a composite term which includes fatigue and asthenia

^cEdema peripheral is a composite term which includes edema peripheral and peripheral swelling

^dMusculoskeletal pain is a composite term which includes back pain, myalgia, neck pain, pain in extremity

^eDyspnea is a composite term that includes dyspnea and dyspnea exertional

^fRash is a composite term which includes rash maculo-papular, erythema and dermatitis bullous

^gPruritus is a composite term that includes pruritus and pruritus generalized

The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology.

Immune-mediated pneumonitis

Immune-mediated pneumonitis occurred in patients receiving BAVENCIO. Across clinical studies in patients with advanced solid tumours (Study 001 and Study 003) 1.2% (21/1738) of patients developed immune-mediated pneumonitis. Of these patients, there was 1 (0.1%) patient with a fatal outcome, 1 (0.1%) patient with Grade 4, 5 (0.3%) patients with Grade 3, 11 (0.6%) patients with Grade 2 and 3 (0.2%) patients with Grade 1 immune-mediated pneumonitis.

The median time to onset of immune-mediated pneumonitis was 11 weeks (range: 3 days to 11 months). The median duration was 35 days (range: 4 days to more than 4 months).

BAVENCIO was discontinued in 3 patients and all 21 patients were treated with corticosteroids. Immune-mediated pneumonitis resolved in 12 patients at the time of data cut off.

In Study 003, none of the 88 patients with metastatic MCC developed immune-mediated pneumonitis.

Immune-mediated hepatitis

Immune-mediated hepatitis occurred in patients receiving BAVENCIO. Across clinical studies in patients with advanced solid tumours, 0.9% (16/1738) of patients developed immune-mediated hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, 11 (0.6%) patients with Grade 3, 2 (0.1%) patients with Grade 2 and 1 (0.1%) patient with Grade 1 immune-mediated hepatitis.

The median time to onset of immune-mediated hepatitis was 14 weeks (range: 1 week to 15 months). The median duration was 26 days (range: 1 day to 5 months).

BAVENCIO was discontinued in 9 patients and all 16 patients were treated with corticosteroids. Immune-mediated hepatitis resolved in 11 of the 16 patients at the time of data cut off.

In Study 003, 2% (2/88) of patients with metastatic MCC developed immune-mediated hepatitis, which was Grade 3 in severity.

Immune-mediated colitis

Immune-mediated colitis, including immune-mediated diarrhea, occurred in patients receiving BAVENCIO. Across clinical studies in patients with advanced solid tumours, 1.5% (26/1738) of patients developed immune-mediated colitis or immune-mediated diarrhea. Of these patients there were 7 (0.4%) patients with Grade 3, 13 (0.7%) patients with Grade 2 and 6 (0.3%) patients with Grade 1 immune-mediated colitis.

The median time to onset of immune-mediated colitis was 9 weeks (range: 2 days to 11 months). The median duration was 26 days (range: 1 day to more than 14 months).

BAVENCIO was discontinued in 8 patients and all 26 patients were treated with corticosteroids. Immune-mediated colitis resolved in 20 patients at the time of data cut off.

In Study 003, 2% (2/88) of patients with metastatic MCC developed Grade 2 immune-mediated colitis.

Immune-mediated endocrinopathies

Immune-mediated thyroid disorders, immune-mediated adrenal insufficiency and type 1 diabetes mellitus occurred in patients receiving BAVENCIO.

Thyroid disorders (Hypothyroidism/Hyperthyroidism)

Across clinical studies in patients with advanced solid tumours, 5.6% (98/1738) of patients developed immune-mediated thyroid disorders, of which 90 (5.2%) patients with hypothyroidism, 7 (0.4%) with hyperthyroidism, and 4 (0.2%) with thyroiditis. Of these patients there were 3 (0.2%) patients with Grade 3, 70 (4.0%) patients with Grade 2 and 25 (1.4%) patients with Grade 1 immune-mediated thyroid disorders.

The median time to onset of thyroid disorders was 12 weeks (range: 2 weeks to 13 months). The median duration was not estimable (range: 6 days to more than 21 months).

BAVENCIO was discontinued in 1 (0.1%) patient. Thyroid disorders resolved in 22 patients at the time of data cut off.

