Product Monograph

Including Patient Medication Information

PrTEVIMBRA®

tislelizumab for injection

Recombinant monoclonal antibody

Concentrate for solution for intravenous infusion

100 mg/10 mL of tislelizumab

Professed Standard

Antineoplastic agent, monoclonal antibody

BeOne Medicines I GmbH
Aeschengraben 27
21st floor
4051 Basel
www.beonemed.com

Date of Authorisation:
December 18, 2025

Canadian Distributor:
Innomar Strategies Inc.
Milton, ON, L9T 6W3

Submission Control Number: 293878

Recent Major Label Changes

Not Applicable	

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

TEVIMBRA (tislelizumab for injection) in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adult patients with recurrent or metastatic nasopharyngeal carcinoma (NPC).

1.1 Pediatrics

Pediatrics (below 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Based on population pharmacokinetic (PK) analysis, no clinically relevant differences in the PK of TEVIMBRA were observed between patients aged <65 years, patients aged between 65 and 75 years, and patients aged >75 years. Limited safety and efficacy information is available for TEVIMBRA in NPC patients ≥ 65 years. (see 4 Dosage and Administration).

2 Contraindications

TEVIMBRA 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 of ingredients, (see 6 Dosage Forms, Strengths, Composition and Packaging).

3 Serious Warnings and Precautions Box

- TEVIMBRA may cause severe and fatal immune-mediated adverse reactions, in any organ system or tissue including: colitis, endocrinopathies, hepatitis, myocarditis, myositis, nephritis with renal dysfunction, organ transplant rejection, pancreatitis, pneumonitis, and severe cutaneous adverse reactions (SCARS eg Steven's Johnson Syndrome, and Toxic Epidermal Necrolysis) (see 7. Warnings and Precautions).
- TEVIMBRA can cause severe or life-threatening infusion-related reactions including hypersensitivity and anaphylaxis (see 7. Warnings and Precautions).
- 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 (see 7. Warnings and Precautions).

4 Dosage and Administration

4.1 Dosing Considerations

TEVIMBRA is administered as an intravenous infusion. The first infusion should be administered over 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes.

No dose reductions of TEVIMBRA are recommended.

TEVIMBRA is for intravenous infusion after dilution (see 4.3 Reconstitution; 4.4 Administration).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage for recurrent or metastatic Nasopharyngeal Carcinoma

- The recommended dose of TEVIMBRA is 200 mg once every 3 weeks in combination with cisplatin and gemcitabine chemotherapy for 4 to 6 cycles then continued as monotherapy until unacceptable toxicity or disease progression.
- When administering TEVIMBRA in combination with chemotherapy, administer TEVIMBRA before chemotherapy when both are given on the same day. Refer to the Product Monographs for the chemotherapy agents administered in combination with TEVIMBRA for recommended dosing information, as appropriate.

Dose modifications for adverse reactions
Dose reduction of TEVIMBRA is not recommended.
Recommended treatment modifications to manage immune-related adverse reactions (ARs) are provided in Table 1.

Detailed guidelines for the management of immune-related ARs are described in Section 7 Warnings and Precautions.

Table 1 Recommended treatment modifications for TEVIMBRA

Immune-related ADR	Severity[1]	TEVIMBRA treatment modification
Pneumonitis	Grade 2	Withhold[2]
	Recurrent Grade 2; Grade 3 or 4	Permanently discontinue
Hepatitis	ALT or AST >3 and up to 8 times ULN (or) total bilirubin >1.5 and up to 3 times ULN	Withhold[2]
	ALT or AST >8 times ULN (or) total bilirubin >3 times ULN	Permanently discontinue
Rash	Grade 3	Withhold[2]
	Grade 4	Permanently discontinue
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including Steven's Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)	Withhold[2] For suspected SCARs (SJS or TEN), do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist.

Immune-related ADR	Severity[1]	TEVIMBRA treatment modification
	Confirmed SCARs, including SJS or TEN	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[2]
	Recurrent Grade 3; Grade 4	Permanently discontinue
Myositis/Rhabdomyolysis	Grade 2 or 3	Withhold[2]
	Recurrent Grade 3; Grade 4	Permanently discontinue
Endocrinopathies	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption
	Grade 3 or 4 adrenal insufficiency or symptomatic hypophysitis Hyperthyroidism Grade ≥3	Withhold[2] Grade 3 or Grade 4 that improved to Grade ≤2 and are controlled with HRT, if indicated, continuation of TEVIMBRA may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Diabetes mellitus associated with Grade ≥3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis	Withhold[2] Grade 3 or 4 that improved to Grade ≤2, with insulin therapy, if indicated, continuation of TEVIMBRA may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.
	Grade 2 adrenal insufficiency and hypophysitis	Consider withholding treatment until controlled by HRT
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5 to 3 times baseline or >1.5 to 3 times ULN)	Withhold[2]

Immune-related ADR	Severity[1]	TEVIMBRA treatment modification
	Grade 3 (creatinine >3 times baseline or >3 to 6 times ULN) Grade 4 (creatinine >6 times ULN)	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological toxicities, ie myasthenia gravis, Guillain-Barre syndrome and encephalitis	Grade 2	Withhold[2]
	Grade 3 or 4	Permanently discontinue
Pancreatitis	Grade 2 pancreatitis	Withhold if clinically significant
	Grade 3 pancreatitis or Grade 3 or Grade 4 serum amylase or lipase levels increased (>2 times ULN)	Withhold[2]
	Grade 4	Permanently discontinue
Other immune-related ADRs	Grade 3	Withhold[2]
	Recurrent Grade 3; Grade 4	Permanently discontinue
Other ARs		
Infusion-related reactions	Grade 1	Consider pre-medication for prophylaxis of subsequent infusion reactions. Slow the rate of infusion by 50%
	Grade 2	Interrupt infusion[3]
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BSA = body surface area, HRT= hormone replacement therapy, ULN = upper limit of normal

[1]Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4).

[2] 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 corticosteroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

[3] Resume infusion if resolved or decreased to Grade 1 and slow the rate of infusion by 50%.

Special Populations

Pediatrics (below 18 years): Health Canada has not authorized an indication for pediatric use.

Geriatrics (65 years or above): No dose adjustment of TEVIMBRA is required in patients aged 65 years or above (see section 10 Clinical Pharmacology).

Renal Impairment: Based on population pharmacokinetic analysis, no dose adjustment of TEVIMBRA is necessary in patients with mild (CLcr 60 to 89 mL/min) or moderate (CLcr 30 to 59 mL/min) renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions for this population (see section 10 Clinical Pharmacology).

Hepatic Impairment: Based on population pharmacokinetic analysis, no dose adjustment of TEVIMBRA is necessary in patients with mild (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 x ULN and any AST) or moderate (bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. Data from patients with severe hepatic impairment are too limited to draw conclusions for this population (see section 10 Clinical Pharmacology).

4.3 Reconstitution

Preparation for Intravenous Infusion

Vials are for single use only. Each vial contains 100 mg of tislelizumab. This product must not be mixed with products except sodium chloride, which is used to prepare diluted solution.

1. The diluted solution for infusion (sterile concentrate) should be prepared by a healthcare professional using aseptic technique. Two TEVIMBRA vials are required for each dose. Remove the vials from the refrigerator, taking care not to shake them.
2. Inspect each vial visually for particulate matter and discoloration prior to administration. The concentrate is a clear to slightly opalescent, colorless to slightly yellowish solution. Do not use a vial if the solution is cloudy or if visible particles or discoloration are observed.
3. Invert the vials gently, without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 mL) and transfer into an intravenous (I.V.) infusion bag containing sodium chloride 9 mg/mL (0.9%) to prepare a diluted solution with a final concentration ranging from 2 to 5 mg/mL. Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

4.4 Administration

TEVIMBRA is for intravenous use only.

When TEVIMBRA is administered in combination with chemotherapy, it should be administered before chemotherapy when both are given on the same day. Refer to the Product Monograph for details of any chemotherapy administered in combination with TEVIMBRA.

The diluted solution must be administered by infusion, given via an intravenous line containing a

sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter.

The first TEVIMBRA infusion of 200 mg should be administered over 60 minutes. If this is well-tolerated, subsequent infusions may be administered over a period of 30 minutes.

