PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**BAVENCIO®**

Avelumab for injection

Solution for Intravenous Infusion

20 mg/mL single-use vial

Professed Standard

Antineoplastic

BAVENCIO 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. For further information for BAVENCIO please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.

BAVENCIO is indicated for the treatment of:

- *Adult patients with metastatic Merkel cell carcinoma (MCC).*
- *Patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy.*

Importer & Distributor:

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Co-developed with:

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Submission Control No: 225974

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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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NOC/c

Metastatic Merkel Cell Carcinoma

BAVENCIO (avelumab for injection) is indicated for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).

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).

NOC/c

Locally Advanced or Metastatic Urothelial Carcinoma

BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy.

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 disease progression or unacceptable 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**

Treatment-related Adverse Reaction	Severity*	Treatment Modification
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN (Grade 3 or 4)	Permanently discontinue
Colitis/diarrhea	Grade 2 or Grade 3	Withhold**
	Grade 4 or recurrent Grade 3	Permanently discontinue
Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, hyperglycemia)	Grade 3 or Grade 4	Withhold**
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 (imARs) (including but not limited to myocarditis, pancreatitis, 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**
	For any of the following: • Life-threatening or Grade 4 reactions except for endocrinopathies that are controlled with replacement hormones • Requirement of prednisone ≥ 10 mg/day or equivalent for more than 12 weeks • Persistent Grade 2 or 3 imARs lasting ≥ 12 weeks • Reoccurrence of imARs at ≥ Grade 3	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.

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 discolouration. 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 (see section 10 STORAGE, STABILITY AND DISPOSAL).

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.

NOC/c

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 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). Patients should be advised not to drive or operate machinery until they are sure they are feeling well.

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 Part A (Study 003 Part A) (N=88) in patients with previously treated metastatic MCC with a median duration of treatment of 12 weeks in Study 001 and 17 weeks in Study 003 Part A at the time of data cut-off. In addition, the immune-mediated adverse drug reactions described below reflect the exposure to BAVENCIO in a total of 116 patients in Study EMR100070-003 Part B (Study 003 Part B) (N=116) in treatment-naïve patients with metastatic MCC with a median duration of treatment of 24 weeks 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 for Grade ≥ 2 immune-mediated hepatitis (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. Hypothyroidism should be managed 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 ≥ 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 ≥ 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.

Immune-mediated pancreatitis has been observed in patients receiving BAVENCIO. In one clinical trial with BAVENCIO in combination with axitinib, cases of immune-mediated pancreatitis with fatal outcomes have been observed (see section 7.2 ADVERSE REACTIONS, Clinical Trial Adverse Reactions).

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 ≥ 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 BAVENCIO 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 breast-feed during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breast-fed 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):

Metastatic Merkel Cell Carcinoma

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

Locally Advanced or Metastatic Urothelial Carcinoma

Of the 242 patients with locally advanced or metastatic UC treated with BAVENCIO, 68% were 65 years or over and 28% were 75 years or over. Among patients 65 years or over who were followed for at least 12 months, 17% (28/165) responded to BAVENCIO and 67% (111/165) developed a Grade 3 - 4 adverse reaction. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

NOC/c

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety of BAVENCIO at doses of 10 mg/kg intravenously every 2 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) including patients with locally advanced or metastatic UC (N = 242) and in Study 003 Part A, a single arm, multi-center study in patients with previously treated metastatic MCC (N = 88). In addition, the safety of BAVENCIO at doses of 10 mg/kg

intravenously every 2 weeks has been evaluated in treatment-naïve patients with metastatic MCC in Study 003 Part B (N = 116).

The study population characteristics of the 1738 patients (Study 001 and Study 003 Part A) 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, 25% of patients were exposed to BAVENCIO for ≥ 6 months and 8% were exposed to BAVENCIO for ≥ 12 months.

The study population characteristics of the 116 patients in Study 003 Part B were median age of 74 years (range: 41 to 93 years); 69.8% male; 64.7% White, 2.6% Asian, 1.7% Black or African American; and ECOG performance score of 0 (62.1%) or 1 (37.9%).

Metastatic Merkel Cell Carcinoma

In Study 003 Part A, 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 95 doses). In this ongoing study, 39.8% of patients received BAVENCIO for more than 6 months and 26.1% for more than one year.

In Study 003 Part B, the median duration of exposure to BAVENCIO was 24 weeks (range: 2 weeks to 122 weeks) with a median of 11.5 doses (range: 1 dose to 61 doses). In this ongoing study, 48.3% of patients received BAVENCIO for more than 6 months and 25.0% for more than one year.

Locally Advanced or Metastatic Urothelial Carcinoma

In Study 001, the median duration of exposure to BAVENCIO for patients with locally advanced or metastatic UC was 12 weeks (range: 2 weeks to 134 weeks) with a median of 6 doses (range: 1 dose to 67 doses); 26.9% of patients received BAVENCIO for more than 6 months.

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.

Metastatic Merkel Cell Carcinoma

The safety of BAVENCIO was investigated in Study 003, a single-arm multi-center study with two parts. Part A included 88 patients with metastatic MCC whose disease had progressed after at least one chemotherapy treatment. Part B included 116 patients with histologically confirmed metastatic MCC who were treatment-naïve to systemic therapy in the metastatic setting.