In Study 003, 6% (5/88) of patients with metastatic MCC developed Grade 3 (1 patient), Grade 2 (2 patients) and Grade 1 (2 patients) immune-mediated thyroid disorders, including 4 patients with hypothyroidism and 1 patient with hyperthyroidism.

Adrenal insufficiency

Across clinical studies in patients with advanced solid tumours, 0.5% (8/1738) of patients developed immune-mediated adrenal insufficiency. Of these patients there was 1 (0.1%) patient with Grade 3, 6 (0.3%) patients with Grade 2 and 1 (0.1%) patient with Grade 1 immune-mediated adrenal insufficiency.

The median time to onset of immune-mediated adrenal insufficiency was 11 weeks (range: 1 day to 9 months). The median duration was not estimable (range: 2 days to more than 8 months).

BAVENCIO was discontinued in 1 patient and all 8 patients were treated with corticosteroids, 4 (0.2%) patients received high dose systemic corticosteroids (≥ 40 mg prednisone or equivalent) followed by a taper. Adrenal insufficiency resolved in 1 patient at the time of data cut off.

In Study 003, none of the 88 patients with metastatic MCC developed immune-mediated adrenal

insufficiency.

Type 1 diabetes mellitus

New onset of type 1 diabetes mellitus including diabetic ketoacidosis occurred in patients receiving BAVENCIO. Across clinical studies in patients with advanced solid tumours, type 1 diabetes mellitus, without an alternative etiology occurred in 0.1% (2/1738) of patients.

Immune-mediated nephritis and renal dysfunction

Immune-mediated nephritis occurred in 0.1% (1/1738) of patients receiving BAVENCIO, leading to permanent discontinuation of BAVENCIO.

Other immune-mediated adverse drug reactions

Myocarditis

Immune-mediated myocarditis was observed in studies outside of Study 003 and Study 001, in 2 patients treated with BAVENCIO including one case with fatal outcome.

Myositis

Across clinical studies in patients with advanced solid tumours, 0.5% (9/1738) patients developed immune-mediated myositis. Of these patients there was 3 (0.2%) patients with Grade 4, 2 (0.1%) patients with Grade 3, 3 (0.2%) patients with Grade 2 and 1 (0.1%) patient with Grade 1 immune-mediated myositis.

Infusion reactions

Infusion reactions occurred in patients in clinical studies receiving BAVENCIO. Grade 3 and 4 infusion reactions have been reported in 0.7% (12/1738) of patients receiving BAVENCIO, 0.6% (11/1738) of patients with Grade 3 or 4 infusion adverse reactions received corticosteroids intravenously.

Immunogenicity

As with all therapeutic proteins, BAVENCIO has the potential for immunogenicity. Of 1738 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks, 1558 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 64 (4.1%) tested positive. Based on data available, ADA against BAVENCIO did not appear to impact pharmacokinetics or risk of infusion-related reactions.

7.3 Less Common Clinical Trial Adverse Reactions

All adverse reactions observed in Study 003 are included in Table 3. Due to the limited size of Study 003 (N=88), no adverse reactions < 1% were possible to be observed.

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 4 summarizes selected Grade 3 – 4 laboratory abnormalities that occurred in ≥ 1% of patients treated with BAVENCIO in Study 003.

Table 4 – Selected Laboratory Abnormalities with On-Treatment Worsening in ≥ 1% of Patients in Study 003

Laboratory Tests	Any Grade (N = 88) n (%)	Grade 3-4 (N = 88) n (%)
Chemistry		
Increased aspartate aminotransferase (AST)	29 (34)	1 (1)
Increased alanine aminotransferase (ALT)	17 (20)	4 (5)
Increased lipase	11 (14)	3 (4)
Increased amylase	6 (8)	1 (1)
Increased bilirubin	5 (6)	1 (1)
Hyperglycemia*	-	6 (7)
Hematology		
Anemia	30 (35)	8 (9)
Lymphopenia	41 (49)	16 (19)
Thrombocytopenia	23 (27)	1 (1)
Neutropenia	5 (6)	1 (1)

*Hyperglycemia illustrated for Grade ≥ 3 only due to non-fasting measurements

8 DRUG INTERACTIONS

8.1 Overview

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.

