Adverse Reaction Checklist

This checklist should be printed and used only by healthcare providers to help identify certain adverse reactions that patients may experience during treatment with BAVENCIO® (avelumab) in combination with INLYTA® (axitinib). This checklist is intended to be used prior to each infusion. Click to download and print the full **BAVENCIO Prescribing Information** and the full **INLYTA Prescribing Information** to provide to your patient. Remember to also print a copy of both for your reference. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.

Patients should be encouraged to contact their healthcare provider right away if they experience any adverse reactions during treatment.

PATIENT NAME: _____ **DATE:** _____

INDICATION

BAVENCIO® (avelumab) in combination with INLYTA® (axitinib) is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION FOR BAVENCIO AND INLYTA

BAVENCIO (avelumab)

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis, and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% of patients, including one (0.1%) patient with fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% of patients, including two (0.1%) patients with fatal, and 11 (0.6%) with Grade 3.

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INLYTA (axitinib)

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for, or who have a history of, these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

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Adverse Reaction Checklist

These are not all of the possible side effects.

BAVENCIO® avelumab Injection 20 mg/mL + Inlyta® axitinib 1mg and 5mg tablets

PATIENT NAME: **DATE:**

BAVENCIO severe adverse reactions

LUNG PROBLEMS (pneumonitis). Symptoms of pneumonitis include:
- ☐ new or worsening cough
- ☐ shortness of breath
- ☐ chest pain

LIVER PROBLEMS, including hepatitis. Symptoms of liver problems include:
- ☐ yellowing of the skin or the whites of the eyes
- ☐ severe nausea or vomiting
- ☐ pain on the right side of the stomach area (abdomen)
- ☐ drowsiness
- ☐ dark urine (tea colored)
- ☐ bleeding or bruising more easily than normal

INTESTINAL PROBLEMS (colitis). Symptoms of colitis include:
- ☐ diarrhea (loose stools) or more bowel movements than usual
- ☐ blood in the stools or dark, tarry, sticky stools
- ☐ severe stomach area (abdomen) pain or tenderness

HORMONE GLAND PROBLEMS (especially the adrenal glands, thyroid, and pancreas). Symptoms that the hormone glands are not working properly include:
- ☐ rapid heartbeat
- ☐ increased sweating
- ☐ extreme tiredness
- ☐ weight gain or weight loss
- ☐ feeling more hungry or thirsty than usual
- ☐ hair loss
- ☐ changes in mood or behavior, such as irritability or forgetfulness
- ☐ constipation
- ☐ voice gets deeper
- ☐ very low blood pressure
- ☐ urinating more often than usual
- ☐ dizziness or fainting
- ☐ nausea or vomiting
- ☐ stomach area (abdomen) pain
- ☐ feeling cold

KIDNEY PROBLEMS, including nephritis. Symptoms of kidney problems include:
- ☐ decrease in the amount of urine
- ☐ blood in the urine
- ☐ swelling in the ankles
- ☐ loss of appetite

PROBLEMS IN OTHER ORGANS. Symptoms include:
- ☐ severe muscle weakness
- ☐ severe or persistent muscle or joint pains
- ☐ chest pain and tightness
- ☐ trouble breathing
- ☐ skin rash, blisters, or peeling
- ☐ changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation
- ☐ tiredness, sleepiness
- ☐ swelling of the feet and legs
- ☐ dizziness or fainting
- ☐ fever, flu-like symptoms
- ☐ changes in eyesight

SEVERE INFUSION REACTIONS. Symptoms of severe infusion reactions include:
- ☐ chills or shaking
- ☐ hives
- ☐ flushing
- ☐ shortness of breath or wheezing
- ☐ low blood pressure
- ☐ fever
- ☐ back pain
- ☐ stomach area (abdomen) pain

HEART PROBLEMS. When BAVENCIO is used with the medicine INLYTA, severe heart problems can happen and can lead to death. Symptoms of heart problems include:
- ☐ swelling of the stomach area (abdomen), legs, hands, feet, or ankles
- ☐ shortness of breath
- ☐ nausea or vomiting
- ☐ chest discomfort, including pain or pressure
- ☐ weight gain
- ☐ pain or discomfort in the arms, back, neck, or jaw
- ☐ breaking out in a cold sweat
- ☐ feeling lightheaded or dizzy

