



October 4, 2024

Ms. Carmen Chinchilla
Nebraska Oncology Society
1045 Lincoln Mall, Suite 200
Lincoln, NE 68508

Dear Ms. Chinchilla,

We are sending this communication on behalf of BeiGene USA, Inc. to announce **WAC pricing** and that the Centers for Medicare & Medicaid Services (CMS) has assigned a **permanent drug-specific J-code TEVIMBRA® (tislelizumab-jsgr)** injection, for intravenous use, effective October 1, 2024.¹ The J-code (J9329) and WAC are detailed below. Additionally, TEVIMBRA is now available.

Please see Indication and Important Safety Information below and the enclosed Full Prescribing Information for TEVIMBRA.

Trade Name	Permanent Drug-Specific HCPCS Code	CMS Long Descriptor	Effective Date
TEVIMBRA® (tislelizumab-jsgr) injection, for intravenous use	J9329	Injection, tislelizumab-jsgr, 1 mg	October 1, 2024

Trade Name	Packaging	National Drug Code (NDC) ²	WAC
TEVIMBRA® (tislelizumab-jsgr) injection, for intravenous use	100 mg/10 mL (10 mg/mL) single-dose vial	72579- 0 121-01*	\$5,204

*NDC has been “zero-filled” to ensure creation of an 11-digit code that meets HIPAA standards.² The zero-fill location is indicated in bold. HIPAA=Health Insurance Portability and Accountability Act.

TEVIMBRA® (tislelizumab-jsgr), as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.³

The recommended dose of TEVIMBRA is 200 mg as an intravenous infusion once every 3 weeks. Administer the first infusion over 60 minutes. If tolerated, subsequent infusions may be administered over 30 minutes.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

TEVIMBRA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated reactions.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TEVIMBRA depending on severity. In general, if TEVIMBRA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Immune-Mediated Pneumonitis

TEVIMBRA can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3.8% (75/1972) of patients receiving TEVIMBRA, including fatal (0.2%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.7%) adverse reactions. Pneumonitis led to permanent discontinuation of TEVIMBRA in 35 (1.8%) patients and withholding of TEVIMBRA in 27 (1.4%) patients.

Systemic corticosteroids were required in all patients with pneumonitis. Immune-mediated pneumonitis resolved in 47% of the 75 patients. Of the 27 patients in whom TEVIMBRA was withheld for pneumonitis, 18 reinitiated TEVIMBRA after symptom improvement; of these, 3 (17%) patients had recurrence of pneumonitis.

Immune-Mediated Colitis

TEVIMBRA can cause immune-mediated colitis, which can be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 0.9% (17/1972) of patients receiving TEVIMBRA, including Grade 3 (0.4%), and Grade 2 (0.5%) adverse reactions. Colitis led to permanent discontinuation of TEVIMBRA in 2 (0.1%) patients and withholding of TEVIMBRA in 10 (0.5%) patients. All 17 patients received systemic corticosteroids. Twelve (71%) of the 17 patients received high-dose systemic corticosteroids. Two (12%) of the 17 patients received immunosuppressive treatment. Immune-mediated colitis resolved in 88% of the 17 patients. Of the 10 patients in whom TEVIMBRA was withheld for colitis, 8 reinitiated TEVIMBRA after symptom improvement; of these, 1 (13%) patient had recurrence of colitis.

Immune-Mediated Hepatitis

TEVIMBRA can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 1.7% (34/1972) of patients receiving TEVIMBRA, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1%), and Grade 2 (0.6%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation in 9 (0.5%) patients and withholding of TEVIMBRA in 20 (1%) patients. All patients received systemic corticosteroids. Twenty-nine (85%) of the 34 patients received high-dose systemic corticosteroids. One patient (2.9%) of the 34 patients received immunosuppressive treatment. Immune-mediated hepatitis resolved in 59% of the 34 patients. Of the 20 patients in whom TEVIMBRA was withheld for hepatitis, 12 reinitiated TEVIMBRA after symptom improvement; of these, 2 (17%) patients had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TEVIMBRA can cause immune-mediated adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold TEVIMBRA depending on severity.

Immune-mediated adrenal insufficiency occurred in 0.3% (6/1972) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (0.1%), and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 5 out of the 6 patients. All 6 patients received systemic corticosteroids. Two (33%) of the 6 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 17% of the 6 patients.

Hypophysitis

TEVIMBRA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity.

Hypophysitis/hypopituitarism occurred in 0.1% (1/1972) of patients receiving TEVIMBRA, including a Grade 2 (0.1%) adverse reaction. No TEVIMBRA treatment discontinuation or withholding was required.

Thyroid Disorders

TEVIMBRA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity.

Thyroiditis: Immune-mediated thyroiditis occurred in 0.4% (7/1972) of patients receiving TEVIMBRA, including Grade 2 (0.3%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 1 (0.1%) patient. One (14%) of the 7 patients received systemic corticosteroids. Thyroiditis resolved in 29% of the 7 patients.

Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 0.6% (12/1972) of patients receiving TEVIMBRA, including Grade 3 (0.1%), and Grade 2 (0.5%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of TEVIMBRA in 1 (0.1%) patient and withholding of TEVIMBRA in 1 (0.1%) patient. One (8%) of the 12 patients received systemic corticosteroids. Hyperthyroidism resolved in 92% of the 12 patients.

Hypothyroidism: Immune-mediated hypothyroidism occurred in 7% (132/1972) of patients receiving TEVIMBRA, including Grade 4 (0.1%) and Grade 2 (5%) adverse reactions. TEVIMBRA was not permanently discontinued in any patient, while treatment was withheld in 6 (0.3%) patients. Two (1.5%) of the 132 patients received systemic corticosteroids. All 132 patients received hormone replacement therapy. Hypothyroidism resolved in 27% of the 132 patients. The majority (86%) of patients with hypothyroidism required long-term thyroid hormone replacement.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Type 1 diabetes mellitus has been reported with PD-1/PD-L1 blocking antibodies. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity.

Immune-Mediated Nephritis with Renal Dysfunction

TEVIMBRA can cause immune-mediated nephritis, which can be fatal.

Immune-mediated nephritis with renal dysfunction occurred in 0.4% (7/1972) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (0.1%), and Grade 2 (0.2%) adverse reactions. TEVIMBRA was permanently discontinued in 3 (0.2%) patients and treatment was withheld in 3 (0.2%) patients. All patients received systemic corticosteroids. Nephritis with renal dysfunction resolved in 57% of the 7 patients. Of the 3 patients in whom TEVIMBRA was withheld for nephritis, 2 reinitiated TEVIMBRA after symptom improvement and one patient had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TEVIMBRA can cause immune-mediated rash or dermatitis. Cases of severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported, some with fatal outcome. Topical emollients and/or topical

corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TEVIMBRA depending on severity.

Immune-mediated dermatologic adverse reactions occurred in 1.2% (24/1972) of patients receiving TEVIMBRA, including Grade 4 (0.2%), Grade 3 (0.4%), and Grade 2 (0.4%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TEVIMBRA in 3 (0.2%) patients and withholding of TEVIMBRA in 9 (0.5%) patients. Twenty-three (96%) of the 24 patients received systemic corticosteroids. Immune-mediated skin reactions resolved in 58% of the 24 patients. Of the 9 patients in whom TEVIMBRA was withheld for dermatologic adverse reactions, 8 reinitiated TEVIMBRA after symptom improvement; of these, 2 (25%) patients had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1972 patients who received TEVIMBRA: myositis, myocarditis, arthritis, polymyalgia rheumatica, and pericarditis.

The following additional clinically significant immune-mediated adverse reactions have been reported with other PD-1/PD-L1 blocking antibodies, including severe or fatal cases.

Cardiac/Vascular: Vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Polymyositis, rhabdomyolysis and associated sequelae including renal failure

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Infusion-Related Reactions

TEVIMBRA can cause severe or life-threatening infusion-related reactions. Infusion-related reactions occurred in 4.2% (83/1972) patients receiving TEVIMBRA, including Grade 3 or higher (0.3%) reactions. Monitor patients for signs and symptoms of infusion-related reactions.

Slow the rate of infusion for mild (Grade 1) and interrupt the infusion for moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue TEVIMBRA.

Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action, TEVIMBRA can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose.

ADVERSE REACTIONS

Permanent discontinuation of TEVIMBRA due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation in $\geq 1\%$ of patients were hemorrhage, pneumonitis (including pneumonitis and immune-mediated pneumonitis), and pneumonia.

Dosage interruptions of TEVIMBRA due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dosage interruptions in $\geq 2\%$ of patients were pneumonia, pneumonitis, and fatigue.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were increased glucose, decreased hemoglobin, decreased lymphocytes, decreased sodium, decreased albumin, increased alkaline phosphatase, anemia, fatigue, increased AST, musculoskeletal pain, decreased weight, increased ALT, and cough.

Please see the enclosed full Prescribing Information for more information.

Sincerely,

Marisa Price

Consultant

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References:

1. Centers for Medicare & Medicaid Services. 2024 HCPCS Application Summary for Quarter 2, 2024 Drugs and Biologicals. <https://www.cms.gov/files/document/2024-hcpcs-application-summary-quarter-2-2024-drugs-and-biologicals.pdf>. Accessed 8/12/2024.
2. U.S. Food and Drug Administration. National Drug Code Background Information. <https://www.fda.gov/drugs/development-approval-process-drugs/national-drug-code-database-background-information>. Accessed 8/12/2024.
3. BeiGene USA, Inc. San Mateo, CA. TEVIMBRA Full Prescribing Information. <https://www.beigene.com/PDF/TEVIMBRAUSPI.pdf>.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TEVIMBRA safely and effectively. See full prescribing information for TEVIMBRA.