- TEVIMBRA must not be administered as an intravenous push or single bolus injection. Other drugs should not be co-administered through the same infusion line.
- TEVIMBRA does not contain any preservatives. It is recommended to prepare the solution immediately after taking it out of the refrigerator. From a microbiological point of view, once infusion is prepared, it is recommended to use the solution immediately after dilution.
- The diluted solution may be stored at 2°C to 8°C for up to 20 hours, followed by up to four hours at room temperature (25°C and below). This includes the time to reach room temperature as well as completing the infusion.
- The diluted solution must not be frozen.
- TEVIMBRA vials are for single use only. Discard any unused portion left in the vial.

The intravenous line must be flushed at the end of the infusion.

4.5 Missed Dose

If a planned dose of TEVIMBRA is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 Overdose

There is no information on overdose with TEVIMBRA. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Concentrate for solution for infusion/ 100 mg tislelizumab/100 mg/10 mL (10mg/mL)	Citric acid monohydrate, L-histidine, L-histidine hydrochloride monohydrate, polysorbate-20, sodium citrate dihydrate, trehalose dihydrate and water for injection (WFI).

Each single-use vial contains 100 mg of tislelizumab in 10 mL solution, at a concentration of 10 mg/mL.

Description

TEVIMBRA is a preservative free, clear to slightly opalescent, colourless to slightly yellowish solution. TEVIMBRA concentrate (100mg/10mL) is provided in a single-use, clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating, and a seal cap with a flip-off button.

Each carton contains one vial.

7 Warnings and Precautions

See 3. Serious Warnings and Precautions Box.

General

TEVIMBRA should be administered under the supervision of a healthcare professional experienced in the treatment of cancer.

Driving and Operating Machinery

No studies on the effects on the ability to drive and to use machines have been performed. Caution when driving or using machines is advised for patients who report dizziness, fatigue, asthenia, and/or malaise during treatment with TEVIMBRA (see 8 Adverse Drug Reactions).

Immune

Severe, including fatal, cases of pneumonitis and hepatitis have been reported. Most immune-related adverse reactions occurring during treatment with TEVIMBRA were reversible and managed with interruptions of TEVIMBRA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of TEVIMBRA. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-related adverse reactions, adequate evaluation to confirm etiology or exclude alternative etiologies, including infection, should be ensured. Based on the severity of the adverse reaction, TEVIMBRA should be withheld and corticosteroids administered. Administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid therapy (see 4 Dosage And Administration and 8 Adverse Reactions).

Immune-related pneumonitis

Immune-related pneumonitis, including fatal cases, has been reported in patients receiving TEVIMBRA. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and infectious or disease-related etiologies should be excluded. Patients with immune-related pneumonitis should be managed according to the treatment modifications as recommended in Table 1 (4.2 Recommended Dose And Dosage Adjustment).

Immune-related hepatitis

Immune-related hepatitis has been reported in patients treated with TEVIMBRA, including fatal cases. Patients should be monitored for signs and symptoms of hepatitis and changes in liver function. Liver function test (LFT) should be performed at baseline and periodically during treatment. Patients with immune-related hepatitis should be managed according to the treatment modifications as recommended in Table 1 (see 4.2 Recommended Dose And Dosage Adjustment).

Immune-related skin reactions

Immune-related skin rash or dermatitis has been reported in patients receiving TEVIMBRA. Patients should be monitored for signs and symptoms of suspected skin reactions, and other causes should be excluded. Depending on the severity of the skin adverse reactions, TEVIMBRA should be withheld or permanently discontinued as recommended in Table 1(see 4.2 Recommended Dose And Dosage Adjustment)

Cases of severe cutaneous adverse reactions (SCARs), including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving TEVIMBRA (see 8 Adverse Reactions). Patients should be monitored for signs or symptoms of SCARs (e.g., a prodrome of fever, flu-like symptoms, mucosal lesions, or progressive skin rash) and other causes should be excluded. For suspected SCARs, TEVIMBRA should be withheld, and the patient should be referred to specialized care for assessment and treatment. If SCARs is confirmed, TEVIMBRA should be permanently discontinued (see 4.2 Recommended Dose And Dosage Adjustment).

Immune-related colitis

Immune-related colitis, frequently associated with diarrhea, has been reported in patients treated with TEVIMBRA. Patients should be monitored for signs and symptoms of colitis. Infectious and disease-related etiologies should be excluded. Patients with immune-related colitis should be managed according to treatment modifications as recommended in Table 1(see 4.2 Recommended Dose And Dosage Adjustment).

Immune-related endocrinopathies

Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, hypophysitis and diabetes mellitus have been reported with TEVIMBRA, which may require supportive treatment.

Patients with immune-related endocrinopathies should be managed according to treatment modifications as recommended in Table 1(see 4.2 Recommended Dose And Dosage Adjustment).

Thyroid disorders

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis have been reported in patients treated with TEVIMBRA. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. 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 clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with hormone replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically.

Adrenal insufficiency

Adrenal insufficiency has been reported in patients treated with TEVIMBRA. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered as clinically indicated. Corticosteroids and hormone replacement should be administered as clinically indicated.

Hypophysitis/hypopituitarism

Hypophysitis/hypopituitarism has been reported in patients treated with TEVIMBRA. Hypophysitis can cause hypopituitarism. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered

as clinically indicated. Corticosteroids and hormone replacement should be administered as clinically indicated.

Diabetes mellitus

Diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with TEVIMBRA. Patients should be monitored for hyperglycemia or other signs and symptoms of diabetes. Insulin should be administered as clinically indicated for diabetes. In patients with severe hyperglycemia or ketoacidosis (Grade ≥3), TEVIMBRA should be withheld, and anti-hyperglycemic treatment should be administered. Treatment with TEVIMBRA should be resumed when metabolic control is achieved. (see 4.2 Recommended Dose And Dosage Adjustment).

Immune-related nephritis with renal dysfunction

Immune-related nephritis with renal dysfunction has been reported in patients treated with TEVIMBRA. Patients should be monitored for changes in renal function (elevated serum creatinine) and other causes of renal dysfunction should be excluded. Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications as recommended in Table 1 (see 4.2 Recommended Dose And Dosage Adjustment).

Other immune-related ADRs

Other clinically important immune-related ADRs were reported in patients treated with TEVIMBRA: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis, immune thrombocytopenia, encephalitis, myasthenia gravis, Sjogren's syndrome, Guillain-Barré syndrome, and hemophagocytic lymphohistiocytosis (HLH).

Patients with other immune-related ADRs should be managed according to the treatment modifications as recommended in Table 1(see 4.2 Recommended Dose And Dosage Adjustment).

Solid organ transplant rejection

Solid organ transplant rejection has been reported in the post marketing setting in patients treated with PD-1 inhibitors. Treatment with TEVIMBRA may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with TEVIMBRA versus the risk of possible organ rejection should be considered in these patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Cases of graft-versus-host disease (GvHD) have been reported in patients treated with PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant. This complication may occur despite intervening therapy between PD-1/PD-L1 blockade and the allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly.

Infusion-related reactions

Severe infusion-related reactions (Grade 3 or higher) have been reported in patients receiving TEVIMBRA. Cases of anaphylaxis, including anaphylactic reaction and anaphylactic shock, have been reported in the post marketing setting. Patients should be monitored for signs and symptoms of infusion-related reactions.

Infusion-related reactions should be managed as recommended in Table 1(see 4.2 Recommended Dose And Dosage Adjustment).

Monitoring and Laboratory Tests

Monitor liver function including AST, ALT, and bilirubin, renal function, pituitary, adrenal and thyroid function prior to initiation and as indicated based on clinical evaluation. Refer to Section 4 Dosage And Administration for recommended dosing adjustments.

Reproductive Health

Fertility

No data are available on the possible effects of TEVIMBRA on fertility.

No reproductive and development toxicity studies have been conducted with tislelizumab. Based on a 3-month repeat-dose toxicity study, there were no notable effects in the male and female reproductive organs in cynomolgus monkeys when given tislelizumab (See 16 Non-Clinical Toxicology).

Contraception

Sexually active females of reproductive potential should be advised to use effective contraception (methods that result in less than 1 % pregnancy rates) during treatment with TEVIMBRA and for at least 4 months after the last dose of TEVIMBRA.

7.1 Special Populations

7.1.1 Pregnancy

There are no available data on the use of TEVIMBRA in pregnant women. Based on its mechanism of action, TEVIMBRA can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Human IgG4 (immunoglobulins) are known to cross the placental barrier. Therefore, TEVIMBRA, being an IgG4 variant, has the potential to be transmitted from the mother to the developing fetus.