INLYTA severe adverse reactions

HIGH BLOOD PRESSURE (hypertension). High blood pressure is common with INLYTA, and may sometimes be severe.
- ☐ high blood pressure

BLOOD CLOTS IN VEINS OR ARTERIES. INLYTA can cause blood clots which can be serious, and sometimes lead to death. Symptoms include:
- ☐ chest pain or pressure
- ☐ pain in arms, back, neck, or jaw
- ☐ shortness of breath
- ☐ numbness or weakness on one side of the body
- ☐ trouble talking
- ☐ headache
- ☐ vision changes

BLEEDING. INLYTA can cause bleeding which can be serious, and sometimes lead to death. Symptoms include:
- ☐ unexpected bleeding or bleeding that lasts a long time, such as:
  - ☐ unusual bleeding from the gums
  - ☐ menstrual bleeding or vaginal bleeding that is heavier than normal
  - ☐ bleeding that is severe or that the patient cannot control
  - ☐ pink or brown urine
  - ☐ red or black stools (looks like tar)
  - ☐ bruises that happen without a known cause or get larger
  - ☐ cough up blood or blood clots
  - ☐ vomit blood or the vomit looks like "coffee grounds"
- ☐ unexpected pain, swelling, or joint pain
- ☐ headaches, feeling dizzy or weak

HEART FAILURE. Heart failure can be serious and can sometimes lead to death. Symptoms include:
- ☐ tiredness
- ☐ swelling of the stomach area (abdomen), legs, or ankles
- ☐ shortness of breath
- ☐ protruding neck veins

TEAR IN THE STOMACH OR INTESTINAL WALL (perforation). A tear in stomach or intestinal wall can be serious and can sometimes lead to death. Symptoms include:
- ☐ severe stomach area (abdominal) pain or stomach area pain that does not go away
- ☐ vomit blood
- ☐ red or black stools

THYROID GLAND PROBLEMS. Symptoms include:
- ☐ tiredness that worsens or that does not go away
- ☐ feeling hot or cold
- ☐ voice deepens
- ☐ weight gain or weight loss
- ☐ hair loss
- ☐ muscle cramps and aches

RISK OF WOUND HEALING PROBLEMS. Wounds may not heal properly during INLYTA treatment:
- ☐ planned surgery; if yes: discuss plan to stop and restart INLYTA

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME (RPLS). Symptoms include:
- ☐ headache
- ☐ seizures
- ☐ weakness
- ☐ confusion
- ☐ high blood pressure
- ☐ blindness or change in vision
- ☐ problems thinking

PROTEIN IN URINE.
- ☐ protein in urine

LIVER PROBLEMS.
- ☐ change in liver function

MOST COMMON ADVERSE REACTIONS of BAVENCIO in combination with INLYTA:
- ☐ diarrhea
- ☐ feeling tired
- ☐ high blood pressure
- ☐ muscle and bone pain
- ☐ nausea
- ☐ mouth sores
- ☐ liver problems
- ☐ rash, redness, itching, or peeling of your skin on your hands and feet
- ☐ hoarseness
- ☐ decreased appetite
- ☐ low levels of thyroid hormone
- ☐ rash
- ☐ shortness of breath
- ☐ cough
- ☐ stomach area (abdomen) pain
- ☐ headache

Please see Important Safety Information throughout. Click for the full Prescribing Information and Medication Guide for BAVENCIO and full Prescribing Information/ Patient Information for INLYTA, or visit BAVENCIO.com.

Adverse Reaction Checklist

IMPORTANT SAFETY INFORMATION FOR BAVENCIO AND INLYTA (cont'd)

BAVENCIO (avelumab)

BAVENCIO in combination with INLYTA can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold BAVENCIO and INLYTA for moderate (Grade 2) hepatotoxicity and permanently discontinue the combination for severe or life-threatening (Grade 3 or 4) hepatotoxicity. Administer corticosteroids as needed. In patients treated with BAVENCIO in combination with INLYTA, Grades 3 and 4 increased ALT and AST occurred in 9% and 7% of patients, respectively, and immune-mediated hepatitis occurred in 7% of patients, including 4.9% with Grade 3 or 4.

