Product Monograph

Including Patient Medication Information

[Pr]LOQTORZI™

toripalimab for injection

Produced in Chinese hamster ovary cells by recombinant DNA technology

Concentrate for solution for intravenous infusion

40 mg/mL

Antineoplastic agent, monoclonal antibody

Apotex Inc.
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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

LOQTORZI (toripalimab for injection) is indicated:

- in combination with cisplatin and gemcitabine, for the first-line treatment of adults with metastatic or with recurrent, locally advanced nasopharyngeal carcinoma (NPC).
- as a single agent, for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

1.1. Pediatrics

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

1.2. Geriatrics

Geriatrics (≥65 years of age): No overall differences in safety were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population. Clinical studies of LOQTORZI did not include sufficient numbers of patients aged 65 years and over with NPC to determine whether they respond differently from younger patients. (see 7.1.4. Geriatrics).

2. Contraindications

LOQTORZI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6. Dosage Forms, Strengths, Composition and Packaging.

3. Serious Warnings and Precautions Box

- LOQTORZI can cause severe and fatal immune-mediated adverse reactions, which can occur in any organ system or tissue, including the following: pneumonitis, colitis, hepatitis, myocarditis, pancreatitis, myositis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, and solid organ transplant rejection (see **Error! Reference source not found.. Error! Reference source not found., Error! Reference source not found.**).
- LOQTORZI 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

- LOQTORZI is for intravenous infusion after dilution (see 4.3 Reconstitution, and 4.4 Administration).

- LOQTORZI should be administered over 60 minutes for the first infusion. If no infusion-related reactions occur during the first infusion, subsequent infusions may be administered over 30 minutes (see 4.2 Recommended Dose and Dosage Adjustment, and 4.4 Administration).

4.2. Recommended Dose and Dosage Adjustment

First-line metastatic or recurrent, locally advanced nasopharyngeal carcinoma

- LOQTORZI 240 mg intravenously every three weeks in combination with cisplatin and gemcitabine for up to 6 cycles, followed by LOQTORZI 240 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

Previously treated unresectable or metastatic nasopharyngeal carcinoma

- LOQTORZI 3 mg/kg body weight intravenously every two weeks. Administer until disease progression or unacceptable toxicity.

Treatment Modifications

No dose reductions of LOQTORZI are recommended. In general, withhold LOQTORZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LOQTORZI 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 prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

Treatment modifications for LOQTORZI for adverse reactions that require management different from these general guidelines are summarized in Table 1 below.

Table 1: Recommended Treatment Modifications for Adverse Reactions

Adverse Reaction	Severity[1]	Treatment Modification
Immune-Related Adverse Reactions		
Pneumonitis	Grade 2	Withhold[2]
	Grades 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[2]
	Grade 4	Permanently discontinue
Myositis	Grade 2 or 3	Withhold or permanently discontinue depending on severity[2]
	Grade 4	Permanently discontinue
Pancreatitis	Grade 2 or 3	Withhold or permanently discontinue depending on severity[2]
	Grade 4	Permanently discontinue

Adverse Reaction	Severity[1]	Treatment Modification
Hepatitis with no tumor involvement of the liver	AST/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[2]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[3]	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[2]
	Baseline AST or ALT is above the ULN and increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Adrenal Insufficiency	Grade 2 to 4	Withhold until clinically stable on hormone replacement therapy[2]
Hypophysitis	Grade 2 to 4	Withhold until clinically stable on hormone replacement therapy[2]
Hyperthyroidism	Grade 3 or 4	Withhold until clinically stable on appropriate medical management
Thyroiditis	Grade 3 or 4	Withhold until clinically stable on appropriate medical management
Type I Diabetes Mellitus	Grade 3 or 4	Withhold until clinically stable on appropriate medical management
Hypothyroidism	Grade 3 or 4	Withold until clinically stable on hormone replacement therapy[2]
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[2]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[2]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold [2]
	Grade 3-4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion

Adverse Reaction	Severity[1]	Treatment Modification
	Grade 3 or 4	Stop infusion. Permanently discontinue

[1] Based on National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) version 5.0

[2] Resume LOQTORZI in patients with complete or partial resolution to Grade 0-1 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 or for endocrinopathies that cannot be clinically stabilized on hormone replacement therapy.

[3] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue LOQTORZI based on recommendations for hepatitis with no liver involvement.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, DRESS=drug rash with eosinophilia and systemic symptoms, SJS=Stevens Johnson syndrome, TEN=toxic epidermal necrolysis, ULN=upper limit of normal

4.3. Reconstitution

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute LOQTORZI prior to intravenous administration.
- Withdraw the required volume of LOQTORZI and inject slowly into a 100 mL or 250 mL infusion bag containing 0.9% Sodium Chloride Injection, USP. **Mix diluted solution by gentle inversion. Do not shake.** The final concentration of the diluted solution should be between 1 mg/mL to 3 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solution

LOQTORZI does not contain a preservative. If the diluted solution is not administered immediately, store either:

- At room temperature, 20°C to 25°C, for no more than 8 hours from the time of dilution to the completion of the infusion. Discard diluted solution stored at room temperature after 8 hours.

Or

- Refrigerated at 2°C to 8°C for no more than 24 hours from the time of dilution to the completion of the infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Discard the refrigerated diluted solution after 24 hours. Do not freeze.

4.4. Administration

- Administer diluted solution intravenously via an infusion pump using an in-line aseptic filter (0.2 or 0.22 micron).
- First Infusion: Infuse over at least 60 minutes.
- Subsequent infusions: If no infusion-related reactions occurred during the first infusion, subsequent infusions may be administered over 30 minutes (see 4.2. Recommended Dose and Dosage Adjustment).
- Do not co-administer other drugs through the same intravenous line.

- When administered on the same day as chemotherapy, LOQTORZI should be administered prior to chemotherapy.
- Refer to the product labelling for cisplatin and gemcitabine for recommended dosing information.

4.5. Missed Dose

If a planned dose of LOQTORZI 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 known antidote for overdosage of LOQTORZI. In case of overdosage, the patient should be closely monitored for adverse reactions and supportive treatment should be administered.

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, 240 mg toripalimab/6 mL (40 mg/mL)	Citric acid monohydrate, mannitol, polysorbate 80, sodium chloride, sodium citrate, and Water for Injection.

Description

LOQTORZI is provided as a sterile, clear to slightly opalescent, colorless to slightly yellow solution in a single-use vial. Each vial of 6 mL contains 240 mg of toripalimab.

7. Warnings and Precautions

See 3. Serious Warnings and Precautions Box.

General

Treatment with LOQTORZI should be initiated and supervised by a healthcare professional experienced in the treatment of cancer. LOQTORZI is administered by intravenous infusion only.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Immune

LOQTORZI 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

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting 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 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 LOQTORZI depending on severity (see 4.2. Recommended Dose and Dosage Adjustment). In general, if LOQTORZI 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 corticosteroid therapy.

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

LOQTORZI can cause immune-mediated pneumonitis (see 8 Adverse Reactions). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Manage patients with LOQTORZI treatment modifications and corticosteroids, and withhold or permanently discontinue treatment depending on severity (see 4.2 Recommended dose and dosage adjustment).

Immune-mediated Colitis

LOQTORZI can cause immune-mediated colitis, which may present with diarrhea (see 8 Adverse Reactions). Manage patients with LOQTORZI treatment modifications and corticosteroids, and withhold

or permanently discontinue treatment depending on severity (see 4.2 Recommended Dose and Dosage Adjustment). Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Hepatotoxicity and Immune-mediated Hepatitis

LOQTORZI can cause immune-mediated hepatitis (see 8 Adverse Reactions). Patients should be monitored for changes in liver function prior to and periodically during treatment and as indicated based on clinical evaluation. Manage patients with LOQTORZI treatment modifications and corticosteroids, and withhold or permanently discontinue treatment depending on severity (see 4.2 Recommended Dose and Dosage Adjustment).

Immune-mediated Endocrinopathies

Adrenal Insufficiency

LOQTORZI can cause primary or secondary adrenal insufficiency (see 8 Adverse Reactions). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Manage patients with LOQTORZI treatment modifications, and withhold or permanently discontinue LOQTORZI depending on severity (see 4.2. Recommended Dose and Dosage Adjustment).

Hypophysitis

LOQTORZI can cause immune-mediated hypophysitis (see 8 Adverse Reactions). Hypophysitis can present with acute symptoms associated with mass effects such as headache, photophobia, or visual field defects.

Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Patients should be monitored for signs and symptoms of hypophysitis and managed with LOQTORZI treatment modifications. Withhold or permanently discontinue LOQTORZI depending on severity (see 4.2. Recommended Dose and Dosage Adjustment).