Part A - Previously treated metastatic MCC:

In Part A, the most common adverse reactions (≥ 20%) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion related reaction, rash, peripheral edema and decreased appetite (see Table 3). The most common Grade ≥ 3 treatment emergent adverse events (≥ 3%) were anemia, lymphopenia, abdominal pain, disease progression, alanine aminotransferase increased, blood

creatine phosphokinase increased, gamma-glutamyltransferase increased, lipase increased and hypertension. Serious treatment emergent adverse events that occurred in more than one patient were anemia, abdominal pain, disease progression, general physical health deterioration, cellulitis, lung infection, squamous cell carcinoma of skin and acute kidney injury.

BAVENCIO was permanently discontinued in 10 (11.4%) patients due to treatment emergent adverse events of anemia, thrombocytopenia, pericardial effusion, autoimmune colitis, ileus, autoimmune disorder, alanine aminotransferase increased, blood creatine phosphokinase increased, gamma-glutamyltransferase increased, neutrophil count decreased and transaminases increased.

BAVENCIO was temporarily discontinued in 36 (40.9%) patients for treatment emergent adverse events, excluding temporary dose interruption for infusion related reactions where infusion was restarted the same day. Anemia, gastric hemorrhage, lung infection, infusion related reaction and back pain were the reasons for temporary discontinuation of BAVENCIO reported in more than one patient.

Part B - Treatment-naïve metastatic MCC:
In Part B, the most common adverse reactions (≥ 20%) were fatigue, infusion related reaction, constipation, nausea, cough and rash (see Table 3). The most common Grade ≥ 3 treatment emergent adverse events (≥ 3%) were disease progression, general physical health deterioration, lipase increased, aspartate aminotransferase increased, sepsis, hypertension, decreased appetite and hyponatremia. Serious treatment emergent adverse events that occurred in more than one patient were infusion related reaction, abdominal pain, dysphagia, vomiting, asthenia, disease progression, general physical health deterioration, sepsis, dehydration, diabetes mellitus, hyponatremia, malignant neoplasm progression, metastases to central nervous system, pulmonary embolism and lymphoedema.

BAVENCIO was permanently discontinued in 28 (24.1%) patients due to treatment emergent adverse events. Disease progression, general physical health deterioration, infusion related reaction and aspartate aminotransferase increased were the reasons for permanent discontinuation of BAVENCIO reported in more than one patient. One patient permanently discontinued BAVENCIO due to the treatment emergent adverse event of tumour lysis syndrome.

BAVENCIO was temporarily discontinued in 53 (45.7%) patients for treatment emergent adverse events, excluding temporary dose interruption for infusion related reactions where infusion was restarted the same day. Diarrhea, pyrexia, nasopharyngitis, infusion related reaction, abnormal laboratory values (alanine aminotransferase increased, amylase increased, aspartate aminotransferase increased), hyponatremia, back pain and hydronephrosis were the reasons for temporary discontinuation of BAVENCIO reported in more than one patient.

Table 3 summarizes the adverse reactions that occurred in at least 1% of patients receiving BAVENCIO in Study 003 Part A (previously treated) and Part B (treatment-naïve).

Table 3 – All Grade Adverse Reactions in ≥ 1% of Patients with Metastatic MCC in Study 003 Part A (previously treated) and Part B (treatment-naïve)

MedDRA System Organ Class and Preferred Term	BAVENCIO (N = 88)		BAVENCIO (N = 116)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Blood and lymphatic system disorder				
Anemia	16 (18.2)	10 (11.4)	19 (16.4)	3 (2.6)
Endocrine disorders				
Hypothyroidism*	5 (5.7)	1 (1.1)	5 (4.3)	0
Hyperthyroidism*	1 (1.1)	0	1 (0.9)	0
Adrenal insufficiency	0	0	3 (2.6)	0
Gastrointestinal disorders				
Nausea	24 (27.3)	0	23 (19.8)	0
Diarrhea	23 (26.1)	0	18 (15.5)	1 (0.9)
Constipation	16 (18.2)	1 (1.1)	28 (24.1)	0
Vomiting	13 (14.8)	0	12 (10.3)	2 (1.7)
Abdominal pain[a]	17 (19.3)	4 (4.5)	14 (12.1)	3 (2.6)
Autoimmune colitis	1(1.1)	0	0	0
General disorders and administration site conditions				
Fatigue[b]	46 (52.3)	2 (2.3)	49 (42.2)	4 (3.4)
Pyrexia#	2 (2.3)	0	7 (6.0)	0
Edema peripheral[c]	20 (22.7)	0	12 (10.3)	0
Chills#	2 (2.3)	0	10 (8.6)	0
Immune system disorders				
Drug hypersensitivity#	1 (1.1)	0	0	0
Hypersensitivity#	1 (1.1)	0	0	0
Autoimmune disorder	1(1.1)	1(1.1)	0	0
Haemophagocytic lymphohistiocytosis	1(1.1)	0	0	0
Injury, poisoning and procedural complications				
Infusion related reaction#	19 (21.6)	0	33 (28.4)	1 (0.9)
Investigations				
Weight decreased	14 (15.9)	0	19 (16.4)	1 (0.9)
Aspartate aminotransferase (AST) increased*	1(1.1)	0	3 (2.6)	2 (1.7)
Alanine aminotransferase (ALT) increased*	1 (1.1)	1 (1.1)	3 (2.6)	1 (0.9)
Transaminases increased*	1 (1.1)	1 (1.1)	0	0
Thyroid function test abnormal	1 (1.1)	0	0	0
Blood thyroid stimulating hormone decreased	0	0	2 (1.7)	0
Metabolism and nutrition disorders				
Decreased appetite	21 (23.9)	1 (1.1)	16 (13.8)	5 (4.3)
Musculoskeletal and connective tissue disorders				
Back pain#	1 (1.1)	0	3 (2.6)	0
Musculoskeletal pain[d]	35 (39.8)	3 (3.4)	23 (19.8)	0
Arthralgia	16 (18.2)	1 (1.1)	8 (6.9)	0
Nervous system disorders				
Dizziness	12 (13.6)	0	4 (3.4)	0
Headache	10 (11.4)	0	4 (3.4)	0