For women of childbearing potential, pregnancy status should be established prior to initiating TEVIMBRA. Women should be advised to use highly effective contraception (methods that result in less than 1% pregnancy rates) and take active measures to avoid pregnancy while undergoing TEVIMBRA treatment and for at least 4 months after the last dose (See 16 Non-Clinical Toxicology).

If TEVIMBRA is used during pregnancy or if the patient becomes pregnant while taking TEVIMBRA, the patient should be apprised of the potential hazard to the fetus.

7.1.2 Breastfeeding

It is unknown whether TEVIMBRA is excreted in human milk. Its effects on breast-fed newborns/infants and on milk production are also unknown.

Because of the potential for serious adverse reactions in breastfed children from TEVIMBRA, women should be advised not to breastfeed during treatment and for at least 4 months after the last dose of TEVIMBRA.

7.1.3 Pediatrics

Pediatrics (below 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Based on population pharmacokinetic (PK) analysis, no clinically relevant differences in PK of TEVIMBRA were observed between patients aged <65 years, patients aged between 65 and 75 years, and patients aged >75 years. Limited safety and efficacy information is available for TEVIMBRA in NPC patients ≥ 65 years; therefore, efficacy and safety is not well established in patients over 65 years of age. (see 4 Dosage And Administration).

8 Adverse Reactions

8.1 Adverse Reaction Overview

The following clinically significant treatment emergent adverse events have been observed in patients treated with TEVIMBRA and are detailed under 7 Warnings And Precautions:

• Severe and fatal immune-mediated adverse reactions (see 7. Warnings and Precautions, Immune and 8.2 Clinical Trial Adverse Reactions)

• Infusion-related reactions (see 7. Warnings and Precautions, Immune and 8.2 Clinical Trial Adverse Reactions)

The overall safety profile of TEVIMBRA is based on pooled data from 1952 patients receiving TEVIMBRA as monotherapy across multiple tumour types and 133 patients receiving TEVIMBRA in combination with gemcitabine and cisplatin for NPC.

Tislelizumab as Monotherapy

In the monotherapy pool the most common treatment emergent adverse events (TEAEs) (≥ 10%) were anemia, AST increased, ALT increased, pyrexia, cough, decreased appetite, weight decreased, blood bilirubin increased, hypoalbuminemia, constipation, pruritus, rash, diarrhea, hypothyroidism, nausea, and asthenia.

Tislelizumab in Combination with Gemcitabine and Cisplatin

In combination therapy with gemcitabine and cisplatin, the most common treatment emergent adverse events (TEAEs) (≥ 20%) were anemia (87%), neutrophil count decreased, (62%), white blood cell count decreased (62%), nausea (59%), platelet count decreased (54%), decreased appetite (48%), vomiting (41%), neutropenia (35%), constipation (35%), leukopenia (35%), hyponatremia (31%), hypothyroidism (31%), AST increased (29%), ALT increased (29%), pyrexia (26%), rash (26%), blood creatinine increased (24%), hypokalemia (23%), cough (22%), malaise (22%) pruritus (22%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Nasopharyngeal Carcinoma (NPC)

The safety of TEVIMBRA was evaluated in patients with recurrent or metastatic NPC in RATIONALE-309. Patients received tislelizumab 200 mg once every 3 weeks in combination with gemcitabine plus cisplatin (T+GC arm). The median duration of exposure to tislelizumab was 10.51 months (range 0.3 to 53.1 months).

Serious treatment emergent adverse events (TEAEs) occurred in 35% of patients who received tislelizumab; the most frequent serious adverse reactions (≥2%) were platelet count decreased (6.8%), sepsis (3%), thrombocytopenia (3%), anemia, neutrophil count decreased, and white blood cell count decreased (2%). In the placebo plus chemotherapy arm, serious TEAEs occurred in 35.4% of patients, the most frequent TEAEs (>2%) were platelet count decreased, neutrophil count decreased, white blood cell count decreased, anemia, thrombocytopenia, leukopenia, pneumonia, and hypokalemia. There were 6 fatal TEAEs in the tislelizumab arm: depressed level of consciousness (1), pharyngeal hemorrhage (1), pneumonia aspiration and hypoxia (1) myelodysplastic syndrome (1), accidental death (1) and death (1), and 2 in the placebo arm of the trial: arrhythmia (1) and hypernatremia (1).

TEAEs leading to discontinuation of tislelizumab occurred in 9% of patients; the most common (>1%) TEAE resulting in permanent discontinuation was myocarditis (1.5%). TEAEs leading to discontinuation of placebo occurred in 5% of patients in the placebo plus chemotherapy arm, with no TEAE occurring at an incidence of more than 1%.

TEAEs leading to the dose interruption of tislelizumab occurred in 50% of patients; the most common TEAEs leading to dose interruptions of tislelizumab (≥2%) were anemia (10%), neutropenia (9%), white blood cell count decreased (9%), leukopenia (8%), neutrophil count decreased (7%), platelet count decreased (6%), ALT increased (3%), AST increased (3%), and pneumonia (2%). In the placebo plus chemotherapy arm, 41 % of patients experienced a dose reduction due to TEAEs, the most common (≥2%) were anemia (12%), white blood cell count decreased (11%), neutrophil count decreased (11%), platelet count decreased (9%), leucopenia (8%), neutropenia (6%), lymphocyte count decreased (2%), and pneumonia (2%).

Treatment Emergent Adverse Events are listed in Table 3.

Table 3: Treatment-Emergent Adverse Events With Incidence ≥ 5% by System Organ Class and Preferred Term (Safety Analysis Set)

	Tislelizumab + Gemcitabine + Cisplatin (N = 133)		Placebo + Gemcitabine + Cisplatin (N = 130)	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Patients With at Least One Event	133 (100.0)	85 (63.9)	129 (99.2)	79 (60.8)
Blood and lymphatic system disorders	120 (90.2)	63 (47.4)	122 (93.8)	63 (48.5)
Anaemia	116 (87.2)	41 (30.8)	118 (90.8)	43 (33.1)
Neutropenia	47 (35.3)	30 (22.6)	38 (29.2)	23 (17.7)
Leukopenia	46 (34.6)	29 (21.8)	45 (34.6)	20 (15.4)
Thrombocytopenia	15 (11.3)	6 (4.5)	17 (13.1)	10 (7.7)
Metabolism and nutrition disorders	115 (86.5)	22 (16.5)	106 (81.5)	13 (10.0)