TEVIMBRA® (tislelizumab-jsgf) injection, for intravenous use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

TEVIMBRA is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. (1)

DOSAGE AND ADMINISTRATION

Recommended Dosage: 200 mg as an intravenous infusion once every 3 weeks. Administer the first infusion over 60 minutes. If tolerated, subsequent infusions may be administered over 30 minutes. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL (10 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Immune-Mediated Adverse Reactions:** (5.1)
 - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated

nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.

- Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
- Withhold or permanently discontinue TEVIMBRA based on the severity of reaction.
- **Infusion-Related Reactions:** Slow the rate of infusion, interrupt, or permanently discontinue based on severity of infusion reaction. (5.2)
- **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT):** Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use of effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 20 %), including laboratory abnormalities with TEVIMBRA were: increased glucose, decreased hemoglobin, decreased lymphocytes, decreased sodium, decreased albumin, increased alkaline phosphatase, anemia, fatigue, increased AST, musculoskeletal pain, decreased weight, increased ALT, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BeiGene at 1-877-828-5596 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2024

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TEVIMBRA (tislelizumab-jsgr), as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of TEVIMBRA is 200 mg administered as an intravenous infusion once every 3 weeks, until disease progression or unacceptable toxicity.

Administer the first infusion over 60 minutes. If tolerated, subsequent infusions may be administered over 30 minutes.

2.2 Dosage Modifications for Adverse Reactions

No dose reduction of TEVIMBRA is recommended. In general, withhold TEVIMBRA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TEVIMBRA for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids [see *Warnings and Precautions (5.1)*].

Dosage modifications for TEVIMBRA for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction ^a	Dosage Modifications
Immune-Mediated Adverse Reactions [see <i>Warnings and Precautions (5.1)</i>]		
Pneumonitis	Grade 2	Withhold ^b
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold ^b
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold ^b
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue

Adverse Reaction	Severity of Adverse Reaction ^a	Dosage Modifications
Immune-Mediated Adverse Reactions [see <i>Warnings and Precautions</i> (5.1)]		
Hepatitis with tumor involvement of the liver ^c	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold ^b
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold ^b
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Grade 3, or suspected SJS, TEN, or DRESS	Withhold ^b
	Grade 4, or confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions [see <i>Warnings and Precautions</i> (5.2)].	Grade 1	Slow infusion rate by 50%
	Grade 2	Interrupt infusion ^d
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, SJS = Stevens Johnson syndrome, TEN = Toxic epidermal necrolysis

^a Based on Common Terminology Criteria for Adverse Events Version 4.

^b Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

^c If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TEVIMBRA based on recommendations for hepatitis with no liver involvement.

^d Resume infusion if resolved or decreased to Grade 1, and slow rate of infusion by 50% of the previous rate.

2.3 Preparation and Administration

Preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. TEVIMBRA is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or contains visible particles. Do not shake the vial.

Prepare the solution for infusion as follows:

- Withdraw 20 mL of TEVIMBRA from two vials of TEVIMBRA 100 mg (for a total of 200 mg in 20 mL).
- Transfer solution into an intravenous (IV) infusion bag containing 0.9% Sodium Chloride Injection, USP to prepare an infusion with a final concentration between 2 mg/mL to 5 mg/mL.
- Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution. Do not shake.
- TEVIMBRA is for single use only. Discard any unused portion left in the vial.

Storage of Diluted Solution

This product does not contain any preservatives. Store the TEVIMBRA diluted solution either:

- At room temperature for no more than 4 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of the infusion
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 20 hours. If refrigerated, allow the diluted solution to come to room temperature prior to administration

Discard the diluted solution after 4 hours at room temperature or after 20 hours under refrigeration.

Do not freeze the diluted solution.

Administration

- Administer diluted solution by intravenous infusion through an intravenous line with a sterile, nonpyrogenic, low-protein binding 0.2 micron or 0.22 micron in-line or add-on filter.
- The initial infusion should be delivered over 60 minutes. If tolerated, all subsequent infusions may be administered over 30 minutes.
- Do not co-administer other drugs through the same infusion line.
- Do not administer TEVIMBRA as an intravenous push or single bolus injection.
- The intravenous line must be flushed at the end of infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

TEVIMBRA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TEVIMBRA depending on severity [*see Dosage and Administration (2.2)*]. In general, if TEVIMBRA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TEVIMBRA can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3.8% (75/1972) of patients receiving TEVIMBRA, including fatal (0.2%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.7%) adverse reactions. Pneumonitis led to permanent discontinuation of TEVIMBRA in 35 (1.8%) patients and withholding of TEVIMBRA in 27 (1.4%) patients.

Systemic corticosteroids were required in all patients with pneumonitis. Immune-mediated pneumonitis resolved in 47% of the 75 patients. Of the 27 patients in whom TEVIMBRA was withheld for pneumonitis, 18 reinitiated TEVIMBRA after symptom improvement; of these, 3 (17%) patients had recurrence of pneumonitis.