Thyroid Disorders

LOQTORZI can cause immune-mediated thyroid disorders (see 8 Adverse Reactions). Patients should be monitored for signs and symptoms of thyroid disorders prior to and periodically during treatment, and as indicated based on clinical evaluation. 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. Manage patients with LOQTORZI treatment modifications, and withhold or permanently discontinue LOQTORZI depending on severity (see 4.2. Recommended Dose and Dosage Adjustment).

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

LOQTORZI can cause immune-mediated type I diabetes mellitus (see 8 Adverse Reactions). Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue LOQTORZI depending on severity (see 4.2. Recommended Dose and Dosage Adjustment).

Immune-mediated Nephritis with Renal Dysfunction

LOQTORZI can cause immune-mediated nephritis (see 8 Adverse Reactions). Patients should be monitored for changes in renal function and other causes of renal dysfunction excluded. Manage patients with LOQTORZI treatment modifications and corticosteroids, and withhold or permanently discontinue treatment depending on severity (see 4.2 Recommended Dose and Dosage Adjustment).

Immune-mediated Myocarditis

LOQTORZI can cause immune-mediated myocarditis. Patients should be monitored for signs and symptoms of myocarditis. If myocarditis is suspected, high-dose steroids should be promptly initiated with cardiology consultation and diagnostic workup according to current clinical guidelines. Patients should be managed with LOQTORZI treatment modifications (see section 4.2 Recommended Dose and Dose Adjustment) and corticosteroids, as clinically indicated. Consider the addition of immunosuppressants if the event does not improve within 48 hours after start of corticosteroid therapy. Permanently discontinue LOQTORZI for Grade 2 or higher immune-mediated myocarditis.

Immune-mediated Myositis

LOQTORZI can cause immune-mediated myositis. Patients should be monitored for signs and symptoms of myositis and managed with LOQTORZI treatment modifications (see section 4.2 Recommended Dose and Dose Adjustment) and corticosteroids, as clinically indicated. Withhold or permanently discontinue LOQTORZI depending on severity.

Immune-mediated Pancreatitis

LOQTORZI can cause immune-mediated pancreatitis. Patients should be monitored for signs and symptoms of pancreatitis and managed with LOQTORZI treatment modifications (see section 4.2 Recommended Dose and Dose Adjustment) and corticosteroids, as clinically indicated. Withhold or permanently discontinue LOQTORZI depending on severity.

Immune-mediated Skin Reactions

LOQTORZI can cause immune-mediated skin reactions including rash or dermatitis (see 8 Adverse Reactions). Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Manage patients with LOQTORZI treatment modifications and corticosteroids, and withhold or permanently discontinue LOQTORZI depending on severity (see 4.2 Recommended Dose and Dosage Adjustment).

Other Immune-mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions were reported in less than 1% of patients treated with LOQTORZI or were reported with the use of other PD-1/PD-L1 blocking antibodies. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed with LOQTORZI treatment modifications as clinically indicated (see 4.2 Recommended Dose and Dosage Adjustment).

Cardiac/Vascular: Pericarditis, vasculitis, pericardial effusion

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré 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: Gastritis, duodenitis

Musculoskeletal and Connective Tissue: Rhabdomyolysis (and associated sequelae, including renal failure), arthritis, polymyalgia rheumatica, dermatomyositis

Endocrine: Hypoparathyroidism

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

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who received an allogeneic haematopoietic 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 the allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. The benefits of treatment with LOQTORZI versus the risks listed above should be considered in patients who have received or who may receive an allogeneic HSCT.

Infusion Related Reactions

LOQTORZI can cause severe or life-threatening infusion-related reactions including hypersensitivity and anaphylaxis. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue LOQTORZI (see 4.2 Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

Routine laboratory assessments for organ function (i.e. renal function test, liver function tests, thyroid function tests), ECGs, and immunogenicity testing should be performed at baseline and during treatment. Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests

Reproductive Health

Advise females of reproductive potential to use effective contraception during treatment with LOQTORZI and for 4 months after the last dose (see 7.1.1. Pregnancy).

- **Fertility**

  There are no data on the effect of LOQTORZI on fertility.

7.1. Special Populations

7.1.1. Pregnancy

Based on its mechanism of action, LOQTORZI can cause fetal harm when administered to a pregnant woman (see 10.1. Mechanism of Action). There are no available data on the use of LOQTORZI 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 and result in fetal death (see **Error! Reference source not found.**. **Error! Reference source not found.**). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LOQTORZI can potentially be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus. LOQTORZI is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risks.

Verify the pregnancy status of females of reproductive potential prior to initiating LOQTORZI.

7.1.2. Breastfeeding

There are no data on the presence of toripalimab in human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to toripalimab are unknown. Because of the potential for serious adverse reactions in breastfed children, advise lactating women not to breastfeed during treatment with LOQTORZI and for 4 months after the last dose.

7.1.3. Pediatrics

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

7.1.4. Geriatrics

Geriatrics (≥65 years of age)

Of the 146 patients with NPC who were treated with LOQTORZI in combination with cisplatin and gemcitabine, 7 (4.8%) were 65 years or older; there were no patients 75 years and older. Clinical studies of LOQTORZI in combination with cisplatin and gemcitabine did not include a sufficient number of patients aged 65 years and over with NPC to determine whether they respond differently from younger patients.

Of the 190 patients with NPC treated with LOQTORZI as single agent, 10 (5%) patients were 65 years or older; there were no patients 75 years and older. Clinical studies of LOQTORZI did not include sufficient numbers of patients aged 65 years and over with NPC to determine whether they respond differently from younger patients.

Of the 851 patients with tumor types including nasopharyngeal carcinoma or other types of tumors from the safety pool treated with LOQTORZI as a single agent (see 8.1. Adverse Reaction Overview), 171 (20%) patients were 65 years or older and 13 (1.5%) patients were 75 years and older. No overall differences in safety were observed between elderly patients and younger patients.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The following clinically significant adverse reactions have been observed in patients treated with LOQTORZI and are detailed under WARNINGS AND PRECAUTIONS:

- Severe and fatal immune-mediated adverse reactions (see 7. Warnings and Precautions, Immune and 8.2. Clinical Trial Adverse Reactions, Additional Information on Selected Adverse Reactions)
- Infusion-related reactions (see 7. Warnings and Precautions, Immune and 8.2. Clinical Trial Adverse Reactions, Additional Information on Selected Adverse Reactions)

In clinical trials of LOQTORZI, the most common adverse reactions were:

LOQTORZI in Combination with Cisplatin and Gemcitabine

The most common adverse reactions (≥ 20%) were: nausea (71%), vomiting (68%), decreased appetite (55%), constipation (39%), hypothyroidism (38%), rash (36%), pyrexia (32%), diarrhea (31%), peripheral neuropathy (30%), cough (26%), musculoskeletal pain (25%), upper respiratory infection (23%), insomnia (23%), dizziness (21%), and malaise (21%).

LOQTORZI as a Single Agent

The data described is from 851 patients treated with LOQTORZI at a dose of 3 mg/kg IV every 2 weeks across 12 trials: one randomized, active-controlled trial and 11 open-label, non-randomized trials. The tumor types included nasopharyngeal carcinoma (n=193) or other types of tumors (n=658). In this pooled safety population, the most common (≥20%) adverse reactions were: fatigue (22%), hypothyroidism (20%), and musculoskeletal pain (20%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

First-line Treatment of Metastatic or Recurrent, Locally Advanced Nasopharyngeal Carcinoma (NPC)

The safety of LOQTORZI in combination with cisplatin and gemcitabine was evaluated in JUPITER-02 (see 14 Clinical Trials). Key eligibility criteria were recurrent locally advanced or metastatic nasopharyngeal carcinoma (NPC) not previously treated with systemic chemotherapy for recurrent or metastatic disease. Patients with recurrent NPC after treatment with curative intent were required to have an interval of at least 6 months between the last dose of radiotherapy or chemotherapy and recurrence. Patients received LOQTORZI 240 mg (n=146) or placebo (n=143) intravenously (IV) every 3 weeks, in combination with cisplatin 80 mg/m^2 IV every 3 weeks and gemcitabine 1000 mg/m^2 IV days 1 and 8 for up to 6 cycles followed by LOQTORZI 240 mg or placebo IV every 3 weeks until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Among patients who received LOQTORZI, 73% were exposed for 6 months or longer and 54% were exposed for greater than one year.

The most common adverse reactions (≥ 20%) were: nausea (71%), vomiting (68%), decreased appetite (55%), constipation (39%), hypothyroidism (38%), rash (36%), pyrexia (32%), diarrhea (31%), peripheral neuropathy (30%), cough (26%), musculoskeletal pain (25%), upper respiratory infection (23%), insomnia (23%), dizziness (21%), and malaise (21%).