	Tislelizumab + Gemcitabine + Cisplatin (N = 133)		Placebo + Gemcitabine + Cisplatin (N = 130)	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Decreased appetite	64 (48.1)	1 (0.8)	65 (50.0)	1 (0.8)
Hyponatraemia	41 (30.8)	4 (3.0)	37 (28.5)	1 (0.8)
Hypokalaemia	30 (22.6)	7 (5.3)	30 (23.1)	8 (6.2)
Hypocalcemia	25 (18.8)	1 (0.8)	17 (13.1)	0 (0.0)
Hyperuricemia	24 (18.0)	2 (1.5)	25 (19.2)	1 (0.8)
Hypoalbuminaemia	22 (16.5)	1 (0.8)	29 (22.3)	0 (0.0)
Hypomagnesaemia	22 (16.5)	3 (2.3)	16 (12.3)	3 (2.3)
Hypochloremia	16 (12.0)	0 (0.0)	22 (16.9)	0 (0.0)
Hypertriglyceridemia	12 (9.0)	3 (2.3)	6 (4.6)	0 (0.0)
Hypoproteinemia	12 (9.0)	0 (0.0)	7 (5.4)	0 (0.0)
Hypophosphatasemia	8 (6.0)	0 (0.0)	8 (6.2)	0 (0.0)
Hyperglycemia	7 (5.3)	0 (0.0)	4 (3.1)	0 (0.0)
Gastrointestinal disorders	114 (85.7)	2 (1.5)	118 (90.8)	6 (4.6)
Nausea	78 (58.6)	0 (0.0)	94 (72.3)	2 (1.5)
Vomiting	55 (41.4)	1 (0.8)	69 (53.1)	2 (1.5)
Constipation	46 (34.6)	0 (0.0)	60 (46.2)	0 (0.0)
Diarrhoea	21 (15.8)	0 (0.0)	14 (10.8)	1 (0.8)
Abdominal distension	18 (13.5)	0 (0.0)	15 (11.5)	0 (0.0)
Dry mouth	17 (12.8)	0 (0.0)	6 (4.6)	0 (0.0)
Abdominal pain	10 (7.5)	0 (0.0)	9 (6.9)	0 (0.0)
Mouth ulceration	10 (7.5)	0 (0.0)	3 (2.3)	0 (0.0)
Abdominal discomfort	9 (6.8)	0 (0.0)	8 (6.2)	0 (0.0)
Toothache	9 (6.8)	0 (0.0)	4 (3.1)	0 (0.0)
Gingival pain	7 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	5 (3.8)	0 (0.0)	8 (6.2)	1 (0.8)
Abdominal pain upper	1 (0.8)	0 (0.0)	9 (6.9)	0 (0.0)
General disorders and administration site conditions	91 (68.4)	6 (4.5)	77 (59.2)	3 (2.3)
Pyrexia	35 (26.3)	2 (1.5)	13 (10.0)	0 (0.0)
Malaise	29 (21.8)	1 (0.8)	31 (23.8)	2 (1.5)
Fatigue	17 (12.8)	1 (0.8)	17 (13.1)	0 (0.0)
Asthenia	13 (9.8)	0 (0.0)	11 (8.5)	0 (0.0)
Chest discomfort	9 (6.8)	0 (0.0)	8 (6.2)	0 (0.0)
Oedema peripheral	5 (3.8)	0 (0.0)	8 (6.2)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	71 (53.4)	1 (0.8)	44 (33.8)	1 (0.8)
Cough	29 (21.8)	0 (0.0)	13 (10.0)	0 (0.0)
Productive cough	22 (16.5)	0 (0.0)	10 (7.7)	0 (0.0)
Hiccups	17 (12.8)	0 (0.0)	10 (7.7)	0 (0.0)
Oropharyngeal pain	12 (9.0)	0 (0.0)	10 (7.7)	0 (0.0)
Epistaxis	9 (6.8)	0 (0.0)	12 (9.2)	0 (0.0)
Rhinorrhea	8 (6.0)	0 (0.0)	2 (1.5)	0 (0.0)
Haemoptysis	7 (5.3)	0 (0.0)	3 (2.3)	0 (0.0)
Nasal congestion	7 (5.3)	0 (0.0)	2 (1.5)	0 (0.0)
Infections and infestations	62 (46.6)	14 (10.5)	35 (26.9)	9 (6.9)

	Tislelizumab + Gemcitabine + Cisplatin (N = 133)		Placebo + Gemcitabine + Cisplatin (N = 130)	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Upper respiratory tract infection	22 (16.5)	0 (0.0)	12 (9.2)	1 (0.8)
Pneumonia	12 (9.0)	3 (2.3)	7 (5.4)	4 (3.1)
Otitis media	7 (5.3)	0 (0.0)	2 (1.5)	0 (0.0)
Skin and subcutaneous tissue disorders	61 (45.9)	6 (4.5)	53 (40.8)	0 (0.0)
Rash	34 (25.6)	5 (3.8)	29 (22.3)	0 (0.0)
Pruritus	29 (21.8)	0 (0.0)	18 (13.8)	0 (0.0)
Alopecia	10 (7.5)	0 (0.0)	11 (8.5)	0 (0.0)
Nervous system disorders	54 (40.6)	6 (4.5)	49 (37.7)	5 (3.8)
Dizziness	23 (17.3)	1 (0.8)	19 (14.6)	0 (0.0)
Hypoaesthesia	20 (15.0)	0 (0.0)	20 (15.4)	0 (0.0)
Headache	15 (11.3)	1 (0.8)	23 (17.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	48 (36.1)	2 (1.5)	47 (36.2)	1 (0.8)
Back pain	23 (17.3)	1 (0.8)	18 (13.8)	1 (0.8)
Arthralgia	18 (13.5)	1 (0.8)	17 (13.1)	0 (0.0)
Pain in extremity	17 (12.8)	0 (0.0)	10 (7.7)	0 (0.0)
Muscular weakness	10 (7.5)	0 (0.0)	5 (3.8)	0 (0.0)
Neck pain	5 (3.8)	0 (0.0)	10 (7.7)	0 (0.0)
Endocrine disorders	45 (33.8)	1 (0.8)	21 (16.2)	0 (0.0)
Hypothyroidism	41 (30.8)	1 (0.8)	20 (15.4)	0 (0.0)
Ear and labyrinth disorders	18 (13.5)	1 (0.8)	20 (15.4)	1 (0.8)
Tinnitus	11 (8.3)	1 (0.8)	8 (6.2)	0 (0.0)
Psychiatric disorders	17 (12.8)	0 (0.0)	20 (15.4)	0 (0.0)
Insomnia	14 (10.5)	0 (0.0)	17 (13.1)	0 (0.0)

Events were sorted by decreasing frequency of system organ class in the 'All Grades' of Tislelizumab group.

Additional Information on Selected Adverse Reactions

The selected adverse reactions described below are based on the safety of TEVIMBRA 200 mg Q3W in combination with gemcitabine and cisplatin in 133 patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma treated in the RATIONALE 309 trial, and on the safety of TEVIMBRA 200 mg/kg Q3W as a single agent in the monotherapy pool consisting of 1952 patients across various tumor types. There were no fatal IMAEs in RATIONALE 309. (see 8.1.Adverse Reaction Overview for additional details). For information on management of these adverse reactions, see 4.2 Recommended Dose And Dosage Adjustment and 7 Warnings and Precautions.

Immune-mediated Pneumonitis

TEVIMBRA in combination with gemcitabine and cisplatin:

Immune-mediated pneumonitis occurred in 2.3% (3/133) of patients receiving TEVIMBRA. All AEs were ≤ Grade 2. One patient received corticosteroid treatment and pneumonitis resolved in one of these patients. No patients discontinued due to IMAEs.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related pneumonitis occurred in 5.1% of patients, including Grade 1 (1.3%), Grade 2 (2.1%), Grade 3 (1.3%), Grade 4 (0.3%) and Grade 5 (0.1%) events.

Tislelizumab was permanently discontinued in 1.8% of patients and tislelizumab treatment was interrupted in 1.9% of patients and 47.0% of patients with pneumonitis recovered.

Immune-mediated Colitis

TEVIMBRA in combination with gemcitabine and cisplatin:

Immune-mediated colitis occurred in 0.8% (1/133) of patients receiving TEVIMBRA. The one reported IMAE was ⩽Grade 2. No patients discontinued due to IMAEs.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related colitis occurred in 0.6% of patients, including Grade 2 (0.4%) and Grade 3 (0.2%) events.

Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.4% of patients, and 81.8% of patients recovered.

Hepatotoxicity and Immune-mediated Hepatitis

TEVIMBRA in combination with gemcitabine and cisplatin:

Immune-mediated hepatitis occurred in 0.8% (1/133) of patients receiving TEVIMBRA, the one reported IMAE was Grade 1. No patients discontinued due to IMAEs.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related hepatitis occurred in 1.2% of patients, including Grade 1 (0.1%), Grade 2 (0.2%), Grade 3 (0.6%) and Grade 4 (0.3%) events.

Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 0.8% of patients for immune-related hepatitis, and 60.9% of patients with hepatitis recovered.

Immune-mediated Endocrinopathies

Adrenal Insufficiency

TEVIMBRA in combination with gemcitabine and cisplatin:

No IMAEs of adrenal insufficiency were reported.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, adrenal insufficiency occurred in 0.5% of patients, including Grade 2 (0.3%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.4% of patients, and 30.0% of patients with Adrenal insufficiency recovered.

Hypophysitis

TEVIMBRA in combination with gemcitabine and cisplatin:

Hypophysitis occurred in 0.8% (1/1952) of the patients receiving combination therapy. The one reported IMAE was Grade 2. No patients discontinued due to IMAEs.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, hypophysitis (Grade 2) occurred in 0.3% of patients.

Tislelizumab was not permanently discontinued in any patients and tislelizumab treatment was not interrupted in any patients. Twenty percent (20%) of patients with hypophysitis recovered.

Thyroid Disorders

TEVIMBRA in combination with gemcitabine and cisplatin:

Thyroiditis was not reported as an IMAE.

Hyperthyroidism occurred in 4.5% (6/133) of patients receiving TEVIMBRA in combination with gemcitabine and cisplatin. All AEs were ≤ Grade 2, 1 patient required hormone therapy, 5 of 6 patients fully recovered. No patients discontinued due to IMAEs.