NOC/c 9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells and can contribute to the inhibition of the anti-tumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

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*.

9.2 Pharmacodynamics

In peripheral blood of patients who received avelumab 10 mg/kg every 2 weeks, a PD-L1 target occupancy of over 90% was observed throughout the dose interval. Transient increases in IFN γ and TNF α were observed.

9.3 Pharmacokinetics

Table 5 – Summary of Avelumab Pharmacokinetics at 10 mg/kg Once Every 2 Weeks in Subjects with Malignant Tumours

	C_{max}	T_{max}	t_{1/2}	AUC_{0-tau}	CL	V_{ss}
Means, Range or Population Estimate	294 $\mu\text{g/mL}$ *	1.5 hours**	6.1 days §	26214 $\mu\text{g}\cdot\text{hr/mL}$ ***	0.59 L/day §	4.72 L §

CL = total systemic clearance; V_{ss} = volume of distribution at steady state

*observed largest geometric mean (CV=32.5%) of C_{max} in Study 001

**observed median after first dose at 10 mg/kg in Study 001

***estimated steady state geometric mean (CV=35.4%) based on a population pharmacokinetic (PK) analysis

§ based on a population PK analysis

Absorption: Avelumab is administered intravenously and is 100% bioavailable in the blood circulation.

Distribution: Avelumab is expected to be distributed in the systemic circulation and to a lesser extent in the extracellular space. The volume of distribution at steady state was 4.72 L.

Metabolism: Avelumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination: Based on a population PK analysis from 1629 patients, the value of the parameter systemic clearance (CL) in this population PK model is 0.59 L/day.

Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (2 to 3 cycles) of repeated dosing at 10 mg/kg every 2 weeks, and systemic accumulation was approximately 1.25-fold in C_{max} values and 1.66-fold in the C_{trough} values after 24 weeks of treatment.

The elimination half-life (t_{1/2}) at the recommended dose is 6.1 days based on the population PK analysis. Following IV administration of a 10 mg/kg dose, the mean clearance determined by non-compartmental analysis was 0.36 mL/h/kg. The corresponding mean half-life was 95 h (~4 days).

Linearity/Nonlinearity: The avelumab exposure increased dose-proportionally in the dose range of 10 mg/kg to 20 mg/kg every 2 weeks.

Special Populations and Conditions

A covariate analysis with the current population PK model could not detect any significant effect on the CL parameter with the covariates of age, gender, race, PD-L1 status, tumour burden, renal impairment and mild or moderate hepatic impairment.

The covariate of body weight had a positive correlation with the CL and V1 parameters in the population PK model.

Hepatic Insufficiency:

A population PK analysis suggested no clinically important effect on the CL parameter in the model by the covariates of mild hepatic impairment (bilirubin less than or equal to the upper limit of normal (ULN) and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n = 217), or moderate hepatic impairment (bilirubin between 1.5 and 3 times ULN, n = 4), and normal hepatic function (bilirubin and AST less than or equal to ULN, n = 1388).

Avelumab has not been studied in patients with severe hepatic impairment (bilirubin greater than 3 times ULN).

Renal Insufficiency:

No clinically important differences in the clearance of avelumab were found between patients with mild (glomerular filtration rate (GFR) 60 to 89 mL/min, Cockcroft-Gault Creatinine Clearance (CrCL); n = 623), moderate (GFR 30 to 59 mL/min, n = 320) or severe (GFR 15 to 29 mL/min, n = 4) renal impairment and patients with normal (GFR ≥ 90 mL/min, n = 671) renal function.

10 STORAGE, STABILITY AND DISPOSAL

Storage of vials

Store at 2°C to 8°C, do not freeze. Store in the original package in order to protect from light.

The container closure does not contain natural rubber latex material.

Storage of the diluted solution for infusion

BAVENCIO does not contain a preservative.

If BAVENCIO is not infused immediately, the diluted solution can be stored up to 8 hours at room temperature or up to 24 hours in the refrigerator at 2°C to 8°C. If refrigerated, allow the diluted solution to come to room temperature prior to administration. This storage time includes the storage of the infusion solution in the infusion bag, and the duration of infusion.