Serious adverse reactions occurred in 43% of patients receiving LOQTORZI in combination with cisplatin and gemcitabine. Serious adverse drug reactions in ≥ 2% were thrombocytopenia (14%), neutrophil count decreased (10%), pneumonia (10%), anemia (9%), abnormal hepatic function (2.7%), and rash (2.1%). Of the patients who received LOQTORZI in combination with cisplatin and gemcitabine, there were three fatal adverse reactions (2.1%) one due to epistaxis; one due to intracranial hemorrhage associated with immune-related thrombocytopenia and coagulopathy; and one due to pneumonia.

Permanent discontinuation of LOQTORZI, when given in combination with cisplatin and gemcitabine, due to an adverse reaction occurred in 12% of patients. Adverse reactions resulting in permanent discontinuation of LOQTORZI in ≥1% were pneumonia (2.1%), pulmonary tuberculosis (1.4%), rash (1.4%), and vomiting (1.4%).

Dosage interruptions of LOQTORZI due to an adverse reaction occurred in 50% of patients. Adverse reactions which required dosage interruption in ≥2% were anemia (17%), decreased neutrophils (12%), thrombocytopenia (12%), acute kidney injury (4.1%), pneumonia (6%), fatigue (2.7%), upper respiratory infection (2.7%), and hypothyroidism (2.1%).

Table 3: Adverse Reactions (≥ 5%) in Patients with Recurrent, Locally Advanced or Metastatic NPC Who Received LOQTORZI in Combination with Cisplatin and Gemcitabine in JUPITER-02

Adverse Reaction[1]	**LOQTORZI Cisplatin/Gemcitabine N = 146**		**Placebo Cisplatin/Gemcitabine N = 143**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Ear and labyrinth disorders				
Tinnitus	8 (5.5)	0	12 (8.4)	0
Endocrine disorders				

Adverse Reaction[1]	LOQTORZI Cisplatin/Gemcitabine N = 146		Placebo Cisplatin/Gemcitabine N = 143	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hypothyroidism[2]	56 (38.4)	1 (0.7)	25 (17.5)	0
Gastrointestinal disorders				
Nausea	103 (70.5)	2 (1.4)	121 (84.6)	4 (2.8)
Vomiting	99 (67.8)	3 (2.1)	95 (66.4)	3 (2.1)
Constipation	58 (39.7)	0	66 (46.2)	0
Diarrhoea	45 (30.8)	2 (1.4)	33 (23.1)	0
Abdominal pain	24 (16.4)	0	15 (10.5)	0
Stomatitis[3]	17 (11.6)	0	12 (8.4)	1 (0.7)
Dry mouth	14 (9.6)	0	11 (7.7)	0
Abdominal distension	14 (9.6)	0	10 (7.0)	0
Oropharyngeal pain	13 (8.9)	0	9 (6.3)	0
Toothache	12 (8.2)	0	3 (2.1)	0
General disorders and administration site conditions				
Pyrexia	47 (32.2)	2 (1.4)	35 (24.5)	1 (0.7)
Malaise	31 (21.2)	1 (0.7)	28 (19.6)	0
Fatigue[4]	28 (19.2)	1 (0.7)	31 (21.7)	3 (2.1)
Oedema	11 (7.5)	0	17 (11.9)	0
Chest discomfort	10 (6.8)	0	11 (7.7)	0
Hepatobiliary disorders				
Hepatic function abnormal	12 (8.2)	2 (1.4)	10 (7.0)	4 (2.8)
Infections and infestations				
Upper respiratory infection[5]	35 (24.0)	5 (3.4)	19 (13.3)	4 (2.8)
Pneumonia[6]	26 (17.8)	17 (11.6)	10 (7.0)	5 (3.5)
Investigations				
Weight decreased	16 (11.0)	0	13 (9.1)	0
Metabolism and nutrition disorders				
Decreased appetite	81 (55.5)	1 (0.7)	90 (62.9)	0

Adverse Reaction[1]	LOQTORZI Cisplatin/Gemcitabine N = 146		Placebo Cisplatin/Gemcitabine N = 143	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[7]	37 (25.3)	0	36 (25.2)	1 (0.7)
Nervous system disorders				
Neuropathy peripheral[8]	44 (30.1)	0	45 (31.5)	1 (0.7)
Dizziness	31 (21.2)	0	31 (21.7)	1 (0.7)
Headache	27 (18.5)	0	33 (23.1)	1 (0.7)
Psychiatric Disorders				
Insomnia	33 (22.6)	0	24 (16.8)	0
Renal and urinary disorders				
Renal injury	7 (4.8)	1 (0.7)	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders				
Cough[9]	38 (26.0)	0	38 (26.6)	0
Epistaxis	14 (9.6)	3 (2.1)	19 (13.3)	4 (2.8)
Rhinorrhoea	13 (8.9)	0	10 (7.0)	0
Skin and subcutaneous tissue disorders				
Rash[10]	51 (34.9)	5 (3.4)	40 (28.0)	4 (2.8)
Pruritus	25 (17.1)	0	11 (7.7)	0
Alopecia	7 (4.8)	0	11 (7.7)	0
Vascular disorders				
Hypertension[11]	15 (10.3)	9 (6.2)	8 (5.6)	6 (4.2)
Thrombosis	7 (4.8)	1 (0.7)	12 (8.4)	1 (0.7)

[1] NCI CTCAE v5.0. See Table below for aggregation rules

[2] Includes hypothyroidism, tri-iodothyronine decreased, tri-iodothyronine free decreased, and thyroiditis.

[3] Includes mouth ulceration, stomatitis, and radiation stomatitis.

[4] Includes asthenia and fatigue.

[5] Includes acute sinusitis, bronchitis, laryngitis, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.

[6] Includes aspiration pneumonia and pneumonia

[7] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, pain in jaw.

[8] Includes hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy.

[9] Includes cough and productive cough.
[10] Includes acneiform dermatitis, allergic dermatitis, catheter-site rash, dermatitis, drug eruption, eczema, erythema, macule, maculopapular rash, palmar-plantar erythrodysesthesia syndrome, papule, pruritic rash, rash, and urticaria.
[11] Includes blood pressure increased, blood pressure systolic increased, hypertension, and hypertensive crisis.

Previously Treated, Unresectable or Metastatic Nasopharyngeal Carcinoma (NPC)

The safety of LOQTORZI was evaluated in POLARIS-02. Eligible patients had previously treated unresectable or metastatic NPC. Patients received LOQTORZI 3 mg/kg every 2 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Among patients who received LOQTORZI, 33% were exposed for 6 months or longer and 21% were exposed for greater than one year.

The median age of patients who received LOQTORZI was 46 years (range: 22 to 71), 83% male, 100% Asian, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 (35%) or 1 (65%) and median weight 59 kg (range: 32 to 101 kg).

Serious adverse reactions occurred in 24% of patients who received LOQTORZI. Serious adverse drug reactions (≥2%) were pneumonia (4.7%), abnormal hepatic function (2.6%), and hyperbilirubinemia (2.1%). Fatal adverse reactions occurred in 4.7% of patients who received LOQTORZI, including death not otherwise specified (1.6%), tumor hemorrhage (0.5%), ascites (0.5%), lung infection (0.5%), thrombocytopenia (0.5%), hyponatremia (0.5%), and sudden death (0.5%).

Permanent discontinuation of LOQTORZI due to an adverse reaction occurred in 9% of patients. Adverse reactions resulting in permanent discontinuation of LOQTORZI in ≥1% of patients included pneumonia (1.1%), abnormal hepatic function (1.1%), and hyperbilirubinemia (1.1%).

Dosage interruptions due to an adverse reaction occurred in 23% of patients. Adverse reactions which required dosage interruption in ≥1% of patients were pneumonia (2.1%), thrombocytopenia (2.1%), fatigue (1.6%), hyperbilirubinemia (1.6%), anemia (1.1%), decreased appetite (1.1%), abnormal hepatic function (1.1%), hypothyroidism (1.1%), and pneumonitis (1.1%).