Hypothyroidism occurred in 29.3% (39/133) of patients receiving TEVIMBRA in combination with gemcitabine and cisplatin. There were 38 patients who experienced AE of Grade 1 or 2. One patient experienced an AE of Grade 3 which led to modified treatment, 29/39 patients required hormone replacement therapy, 16 patients fully recovered, and 2 patients discontinued treatment. No patients discontinued due to IMAEs.

TEVIMBRA as monotherapy:

Thyroiditis occurred in 1.1% of patients treated with tislelizumab as monotherapy, including Grade 1 (0.5%) and Grade 2 (0.6%) events.

Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.2% of patients and 38.1% of patients with thyroiditis recovered.

Hyperthyroidism occurred in 5.1% of patients treated with tislelizumab as monotherapy, including Grade 1 (4.4%) and Grade 2 (0.7%) events.

Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.3% of patients and 77.0% of patients with hyperthyroidism recovered.

Hypothyroidism occurred in 13.8% of patients treated with tislelizumab as monotherapy, including Grade 1 (6.4%), Grade 2 (7.3%), Grade 3 (0.1%) and Grade 4 (0.1%) events.

Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.6% of patients and 36.4% of patients with hypothyroidism recovered.

Type 1 Diabetes Mellitus

TEVIMBRA in combination with gemcitabine and cisplatin:

No IMAEs of Diabetes mellitus were reported.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 0.6% of patients, including Grade 1 (0.1%), Grade 2 (0.3%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.2% of patients and 8.3% of patients with Type 1 diabetes mellitus recovered.

Immune-mediated Nephritis with Renal Dysfunction

TEVIMBRA in combination with gemcitabine and cisplatin:

No IMAEs of Nephritis were reported.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 0.2% of patients, including Grade 1 (0.1%), Grade 2 (0.1%) and Grade 3 (0.1%) events.

Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients and 50.0% of patients with immune-related nephritis and renal dysfunction recovered.

Immune-mediated Myocarditis

TEVIMBRA in combination with gemcitabine and cisplatin:

Immune-mediated myocarditis occurred in 1.5% (2/133) of patients receiving TEVIMBRA, 1 patient required corticosteroid treatment. Both IMAEs were Grade 2, and both patients discontinued treatment.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related myocarditis occurred in 0.8% of patients, including Grade 1 (0.4%), Grade 2 (0.2%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

Tislelizumab was permanently discontinued in 0.4% of patients and tislelizumab treatment was interrupted in 0.4% of patients and 60.0% of patients with myocarditis recovered.

Immune-mediated Myositis

TEVIMBRA in combination with gemcitabine and cisplatin:

Immune-mediated myositis occurred in 1.5% (2/1952) of patients receiving TEVIMBRA, all adverse events were ≤ Grade 2. One patient required corticosteroid treatment. One patient (0.8%) had treatment interruption.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related myositis/rhabdomyolysis occurred in 0.8% of patients, including Grade 1 (0.3%), Grade 2 (0.3%), Grade 3 (0.2%) and Grade 4 (0.1%) events.

Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.5% of patients and 75.0% of patients with myositis/rhabdomyolysis recovered.

Immune-mediated Pancreatitis

TEVIMBRA in combination with gemcitabine and cisplatin:

No IMAEs of pancreatitis were reported.

TEVIMBRA as monotherapy:

Immune-mediated pancreatitis occurred in 0.3% (5/1952) of patients receiving TEVIMBRA, all IMAEs were Grade 3. Tislelizumab was treatment interrupted in 0.3% of patients and 100% of patients recovered.

Immune-mediated Skin Reactions

TEVIMBRA in combination with gemcitabine and cisplatin:

Immune-mediated dermatologic adverse reactions occurred in 29.3% (39/133) of patients receiving TEVIMBRA, 2 patients required treatment modification, 3.8% of patients experienced a reaction ≥ Grade 3, and 12.8% of patients required corticosteroid treatment. No patients discontinued due to IMAEs. Skin adverse reactions resolved in 92.3% of patients.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 12.6% of patients, including Grade 1 (7.7%), Grade 2 (3.7%), Grade 3 (1.0%) and Grade 4 (0.1%) events.

Tislelizumab was permanently discontinued in 0.1% of patients, and tislelizumab treatment was interrupted in 1.3% of patients and 76.6% of patients with skin adverse reactions recovered.

Infusion Related Reactions

TEVIMBRA in combination with gemcitabine and cisplatin:

Infusion-related reactions have been reported in 5.3 % (7/133) of patients receiving TEVIMBRA in combination with gemcitabine and cisplatin, no ≥ Grade 3 reactions were reported.

TEVIMBRA as monotherapy:

In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 3.0% of patients, including Grade 3 (0.1%) events. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients.

8.3 Less Common Clinical Trial Adverse Reactions

The following are clinically important less common adverse events, reported in <5% of patients treated with TEVIMBRA in study RATIONALE-309.

Blood and lymphatic System Disorders: Myelosuppression.

Cardiac disorders: Myocarditis

Endocrine disorders: Central hypothyroidism, Hyperthyroidism

Gastrointestinal disorders: Chronic gastritis, Colitis, Duodenitis, Enteritis

Hepatobiliary disorders: Drug-induced liver injury, Hepatic function abnormal .

Infections and infestations: COVID-19, Periodontitis, Sepsis

Metabolism and nutrition disorders: Hypoglycemia, Type 2 diabetes mellitus

Musculoskeletal and connective tissue disorders: Myositis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Myelodysplastic syndrome

Nervous system disorders: Peripheral sensory neuropathy

Renal and urinary disorders: Acute kidney injury

Respiratory, thoracic and mediastinal disorders: Pneumonitis

Skin and subcutaneous tissue disorders: Vitiligo

Vascular disorders: Venous thrombosis limb

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

Clinical Trial Findings

Nasopharyngeal Carcinoma

Table 4 summarizes the Hematological and Chemistry laboratory abnormalities in study RATIONALE-309.

Table 4 Laboratory abnormalities worsening from baseline with TEVIMBRA in Study RATIONALE-309

	Tislelizumab Gemcitabine + Cisplatin N = 133		Placebo Gemcitabine + Cisplatin N=130	
Laboratory abnormality parameter*	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Hematology				
Haemoglobin increased	5 (3.8)	0 (0.0)	1 (0.8)	0 (0.0)
Haemoglobin decreased	130 (99.2)	43 (32.8)	125 (97.7)	47 (36.7)
Leukocytes decreased	123 (93.9)	69 (52.7)	121 (94.5)	73 (57.0)
Lymphocytes increased	8 (6.1)	1 (0.8)	4/ (3.2)	0 (0.0)
Lymphocytes decreased	111 (84.7)	76 (58.0)	119 (94.4)	72 (57.1)
Neutrophils decreased	118 (90.1)	66 (50.4)	116 (92.1)	77 (61.1)
Platelets decreased	90 (68.7)	34 (26.0)	99 (77.3)	41 (32.0)
Chemistry				
Alanine aminotransferase increased	53 (40.8)	3 (2.3)	46 (36.2)	2 (1.6)
Albumin decreased	51 (39.2)	1 (0.8)	62 (48.8)	0 (0.0)
Alkaline phosphatase increased	34 (26.2)	0 (0.0)	31 (24.6)	0 (0.0)
Aspartate aminotransferase increased	53 (40.5)	1 (0.8)	45 (35.4)	2 (1.6)
Bilirubin increased	18 (13.8)	3 (2.3)	12 (9.4)	1 (0.8)
Creatine kinase increased	42 (32.6)	5 (3.9)	21 (16.5)	2 (1.6)
Creatinine increased	49 (37.7)	0 (0.0)	42 (33.1)	0 (0.0)
Glucose increased	57 (43.8)	0 (0.0)	51 (40.5)	0 (0.0)
Glucose decreased	30 (23.1)	1 (0.8)	23 (18.3)	1 (0.8)
Potassium increased	11 (8.4)	1 (0.8)	10 (7.8)	0 (0.0)
Potassium decreased	50 (38.2)	12 (9.2)	38 (29.7)	11 (8.6)
Sodium increased	4 (3.1)	0 (0.0)	1 (0.8)	1 (0.8)
Sodium decreased	78 (59.5)	16 (12.2)	80 (62.5)	16 (12.5)

*Each test incidence is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement available:
n is the number of patients for whom the laboratory abnormalities deteriorated by ≥1 CTCAE toxicity grade from baseline.