BAVENCIO can cause **immune-mediated colitis**. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO for moderate or severe (Grade 2 or 3) colitis until resolution. Permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon reinitiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% of patients, including seven (0.4%) with Grade 3.

BAVENCIO can cause **immune-mediated endocrinopathies**, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of **adrenal insufficiency** during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% of patients, including one (0.1%) with Grade 3.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders, including hypothyroidism, hyperthyroidism, and thyroiditis, were reported in 6% of patients, including three (0.2%) with Grade 3.

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer antihyperglycemics or insulin in patients with severe or life-threatening (Grade ≥3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% of patients, including two cases of Grade 3 hyperglycemia.

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% of patients.

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INLYTA (axitinib)

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

INLYTA has the potential to adversely affect **wound healing.** Withhold INLYTA for at least 2 days prior to elective surgery. Do not administer INLYTA for at least 2 weeks following major surgery and until adequate wound healing. The safety of resuming INLYTA after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment with INLYTA.

INLYTA in combination with BAVENCIO® (avelumab) can cause **hepatotoxicity** with higher than expected frequencies of Grades 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used for monotherapy. Consider withholding INLYTA and/or BAVENCIO, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

For patients with moderate **hepatic impairment,** the starting dose of INLYTA should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

INLYTA in combination with BAVENCIO can cause severe and fatal **major adverse cardiovascular events (MACE).** Consider baseline and periodic evaluations of left ventricular ejection fraction and monitor for signs and symptoms of cardiovascular events. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue INLYTA and BAVENCIO for Grade 3 or 4 cardiovascular events.

INLYTA can cause **fetal harm.** Advise patients of the potential risk to the fetus and to use effective contraception.

Avoid strong **CYP3A4/5 inhibitors.** If unavoidable, reduce the dose of INLYTA. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

Adverse Reaction Checklist

IMPORTANT SAFETY INFORMATION FOR BAVENCIO AND INLYTA (cont'd)

BAVENCIO (avelumab)

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO as a single agent or in 489 patients who received *BAVENCIO in combination with INLYTA*: myocarditis including fatal cases, pancreatitis including fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO in combination with INLYTA can cause **major adverse cardiovascular events (MACE)** including severe and fatal events. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue BAVENCIO and INLYTA for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with INLYTA compared to 3.4% treated with sunitinib. These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%).

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

ADVERSE REACTIONS (BAVENCIO + INLYTA)

Fatal adverse reactions occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving BAVENCIO in combination with INLYTA. These included sudden cardiac death (1.2%), stroke (0.2%), myocarditis (0.2%), and necrotizing pancreatitis (0.2%).

The most common adverse reactions (all grades, ≥20%) in patients with **advanced RCC** receiving BAVENCIO in combination with INLYTA (vs sunitinib) were diarrhea (62% vs 48%), fatigue (53% vs 54%), hypertension (50% vs 36%), musculoskeletal pain (40% vs 33%), nausea (34% vs 39%), mucositis (34% vs 35%), palmar-plantar erythrodysesthesia (33% vs 34%), dysphonia (31% vs 3.2%), decreased appetite (26% vs 29%), hypothyroidism (25% vs 14%), rash (25% vs 16%), hepatotoxicity (24% vs 18%), cough (23% vs 19%), dyspnea (23% vs 16%), abdominal pain (22% vs 19%), and headache (21% vs 16%).

Selected laboratory abnormalities (all grades, ≥20%) worsening from baseline in patients with **advanced RCC** receiving BAVENCIO in combination with INLYTA (vs sunitinib) were blood triglycerides increased (71% vs 48%), blood creatinine increased (62% vs 68%), blood cholesterol increased (57% vs 22%), alanine aminotransferase increased (ALT) (50% vs 46%), aspartate aminotransferase increased (AST) (47% vs 57%), blood sodium decreased (38% vs 37%), lipase increased (37% vs 25%), blood potassium increased (35% vs 28%), platelet count decreased (27% vs 80%), blood bilirubin increased (21% vs 23%), and hemoglobin decreased (21% vs 65%).

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