Table 4: Adverse Reactions (≥2%) in Patients with Previously Treated, Unresectable or Metastatic NPC Who Received LOQTORZI in POLARIS-02

Adverse Reaction*	LOQTORZI N=190	
	All Grades n (%)	Grade 3 or 4 n (%)
Cardiac disorders		
Pericardial effusion	5 (2.6)	1 (0.5)
Endocrine disorders		
Hypothyroidism[1]	52 (27.4)	0
Hyperthyroidism	7 (3.7)	0
Eye disorders		
Vision blurred	7 (3.7)	0
Gastrointestinal disorders		
Constipation	21 (11.1)	0
Diarrhoea	12 (6.3)	0
Nausea	10 (5.3)	0

Adverse Reaction*	LOQTORZI N=190	
	All Grades n (%)	Grade 3 or 4 n (%)
Stomatitis	10 (5.3)	1 (0.5)
Vomiting	9 (4.7)	0
Abdominal pain	7 (3.7)	0
Toothache	7 (3.7)	0
Abdominal distension	5 (2.6)	0
Ascites	5 (2.6)	2 (1.1)
Dysphagia	4 (2.1)	2 (1.1)
General disorders and administration site conditions		
Fatigue[2]	42 (22.1)	6 (3.2)
Pyrexia	31 (16.3)	0
Oedema peripheral	10 (5.3)	0
Face oedema	6 (3.2)	0
Facial pain	5 (2.6)	0
Non-cardiac chest pain	5 (2.6)	0
Chest discomfort	4 (2.1)	0
Death	4 (2.1)	4 (2.1)
Hepatobiliary disorders		
Hepatic function abnormal	10 (5.3)	4 (2.1)
Infections and infestations		
Lung infection[3]	17 (8.9)	6 (3.2)
Upper respiratory tract infection	15 (7.9)	4 (2.1)
Otitis media	9 (4.7)	1 (0.5)
Nasopharyngitis	7 (3.7)	0
Urinary tract infection	7 (3.7)	0
Gingivitis	5 (2.6)	1 (0.5)
Sinusitis	5 (2.6)	0
Investigations		
Weight decreased	20 (10.5)	3 (1.6)
Weight increased	5 (2.6)	2 (1.1)
Metabolism and nutrition disorders		
Decreased appetite	24 (12.6)	2 (1.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[4]	35 (18.4)	2 (1.1)
Muscular weakness	6 (3.2)	1 (0.5)
Arthralgia	4 (2.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cancer pain	4 (2.1)	1 (0.5)
Nervous system disorders		
Dizziness	11 (5.8)	0
Headache	8 (4.2)	2 (1.1)
Hypoaesthesia	5 (2.6)	0
Psychiatric disorders		

Adverse Reaction*	LOQTORZI N=190	
	All Grades n (%)	Grade 3 or 4 n (%)
Insomnia	11 (5.8)	0
Respiratory, thoracic and mediastinal disorders		
Cough[5]	38 (20.0)	0
Dyspnoea	5 (2.6)	0
Pleural effusion	4 (2.1)	1 (0.5)
Pneumonitis	4 (2.1)	0
Rhinorrhoea	4 (2.1)	0
Skin and subcutaneous tissue disorders		
Pruritus	20 (10.5)	0
Rash[6]	20 (10.5)	0
Vascular disorders		
Haemorrhage	16 (8.4)	0
Hypotension	5 (2.6)	2 (1.1)

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

[1] Includes hypothyroidism, thyroiditis, tri-iodothyronine decreased, and tri-iodothyronine free decreased

[2] Includes fatigue and asthenia

[3] Includes lung infection, pneumonia

[4] Includes musculoskeletal pain and myalgia.

[5] Includes cough and productive cough.

[6] Includes dermatitis allergic, eczema, and rash.

Additional Information on Selected Adverse Reactions

The selected adverse reactions described below are based on the safety of LOQTORZI 240 mg Q3W in combination with cisplatin and gemcitabine in 146 patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma treated in the JUPITER-02 trial, and on the safety of LOQTORZI 3 mg/kg Q2W as a single agent in a pooled population of 851 patients from 12 clinical trials (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

LOQTORZI in Combination with Cisplatin and Gemcitabine

Immune-mediated pneumonitis occurred in 2.1% (3/146) of patients receiving LOQTORZI, including Grade 2 (1.4%) adverse reactions. Pneumonitis resolved in 67% (2/3) of these patients.

LOQTORZI as a Single-Agent

Immune-mediated pneumonitis occurred in 2.6% (22/851) of patients receiving LOQTORZI, including fatal (0.2%), Grade 3 (0.7%), and Grade 2 (1.1%) adverse reactions. Systemic corticosteroids were required in 82% (18/22) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of LOQTORZI in 1.2% (10/851) of patients. Pneumonitis resolved in 23% (5/22) of these patients.

Immune-mediated Colitis

LOQTORZI as a Single-Agent

Immune-mediated colitis occurred in 0.4% (3/851) of patients receiving LOQTORZI, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Colitis resolved in all 3 patients.

Hepatotoxicity and Immune-mediated Hepatitis

LOQTORZI in Combination with Cisplatin and Gemcitabine

Immune-mediated hepatitis occurred in 0.7% (1/146) of patients receiving LOQTORZI in combination with cisplatin and gemcitabine, which was a Grade 3 (0.7%) adverse reaction. The patient with immune-mediated hepatitis required systemic corticosteroids.

LOQTORZI as a Single-Agent

Immune-mediated hepatitis occurred in 3.3% (28/851) of patients receiving LOQTORZI, including Grade 4 (0.8%), Grade 3 (2.1%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of LOQTORZI in 1.1% of patients and withholding of LOQTORZI in 0.8% of patients. Hepatitis resolved in 54% (15/28) of these patients.

Immune-mediated Endocrinopathies

Adrenal Insufficiency

LOQTORZI as a Single-Agent

Adrenal insufficiency occurred in 0.5% (4/851) of the patients receiving LOQTORZI, including Grade 2 (0.4%) and Grade 1 (0.1%) adverse reactions. Systemic corticosteroids were required in 75% (3/4) of the patients with adrenal insufficiency. Adrenal insufficiency led to withholding of LOQTORZI in 0.1% (1/851) of patients. In the one patient in whom LOQTORZI was withheld, LOQTORZI was reinitiated after symptom improvement.

Hypophysitis

LOQTORZI as a Single-Agent

Hypophysitis occurred in 0.4% (3/851) of patients receiving LOQTORZI, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. All three patients received systemic corticosteroids.

Hypophysitis led to permanent discontinuation of LOQTORZI in 0.1% (1/851) of patients and withholding of LOQTORZI in 0.1% (1/851) of patients. The one patient in whom LOQTORZI was withheld reinitiated LOQTORZI.

Thyroid Disorders

LOQTORZI in Combination with Cisplatin and Gemcitabine

Thyroiditis occurred in 2.1% (3/146) of patients receiving LOQTORZI in combination with cisplatin and gemcitabine, including Grade 2 (1.4%). Three patients required thyroid hormone replacement therapy. Thyroiditis resolved in one of the 3 patients.

Hyperthyroidism occurred in 1.4% (2/146) of patients receiving LOQTORZI in combination with cisplatin and gemcitabine. Hyperthyroidism resolved in these 2 patients.

Hypothyroidism occurred in 30% (44/146) of patients receiving LOQTORZI in combination with cisplatin and gemcitabine, including Grade 2 (24%) and Grade 1 (6%). Eighty percent of the 44 patients required thyroid hormone replacement therapy. LOQTORZI was withheld in 2.1% (3/146) of the patients. Of the 3 patients in whom LOQTORZI was withheld, 2 patients reinitiated LOQTORZI.

LOQTORZI as a Single-Agent

Thyroiditis occurred in 0.6% (5/851) of patients receiving LOQTORZI, including Grade 2 (0.1%). Two of these 5 patients received systemic corticosteroids and 2 required thyroid hormone replacement therapy. Thyroiditis resolved in 2 of the 5 patients.

Hyperthyroidism occurred in 7% (55/851) of patients receiving LOQTORZI, including Grade 2 (1.9%). Hyperthyroidism resolved in 85% (47/55) of the patients.

Hypothyroidism occurred in 15% (128/851) of patients receiving LOQTORZI, including Grade 2 (8%). Sixty three percent of the 128 patients required thyroid hormone replacement therapy. LOQTORZI was withheld in 0.5% of patients. Of the 4 patients in whom LOQTORZI was withheld, 3 patients reinitiated LOQTORZI.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

LOQTORZI as a Single-Agent

Diabetes mellitus occurred in 0.9% (8/851) of patients receiving LOQTORZI, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (0.1%). Diabetes mellitus led to permanent discontinuation in 0.4% of patients. Six of the 8 (75%) patients with diabetes mellitus required long-term insulin therapy.

Immune-mediated Nephritis with Renal Dysfunction

LOQTORZI in Combination with Cisplatin and Gemcitabine

Immune-mediated nephritis occurred in 0.7% (1/146) of patients receiving LOQTORZI. The one patient with immune-mediated nephritis (Grade 4) required systemic corticosteroids and nephritis led to discontinuation of LOQTORZI. Nephritis resolved in this patient.