8.5 Post-Market Adverse Reactions

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)

- Immune system disorders: immune-mediated cystitis
- Anaphylaxis, including anaphylactic reaction and anaphylactic shock

9 Drug Interactions

9.2 Drug Interactions Overview

No formal pharmacokinetic drug interaction studies have been conducted. Since tislelizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

9.4 Drug-Drug Interactions

The use of systemic corticosteroids and other immunosuppressants, before starting TEVIMBRA, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy. However, systemic corticosteroids and other immunosuppressants can be used after starting TEVIMBRA to treat immune-related ADRs (see 7 Warnings And Precautions).

10 Clinical Pharmacology

10.1 Mechanism of Action

Tislelizumab is a humanized immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1. Binding to the extracellular domain of PD-1 receptor blocks the interaction with both PD-L1 and PD-L2 ligands, inhibiting 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 does not bind to Fc gamma receptors (FcγRs) and *C1q*, and therefore not induce antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) or complement-dependent cytotoxicity (CDC).

10.3 Pharmacokinetics

The pharmacokinetics (PK) of tislelizumab was assessed following administration as monotherapy and in combination with chemotherapy. The PK of tislelizumab was characterized using population PK analysis with concentration data from 2,596 patients with advanced malignancies who received tislelizumab doses of 0.5 to 10 mg/kg every 2 weeks, 2.0 and 5.0 mg/kg every 3 weeks, and 200 mg every 3 weeks (Q3W). The PK of tislelizumab in patients dosed with 200 mg Q3W is described below.

200 mg Q3W	**C_{max}** (mg/mL) (%CV)	**C_{trough}** (mg/mL) (%CV)	**AUC** (mg/mL*day) (%CV)	**CL** (mL/day) (%CV)	**Vd** (L) (%CV)	**$T_{1/2}$** (d) (%CV)
First dose	67.8 (18.1)	16.5 (27.0)	601.0 (17.7)	153.0 (26.3)	6.5 (32.6)	23.8 (31.0)
Steady state	110.0 (22.2)	41.0 (38.3)	1283.0 (28.7)			

[a] PK parameters are reported as geometric mean (CV%) based on population pharmacokinetic analysis. AUC: area under the concentration time curve from the last dose to the next dose; CL: clearance; Cmax: maximum concentration; C_{trough}: trough concentration; T1/2: terminal elimination half-life; Vd: volume of distribution.

Peak concentrations were observed at the end of the infusion. The time to reach 90% steady-state level is approximately 84 days (12 weeks) after 200 mg Q3W doses, and the steady-state accumulation ratio of tislelizumab after repeat dosing is approximately 2.1-fold.

Absorption

Tislelizumab is administered via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

A population PK analysis indicates that the steady state volume of distribution is 6.42 L, which is typical of monoclonal antibodies with limited distribution.

Metabolism

Tislelizumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Based on population PK analysis, the clearance of tislelizumab was 0.153 L/day with an inter-individual variability of 26.3% and the geometrical mean terminal half-life was approximately 23.8 days with a coefficient variation (CV) of 31%. Time-varying clearance was not observed in tislelizumab PK.

At the dosing regimens of 0.5 mg/kg to 10 mg/kg once every 2 or 3 weeks (including 200 mg once every 3 weeks), PK of tislelizumab were observed to be linear and dose proportional, suggesting saturation of the target-mediated drug disposition.

Special Populations and Conditions

- **Pediatrics:** PK of tislelizumab have not been evaluated in children and adolescents <18 years of age. Health Canada has not authorized tislelizumab for pediatric use.
  Geriatrics: Based on population PK analysis, no clinically relevant differences in PK of tislelizumab were observed between patients aged <65 years (n=1750), patients aged between 65 and 75 years (n=737), and patients aged >75 years (n=109) (see 4 Dosage And Administration).
- **Ethnic Origin:** Population PK analysis showed that exposures in Asian patients were 12% to 21% higher than those of Caucasian patients; however, the differences were not considered clinically relevant**.**
- **Hepatic Insufficiency:** No dedicated studies of tislelizumab have been conducted in patients with hepatic impairment. In the population PK analyses of tislelizumab, no clinically important differences in the clearance of tislelizumab were found between patients with mild hepatic impairment (bilirubin ≤ULN and AST >ULN or bilirubin >1.0 to 1.5 × ULN and any AST, n=396) or moderate hepatic impairment (bilirubin >1.5 to 3 × ULN and any AST, n=12) and patients with normal hepatic function (bilirubin ≤ULN and AST ≤ULN, n=2,182). Data in patients with severe hepatic impairment (bilirubin >3 × ULN and any AST, n=2) were too limited to draw any conclusions (see 4 Dosage And Administration).
- **Renal Insufficiency:** No dedicated studies of tislelizumab have been conducted in patients with renal impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild renal impairment (CLcr) 60 to 89 mL/min, n=1,046) or moderate renal impairment (CLcr 30 to 59 mL/min, n=320) and patients with normal renal function (CLcr ≥90 ml/min, n=1223). Mild and

moderate renal impairment had no effect on the exposure of TEVIMBRA). Data in patients with severe renal impairment (CLcr 15 to 29 mL/min, n=5) were too limited to draw any conclusions (see 4 Dosing And Administration).

- **Body Weight:** Population PK analysis showed that increased body weight was associated with increased clearance (CL and Vc), resulting in decreased exposure. However, no clinically meaningful differences in the PK of tislelizumab based on body weight (32 to 130 kg) was observed.

10.4 Immunogenicity

Overall, a 19.3% incidence (656 of 3395 anti-drug antibody (ADA) evaluable patients) of treatment-emergent ADA was observed following tislelizumab administration across all dose levels, including 0.5 to 10 mg/kg once every 2 weeks, 2 to 5 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. Neutralizing antibodies were detected in 27 of these 3395 patients (0.8%).

Of 3034 ADA evaluable patients treated at the recommended dose of 200 mg once every 3 weeks with tislelizumab as monotherapy or in combination with chemotherapies, 593 patients (19.5%) had treatment-emergent ADAs, the incidence of treatment-emergent ADA was 16.5% (236 of 1427 patients) for monotherapy and 22.2% (357 of 1607 patients) for combination therapy. Neutralizing antibodies (Nabs) were detected in 27 (0.9%) patients. The incidence of neutralizing antibodies was 0.8% (11 of 1427 patients) for monotherapy and 1.0% (16 of 1607 patients) for combination therapy. Population PK analysis showed that the presence of treatment-emergent ADA against tislelizumab did not appear to have any clinically relevant impact on pharmacokinetics, efficacy, or safety.

11 Storage, Stability and Disposal

Store under refrigeration at 2°C to 8°C in the original carton to protect from light. Do not freeze. Do not shake.

For storage conditions after dilution of the medicinal product,(See 4 Dosage And Administration).

12 Special Handling Instructions

Any unused product or waste material should be disposed of in accordance with local requirements.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper name: tislelizumab for injection

Chemical name: Anti-human PD-1, Immunoglobulin G4 (IgG4) variant monoclonal antibody

Molecular formula and molecular mass: The molecular weight of the intact tislelizumab molecule calculated from the complementary DNA (cDNA) sequence is 144,044 Daltons excluding the glycan moiety or 146,972 Daltons if including two A2FG1 glycan chains.

Structure:

Tislelizumab is a humanized IgG4 variant monoclonal antibody. The binding target of tislelizumab is PD-1. Tislelizumab is composed of two heterodimers. Each of the heterodimers is composed of a heavy and a light polypeptide chain. The heavy chains (HCs) of the antibody molecule are linked together by two disulfide bonds and the light chains (LCs) are linked to the HCs by one disulfide bond each.

Physicochemical properties: Clear to slightly opalescent, colorless to slightly yellowish solution.

The solution has a pH of approximately 6.5 and an osmolality of approximately 270 to 330 mOsm/kg.

Pharmaceutical standard: Professed

Product Characteristics:

Tislelizumab is an Fc-engineered humanized IgG4 variant monoclonal antibody produced in recombinant Chinese Hamster Ovary cells, followed by purification and formulation.

14 Clinical Trials

14.1 Clinical Trials by Indication

Nasopharyngeal Carcinoma (NPC)

RATIONALE-309 (NCT03924986) was a randomized, multi-center, double-blind, placebo-controlled phase 3 study comparing the efficacy and safety of TEVIMBRA in combination with gemcitabine and cisplatin versus placebo in combination with gemcitabine and cisplatin as first-line treatment in patients with recurrent or metastatic nasopharyngeal carcinoma (NPC).