Do not freeze or shake the diluted solution.

PART II: SCIENTIFIC INFORMATION

BAVENCIO, indicated for the treatment of metastatic Merkel cell carcinoma (MCC) in previously treated adults, has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for BAVENCIO please refer to Health Canada's [Notice of Compliance with conditions - drug products](#) web site.

11 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Avelumab

Chemical name: Recombinant human IgG1 monoclonal antibody directed against human PD-L1

Molecular formula and molecular mass: The molecular formula for the heterodimer (including disulfide bridge) is $C_{6374}+H_{9898}+N_{1694}+O_{2010}+S_{44}$. The molecular mass of intact avelumab, calculated on the basis of the amino acid composition and predicted disulfide bonding without glycans is 143, 832 Da, the mass including glycans is approximately 147, 000 Da.

Structural formula: Avelumab is a recombinant human IgG1 monoclonal antibody. It consists of two heavy chains (HC) of 450 amino acid residues each and two light chains (LC) of 216 amino acid residues each with typical IgG1 inter- and intra- chain disulfide bonds.

Physicochemical properties: Avelumab is a clear, colourless to slightly yellow concentrate for solution for infusion, practically free from visible particles. The pH of the solution is in the range of 5.0 - 5.6 and the osmolality is between 270 and 330 mOsm/kg.

NOC/c 12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Table 6 – Summary of Patient Demographics for Clinical Trial 003 in Metastatic MCC

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
EMR 1000070-003 Part A (Study 003 Part A)	Single-arm, multi-center	10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity	88	69.7 years 33 to 88 years	Male: n = 65 (74%) Female: n = 23 (26%)

Study 003 Part A was an open-label, single-arm, multi-center study in 88 patients with histologically confirmed metastatic MCC whose disease had progressed after at least one chemotherapy treatment for distant metastatic disease. The study excluded patients with autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies; central nervous system (CNS) metastases; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score > 2.

Patients received BAVENCIO (avelumab for injection) at a dose of 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression could receive additional doses of treatment unless disease progression was associated with significant clinical deterioration. Tumour response assessments were performed every 6 weeks, as assessed by an Independent Endpoint Review Committee (IERC) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

Of the 88 patients, 73.9% were male, the median age was 72.5 years (33 years to 88 years), 92.0% were Caucasian, and 55.7% and 44.3% had an ECOG performance status 0 and 1, respectively. In the metastatic disease setting, 65% of patients were reported to have had one prior anti-cancer therapy and 35% had two or more prior therapies. Fifty-three percent (53%) of patients had visceral metastases. All patients had tumour samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive ($\geq 1\%$ of tumour cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational immunohistochemistry assay. Archival tumour samples were evaluated for Merkel cell polyomavirus (MCV) using an investigational assay; of the 77 patients with evaluable results, 60% had evidence of MCV. Patients received a median of 7 doses of BAVENCIO (1 dose to 47 doses), and the median duration of treatment was 17 weeks (2 to 102 weeks).

The primary efficacy analysis was confirmed best overall response (BOR). The key secondary efficacy analysis was duration of response (DOR). The efficacy analysis was conducted when the last patient enrolled had completed 12 months of follow-up.

12.2 Study Results

Efficacy results are presented in Table 7. 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 BAVENCIO treated patients. Of 29 patients with objective responses, duration of response ranged from 2.8 to 23.3+ months. Durable response (defined as response \geq 6 months) was achieved in 25 patients (28.4%). A total of 21 patients remained in response at 12 months after the start of treatment.