Immune-Mediated Colitis

TEVIMBRA can cause immune-mediated colitis, which can be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 0.9% (17/1972) of patients receiving TEVIMBRA, including Grade 3 (0.4%), and Grade 2 (0.5%) adverse reactions. Colitis led to permanent discontinuation of TEVIMBRA in 2 (0.1%) patients and withholding of TEVIMBRA in 10 (0.5%) patients. All 17 patients received systemic corticosteroids. Twelve (71%) of the 17 patients received high-dose systemic corticosteroids. Two (12%) of the 17 patients received immunosuppressive treatment. Immune-mediated colitis resolved in 88% of the 17 patients. Of the 10 patients in whom TEVIMBRA was withheld for colitis, 8 reinitiated TEVIMBRA after symptom improvement; of these, 1 (13%) patient had recurrence of colitis.

Immune-Mediated Hepatitis

TEVIMBRA can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 1.7% (34/1972) of patients receiving TEVIMBRA, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1%), and Grade 2 (0.6%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation in 9 (0.5%) patients and withholding of TEVIMBRA in 20 (1%) patients. All patients received systemic corticosteroids. Twenty-nine (85%) of the 34 patients received high-dose systemic corticosteroids. One patient (2.9%) of the 34 patients received immunosuppressive treatment. Immune-mediated hepatitis resolved in 59% of the 34 patients. Of the 20 patients in whom TEVIMBRA was withheld for hepatitis, 12 reinitiated TEVIMBRA after symptom improvement; of these, 2 (17%) patients had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TEVIMBRA can cause immune-mediated adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold TEVIMBRA depending on severity [see *Dosage and Administration (2.2)*].

Immune-mediated adrenal insufficiency occurred in 0.3% (6/1972) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (0.1%), and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 5 out of the 6 patients. All 6 patients received systemic corticosteroids. Two (33%) of the 6 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 17% of the 6 patients.

Hypophysitis

TEVIMBRA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity [see *Dosage and Administration (2.2)*].

Hypophysitis/hypopituitarism occurred in 0.1% (1/1972) of patients receiving TEVIMBRA, including a Grade 2 (0.1%) adverse reaction. No TEVIMBRA treatment discontinuation or withholding was required.

Thyroid Disorders

TEVIMBRA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity [see *Dosage and Administration (2.2)*].

Thyroiditis: Immune-mediated thyroiditis occurred in 0.4% (7/1972) of patients receiving TEVIMBRA, including Grade 2 (0.3%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TEVIMBRA.

TEVIMBRA was withheld in 1 (0.1%) patient. One (14%) of the 7 patients received systemic corticosteroids. Thyroiditis resolved in 29% of the 7 patients.

Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 0.6% (12/1972) of patients receiving TEVIMBRA, including Grade 3 (0.1%), and Grade 2 (0.5%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of TEVIMBRA in 1 (0.1%) patient and withholding of TEVIMBRA in 1 (0.1%) patient. One (8%) of the 12 patients received systemic corticosteroids. Hyperthyroidism resolved in 92% of the 12 patients.

Hypothyroidism: Immune-mediated hypothyroidism occurred in 7% (132/1972) of patients receiving TEVIMBRA, including Grade 4 (0.1%) and Grade 2 (5%) adverse reactions. TEVIMBRA was not permanently discontinued in any patient, while treatment was withheld in 6 (0.3%) patients. Two (1.5%) of the 132 patients received systemic corticosteroids. All 132 patients received hormone replacement therapy. Hypothyroidism resolved in 27% of the 132 patients. The majority (86%) of patients with hypothyroidism required long-term thyroid hormone replacement.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Type 1 diabetes mellitus has been reported with PD-1/PD-L1 blocking antibodies. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity [*see Dosage and Administration (2.2)*].

Immune-Mediated Nephritis with Renal Dysfunction

TEVIMBRA can cause immune-mediated nephritis, which can be fatal.

Immune-mediated nephritis with renal dysfunction occurred in 0.4% (7/1972) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (0.1%), and Grade 2 (0.2%) adverse reactions. TEVIMBRA was permanently discontinued in 3 (0.2%) patients and treatment was withheld in 3 (0.2%) patients. All patients received systemic corticosteroids. Nephritis with renal dysfunction resolved in 57% of the 7 patients. Of the 3 patients in whom TEVIMBRA was withheld for nephritis, 2 reinitiated TEVIMBRA after symptom improvement and one patient had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TEVIMBRA can cause immune-mediated rash or dermatitis. Cases of severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and Toxic epidermal necrolysis (TEN), have been reported, some with fatal outcome. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TEVIMBRA depending on severity [*see Dosage and Administration (2.2)*].