LOQTORZI as a Single-Agent

Immune-mediated nephritis occurred in 0.5% (4/851) of patients receiving LOQTORZI, including Grade 3 (0.5%) adverse reactions. Nephritis resolved in 75% (3/4) of these patients.

Immune-mediated Myocarditis

LOQTORZI in Combination with Cisplatin and Gemcitabine:

Immune-mediated myocarditis occurred in 0.7% (1/146) of patients receiving LOQTORZI, including Grade 4 (0.7%) adverse reactions. Systemic corticosteroids were required in this patient with myocarditis. Myocarditis did not resolve in this patient.

LOQTORZI as a Single-Agent

Immune-mediated myocarditis occurred in 0.4% (3/851) of patients receiving LOQTORZI, including Grade 3 (0.1%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 100% (3/3) of patients with myocarditis. Myocarditis led to permanent discontinuation of LOQTORZI in 0.4% (3/851) of patients. Myocarditis resolved in 66.7% (2/3) of these patients.

Immune-mediated Myositis

LOQTORZI in Combination with Cisplatin and Gemcitabine

Immune-mediated myositis occurred in 0.7% (1/146) of patients receiving LOQTORZI, including Grade 3 (0.7%) adverse reactions. Systemic corticosteroids were required in this patient with myositis. Myositis led to permanent discontinuation of LOQTORZI and did not resolve in this patient.

LOQTORZI as a Single-Agent

Immune-mediated myositis occurred in 0.4% (3/851) of patients receiving LOQTORZI, including Grade 4 (0.1%), and Grade 3 (0.2%) adverse reactions. Systemic corticosteroids were required in 100% (3/3) of patients with myositis. Myositis led to permanent discontinuation of LOQTORZI in all three patients. Myositis resolved in 66.7% (2/3) of these patients.

Immune-mediated Pancreatitis

LOQTORZI as a Single-Agent

Immune-mediated pancreatitis occurred in 0.5% (4/851) of patients receiving LOQTORZI, including Grade 2 (0.4%) and Grade 1 (0.1%) adverse reactions. Systemic corticosteroids were not required in patients with immune-mediated pancreatitis. Immune-mediated pancreatitis led to permanent discontinuation of LOQTORZI in 0.4% (3/851) of patients. Immune-mediated pancreatitis resolved in 75% (3/4) of these patients.

Immune-mediated Skin Reactions

LOQTORZI in Combination with Cisplatin and Gemcitabine

Immune-mediated dermatologic adverse reactions occurred in 8% (12/146) of patients receiving LOQTORZI, including Grade 3 (3.4%) and Grade 2 (1.4%) adverse reactions. Systemic corticosteroids were required in 25% (3/12) of the patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of LOQTORZI in 2.1% (3) of patients. Immune-mediated dermatologic adverse reactions resolved in 92% (11/12) of these patients.

LOQTORZI as a Single-Agent

Immune-mediated dermatologic adverse reactions occurred in 4% (34/851) of patients receiving LOQTORZI, including Grade 3 (0.4%) and Grade 2 (1.4%) adverse reactions. Immune-mediated dermatologic adverse reactions led to withholding of LOQTORZI in 0.4% (3) of the patients. Systemic corticosteroids were required in 12% (4/34) of the patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 71% (24/34) of these patients.

Infusion Related Reactions

LOQTORZI in Combination with Cisplatin and Gemcitabine

Infusion-related reactions have been reported in 4.1% of patients receiving LOQTORZI in combination with cisplatin and gemcitabine, including Grade 2 (0.7%) reactions.

LOQTORZI as a Single-Agent

Infusion-related reactions occurred in 2% of 851 patients receiving LOQTORZI as single agent, including Grade 3 (0.1%) and Grade 2 (0.6%). LOQTORZI was withheld for one Grade 3 infusion related reaction.

8.3. Less Common Clinical Trial Adverse Reactions

The following clinically important adverse reactions were reported in <5% of patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma treated with LOQTORZI in JUPITER-02.

Blood and lymphatic system disorders: immune-mediated thrombocytopenia

Cardiac disorders: myocarditis

Endocrine disorders: hyperthyroidism, thyroiditis

Gastrointestinal disorders: gastritis

Hepatobiliary disorders: hepatitis

Injury, poisoning and procedural complications: infusion related reaction

Metabolism and nutrition disorders: diabetes mellitus

Musculoskeletal and connective tissue disorders: myositis

Nervous system disorders: encephalopathy

Renal and urinary disorders: cystitis noninfective, immune-mediated renal disorder

Respiratory, thoracic and mediastinal disorders: dyspnea, pneumonitis

The following clinically important adverse reactions were reported in <2% of patients with previously treated unresectable or metastatic nasopharyngeal carcinoma treated with LOQTORZI in POLARIS-02.

Blood and lymphatic system disorders: anaemia, thrombocytopenia

Cardiac disorders: myocarditis

Ear and labyrinth disorders: deafness, hypoacusis, tinnitus

Infections and infestations: appendicitis, catheter site infection, conjunctivitis, osteomyelitis, otitis externa, pharyngitis, rhinitis

Metabolism and nutrition disorders: diabetes mellitus, hyponatremia

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

Clinical Trial Findings

Table 5: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Recurrent, Locally Advanced or Metastatic NPC Who Received LOQTORZI in Combination with Cisplatin and Gemcitabine in JUPITER-02

Laboratory Abnormalities*	LOQTORZI Cisplatin/Gemcitabine		Placebo Cisplatin/Gemcitabine	
	All Grades† (%)	Grade 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased hemoglobin	94	50	97	38
Decreased neutrophils	91	58	95	63
Decreased lymphocytes	88	57	88	49
Decreased platelets	71	33	66	31
Chemistry				
Decreased magnesium	78	4.2	77	8
Decreased sodium	63	9	62	6
Increased alanine aminotransferase	58	6	50	3.5
Increased aspartate aminotransferase	58	2.7	53	4.9
Decreased albumin	49	0	48	0
Decreased calcium	45	3.5	46	4.2
Increased lactate dehydrogenase	42	0	35	0
Increased calcium	39	0	35	0.7
Decreased potassium	40	10	39	8
Increased creatinine	39	0.7	41	0
Increased alkaline phosphatase	27	0	27	0
Decreased glucose	23	1.4	16	0

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: LOQTORZI/chemotherapy (range: 139 to 146 patients) and placebo / chemotherapy (range: 136 to 143 patients).

† Graded per NCI CTCAE v5.0

AKP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 6: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with Previously Treated, Unresectable or Metastatic NPC Who Received LOQTORZI in POLARIS-02

	LOQTORZI	
	All Grades (%)[1]	Grades 3 or 4 (%)[1]
Chemistry		
Decreased albumin	38	0.5
Decreased sodium	35	11
Decreased phosphate	32	3.2
Increased aspartate aminotransferase	30	3.8
Decreased calcium	29	0.5
Increased alkaline phosphatase	28	2.2
Increased triglyceride	26	1.1

	LOQTORZI	
	All Grades (%)[1]	**Grades 3 or 4 (%)[1]**
Increased glucose	24	1.1
Increased alanine aminotransferase	23	1.6
Hematology		
Decreased lymphocytes	52	9
Decreased hemoglobin	43	6

[1] Toxicity graded per NCI CTCAE v4.03. The denominator used to calculate the rate varied from 141 to 186 based on the number of patients with a baseline value and at least one post-treatment value.

8.5. Post-Market Adverse Reactions

Blood and lymphatic system disorders: myelosuppression, white blood cell count decreased

Hepatic disorders: liver function abnormal

Immune system disorders: immune-mediated pneumonitis, solid organ transplant rejection

9. Drug Interactions

9.2. Drug Interactions Overview

No formal drug interaction studies have been conducted with LOQTORZI. Since toripalimab is cleared from the circulation through catabolism, metabolic drug-drug interactions are not expected.

The use of systemic corticosteroids or immunosuppressants before starting LOQTORZI should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of LOQTORZI. However, systemic corticosteroids or other immunosuppressants can be used after starting LOQTORZI to treat immune-mediated adverse reactions (see 7. Warnings and Precautions). Corticosteroids can also be used as premedication, when LOQTORZI is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

9.3. Drug-Behaviour Interactions

Interactions with individual behavioural risks have not been established.

9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. 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. Toripalimab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor 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. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

10.2. Pharmacodynamics

The toripalimab exposure-response relationships and time course of pharmacodynamic response are not fully characterized.