MedDRA System Organ Class and Preferred Term	BAVENCIO (N = 88)		BAVENCIO (N = 116)	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Renal and urinary disorders				
Tubulointerstitial nephritis	1 (1.1)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	16 (18.2)	0	26 (22.4)	0
Dyspnea[e]	12 (13.6)	1 (1.1)	18 (15.5)	1 (0.9)
Skin and subcutaneous tissue disorders				
Rash[f]	23 (26.1)	0	28 (24.1)	0
Pruritus[g]	13 (14.8)	0	17 (14.7)	1 (0.9)
Rash maculo-papular*	1 (1.1)	0	5 (4.3)	0
Erythema*	2 (2.3)	0	1 (0.9)	0
Vascular disorders				
Hypertension	11 (12.5)	6 (6.8)	11 (9.5)	7 (6.0)
Hypotension#	1 (1.1)	0	1 (0.9)	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
[a]Abdominal pain is a composite term which includes abdominal pain and abdominal pain upper
[b]Fatigue is a composite term which includes fatigue and asthenia
[c]Edema peripheral is a composite term which includes edema peripheral and peripheral swelling
[d]Musculoskeletal pain is a composite term which includes back pain, myalgia, neck pain, pain in extremity
[e]Dyspnea is a composite term that includes dyspnea and dyspnea exertional
[f]Rash is a composite term which includes rash maculo-papular, erythema, dermatitis bullous and rash pruritic
[g]Pruritus is a composite term that includes pruritus and pruritus generalized

Locally Advanced or Metastatic Urothelial Carcinoma

In Study 001, the UC group (N=249) included 7 patients who had not received previous platinum-based chemotherapy. The following information is based on UC patients who did receive previous platinum-based therapy (N=242).

In 242 patients with locally advanced or metastatic UC, the most common adverse reactions (≥ 15%) were fatigue, nausea, decreased appetite, infusion related reaction, decreased weight, diarrhea, constipation, urinary tract infection, anemia, vomiting, pyrexia, abdominal pain and dyspnea. The most commonly reported Grade ≥ 3 adverse reaction was anemia (8.3%). Other Grade ≥ 3 adverse reactions reported in ≥ 3% of patients were hypertension, fatigue, urinary tract infection and asthenia.

One of the 242 patients experienced an adverse reaction of immune-mediated pneumonitis which led to death.

Serious adverse reactions reported in ≥ 1 % of patients were infusion related reaction, pneumonitis and diarrhea. Adverse reactions leading to permanent discontinuation were reported in 7.4% of patients, and adverse reactions leading to temporary discontinuation were reported in 11.2% of patients.

Table 4 summarizes the adverse reactions that occurred in ≥ 1% of patients with locally advanced or metastatic UC receiving BAVENCIO in Study 001.

Table 4 – All Grade Adverse Reactions in ≥ 1% of Patients with Locally Advanced or Metastatic UC in Study 001

MedDRA System Organ Class and Preferred Term	BAVENCIO (N = 242)	
	All Grades n (%)	Grade 3-4 n (%)
Blood and lymphatic system disorder		
Anemia	46 (19.0)	20 (8.3)
Endocrine disorders		
Hypothyroidism*	11 (4.5)	0
Gastrointestinal disorders		
Nausea	65 (26.9)	4 (1.7)
Constipation	50 (20.7)	2 (0.8)
Diarrhea	50 (20.7)	3 (1.2)
Abdominal pain[a]	49 (20.2)	5 (2.1)
Vomiting	41 (16.9)	4 (1.7)
General disorders and administration site conditions		
Fatigue[b]	108 (44.6)	19 (7.9)
Edema peripheral[c]	40 (16.5)	1 (0.4)
Pyrexia	39 (16.1)	2 (0.8)
Chills**	13 (5.4)	0
Infections and infestations		
Urinary tract infection[d]	60 (24.8)	16 (6.6)
Injury, poisoning and procedural complications		
Infusion related reaction	56 (23.1)	1 (0.4)
Investigations		
Weight decreased	50 (20.7)	1 (0.4)
Metabolism and nutrition disorders		
Decreased appetite	57 (23.6)	5 (2.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	72 (29.8)	8 (3.3)
Arthralgia	25 (10.3)	3 (1.2)
Renal disorders		
Renal failure[f]	44 (18.2)	8 (3.3)
Respiratory, thoracic and mediastinal disorders		
Dyspnea[g]	48 (19.8)	7 (2.9)
Cough	36 (14.9)	0
Pneumonitis*	5 (2.1)	3 (1.2)
Skin and subcutaneous tissue disorders		
Rash[h]	42 (17.4)	1 (0.4)
Pruritus[i]	27 (11.2)	1 (0.4)
Vascular disorders		
Hypertension	32 (13.3)	16 (6.6)