Immune-mediated dermatologic adverse reactions occurred in 1.2% (24/1972) of patients receiving TEVIMBRA, including Grade 4 (0.2%), Grade 3 (0.4%), and Grade 2 (0.4%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TEVIMBRA in 3 (0.2%) patients and withholding of TEVIMBRA in 9 (0.5%) patients. Twenty-three (96%) of the 24 patients received systemic corticosteroids. Immune-mediated skin reactions resolved in 58% of the 24 patients. Of the 9 patients in whom TEVIMBRA was withheld for dermatologic adverse reactions, 8 reinitiated TEVIMBRA after symptom improvement; of these, 2 (25%) patients had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1972 patients who received TEVIMBRA: myositis, myocarditis, arthritis, polymyalgia rheumatica, and pericarditis.

The following additional clinically significant immune-mediated adverse reactions have been reported with other PD-1/PD-L1 blocking antibodies, including severe or fatal cases.

Cardiac/Vascular: Vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Polymyositis, rhabdomyolysis and associated sequelae including renal failure

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2 Infusion-Related Reactions

TEVIMBRA can cause severe or life-threatening infusion-related reactions. Infusion-related reactions occurred in 4.2% (83/1972) patients receiving TEVIMBRA, including Grade 3 or higher (0.3%) reactions. Monitor patients for signs and symptoms of infusion-related reactions.

Slow the rate of infusion for mild (Grade 1) and interrupt the infusion for moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue TEVIMBRA [see *Dosage and Administration (2.2)*].

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TEVIMBRA can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the label:

- Severe and fatal immune-mediated adverse reactions [see *Warnings and Precautions (5.1)*]
- Infusion-related reactions [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflect exposure to TEVIMBRA as a single agent in 1972 patients enrolled in two randomized open-label, active-controlled studies (RATIONALE-302, BGB-A317-303) and five open-label, single-arm studies (BGB-A317-208, BGB-A317-204, BGB-A317-203, BGB-A317-102, BGB-A317_Study_001), which enrolled 307 patients with esophageal squamous cell carcinoma and 1665 patients with advanced or recurrent tumors. TEVIMBRA was administered at a dose of 200 mg intravenously once every 3 weeks, except in studies BGB-A317_Study_001 where patients also received other dosage regimens. Among the 1972 patients, 37% were exposed for longer than 6 months, and 20% were exposed for longer than 12 months.

Esophageal squamous cell carcinoma

The safety of TEVIMBRA was evaluated in RATIONALE-302, a randomized, active-controlled, open-label, multicenter study in 255 patients with unresectable advanced, recurrent or metastatic ESCC [see *Clinical Studies (14.1)*]. The trial excluded patients who had brain or leptomeningeal metastases that were symptomatic or required treatment, active autoimmune disease, a medical condition requiring systemic corticosteroids or immunosuppressants, or apparent tumor invasion of organs adjacent to the esophageal site.

Patients received TEVIMBRA 200 mg by intravenous infusion over 30-60 minutes every 3 weeks or investigator's choice: paclitaxel 135-175 mg/m² every 3 weeks or 80-100 mg/m² weekly, docetaxel 75 mg/m² every 3 weeks, or irinotecan 125 mg/m² on Days 1 and 8 of every 3-week cycle. Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 2.8 months (range: 0.2 to 28.3 months) in TEVIMBRA-treated patients and 1.5 months (range: 0.2 to 19.2 months) in paclitaxel, docetaxel, or irinotecan-treated patients.

Serious adverse reactions occurred in 41% of patients; the most frequent serious adverse reactions ($\geq 2\%$) were pneumonia, dysphagia, hemorrhage, pneumonitis (including pneumonitis and immune-mediated pneumonitis), and esophageal obstruction. Fatal adverse reactions occurred in 7% of patients who received TEVIMBRA, including the following which occurred in more than one patient: pneumonia/pneumonitis (5 patients), hemorrhage (3 patients), and death due to an unknown cause (3 patients).

Permanent discontinuation of TEVIMBRA due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation in $\geq 1\%$ of patients were hemorrhage, pneumonitis (including pneumonitis and immune-mediated pneumonitis), and pneumonia.

Dosage interruptions of TEVIMBRA due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dosage interruptions in $\geq 2\%$ of patients were pneumonia, pneumonitis, and fatigue.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were increased glucose, decreased hemoglobin, decreased lymphocytes, decreased sodium, decreased albumin, increased alkaline phosphatase, anemia, fatigue, increased AST, musculoskeletal pain, decreased weight, increased ALT, and cough.

Adverse reactions and laboratory abnormalities are listed in Table 2 and Table 3, respectively.