Table 7 – Efficacy Results of Study 003 in Metastatic MCC

Efficacy Endpoints (Tumour assessments per RECIST v1.1, IERC)	Results N = 88
Confirmed Best Overall Response (BOR)	
Complete Response (CR)* n (%)	10 (11.4%)
Partial Response (PR)* n (%)	19 (21.6%)
Objective Response Rate (ORR)	
Response Rate, CR+PR* n (%) (95% CI)	29 (33.0%) (23.3, 43.8)
Duration of Response (DOR)^a	N = 29
Median, months (95% CI)	NR (18.0, not estimated)
Minimum, Maximum	2.8, 23.3+
Patients with DOR \geq 6 months, n (%)	25 (86%)
Patients with DOR \geq 12 months, n (%)	13 (45%)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; NR: Not reached; +denotes a censored value; *CR or PR was confirmed at a subsequent tumour assessment;

^aBased on number of subjects with confirmed response (CR or PR)

13 NON-CLINICAL TOXICOLOGY

Conventional repeat dose toxicity studies were conducted in Cynomolgus monkeys. Intravenous doses of 20, 60 or 140 mg/kg were administered once per week in the 1-month study and 3-month studies, followed by a recovery period (1 month and 2 months, respectively).

Results from these studies did not show any notable effects. The no observed adverse effect level (NOAEL) in both primate studies was \geq 140 mg/kg, which is 10 to 14 times the human clinical exposure based on AUC.

No studies have been conducted to assess the potential of avelumab for genotoxicity or carcinogenicity.

No reproductive or development toxicity studies have been conducted with avelumab

Fertility studies have not been conducted with avelumab. In the 1-month and 3-month repeat dose toxicology studies in Cynomolgus monkeys, there were no notable effects in the male and female

reproductive organs.

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *M. tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

BAVENCIO (buh-VEN-see-oh)
Avelumab for Injection
Solution for Intravenous Infusion, 20 mg/mL

Professed Standard

Antineoplastic

Read this carefully before you start taking **BAVENCIO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BAVENCIO**.

What is BAVENCIO used for?

BAVENCIO is a medicine used to treat a rare type of skin cancer that has spread called metastatic Merkel cell carcinoma in previously treated adults.

BAVENCIO should not be used in children less than 18 years of age.

For the following indication BAVENCIO has been approved *with conditions* (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- For the treatment of metastatic Merkel cell carcinoma (MCC) in previously treated adults

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does BAVENCIO work?

BAVENCIO works by helping your immune system fight your cancer.

What are the ingredients in BAVENCIO?

Medicinal ingredients: Avelumab

Non-medicinal ingredients: D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injection.

BAVENCIO comes in the following dosage forms:

BAVENCIO comes in a 10 mL glass vial containing 200 mg of avelumab. The container closure does not contain natural rubber latex material.

Do not use BAVENCIO if:

- you are allergic to avelumab or any of the other ingredients of this medicine. Talk to your healthcare professional if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BAVENCIO. Talk about any health conditions or problems you may have, including if you have:

- Lung problems such as breathing difficulties or cough. These may include signs of inflammation of the lungs (pneumonitis)
- Inflammation of the liver (hepatitis). Signs and symptoms of hepatitis may include abnormal blood tests (liver function tests), eye or skin yellowing (jaundice), pain on the right side of your stomach area or drowsiness
- Diarrhea (watery, loose or soft stools) or more bowel movements than usual or any symptoms of inflammation of the intestines (colitis), such as stomach pain and mucus or blood in stool
- Problems with your hormone producing glands (the thyroid, adrenal glands or pancreas) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include extreme tiredness, rapid heartbeat, increased sweating, changes in mood or behavior, such as irritability or forgetfulness, feeling cold, very low blood pressure, weight change or headache
- Inflammation of your heart (myocarditis). Inflammation of the heart may include trouble breathing, dizziness or fainting, fever, chest pain and chest tightness or flu like symptoms
- Inflammation of your muscles (myositis). Inflammation of your muscles may include muscle pain or weakness
- Infusion reactions, which may include chills, hives, shortness of breath, fever or back pain
- Had an organ transplant (liver or kidney)
- Kidney problems
- A condition that affects your nervous system
- A condition requiring immunosuppressive drug therapy
- An autoimmune disease (a condition where the body attacks its own cells), such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, or lupus
- Taken other medicines that make your immune system weak. Examples of these may include steroids, such as prednisone

Tell your healthcare professional immediately if you have any of these signs or symptoms or if they get worse. Do not try to treat your symptoms with other medicines on your own. Your healthcare professional may:

- give you other medicines in order to prevent complications and reduce your symptoms;
- withhold the next dose of BAVENCIO; or
- stop your treatment with BAVENCIO altogether.