* Immune-related adverse reaction

** Infusion related 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

[a]Abdominal pain is a composite term which includes abdominal pain, abdominal discomfort, abdominal pain upper and lower

[b]Fatigue is a composite term which includes fatigue, asthenia and malaise

[c]Edema peripheral is a composite term which includes edema peripheral and peripheral swelling

[d]Urinary tract infection is a composite term which includes Urinary Tract Infection, urosepsis, cystitis, kidney infection, urinary tract infection fungal, urinary tract infection bacterial, urinary tract infection enterococcal

[e]Musculoskeletal pain is a composite term which includes musculoskeletal pain, back pain, myalgia, neck pain, pain in extremity

[f]Renal failure is a composite term which includes renal failure, creatinine increased, acute kidney injury, GFR decreased

[g]Dyspnea is a composite term that includes dyspnea and dyspnea exertional

[h]Rash is a composite term which includes rash, rash macular-papular, rash pruritic, rash erythematous, erythema, erythema multiforme, rash macular, rash papular
[i]Pruritus is a composite term that includes pruritus and pruritus generalized

Immune-Mediated Adverse Reactions
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 Part A) 1.3% (23/1738) 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, 6 (0.3%) patients with Grade 3, 12 (0.7%) 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 11.8 months). The median duration was 7 weeks (range: 4 days to more than 4 months). BAVENCIO was discontinued in 3 patients and all 23 patients were treated with corticosteroids. Immune-mediated pneumonitis resolved in 13 patients at the time of data cut off.

In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC and in Part B none of the 116 patients with treatment-naïve metastatic MCC developed immune-mediated pneumonitis.

In Study 001, 2.0% (5/242) of patients with locally advanced metastatic UC developed immune-mediated pneumonitis; 1 patient with Grade 5, 2 patients with Grade 3 and 2 patients with Grade 2 immune-mediated pneumonitis.

Immune-mediated hepatitis
Immune-mediated hepatitis occurred in patients receiving BAVENCIO. Across clinical studies in patients with advanced solid tumours, 1.0 % (18/1738) of patients developed immune-mediated hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 13 (0.7%) 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 16 months). The median duration was 2.8 months (range: 1 day to 8 months). BAVENCIO was discontinued in 11 patients and all 18 patients were treated with corticosteroids. Immune-mediated hepatitis resolved in 11 of the 18 patients at the time of data cut off.

In Study 003 Part A, 2% (2/88) of patients with previously treated metastatic MCC developed immune-mediated hepatitis, which was Grade 3 in severity. In Study 003 Part B, 3% (4/116) of patients with treatment-naïve metastatic MCC developed immune-mediated hepatitis; 3 patients with Grade 3 and 1 patient with Grade 2 immune-mediated hepatitis.

In Study 001, 1.7% (4/242) of patients with locally advanced metastatic UC developed immune-mediated hepatitis; 3 patients with Grade 3 and 1 patient with Grade 1 immune-mediated hepatitis.

Immune-mediated colitis
Immune-mediated colitis, including immune-mediated diarrhea, occurred in patients receiving BAVENCIO. Across clinical studies in patients with advanced solid tumours, 1.6% (27/1738) of patients developed immune-mediated colitis or immune-mediated diarrhea. Of these patients there were 7 (0.4%) patients with Grade 3, 14 (0.8%) 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 11.5 months). The median duration was 4 weeks (range: 1 day to more than 15 months). BAVENCIO was discontinued in 9 patients and all 27 patients were treated with corticosteroids. Immune-mediated colitis resolved in 19 patients at the time of data cut off.

In Study 003 Part A, 3% (3/88) of patients with previously treated metastatic MCC developed Grade 2 immune-mediated colitis. In Study 003 Part B, 1% (1/116) of patients with treatment-naïve metastatic MCC developed Grade 2 immune-mediated colitis.

In Study 001, 0.8% (2/242) of patients with locally advanced metastatic UC developed immune-mediated colitis, including immune-mediated diarrhea, 1 patient with Grade 3 immune-mediated diarrhea.

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, 5.8% (100/1738) of patients developed immune-mediated thyroid disorders, of which 92 (5.3%) 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, 71 (4.1%) patients with Grade 2 and 26 (1.5%) patients with Grade 1 immune-mediated thyroid disorders. The median time to onset of thyroid disorders was 12 weeks (range: 2 weeks to 15 months). The median duration was not estimable (range: 1 day to more than 28 months). BAVENCIO was discontinued in 1 (0.1%) patient. Thyroid disorders resolved in 7 patients at the time of data cut off.

In Study 003 Part A, 8% (7/88) of patients with previously treated metastatic MCC developed Grade 3 (1 patient), Grade 2 (2 patients) and Grade 1 (3 patients) immune-mediated thyroid disorders, including 5 patients with hypothyroidism, 1 patient with hyperthyroidism and 1 patient with an abnormal thyroid function test (not graded). In Study 003 Part B, 6% (7/116) of patients with treatment-naïve metastatic MCC developed Grade 2 (3 patients) and Grade 1 (4 patients) immune-mediated thyroid disorders, including 4 patients with hypothyroidism, 1 patient with hypothyroidism and hyperthyroidism and 2 patients with increased blood thyroid stimulating hormone.