Table 2: Adverse Reactions ($\geq 10\%$) in Patients With ESCC Receiving TEVIMBRA in RATIONALE-302

Adverse Reaction	TEVIMBRA (N=255)		ICC (N=240)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Blood disorders				
Anemia	31	6	45	11
General disorders				
Fatigue ^a	28	2	46	6
Pyrexia	16	0.4	14	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^b	24	1	25	1
Investigations				
Weight decreased	23	1	19	0
Respiratory, thoracic and mediastinal disorders				
Cough ^c	22	0.4	16	0.4
Metabolism and nutrition disorders				
Decreased appetite	16	0.4	35	4
Infections and infestations				
Pneumonia ^d	16	6	12	7
Gastrointestinal disorders				
Constipation	15	0	19	0.4
Nausea	14	0.4	30	3
Diarrhea ^e	13	1	32	7
Dysphagia	11	6	8	3
Abdominal pain ^f	11	0.8	16	2
Vomiting	11	0.8	20	4
Endocrine disorders				
Hypothyroidism ^g	13	0.4	0.8	0
Skin and subcutaneous tissue disorders				
Rash ^h	13	0.4	6	0
Vascular disorders				
Hemorrhage ⁱ	12	2	10	3

ICC = investigator's choice of chemotherapy

^a Fatigue includes asthenia, fatigue, malaise.

^b Musculoskeletal pain includes musculoskeletal pain, spinal pain, arthralgia, back pain, neck pain, musculoskeletal chest pain, myalgia, pain in extremity, non-cardiac chest pain, bone pain, arthritis.

^c Cough includes productive cough, cough.

^d Pneumonia includes pneumonia aspiration, pneumonia, pneumonia bacterial, lower respiratory tract infection.

^e Diarrhea includes diarrhea, colitis.

^f Abdominal pain includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

^g Hypothyroidism includes hypothyroidism, blood thyroid stimulating hormone increased.

^h Rash includes dermatitis, dermatitis acneiform, dermatitis allergic, eczema, erythema, psoriasis, rash, rash follicular, rash maculo-papular, rash pruritic.

ⁱ Hemorrhage includes tumor hemorrhage, upper gastrointestinal hemorrhage, gastrointestinal hemorrhage, hemoptysis, esophageal hemorrhage, hematuria, gastric hemorrhage, epistaxis, tracheal hemorrhage, gingival bleeding, pulmonary hemorrhage, procedural hemorrhage, rectal hemorrhage, stoma site hemorrhage.

Table 3: Laboratory Abnormalities Worsening From Baseline Occurring in $\geq 10\%$ of Patients Receiving TEVIMBRA in RATIONALE-302

Laboratory Abnormality	TEVIMBRA ^a		ICC ^a	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry				
Glucose increased	46	4	40	2
Sodium decreased	34	9	36	8
Albumin decreased	33	0.8	37	1
Alkaline phosphatase increased	32	3	15	0.5
AST increased	27	0.8	12	0.5
ALT increased	23	0.8	15	1
Phosphate decreased	15	4	20	3
Creatine kinase increased	13	1	2	0
Potassium decreased	13	1	15	3
Bilirubin increased	11	2	8	0.5
Glucose decreased	10	0.4	10	0.5
Hematology				
Hemoglobin decreased	45	6	61	10
Lymphocytes decreased	43	11	60	28
Platelets decreased	11	1	11	0.9
Leukocytes decreased	10	0.8	66	31

^a The denominator used to calculate the rate varied from 136 to 240 based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TEVIMBRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Stevens-Johnson-Syndrome, Toxic epidermal necrolysis (including fatal cases)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, TEVIMBRA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on the use of TEVIMBRA in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see *Data*). Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, tislelizumab-jsgr has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TEVIMBRA to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering TEVIMBRA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to tislelizumab-jsgr may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of tislelizumab-jsgr in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose of TEVIMBRA.

8.3 Females and Males of Reproductive Potential

TEVIMBRA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TEVIMBRA [*see Use in Specific Populations (8.1)*].

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose of TEVIMBRA.

8.4 Pediatric Use

The safety and effectiveness of TEVIMBRA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 256 patients with ESCC who were treated with TEVIMBRA in the clinical study RATIONALE-302, 39% were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

11 DESCRIPTION

Tislelizumab-jsgr is a programmed death receptor-1 (PD 1)-blocking antibody. Tislelizumab-jsgr is an Fc-engineered humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 147 kDa. Tislelizumab-jsgr is produced in recombinant Chinese hamster ovary (CHO) cells.

TEVIMBRA (tislelizumab-jsgr) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use, supplied in single-dose vials. Each vial contains a 100 mg of tislelizumab-jsgr monoclonal antibody in 10 mL of solution, with a concentration of 10 mg/mL, and is formulated in: citric acid monohydrate (4.2 mg), histidine (17.2 mg), L-histidine hydrochloride monohydrate (8.2 mg), polysorbate 20 (2 mg), sodium citrate (59.3 mg), trehalose (650.4 mg), and Water for Injection, USP. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Tislelizumab-jsgr binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Tislelizumab-jsgr decreased tumor growth in xenograft models and a human PD-1 transgenic mouse model.

12.2 Pharmacodynamics

The tislelizumab-jsgr exposure-response relationship for efficacy and safety and time course of pharmacodynamic response has not been fully characterized.