Please note that these signs and symptoms are sometimes delayed, and may develop after your last dose. Before treatment, your healthcare professional will check your general health. You will also have blood tests during your treatment.

Pregnancy:

Tell your healthcare professional if you are pregnant or think you might be, or if you are planning to become pregnant. You must not use BAVENCIO if you are pregnant unless your healthcare professional specifically recommends it. BAVENCIO can cause harm to your unborn baby.

If you are a woman who could become pregnant, you must use effective birth control while you are being treated with BAVENCIO and for at least 1 month after your last dose.

Breast-feeding:

Tell your healthcare professional if you are breast-feeding. Do not breast-feed while receiving BAVENCIO and for at least 1 month after your last dose.

It is unknown if BAVENCIO passes into your breast milk. A risk to the breast-fed infant cannot be excluded.

Driving and using machines:

It is not recommended to drive or use machines after you have been given BAVENCIO unless you are sure you are feeling well. Feeling tired is a very common side effect of BAVENCIO. This can affect your ability to drive or to use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How you are given BAVENCIO

You will receive BAVENCIO in a hospital or clinic under the supervision of an experienced healthcare professional.

You will receive BAVENCIO as an infusion (a drip) into a vein (intravenously) over a period of 60 minutes every 2 weeks. Your healthcare professional will determine how many treatments you need.

Usual dose:

The amount of BAVENCIO you will receive will be calculated based on your body weight. The recommended dose is 10 mg of avelumab per kilogram of your body weight.

Overdose:

In case of drug overdose, contact your healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

If you miss any appointments, call your healthcare professional as soon as possible to reschedule your appointment.

What are possible side effects from using BAVENCIO?

These are not all the possible side effects that you may feel when taking BAVENCIO. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported in clinical trials with BAVENCIO:

Very common (may affect more than 1 in 10 people)

- Itching
- High blood pressure
- Headache

Common (may affect up to 1 in 10 people)

- Allergic reaction to the drug, increased tendency of body to have allergic reactions
- Redness of the skin
- Increase liver enzymes in the blood

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Decrease in number of red blood cells		✓	
UNCOMMON Inflammation of the lungs (pneumonitis): new or worsening cough, shortness of breath, chest pain		✓	
Inflammation of the liver (hepatitis): yellowing of your skin or the whites of your eyes, dark urine (tea colored), severe nausea or vomiting, bleeding or bruising more easily than normal, pain on the right side of your stomach area (abdomen), feeling less hungry than usual, drowsiness		✓	
Inflammation of the intestines (colitis): diarrhea (loose stools) or more bowel movements than usual, blood in your stools or dark, tarry, sticky stools, severe stomach area (abdomen) pain or tenderness		✓	
Inflammation of a hormone gland (especially the thyroid, adrenal glands or pancreas): rapid heart-beat, constipation, increased sweating, your voice gets deeper, extreme tiredness, very low blood pressure, weight gain or weight loss, urinating more often than usual,		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
feeling more hungry or thirsty than usual, dizziness or fainting, hair loss, nausea or vomiting, changes in mood or behavior (such as irritability or forgetfulness), stomach area (abdomen) pain, feeling cold			
Blood sugar problems (type 1 diabetes mellitus): hunger or thirst, a need to urinate more often, weight loss		✓	
Inflammation of the kidneys (nephritis): urinating less than usual, swelling in your ankles, blood in your urine, loss of appetite		✓	
Inflammation of the heart (myocarditis): shortness of breath, irregular heartbeat, feeling tired, chest pain		✓	
Inflammation of the muscles (myositis): muscle weakness, swelling, pain		✓	
Severe infusion reactions: chills or shaking, low blood pressure, hives, fever, flushing, back pain, shortness of breath or wheezing, abdominal pain		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or • Calling toll-free at 1-866-234-2345. <p><i>NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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Storage:

Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package to protect from light.

Keep out of reach and sight of children.

If you want more information about BAVENCIO:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); EMD Serono website (<http://www.emdserono.ca>), or by calling EMD Serono at 1-888-737-6668.

This leaflet was prepared by EMD Serono, a Division of EMD Inc., Canada

Co-developed with:
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Last Revised: DEC - 2017