A total of 263 patients were randomized (1:1) to receive either TEVIMBRA in combination with gemcitabine and cisplatin (N = 131) or placebo in combination with gemcitabine and cisplatin (N = 132). Randomization was stratified by gender and metastatic status (based on the presence or absence of liver metastases). Patients received either TEVIMBRA 200 mg or placebo plus cisplatin 80 mg/m^2 on Day 1 plus gemcitabine 1 g/m^2 on Day 1 and Day 8 of each 21-day cycle for 4 to 6 cycles. TEVIMBRA or placebo was administered until disease progression or unacceptable toxicity.

The study included patients with pathologically confirmed recurrent or metastatic NPC who have not received prior systemic treatment and an ECOG performance status of 0 or 1.The RATIONALE-309 study excluded patients who received any approved systemic anticancer therapy including hormonal

therapy within 28 days before initiation of study treatment, prior therapies targeting PD-1 or PD-L1, or who have active leptomeningeal disease or uncontrolled, untreated brain metastasis.

The baseline characteristics for the study population were median age of 50 years (min, max: 23, 74); 91.6% of patients < 65 years old; 78.3% of patients were male; 63.1% with baseline ECOG PS score of 1; 100% Asian (from China, Thailand, and Taiwan); and 95% were never or former smokers.

Table 5 Summary of patient demographics for Study RATIONALE-309

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Min -Max)	Sex (%)
RATIONALE-309	Phase 3, multicenter, double-blind, placebo-controlled, randomized (1:1)	Intravenous infusion Arm A Tislelizumab 200mg Q3W +GC Arm B Placebo + GC	All: 263 Arm A: 131 Arm B: 132	50 (23-74) 50 (26-74) 50 (23-73)	M (78.3) F (21.7)

The primary endpoint was progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per RECIST v1.1 in the Intention-to-Treat (ITT) Analysis Set. The secondary endpoints were descriptive in nature and included Overall Survival (OS), Objective Response Rate (ORR), and Duration of Response (DOR). At the time of the primary PFS analysis, the median follow-up time was 10.2 months.

Efficacy results are shown in Table 6 and Figure 1.

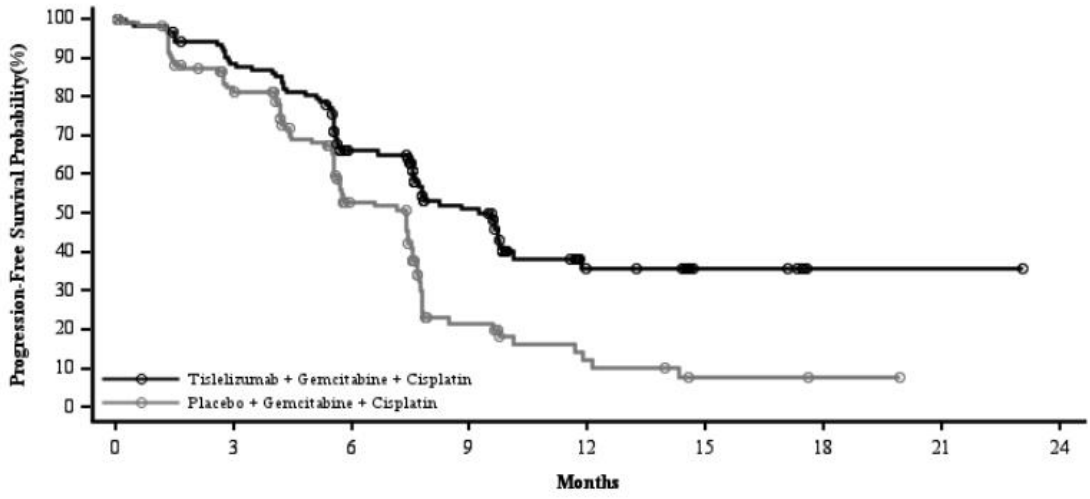
Table 6 Efficacy Results in RATIONALE-309

Endpoint	Tislelizumab + Gemcitabine + Cisplatin (N = 131)	Placebo + Gemcitabine + Cisplatin (N = 132)
PFS		
Events, n (%)	65 (49.6)	87 (65.9)
Median PFS (months) (95% CI) [a]	9.2 (7.6, 10.1)	7.4 (5.6, 7.5)
Hazard Ratio (95% CI) [b, c]	0.52 (0.38, 0.73)	
p-value[c, d]	< 0.0001	

Abbreviations: PFS = progression-free survival

[a] Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley
[b] Estimated from stratified Cox model
[c] Stratified by gender and liver metastases status (with versus without)
[d] One-sided p-value from log-rank test

Figure 1 Kaplan-Meier Plot of Progression-Free Survival in RATIONALE-309



Number At Risk:

Tislelizumab + Gemcitabine + Cisplatin	131	108	70	42	13	6	1	1	0
Placebo + Gemcitabine + Cisplatin	132	98	50	14	6	2	1	0	0

In addition, ORR was 69.5% (95% CI: 60.8%–77.2%) in the TEVIMBRA plus gemcitabine and cisplatin arm and 55.3% (95% CI: 46.4%–64.0%) in the placebo plus gemcitabine and cisplatin arm.

Among responders, the median DOR was 8.5 months (95% CI: 6.5, Not Estimable) in the TEVIMBRA in combination with gemcitabine and cisplatin arm and 6.1 months (95% CI: 4.7, 6.2) in the placebo plus gemcitabine and cisplatin arm.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General toxicology:

In non-clinical toxicology studies in cynomolgus monkeys, no treatment related toxicity was noted at single doses up to 100 mg/kg. In repeat-dose toxicology studies in cynomolgus monkeys, following intravenous infusion at 3, 10, 30 or 60 mg/kg (once every 2 weeks (Q2W), 7 dose administrations) for 13 weeks, no apparent treatment-related toxicity or histopathological changes were observed in any tissues or organs, including the reproductive system of male and females up to 30 mg/kg Q2W, corresponding to 4 to 7 times human exposure than those observed at the clinical dose of 200 mg. A higher dose (60 mg/kg) was associated with article-related adverse histopathology findings in the kidney and vascular changes in multiple tissues corresponding to moderate to severe immunogenic reactions in several animals, which may have been due to ADA development.

Genotoxicity:

No long-term animal studies have been performed to evaluate the genotoxic potential of tislelizumab.

Carcinogenesis:

No long-term animal studies have been performed to evaluate the carcinogenic potential of tislelizumab.

Reproductive and Developmental Toxicity:

No developmental and reproductive toxicity studies or animal fertility studies have been conducted with tislelizumab. In a 13-week 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.

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. IgG4 is also known to cross the placental barrier; hence, tislelizumab has the potential to cross the placenta during pregnancy and cause harm to the fetus.

Special Toxicology:

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**.**

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **TEVIMBRA**™

tislelizumab for injection

This Patient Medication Information is written for the person who will be taking **TEVIMBRA**. This may be you, or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions about the condition this medication is for or want more information about **TEVIMBRA**, talk to a healthcare professional.

Serious Warnings and Precautions Box:

- TEVIMBRA may cause severe and fatal immune-mediated adverse reactions, in any organ system or tissue including: colitis, endocrinopathies, hepatitis, myocarditis, myositis, nephritis with renal dysfunction, organ transplant rejection, pancreatitis, pneumonitis, and severe cutaneous adverse reactions (SCARS) (see 7. Warnings and Precautions).
- TEVIMBRA can cause severe or life-threatening infusion-related reactions including hypersensitivity and anaphylaxis (see 7. Warnings and Precautions).
- 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 (see 7. Warnings and Precautions).

What is TEVIMBRA used for?

- TEVIMBRA in combination with gemcitabine and cisplatin is used to treat patients with a type of head and neck cancer called nasopharyngeal carcinoma that has spread to other parts of the body and/or that has returned after previous therapy.

How does TEVIMBRA work?

TEVIMBRA is a cancer medicine that works by helping your immune system fight your cancer. It can help to slow down or stop the cancer from growing and may shrink the tumour.

If you have any questions about how TEVIMBRA works or why this medicine has been prescribed for you, ask your healthcare professional.