12.3 Pharmacokinetics

Pharmacokinetic parameters are presented as geometric mean (%CV) unless otherwise specified.

The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of tislelizumab-jsgr increased dose proportionally in the dose range of 0.5 (0.2 times the approved recommended dosage in a 70 kg patient) to 10 mg/kg (3.5 times the approved recommended dosage in a 70 kg patient).

The steady-state AUC_{tau} of tislelizumab-jsgr is 1,283 $\mu\text{g/mL}\cdot\text{day}$ (28.7%) and the C_{max} is 110 $\mu\text{g/mL}$ (22.2%) following the approved recommended dosage. Steady-state concentration of tislelizumab-jsgr is reached after 12 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.14-fold.

Distribution

The tislelizumab-jsgr steady-state total volume of distribution is 6.42 L (32.6%).

Elimination

The tislelizumab-jsgr total clearance is 0.153 L/day (29.5%) and the terminal half-life ($t_{1/2}$) is 24 days (31.0%).

Specific Populations

No clinically significant differences in the pharmacokinetics of tislelizumab-jsgr were observed based on age (range: 18 to 90 years), weight (range: 32 to 130 kg), race (White, Asian, or Black), mild to moderate renal impairment ($CLCr \geq 30$ mL/min, estimated by Cockcroft-Gault), mild to moderate hepatic impairment (total bilirubin ≤ 3 times

ULN and any AST, estimated by NCI criteria). The effect of severe hepatic impairment (total bilirubin > 3 times ULN and any AST), severe renal impairment (CLCr 15-29 mL/min), or end stage renal disease (CLCr < 15 mL/min) on the pharmacokinetics of tislelizumab-jsgr is unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of tislelizumab-jsgr products.

In patients who received tislelizumab-jsgr in RATIONALE-302 for up to 22 months, the incidence of anti-tislelizumab antibodies was 14.5% (32/221). Among the anti-tislelizumab antibody-positive patients, the incidence of neutralizing antibodies was 3.1% (1/32).

There was no significant effect of anti-drug antibodies on the pharmacokinetics of tislelizumab-jsgr. The effect of anti-drug antibodies on pharmacodynamics, safety, or effectiveness of tislelizumab-jsgr has not been fully characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of tislelizumab-jsgr for carcinogenicity or genotoxicity.

In a 3-month repeat-dose toxicology study in cynomolgus monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in the study were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. *Mycobacterium 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-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-L1 and PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Esophageal Squamous Cell Cancer

RATIONALE-302 (NCT03430843) was a multicenter, randomized (1:1), open-label trial in 512 adult patients with unresectable advanced or metastatic ESCC who progressed on or after prior systemic chemotherapy.

Patients were enrolled regardless of their tumor PD-L1 expression level. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on both tumor and tumor-associated immune cells. The trial excluded patients who received a prior immune checkpoint inhibitor, had brain or leptomeningeal metastases that were symptomatic or required treatment, active autoimmune disease, a medical condition requiring systemic corticosteroids or immunosuppressants, or apparent tumor invasion of organs adjacent to the esophageal tumor.

Patients were randomized (1:1) to receive either TEVIMBRA 200 mg every 3 weeks or investigator's choice of chemotherapy (ICC), all given intravenously: paclitaxel 135-175 mg/m² every 3 weeks or 80-100 mg/m² weekly, docetaxel 75 mg/m² every 3 weeks, or irinotecan 125 mg/m² on Days 1 and 8 of every 3-week cycle. Patients were treated until disease progression assessed by the investigator or unacceptable toxicity.

Randomization was stratified by geographic region (Asia [excluding Japan] vs Japan vs US/EU), ECOG performance status (0 vs 1), and ICC option. Tumor assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks until disease progression.

The major efficacy outcome measure was overall survival (OS) in the Intent-to-Treat (ITT) population. Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS), overall response rate (ORR), and duration of response (DOR) per RECIST v1.1.

A total of 512 patients were enrolled and randomized to TEVIMBRA (n=256) or ICC (n=256) [irinotecan (46%), paclitaxel (33%), or docetaxel (21%)]. Of the 512 patients, 142 (28%) had PD-L1 \geq 10%, 222 (43%) had PD-L1 < 10%, and 148 (29%) had unknown baseline PD-L1 status.

The trial population characteristics were: median age of 62 years (range: 35 to 86), 38% age \geq 65; 84% male; 19% White and 80% Asian; 95% had metastatic disease. All patients had received at least one prior anti-cancer systemic therapy. Baseline ECOG performance status was 0 (25%) or 1 (75%).

RATIONALE-302 demonstrated a statistically significant improvement in OS for patients randomized to TEVIMBRA as compared with ICC.

Efficacy results are shown in [Table 4](#) and [Figure 1](#).