10.3. Pharmacokinetics

Toripalimab concentrations increased nonlinearly over the dose range of 0.3 to 10 mg/kg every two weeks (0.1 to 3.3 times the approved recommended 3 mg/kg dosage in a 64 kg patient). Steady state was reached by Week 7. The mean accumulation ratio was approximately 1.4 for maximum concentration (C_{max}) and 1.9 for area under the serum concentration curve (AUC) following multiple doses at the approved recommended dosages of 240 mg Q3W in combination with cisplatin and gemcitabine and 3 mg/kg Q2W as monotherapy.

Table 7: Summary of Toripalimab Pharmacokinetic Parameters

	C_{max} (µg/mL)	T_{max}	$t_{½}$ (days)	$AUC_{0-\tau}$ (h*µg/mL)	CL (mL/h)	Vd,ss (L)
Single Dose						
240 mg Q3W	67.1	NA	10 ± 1.5	13386	14.9	3.7
3 mg/kg Q2W	53.9	NA		8894		
Steady State						
240 mg Q3W	97.6	NA	18 ± 9.4	25555	9.5	4.5
3 mg/kg Q2W	93.7	NA		19644		

Absorption: Toripalimab is administered via the intravenous route and therefore is expected to be immediately and completely bioavailable.

Distribution: The mean volume of distribution at steady state (Vss) of toripalimab was 3.7 L (27%).

Metabolism: Toripalimab is expected to be metabolized into small peptides by catabolic pathways.

Elimination: The mean clearance (CL) was 14.9 mL/h (31%) after the first dose and 9.5 mL/h (36%) at steady state. The mean terminal half-life ($t_{1/2}$) (± standard deviation) was 10 ± 1.5 days after the first dose and 18 ± 9.4 days at steady state.

Special Populations and Conditions

No clinically significant differences in the pharmacokinetics were observed based on age (21 to 85 years), body weight (32 to 164 kg), sex, race (White and Asian), concomitant chemotherapy, mild renal impairment (creatinine clearance [CLcr] 60 to 89 mL/min), mild hepatic impairment (total bilirubin > 1 to 1.5 times ULN with any AST or total bilirubin ≤ ULN with AST > ULN), tumor burden and primary cancer.

The effect of moderate (total bilirubin >1.5 to 3 times ULN and any AST) or severe (total bilirubin > 3 times ULN and any AST) hepatic impairment or of moderate (CLcr 30 to 59 mL/min) or severe (CLcr 15 to 29 mL/min) renal impairment on the pharmacokinetics of toripalimab has not been studied.

10.4. Immunogenicity

As with all therapeutic proteins there is the potential for immunogenicity. The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of LOQTORZI or of other toripalimab products.

Of the 146 evaluable patients in JUPITER-02 with nasopharyngeal cancer who received LOQTORZI 240 mg every 3 weeks for a median duration of 15.1 months, in combination with gemcitabine and cisplatin, 3.4% tested positive for treatment-emergent ADA. Of the 190 evaluable patients in study POLARIS-02 with nasopharyngeal cancer who received LOQTORZI 3 mg/kg every 2 weeks for a median duration of 3.3 months, 3.7% of patients developed treatment-emergent ADA and 1.6% developed neutralizing antibodies.

Due to the low incidence of ADA and neutralizing antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, or effectiveness of LOQTORZI is unknown.

11. Storage, Stability, and Disposal

Store vials refrigerated at 2°C to 8°C in original carton to protect from light. Do not freeze. Do not shake.

Storage of Diluted Solution

LOQTORZI is preservative free. If the diluted solution is not administered immediately, store either:

- At room temperature, 20°C to 25°C for no more than 8 hours from the time of dilution to the completion of the infusion. Discard diluted solution stored at room temperature after 8 hours.

Or

- Refrigerated at 2°C to 8°C for no more than 24 hours from the time of dilution to the completion of the infusion. Discard the refrigerated diluted solution after 24 hours.

Do not freeze.

12. Special Handling Instructions

None.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: Toripalimab

Chemical name: Immunoglobulin G4, anti- (human programmed cell death protein 1) (human monoclonal JS001 γ4-chain), disulfide with human monoclonal JS001 κ-chain, dimer

Molecular formula and molecular mass: $C_{6548}H_{10104}N_{1728}O_{2054}S_{44}$, 147 kDa

Structural formula: Toripalimab is comprised of two identical heavy chains and two identical light chains joined by disulfide bonds. Each light chain contains 219 amino acids, and each heavy chain has 452 amino acids.

Physicochemical properties: Toripalimab has a theoretical extinction coefficient of 1.416 (mL/mg) cm^{-1}. The isoelectric point (pI) of the main peak is 6.8.

Product Characteristics:

Toripalimab is a humanized IgG4κ (gamma 4, kappa) monoclonal antibody produced in a stably transfected Chinese hamster ovary (CHO) mammalian cell expression system. No animal-sourced materials are used to manufacture the drug substance.

14. Clinical Trials

14.1. Clinical Trials by Indication

First-line Treatment of Metastatic or Recurrent, Locally Advanced Nasopharyngeal Carcinoma (NPC)

Study Demographics and Trial Design

Table 8: Summary of patient demographics for clinical trials of LOQTORZI as first-line treatment of metastatic or recurrent, locally advanced NPC with cisplatin and gemcitabine

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
JUPITER-02	Randomized, multicenter, single region, double-blind, placebo-controlled	LOQTORZI 240 mg IV every 3 weeks with cisplatin 80 mg/m^2 on Day 1 every 3 weeks, gemcitabine 1000 mg/m^2 on Days 1 and 8 for up to 6 cycles, followed by LOQTORZI 240 mg once every 3 weeks Or	146	46 years (19-72)	M: 124 (85%) F: 22 (15%)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
		Placebo IV every 3 weeks with cisplatin 80 mg/m^2 on Day 1 every 3 weeks, gemcitabine 1000 mg/m^2 on Days 1 and 8 for up to 6 cycles, followed by LOQTORZI 240 mg once every 3 weeks	143	51 years (21-72)	M: 116 (81%) F: 27 (19%)

The efficacy of LOQTORZI in combination with cisplatin and gemcitabine was investigated in JUPITER-02, a randomized, multicenter, single region, double-blind, placebo-controlled trial in 289 patients with metastatic or recurrent, locally advanced NPC who had not received previous systemic chemotherapy for recurrent or metastatic disease. Patients with recurrent NPC after treatment with curative intent were required to have an interval of at least 6 months between the last dose of radiotherapy or chemotherapy and recurrence. Patients with autoimmune disease, other than stable hypothyroidism or Type I diabetes, and patients who required systemic immunosuppression were ineligible.

Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 versus 1) and disease stage (recurrent versus metastatic). Patients were randomized (1:1) to receive one of the following treatments:

- LOQTORZI 240 mg intravenously every 3 weeks in combination with cisplatin 80 mg/m^2 on Day 1 every 3 weeks and gemcitabine 1000 mg/m^2 on Days 1 and 8 for up to 6 cycles, followed by LOQTORZI 240 mg once every 3 weeks, or
- Placebo intravenously every 3 weeks in combination with cisplatin 80 mg/m^2 on Day 1 every 3 weeks and gemcitabine 1000 mg/m^2 on Days 1 and 8 for up to 6 cycles, followed by placebo once every 3 weeks.

Treatment with LOQTORZI or placebo continued until disease progression per RECIST v1.1, unacceptable toxicity, or a maximum of 2 years. Administration of LOQTORZI was permitted beyond radiographic progression if the patient was deriving benefit as assessed by the investigator. Tumour assessments were performed every 6 weeks for the first 12 months and every 9 weeks thereafter. The main efficacy outcome measure was Blinded Independent Review Committee (BIRC)-assessed progression-free survival (PFS) according to RECIST v1.1. Additional efficacy outcome measures include BIRC-assessed objective response rate (ORR) and overall survival (OS).

The study population characteristics were: median age of 48 years (range: 19 to 72), 4.8% age 65 or older, 83% male, 100% Asian, and ECOG PS of 0 (57%) or 1 (43%). Eighty-six percent of patients had metastatic disease at study entry. Histological subtypes of NPC included 98% non-keratinizing, 1% keratinizing squamous cell carcinoma, and 1% did not have the subtype identified.

Efficacy results for JUPITER-02 are summarized in Table 9, Figure 1 and Figure 2.