What are the ingredients in TEVIMBRA

Medicinal ingredients: tislelizumab

Non-medicinal ingredients: Citric acid monohydrate, L-histidine, L-histidine hydrochloride

monohydrate, polysorbate-20, sodium citrate dihydrate, trehalose dihydrate, and water for injection (WFI).

TEVIMBRA comes in the following dosage form:

TEVIMBRA comes in glass vials that contain 10 mL of tislelizumab at a concentration of 10 mg/mL.

Do not use TEVIMBRA if:

- You are allergic to tislelizumab or any other ingredients in TEVIMBRA. If you are not sure about this, talk to your healthcare professional before taking TEVIMBRA.

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

- autoimmune disease (a condition where the body's own defence system attacks normal cells) such as Crohn's disease, ulcerative colitis, or lupus
- inflammation of the liver (hepatitis) or other liver problems
- inflammation of the kidney (nephritis) or other kidney problems
- pneumonia or inflammation of the lungs (pneumonitis) or other lung problems
- inflammation of the large bowel (colitis) or other bowel problems
- inflammation of the heart (myocarditis) or lining of the heart (pericarditis) or other heart problems
- any condition that affects your nervous system such as myasthenia gravis or Guillain-Barre Syndrome
- problems with hormone-producing glands (including the adrenal, pituitary and thyroid glands)
- diabetes mellitus
- have or previously had a severe rash or skin condition
- a solid organ transplant or a hematopoietic stem cell transplant (HSCT)
- infusion-related reaction
- a chronic viral infection of the liver (hepatitis)
- human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- taking medications that affect the immune system such as a steroids
- taking medicine to treat an infection
- have recently received a live, attenuated vaccine

Other warnings you should know about:

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before you are given this medicine.

You should not be given TEVIMBRA if you are pregnant unless your healthcare professional specifically prescribes it for you. The effects of TEVIMBRA in pregnant women are not known, but it is possible that the active substance, tislelizumab, could harm an unborn baby.

If you are a woman who could become pregnant, you must use effective contraception while you are being treated with TEVIMBRA and for at least 4 months following the last dose of TEVIMBRA.

Breast-Feeding
It is not known whether TEVIMBRA passes into breast milk. A risk to the breast-fed infant cannot be ruled out. If you are breast-feeding or plan to breastfeed, tell your healthcare professional. You should not breast-feed during treatment with TEVIMBRA and for at least 4 months after the last dose of TEVIMBRA.

Children and adolescents
TEVIMBRA is not for use in patients under 18 years of age.

Driving and using machines
Please see how you react to TEVIMBRA before driving or operating heavy machinery because TEVIMBRA has been known to cause dizziness, tiredness, and fatigue.

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

How to take TEVIMBRA

TEVIMBRA should be given to you by a healthcare professional who has experience with treating cancer.

- TEVIMBRA is given directly into your bloodstream as an infusion (giving the medicine through a vein) every 3 weeks
- The first dose of TEVIMBRA is given over 60 minutes, and if you tolerate TEVIMBRA well, then the following infusions can be given over 30 minutes
- TEVIMBRA is given before your chemotherapy if both are given on the same day
- Your healthcare professional will determine how many doses of TEVIMBRA you will receive

Usual dose:

The recommended dose for TEVIMBRA is 200 mg every 3 weeks as an infusion.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVIMBRA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

It is important that you make it to all your appointments to receive TEVIMBRA. If you miss your

appointment to receive TEVIMBRA, please contact your healthcare professional to reschedule your visit.

What are possible side effects from using TEVIMBRA?

These are not all the possible side effects you may have when taking TEVIMBRA If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects when TEVIMBRA is used in combination with chemotherapy (may affect more than 1 in 10 people)

- Rash
- Muscle weakness, muscle spasms, abnormal heart rhythm (hypokalemia)
- Underactive thyroid gland with tiredness, weight gain, skin, and hair changes (hypothyroidism)
- Increased blood level of the liver enzymes
- Cough
- Diarrhea
- Itching
- Tiredness
- Fever

Common side effects when TEVIMBRA is used in combination with chemotherapy (may affect up to 1 in 10 people)

- Overactive thyroid gland, which can cause hyperactivity, sweating, weight loss and thirst (hyperthyroidism)
- Increased blood sugar level, thirst, dry mouth, need to pass urine more frequently, tiredness, increased appetite with weight loss, confusion, nausea, vomiting, fruity smelling breath, difficulty breathing and dry or flushed skin (hyperglycemia)
- Mouth sores or ulcers with inflammation of the gums (stomatitis)
- Severe upper stomach pain, nausea, vomiting, fever, tender abdomen – possible symptoms of pancreas problems (pancreatitis)
- Itching or peeling skin, skin sores (erythema multiforme)
- Eye redness, eye pain and swelling – possible symptoms of problems affecting the uvea, the layer beneath the white of the eyeball (uveitis)
- Chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever which may occur during infusion or up to 24 hours after infusion (possible symptoms of infusion-related reactions).

Uncommon side effects (may affect up to 1 in 100 people)

- Skin color change in patches (vitiligo)
  Disorder in which the adrenal glands do not make enough of certain hormones (adrenal insufficiency)
- Frequent headaches, vision changes (either low vision or double vision), fatigue and/or weakness, confusion, decreased blood pressure, dizziness – possible symptoms of pituitary gland problems (hypophysitis).

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Diarrhea/Colitis (**i**nflammation of the intestines): which can cause increased number of bowel movements, watery, loose or soft stools, stools with blood or mucus stomach pain (abdominal pain) and/or cramps		✓	
Hypothyroidism (underactive thyroid gland) tiredness, weight gain, skin and hair changes, constipation, feeling cold		✓	
COMMON			
Arthritis (inflammation of the joints): which may cause joint pain, stiffness, swelling or redness, decreased range of motion in the joints		✓	
Hepatitis (inflammation of the liver): yellowing of the skin or the whites of the eyes, belly (abdominal) pain, nausea, vomiting, loss of appetite, confusion, fatigue, darkening of the urine		✓	
Hyperthyroidism (overactive thyroid gland) which may cause hyperactivity, rapid heartbeat, sweating, weight loss and thirst		✓	
Infusion-related reaction; chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever which may occur during infusion or up to 24 hours after infusion		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Myocarditis (inflammation of the heart muscle): which may cause chest pain, rapid or abnormal heartbeat, shortness of breath at rest or during activity, fluid buildup with swelling of the legs, ankles and feet, tiredness		✓	
Pneumonitis (inflammation of the lung) which may cause trouble breathing, dry cough, chest pain		✓	
Thyroiditis (inflammation of the thyroid): which may cause fatigue, swelling at the base of the neck, pain in front of the throat		✓	
Diabetes mellitus (Blood sugar problems): which may cause hunger or thirst, a need to urinate more often, or weight loss		✓	
UNCOMMON			
Adrenal insufficiency (Disorder in which the adrenal glands do not make enough of certain hormones) which may cause possible weakness and/or low blood pressure		✓	
Hypophysitis (inflammation of the pituitary gland): which may cause frequent headaches, vision changes (either low vision or double vision), fatigue and/or weakness, confusion, decreased blood pressure, dizziness		✓	
Myositis (inflammation of the muscles): which may cause muscle pain, stiffness,		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
weakness, chest pain or severe tiredness			
Nephritis (inflammation of the kidney) which may cause **c**hanges in the amount or colour of the urine (dark tea-coloured urine), swelling of extremities(edema)		✓	
RARE			
Myasthenia gravis (Muscle weakness and tiredness without atrophy) which may cause drooping eyelids, weakness in the arms, hands legs and neck		✓	
Serious Skin Reactions including Stevens-Johnson Syndrome, (SJS, toxic epidermal necrosis (TEN) **(**Serious rash and reddening of the skin on upper body and quickly spreading to other body parts), which may cause blistering of the lips, eyes or mouth, skin peeling, sometimes with flu-like symptoms such as fever, sore throat, cough, and joint pain		✓	
Guillain-Barré syndrome (inflammation of the nerves): which may cause pain, weakness and paralysis in the extremities		✓	
Pericarditis (inflammation of the membrane around the heart/pericardium): which may cause chest pain, fever, cough, palpitations		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about TEVIMBRA

- 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; the manufacturer's website: beonemedicines.com , or by calling 1-877-828-5598.

This leaflet was prepared by BeOne Medicines I GmbH

Distributed by Innomar Strategies Inc.

Milton, ON, L9T 6W3

Date of Authorization

December 18, 2025