In Study 001, 5.4 % (13/242) of patients with locally advanced metastatic UC developed immune-mediated thyroid disorders, all of which were Grade 1 or 2. Eleven (4.5%) patients had hypothyroidism and 2 (0.8%) patients had hyperthyroidism.

Adrenal insufficiency
Across clinical studies in patients with advanced solid tumours, 0.5% (9/1738) of patients developed immune-mediated adrenal insufficiency. Of these patients there were 2 (0.1%) patients 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 14 weeks (range: 1 day to 13.5 months). The median duration was not estimable (range: 2 days to more than 11 months). BAVENCIO was discontinued in 2 patients and all 9 patients were treated with corticosteroids, 4 (44 %) of the 9 patients received high dose systemic corticosteroids (≥ 40 mg prednisone or equivalent) followed by a taper. None of the patients had adrenal insufficiency resolved at the time of data cut off.

In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC had immune-mediated adrenal insufficiency. In Study 003 Part B, 3% (3/116) of patients with treatment-naïve metastatic MCC developed Grade 2 (2 patients) and Grade 1 (1 patient) 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 (Grade 3), without an alternative etiology occurred in 0.1% (2/1738) of patients that led to permanent discontinuation.

In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC had type 1 diabetes. In Study 003 Part B, type 1 diabetes occurred in 0.9% (1/116) of patients with treatment-naïve metastatic MCC reported as Grade 3. The dose of BAVENCIO was not changed.

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.

In Study 003 Part A, immune-mediated nephritis occurred in 1.1% (1/88) of patients with previously treated metastatic MCC reported as tubulointerstitial nephritis Grade 2. In Study 003 Part B, immune-mediated nephritis occurred in 0.9% (1/116) of patients with treatment-naïve metastatic MCC reported as Grade 3. The dose of BAVENCIO was not changed and the patient recovered.

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.

In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC had myocarditis. In Study 003 Part B, immune-mediated myocarditis occurred in 0.9% (1/116) of patients with treatment-naïve metastatic MCC leading to permanent discontinuation of BAVENCIO.

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.

In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC had myositis. In Study 003 Part B, immune-mediated myositis occurred in 0.9% (1/116) of patients with treatment-naïve metastatic MCC leading to permanent discontinuation of BAVENCIO.

Neurologic events
In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC had neurologic events. In Study 003 Part B, immune-mediated autoimmune neuropathy occurred in 0.9% (1/116) of patients with treatment-naïve metastatic MCC reported as Grade 3 leading to permanent discontinuation of BAVENCIO.

Pancreatitis
Immune-mediated pancreatitis has been observed in patients receiving BAVENCIO outside of

Study 003 and 001. In one clinical trial with BAVENCIO in combination with axitinib, rare cases of immune-mediated pancreatitis with fatal outcomes have been observed.

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 intravenous corticosteroids.

In Study 003 Part A, none of the 88 patients with previously treated metastatic MCC had Grade 3 infusion related reactions. In Study 003 Part B, Grade 3 infusion reactions have been reported in 0.9% (1/116) of patients with treatment-naïve metastatic MCC leading to permanent discontinuation.

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

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

Adverse reactions observed in Study 003 Part B at a rate of less than 1% by SOC include:
Autoimmune Disorders: Autoimmune nephritis, Autoimmune neuropathy

Cardiac Disorders: Myocarditis, Myositis

Endocrine Disorders: Hyperthyroidism

Gastrointestinal Disorders: Colitis

Investigations: Blood creatine phosphokinase increased, Liver function test increased

Metabolism and Nutrition Disorders: Diabetes mellitus, Hyperglycaemia

Skin and Subcutaneous Tissue Disorders: Erythema hypotension

Locally Advanced or Metastatic Urothelial Carcinoma

Adverse reactions observed in Study 001 at a rate of less than 1% by SOC include:
Endocrine Disorders: Hyperthyroidism*, Adrenal insufficiency*

Eye Disorders: Uveitis*

Gastrointestinal Disorders: Diarrhea*, Enterocolitis*

Hepatobiliary Disorders: Autoimmune hepatitis*, Hepatitis*

Investigations: Aspartate aminotransferase increased*, Alanine aminotransferase increased*, Blood creatine phosphokinase increased*

Musculoskeletal and Connective Tissue Disorders: Back pain*, Rheumatoid arthritis*

Nervous System Disorders: Guillain-Barre syndrome*

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea**

Skin and Subcutaneous Tissue Disorders: Rash pruritic*, Erythema*, Erythema multiforme*, Pruritis generalized, Rash erythematous*

Vascular Disorders: Flushing**, Hypotension**

* Immune-related adverse reaction
** Infusion related reaction (IRR) based on predefined definition

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

Metastatic Merkel Cell Carcinoma

Table 5 summarizes selected Grade 3 – 4 laboratory abnormalities that occurred in ≥ 1% of patients treated with BAVENCIO in Study 003 Part A (Previously-treated) and Part B (Treatment-naïve).