Table 9: Efficacy Results for JUPITER-02

Endpoints	LOQTORZI + cisplatin and gemcitabine N =146	Placebo + cisplatin and gemcitabine N =143
BIRC-assessed Progression-free Survival (PFS)[1]		
Number of events, n (%)	49 (33.6)	79 (55.2)
Median, months (95% CI)	11.7 (11.0, NE)	8.0 (7.0, 9.5)
Hazard ratio (95% CI)[2]	0.52 (0.36, 0.74)	
p-value[3]	0.0003	
BIRC-assessed Objective Response Rate (ORR)[1]		
Objective response rate, % (95% CI)[4]	77.4 (69.8, 83.9)	66.4 (58.1, 74.1)
Complete response rate (%)	19.2	11.2
Partial response rate (%)	58.2	55.2
p-value[5]	0.0335	
Overall Survival (OS)[1]		
Number of deaths, n (%)	57 (39.0)	76 (53.1)
Median, months (95% CI)	NE (38.7, NE)	33.7 (27.0, 44.2)
Hazard ratio (95% CI)[2]	0.63 (0.45, 0.89)	
p-value[3]	0.0083	

[1]PFS and ORR were based on the data with median follow-up of 10.7 months (pre-specified interim analysis with data cut-off date of 30 May 2020). OS was based on the data with median follow-up of 36.0 months (final analysis with data cut-off date of 18 Nov 2022).

[2]The hazard ratio and its confidence interval were computed using a stratified Cox proportional-hazards model.

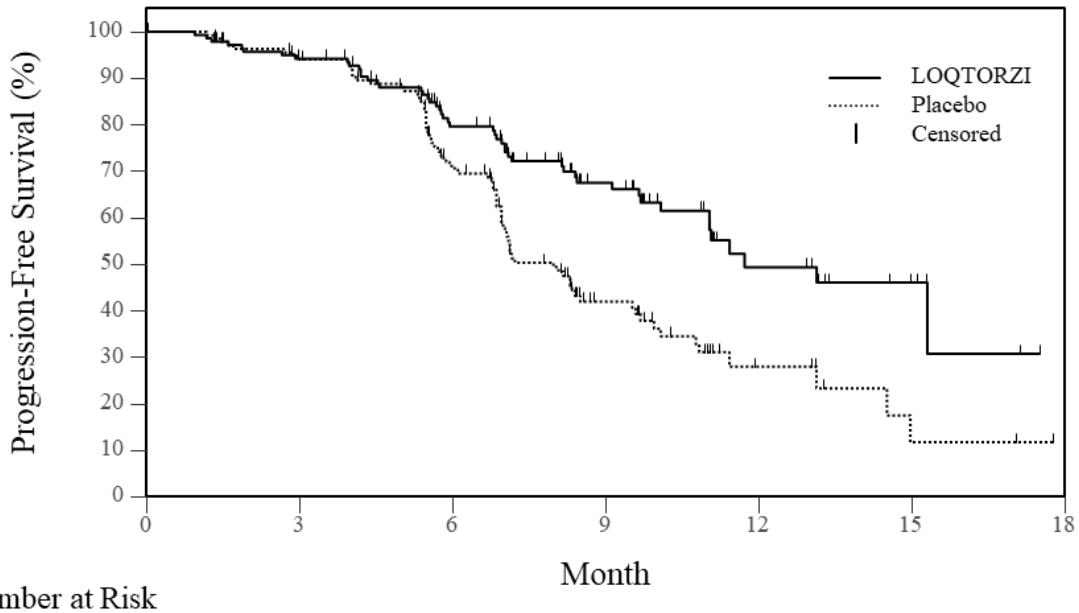
[3] Two-sided p-value, based on the stratified log-rank test.

[4] The confidence interval for ORR for each group was computed using the Clopper-Pearson method.

[5] Two-sided p-value, based on the Cochran-Mantel-Haenszel test.

BIRC=blinded independent review committee; CI= confidence interval; NE=Not estimable

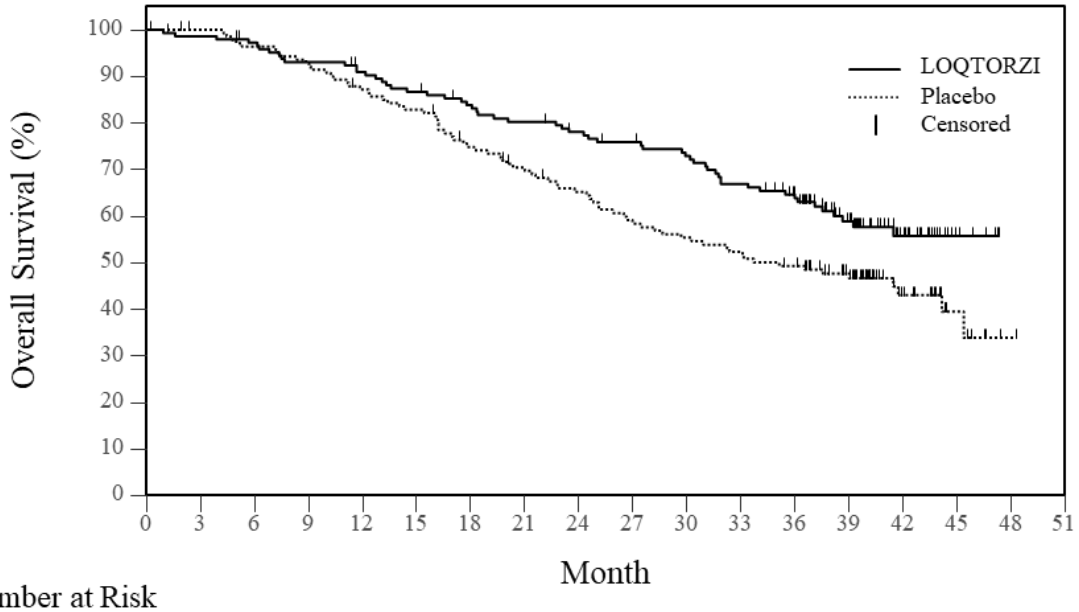
Figure 1: Kaplan-Meier Curves of Progression Free Survival for JUPITER-02



Number at Risk

LOQTORZI	146	125	91	50	17	5	0
Placebo	143	126	85	32	8	2	0

Figure 2: Kaplan-Meier Curves of Overall Survival for JUPITER-02



Number at Risk

LOQTORZI	146	143	139	133	128	122	116	111	106	102	97	89	79	51	25	6	0	0
Placebo	143	140	135	130	121	115	102	94	86	78	73	69	64	49	21	7	1	0

Previously Treated Unresectable or Metastatic NPC

Study Demographics and Trial Design

Table 10: Summary of patient demographics for clinical trials of LOQTORZI as a single agent in patients with previously treated unresectable or metastatic NPC

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
POLARIS-02	Open-label, multicenter, multicohort trial	LOQTORZI 3 mg/kg IV every 2 weeks	190 (safety set)	46 years (22 - 71)	M: 158 (83%) F: 32 (17%)

The efficacy of LOQTORZI was investigated in POLARIS-02, an open-label, multi-centre, multicohort trial conducted in a single country. The trial included a total of 172 patients with unresectable or metastatic NPC who had received prior platinum-based chemotherapy for treatment of recurrent or metastatic NPC or had disease progression within 6 months of completion of platinum-based chemotherapy administered as neoadjuvant, adjuvant, or definitive chemoradiation treatment for locally advanced disease. Key exclusion criteria included active autoimmune disease or other medical conditions requiring immunosuppressive therapy. Patients received LOQTORZI 3 mg/kg intravenously every 2 weeks until disease progression per RECIST v1.1 or unacceptable toxicity. Tumour response assessments were performed every 8 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were confirmed ORR and duration of response (DOR) as assessed by a Blinded Independent Review Committee (BIRC) using RECIST v1.1.

The median age was 45 years (range: 22 to 68), 4.1% age 65 or older, 83% male, 100% Asian, and ECOGPS of 0 (37%). Patients had received a median of 2 prior systemic therapies for recurrent/metastatic disease (range: 1-13). Ninety-nine percent of patients had metastatic disease, 95% had non-keratinizing NPC, 2.9% had keratinizing squamous cell carcinoma and 1.7% did not have the subtype identified.

Efficacy results are summarised in Table 11 below.

Table 11: Efficacy Results for POLARIS-02

Endpoint	LOQTORZI (N=172)
BIRC-Assessed Objective Response Rate[1]	
Objective Response Rate, % (95% CI)	21 (15, 28)
Complete Response Rate, %	2.3
Partial Response Rate, %	19
BIRC-Assessed Duration of Response (DOR)	(N = 36)
Median, months (95% CI)	14.9 (10.3, NE)

CI=confidence interval. n=number. NE=not estimable.

[1] Confirmed objective response rate assessed by BIRC

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology:

Single- dose toxicity

The maximal tolerated dose (MTD) was observed at 203 mg/kg for toripalimab, when administered once via 30-minute IV infusion to male and female cynomolgus monkeys in single dose, exploratory dose range finding and TK study.