Table 4: Efficacy Results in RATIONALE-302 in ITT Population

Endpoint	TEVIMBRA (N=256)	ICC (N=256)
Overall Survival		
Deaths n (%)	197 (77.0)	213 (83.2)
Median (months) ^a (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Hazard ratio ^b (95% CI)	0.70 (0.57, 0.85)	
p-value ^c	0.0001	
Progression-Free Survival		
Disease progression or death (%)	223 (87.1)	180 (70.3)
Median (months) ^a (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Hazard ratio ^b (95% CI)	0.83 (0.67, 1.01)	
Objective Response Rate ^d		
ORR (%) (95% CI)	15.2 (11.1, 20.2)	6.6 (3.9, 10.4)
Complete response n (%)	5 (2.0)	1 (0.4)
Partial response n (%)	34 (13.3)	16 (6.3)
Duration of Response		
Median (months) ^a (95% CI)	10.3 (6.5, 13.2)	6.3 (2.8, 8.5)

CI = confidence interval, ORR = objective response rate

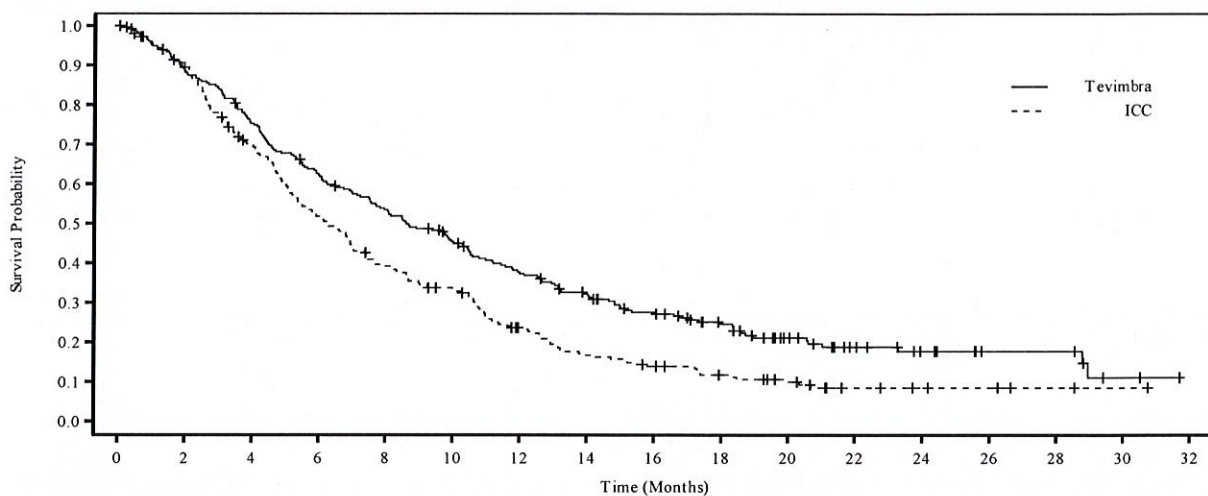
^a Estimated using Kaplan-Meier method.

^b Based on Cox regression model stratified by baseline ECOG status and ICC option.

^c One-sided p-value based on log rank test stratified by ECOG performance status and ICC option.

^d Confirmed response.

Figure 1: Kaplan-Meier Curve for Overall Survival in RATIONALE-302 (ITT)



Number of Patients at Risk:

Tevimbra	256	226	191	157	134	110	88	73	59	44	30	20	13	8	8	2	0
ICC	256	219	167	124	93	77	51	36	29	21	15	7	5	4	2	1	0

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TEVIMBRA injection is a clear to slightly opalescent, colorless to slightly yellow solution supplied in a carton containing one 100 mg/10 mL (10 mg/mL) single-dose vial (NDC 72579-121-01).

Storage

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of TEVIMBRA. These reactions may include:

- **Pneumonitis:** Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions (5.1)*].
- **Colitis:** Advise patients to contact their healthcare provider immediately for diarrhea, or severe abdominal pain [see *Warnings and Precautions (5.1)*].
- **Hepatitis:** Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of the abdomen, or easy bruising or bleeding [see *Warnings and Precautions (5.1)*].

- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, thyroiditis, or Type 1 diabetes mellitus [see *Warnings and Precautions (5.1)*].
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see *Warnings and Precautions (5.1)*].
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS, TEN, or DRESS [see *Warnings and Precautions (5.1)*].
- Other Immune-Mediated Adverse Reactions:
 - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms [see *Warnings and Precautions (5.1)*].
 - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection [see *Warnings and Precautions (5.1)*].

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see *Warnings and Precautions (5.2)*].

Complications of Allogeneic HSCT

Advise patients of potential risk of post-allogeneic hematopoietic stem cell transplantation complications [see *Warnings and Precautions (5.3)*].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1, 8.3)*].

Advise females of reproductive potential to use effective contraception during treatment with TEVIMBRA and for 4 months after the last dose [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.1, 8.3)*].

Lactation

Advise women not to breastfeed during treatment with TEVIMBRA and for 4 months after the last dose [see *Use in Specific Populations (8.2)*].

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San Mateo, CA 94404

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