Table 5 – Selected Laboratory Abnormalities with On-Treatment Worsening in ≥ 1% of Patients in Study 003 Part A (N = 88) and Part B (N = 116)

Laboratory Tests	Any Grade (N = 88) n (%)	Grade 3-4 (N = 88) n (%)	Any Grade (N = 116) n (%)	Grade 3-4 (N = 116) n (%)
Chemistry				
Increased aspartate aminotransferase (AST)	29 (34)	2 (2)	32 (28)	3 (3)
Increased alanine aminotransferase (ALT)	18 (21)	4 (5)	22 (19)	1 (1)
Increased lipase	12 (15)	4 (5)	24 (22)	6 (6)
Increased amylase	6 (8)	1 (1)	14 (13)	5 (5)
Increased bilirubin	5 (6)	1 (1)	16 (14)	0
Hyperglycemia*	-	7 (8)	-	10 (9)
Hematology				
Anemia	33 (39)	8 (9)	47 (41)	4 (4)
Lymphopenia	42 (51)	16 (19)	54 (49)	12 (11)
Thrombocytopenia	25 (29)	3 (4)	21 (18)	1 (1)
Neutropenia	6 (7)	1 (1)	12 (11)	0

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

Locally Advanced or Metastatic Urothelial Carcinoma

Table 6 summarizes selected Grade 3 – 4 laboratory abnormalities that occurred in ≥ 1% patients, with locally advanced or metastatic UC, treated with BAVENCIO in Study 001.

Table 6 – Selected Laboratory Abnormalities with On-Treatment Worsening in ≥ 1% of UC Patients, with Locally Advanced or Metastatic UC, in Study 001

Laboratory Tests	Any Grade (N = 242) n (%)	Grade 3-4 (N = 242) n (%)
Chemistry		
Alanine aminotransferase increased	51 (21.7)	4 (1.7)
Alkaline phosphatase increased	91 (39.1)	18 (7.7)
Aspartate aminotransferase increased	69 (29.4)	9 (3.8)
Blood bilirubin increased	26 (11.3)	3 (1.3)
CPK increased	14 (8.7)	1 (0.6)
Creatinine increased	158 (67.2)	6 (2.6)
GGT increased	60 (31.7)	19 (10.1)
Hypercalcemia	4 (2.0)	1 (0.5)
Hyperglycemia*	-	21 (8.9)
Hyperkalemia	63 (26.8)	8 (3.4)
Hypocalcemia	3 (1.5)	0 (0.0)
Hypoglycemia	19 (8.1)	1 (0.4)
Hypokalemia	26 (11.1)	1 (0.4)
Hypomagnesemia	48 (21.2)	2 (0.9)
Hyponatremia	98 (41.7)	37 (15.7)
Hypophosphatemia	61 (26.5)	12 (5.2)
Lipase increased	34 (18.7)	15 (8.2)
Serum amylase increased	20 (11.5)	5 (2.9)
Hematology		
Anemia	116 (50.9)	22 (9.6)
Lymphocyte count decreased	114 (51.4)	29 (13.1)
Neutrophil count decreased	22 (10.1)	2 (0.9)
Platelet count decreased	46 (20.1)	2 (0.9)

*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 IFNγ and TNFα were observed.

9.3 Pharmacokinetics

Table 7 – Summary of Avelumab Pharmacokinetics at 10 mg/kg Every 2 Weeks in Patients with Malignant Tumours

	C_{max}	T_{max}	$t_{½}$	$AUC_{0\text{-}tau}$	CL	Vss
Means, Range or Population Estimate	294 µg/mL*	1.5 hours**	6.1 days§	26214 µg*hr/mL***	0.59 L/day§	4.72 L§

CL = total systemic clearance; Vss = 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 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. For further information for BAVENCIO please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.

BAVENCIO is indicated for the treatment of:

- *Adult patients with metastatic Merkel cell carcinoma (MCC).*
- *Patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy.*

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.

12 CLINICAL TRIALS

NOC/c

12.1 Trial Design and Study Demographics

Metastatic Merkel Cell Carcinoma

Table 8 – Summary of Patient Demographics for Clinical Trial 003 in Metastatic MCC

Study #	Trial design	Dosage, route of administration and duration	Study patients (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%)
EMR 1000070-003 Part B (Study 003 Part B)	Single-arm, multi-center	10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity	116	74.0 years 41 to 93 years	Male: n = 81 (70%) Female: n = 35 (30%)

Study 003 Part A - Previously treated metastatic MCC:
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 retrospectively for PD-L1 expression; of these, 66% were PD-L1-positive (≥ 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 95 doses), and the median duration of treatment was 17 weeks (2 to 208 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 36 months of follow-up.

Study 003 Part B - Treatment-naïve metastatic MCC:
Study 003 Part B was an open-label, single-arm, multi-center study in 116 patients with metastatic MCC who were systemic treatment-naïve in the metastatic setting. In addition to the exclusion criteria defined in Study 003 Part A, Study 003 Part B also excluded patients with previous malignant disease (other than MCC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (skin, bladder, cervical, colorectal, breast, or low grade prostatic intraepithelial neoplasia or Grade 1 prostate cancer).