Repeat- dose toxicity

Repeat-dose intravenous toxicity studies were conducted for toripalimab in cynomolgus monkeys over periods of 4 and 26 weeks to evaluate its safety and potential adverse effects.

In 4- week study, following multiple toripalimab IV infusions over 30 minutes, every two weeks for four weeks (total of three doses) at doses of 1, 10, 100 mg/kg in both male and female cynomolgus monkeys, there were no toripalimab-related adverse effects on in-life parameters, ophthalmic examination findings, safety pharmacology, clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis), immunologic (immune-phenotype and cytokine analysis), macroscopic and microscopic findings. The No-Observed-Adverse-Effect Level (NOAEL) for this study was determined to be 100 mg/kg. Exposure was 42 times greater in males and 38 times greater in females compared to the human exposure observed at the recommended clinical dose.

In 26- week study, following IV infusions once a week over 26 weeks (total of 27 doses) of toripalimab at doses of 10, 30, 100 mg/kg to male and female cynomolgus monkeys, there were no toripalimab- related adverse effects on in-life parameters, ophthalmic examination findings, safety pharmacology, clinical pathology (clinical chemistry, hematology, coagulation, urinalysis and analysis and fecal occult blood test), immune function parameters, hormone analysis, macroscopic and microscopic findings. The No-Observed-Adverse-Effect Level (NOAEL) for this study was considered 100 mg/kg. Exposure was 21 times greater in males and 30 times greater in females compared to the human exposure observed at the recommended clinical dose.

Genotoxicity:

No studies have been performed to evaluate the genotoxic potential of toripalimab.

Carcinogenicity:

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

Reproductive and Developmental Toxicology:

Animal fertility studies have not been conducted with toripalimab. In 4-week and 26-week repeat-dose toxicology studies in a limited number of sexually mature cynomolgus monkeys, there were no adverse or notable effects in the male and female reproductive organs.

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, toripalimab 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 response 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

PrLOQTORZI™

Toripalimab for Injection

This Patient Medication Information is written for the person who will be taking **LOQTORZI**. 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 more questions about this medication or want more information about **LOQTORZI**, talk to a healthcare professional.

Serious warnings and precautions box

- LOQTORZI can cause severe or fatal reactions of the immune system attacking any organ or tissue, including the lungs, liver, kidneys, heart, skin and bowels.
- LOQTORZI can cause severe or life-threatening infusion reactions including allergic reactions and anaphylaxis.
- Fatal and other serious complications can happen in patients who have a stem cell transplant (HSCT) before or after being treated with medications similar to LOQTORZI.

What LOQTORZI is used for:

- LOQTORZI is used to treat patients with nasopharyngeal carcinoma (NPC), a cancer of the nasopharynx (which is located behind the nose and above the back of the throat).

LOQTORZI may be used together with other medicines called cisplatin and gemcitabine, as your first treatment when your NPC has spread to other parts of your body or has returned in nearby tissues.

LOQTORZI may be used alone to treat your NPC when:

- it has returned and cannot be removed with surgery or
- it has spread (metastatic), and
- you received chemotherapy that contains platinum, and it did not work or is no longer working.

How LOQTORZI works:

LOQTORZI works by helping your immune system fight your cancer.

The ingredients in LOQTORZI are:

Medicinal ingredients: toripalimab

Non-medicinal ingredients: citric acid monohydrate, mannitol, polysorbate 80, sodium chloride, sodium citrate and Water for Injection

LOQTORZI comes in the following dosage forms:

Concentrate for solution for intravenous infusion, 40 mg/mL

Do not use LOQTORZI if:

- You are allergic to toripalimab or to any other ingredients in LOQTORZI. Talk to your healthcare professional if you are not sure.

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

- You have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- You had or will have a stem cell transplant from a donor (allogeneic)
- You have received an organ transplant
- You have received radiation treatment to your chest area
- You have had a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- You are breastfeeding

Other warnings you should know about:

Pregnancy

- You should not use LOQTORZI if you are pregnant. If you are pregnant, think you may be pregnant or are planning to have a baby, talk to your healthcare professional before taking this medicine.
- LOQTORZI can harm your unborn baby.
- If you are a woman who could become pregnant, you should use an effective method of birth control during your treatment and for at least 4 months after the last dose of LOQTORZI.

Breastfeeding

- Tell your healthcare professional if you are breastfeeding or plan to breastfeed.
- Do not breastfeed during treatment and for at least 4 months after the last dose of LOQTORZI. It is not known if LOQTORZI passes into your breastmilk.

LOQTORZI can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after treatment has ended.

Problems can happen in any organ or tissue. Call or see your healthcare professional right away for any new or worsening signs or symptoms, which may include, but are not limited to:

- chest pain, irregular heartbeat, shortness of breath, swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior,
- stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

See the table "**Serious side effects and what to do about them**" for more information.

Rejection of a transplanted organ. Your healthcare professional should tell you what signs and symptoms you should report and monitor, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with LOQTORZI. Your healthcare professional will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare professional will check you for these problems during treatment with LOQTORZI. They may treat you with corticosteroid or hormone replacement medicines. They may also need to delay or completely stop treatment with LOQTORZI if you have severe side effects.

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

We do not know if LOQTORZI can interact with other drugs, food or supplements.

How to take LOQTORZI:

- LOQTORZI will be given to you by a healthcare professional in a hospital or a clinic.
- Your healthcare professional will give you LOQTORZI into your vein through an intravenous (IV) line over 30 or 60 minutes.
- Your healthcare professional will test your blood to check for certain side effects.

Usual dose:

LOQTORZI in combination with cisplatin and gemcitabine for first-line treatment of NPC

The recommended dose is 240 mg of LOQTORZI every 3 weeks in combination with cisplatin and gemcitabine for up to 6 cycles, followed by 240 mg of LOQTORZI every 3 weeks given on its own.

LOQTORZI for treatment of NPC previously treated with platinum chemotherapy

The recommended dose is 3 mg of LOQTORZI for every kg of body weight, every 2 weeks.

Your healthcare professional will decide how many treatments you need.

Overdose:

If you think you, or a person you are caring for, have taken too much LOQTORZI, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X 91-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

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

Possible side effects from using LOQTORZI:

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

- Burning or feeling of pins and needles in feet and toes
- Constipation
- Cough
- Decreased appetite
- Diarrhea
- Diabetes
- Dizziness
- Ear problems
- Feeling generally unwell
- Fever
- Headache
- Low levels of thyroid hormone
- Muscle and bone pain
- Nausea
- Nose bleeds
- Rash
- Sleep problems
- Tiredness
- Upper or lower respiratory infection
- Weight loss
- Vomiting

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	
Common			
Hormone gland problems: headaches that will not go away or unusual headaches, urinating more often than usual, eye sensitivity to light, hair loss, eye problems, feeling cold, rapid heartbeat, constipation, increased sweating, your voice gets deeper, extreme tiredness, dizziness or fainting, weight gain or weight loss, feeling more hungry or thirsty than usual, change in mood or behavior, such as decreased sex drive, irritability, or forgetfulness		✓	

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Intestinal problems: diarrhea (loose stools) or more frequent bowel movements than usual, stools that are black, tarry, sticky, or have blood or mucus, severe stomach-area (abdomen) pain or tenderness or swelling		✓	
Lung problems: Inflammation of the lungs (pneumonitis) which can cause shortness of breath, chest pain, or coughing		✓	
Skin problems: rash, itching, painful sores or ulcers in your mouth or in your nose, throat, or genital area, skin blistering or peeling, fever or flu-like symptoms, swollen lymph nodes, hair loss		✓	
Uncommon			
Cardiac (heart) problems: chest pain, irregular heartbeat, shortness of breath, swelling of ankles, high or low blood pressure, blood clots			✓
Eye problems: double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight		✓	
Infusion reactions: chills or shaking, dizziness, itching or rash, feeling like passing out, flushing, fever, shortness of breath or wheezing, back pain			✓
Kidney problems: decrease in your amount of urine, swelling of your ankles, blood in your urine, loss of appetite		✓	
Liver problems: yellowing of skin or the whites of your eyes, dark urine (tea colored), severe nausea or vomiting, bleeding or bruising more easily than normal, pain on the right side of your stomach-area (abdomen)		✓	
Nervous system problems: confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, muscle weakness, tingling or numbness of the arms or legs, sudden back pain, loss of reflexes		✓	

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

Storage:

LOQTORZI will be kept refrigerated (2°C to 8°C) at the hospital or clinic. You will not bring it home.

If you want more information about LOQTORZI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (Drug Product Database: Access the database; the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto Ontario M9L 1T9.

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