As with Study 003 Part A, patients in Study 003 Part B received BAVENCIO 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 116 patients, 69.8% were male, the median age was 74.0 years (41 to 93 years), 81.0% were ≥ 65 years of age, 64.7% were Caucasian and 62.1% and 37.9% had an ECOG performance status of 0 and 1, respectively. Disease status at study entry included 67.2% of patients with visceral disease, defined as target and nontarget lesion sites categorized as other than skin (including soft tissue or eye) or lymph node per IERC assessment, and 21.6% had lymph node disease only. A total of 6 patients had received prior systemic anti-cancer treatment for non-metastatic disease in the adjuvant or locally advanced setting.

All patients had tumour samples evaluated retrospectively for PD-L1 expression; of these, 18.1% were PD-L1 positive (defined as having ≥ 1% PD-L1 expression on tumour cells), 75.0% were PD-L1 negative, and 6.9% had non-evaluable results by an investigational immunohistochemistry assay. With regards to Merkel cell virus status according to immunohistochemistry method, of the 116 patients, 60.3% were reported as positive, 31.9% were negative, and 7.8% were not evaluable. Patients received a median of 11.5 doses of BAVENCIO (1 dose to 61 doses), and the median duration of treatment was 23.6 weeks (2.0 to 121.6 weeks).

The primary efficacy endpoint was durable response rate (DRR), defined as the proportion of treated patients with an objective response (complete response (CR) or partial response (PR)) with a duration of at least 6 months. Key secondary endpoints included best overall response (BOR) and duration of response (DOR). The efficacy analysis was based on an ad hoc analysis conducted when the last patient enrolled had completed 7 months of follow-up.

Locally Advanced or Metastatic Urothelial Carcinoma

Table 9 – Summary of Patient Demographics for Clinical Trial 001 in Locally Advanced or Metastatic UC After Platinum-based Therapy

Study #	Trial design	Dosage, route of administration and duration	Study patients (n)	Mean age (Range)	Sex
EMR100070-001 (Study 001) – UC Cohorts	Single-arm, multi-center	10 mg/kg i.v every 2 weeks until disease progression or unacceptable toxicity	242*	67.6 years (30 to 89 years)	Male: n = 175 (72%) Female: n = 67 (28%)

*platinum exposed patients only

Study 001 was an open-label, single arm, multi-center study of 242 patients with locally advanced or metastatic UC with disease progression on or after platinum-based therapy or who had disease progression within 12 months of treatment with a platinum-based neoadjuvant or adjuvant chemotherapy regimen. At the time of the first data cut-off, all patients had at least 6 weeks of follow-up, with 161 (67%) having at least 6 months of follow-up. At the time of the second data cut-off, all 242 subjects have been followed up minimally for 12 months after the last enrolled UC subject received the first dose of avelumab.

Patients with active or a history of central nervous system (CNS) metastasis; active or a history of any autoimmune disease (other than type 1 diabetes, vitiligo, psoriasis or thyroid disease not requiring immunosuppressive treatment); other malignancies within the last 5 years; organ transplant; conditions requiring therapeutic immune suppression or active infection with HIV, hepatitis B or C were excluded. Tumour response assessments were performed every 6 weeks by an Independent Endpoint Review Committee (IERC) using the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The primary efficacy outcome measure was confirmed objective response rate (ORR). Duration of response (DOR) was a key secondary outcome. Efficacy was evaluated in patients who were followed for at least 6 and 12 months, respectively, at the time of data cut-off.

Of the 242 patients, 72.3% were male, the median age was 68.0 years (30 years to 89 years), 77.7% were Caucasian, and 35% and 65% of patients enrolled with an ECOG performance status 0 or 1, respectively. Forty-three percent of patients had non-bladder urothelial carcinoma including 23% of patients with upper tract disease and 84% of patients had visceral metastases (baseline target and/or non-target lesions present outside of the lymph nodes). All patients received prior chemotherapy for locally advanced or metastatic disease, 46% of patients had one prior anti-cancer therapy for locally advanced or metastatic UC, 30% with had two prior therapies, 15% had three prior therapies and 7% with had four or more prior therapies. At baseline, 17% of patients had a hemoglobin < 10 g/dL and 34% of patients had liver metastases. Patients were enrolled regardless of their PD-L1 status.

12.2 Study Results

Metastatic Merkel Cell Carcinoma

Study 003 Part A – Previously treated metastatic MCC:
The objective response rate (ORR) in previously treated patients with metastatic MCC was 33.0% (95% CI 23.3, 43.8) (see Table 10).

Table 10 – Efficacy Results of Study 003 Part A 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 (%)	29 (33.0%)
(95% CI)	(23.3, 43.8)
Duration of Response (DOR)[a]	N = 29
Median, months (95% CI)	40.5 (18.0, not estimated)
Minimum, Maximum	2.8, 41.5 +
Time to Response	N = 29
Median, weeks (Range)	6.1 (6 - 36)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; +denotes a censored value; *CR or PR was confirmed at a subsequent tumour assessment;
[a]Based on number of patients with confirmed response (CR or PR)

A higher response rate was observed for patients with PD-L1 positive tumours compared to patients with PD-L1 negative tumours 36.2% (21/58) versus 18.8% (3/16), respectively.

Study 003 Part B - Treatment-naïve metastatic MCC:
An ad hoc analysis conducted after a minimum of 7 months of follow-up in treatment-naïve patients with metastatic MCC reported 32 patients with a response duration of at least 6 months for a DRR of 27.6% (95% CI: 19.7, 36.7). Additional results are presented in Table 11.

Table 11 – Efficacy Results of Study 003 Part B in Metastatic MCC

Efficacy Endpoints (Tumour assessments per RECIST v1.1, IERC)	Results N = 116
Confirmed Best Overall Response (BOR)	
Complete Response (CR)* n (%)	16 (13.8%)
Partial Response (PR)* n (%)	30 (25.9%)
Objective Response Rate (ORR)	
Response Rate, CR+PR* n (%)	46 (39.7%)
(95% CI)	(30.7, 49.2)
Duration of Response (DOR)[a]	N = 46
Median, months (95% CI)	15.2 (10.2, not estimated)
Minimum, Maximum	1.2, 22.1+
Time to Response	N = 46
Median, weeks (Range)	6.1 (5 - 36)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; +denotes a censored value; *CR or PR was confirmed at a subsequent tumour assessment;
[a]Based on number of patients with confirmed response (CR or PR)

A higher response rate was observed for patients with PD-L1 positive tumours compared to patients with PD-L1 negative tumours (61.9% (13/21) versus 33.3% (29/87), respectively). At the time of the ad hoc analysis, the median DOR for PD-L1 positive patients was not reached and the median DOR for PD-L1 negative patients was 15.2 months (95% CI: 10.2, not estimated).

Locally Advanced or Metastatic Urothelial Carcinoma

Efficacy results, for patients with locally advanced or metastatic UC who received prior platinum - based chemotherapy, from Study 001 are presented in Table 12.

Efficacy Results from First Data Cut-Off (≥ 6 Months Follow-Up, N = 161):
The confirmed objective response rate (ORR) as assessed by the IERC was 16.1%, consisting of 8 complete responses and 18 partial responses in BAVENCIO treated patients. The median time to response onset was 11.4 weeks (min, max: 5.6, 48). The 6-month durability of response was 95.8% among 161 patients with at least 6 months of follow-up. Responses were observed among PD-L1 positive and PD-L1 negative patients with a lower response rate observed among patients determined to be PD-L1 negative patients in Study 001 (defined as having less than 5% PD-L1 expression on tumour cells).

Efficacy Results from Second Data Cut-Off (≥ 12 Months Follow-Up, N = 242):
The confirmed ORR as assessed by the IERC was 15.7%, consisting of 11 complete responses and 27 partial responses in BAVENCIO treated patients. The median time to response onset was 11.6 weeks (min, max: 5.6, 47.7). The 6-month and 12-month durability of response was 94.4% and 69.4%, respectively, among 242 patients with at least 12 months of follow-up.

Table 12 – Efficacy Results for Patients with Locally Advanced or Metastatic UC in Study 001

Efficacy Endpoints (Tumour assessments per RECIST v1.1, IERC)	**Results ≥ 6 Months Follow-Up (N = 161)**
Confirmed Best Overall Response (BOR)	
Complete Response (CR)* n (%)	8 (5.0%)
Partial Response (PR)* n (%)	18 (11.2%)
Objective Response Rate (ORR)	
Response Rate, CR+PR* n (%)	26 (16.1%)
(95% CI)	(10.8, 22.8)
Duration of Response (DOR)[a]	
Median, months (95% CI)	NE (9.7, NE)
≥ 6 months by K-M (95% CI)	95.8% (73.9, 99.4)
Minimum, Maximum, months	1.4+, 17.4+

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumours; IERC: Independent Endpoint Review Committee; K-M: Kaplan Meier; +denotes a censored value; NE: Not estimable;
*CR or PR was confirmed at a subsequent tumour assessment
[a]Based on number of patients 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 ≥ 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

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 in adult patients that has spread called metastatic Merkel cell carcinoma.

BAVENCIO is a medicine used to treat bladder cancer that cannot be removed by surgery or has spread and has already been treated with a certain type of chemotherapy, which did not work or is no longer working.

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

For the following indications, 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 adult patients with metastatic Merkel cell carcinoma (MCC)
- For the treatment of bladder cancer that has previously been treated with a certain type of chemotherapy

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 be 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 or pituitary glands) 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 pancreas (pancreatitis). Inflammation of your pancreas may include abdominal pain, nausea and vomiting
- 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 known whether BAVENCIO affects your ability to drive or use tools or machines. However, if you feel tired, do not drive or use tools or machines until you feel better.

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 BAVENCIO per kilogram of your body weight.

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with BAVENCIO unless you have discussed this with your healthcare professional.

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:
It is important to keep your appointments. 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
- Joint pain

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
- Decrease thyroid hormone 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		✓	
COMMON Urinary tract infection		✓	
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 coloured), severe nausea or vomiting, bleeding or bruising more easily than normal, pain on the right side of your stomach area		✓	

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**	
(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 or pituitary glands): 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, feeling more hungry or thirsty than usual, dizziness or fainting, hair loss, changes in mood or behavior (such as irritability or forgetfulness), feeling cold, headache		✓	
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		✓	
Inflammation of the eye (uveitis)		✓	
Nervous system problems (Guillain-Barré Syndrome): pain, numbness, muscle weakness, difficulty in		✓	

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	
walking			
RARE Inflammation of the pancreas (pancreatitis): abdominal pain, nausea and vomiting		✓	

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.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

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

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