# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

LOQTORZI 240 mg concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of concentrate for solution for infusion contains 240 mg of toripalimab.

Each mL of concentrate for solution for infusion contains 40 mg of toripalimab.

Toripalimab is an immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb), produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to slightly yellow solution essentially free from visible particles. The concentrate for solution has a pH of 5.5 – 6.5 and an osmolality of 260 340 mOsmol/kg.

## 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

LOQTORZI, in combination with cisplatin and gemcitabine, is indicated for the first line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.

LOQTORZI, in combination with cisplatin and paclitaxel, is indicated for the first line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

## 4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Posology
The recommended dosing regimen of LOQTORZI is 240 mg every 3 weeks (Q3W) as an intravenous infusion over 60 minutes for the first infusion. If no significant infusion-related reactions occurred during the first infusion, the subsequent infusions may be administered over 30 minutes.

Treatment should continue until disease progression, unacceptable toxicity or up to a maximum duration of 24 months.

*Dose modifications*
Recommended modifications to manage adverse reaction are provided in Table 1.

See the Summary of Product Characteristics (SmPC) of other products to be used in combination with LOQTORZI.

**Table 1: Recommended treatment modifications for LOQTORZI**

| **Adverse reaction** | **Severity[1]** | **Treatment modification** |
|---|---|---|
| **Immune-related adverse reactions** | | |
| Pneumonitis | Grade 2 | Withhold[2] |
| | Grades 3 or 4 | Permanently discontinue |
| Diarrhoea/colitis | Grade 2 or 3 | Withhold[2] |
| | Grade 4 | Permanently discontinue |
| Hepatitis | Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) increases to more than 3 and up to 5 times the upper limit of normal (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 5 times ULN or Total bilirubin increases to more than 3 times ULN | Permanently discontinue |
| Endocrinopathies | Grade 2-4 adrenal insufficiency or hypophysitis | Withhold until clinically stable on hormone replacement therapy[2] |
| | Grades 3 or 4 hyperthyroidism or thyroiditis | Withhold until clinically stable on appropriate medical management |
| | Grade 3-4 diabetes mellitus | Withhold until clinically stable on antihyperglycemic (insulin) therapy |
| | Grade 1-4 hypothyroidism | Manage with hormone replacement therapy without toripalimab interruption |
| Nephritis with renal dysfunction | Grade 2-3 increased blood creatinine | Withhold[2] |
| | Grade 4 increased blood creatinine | Permanently discontinue |

| Adverse reaction | Severity[1] | Treatment modification |
|---|---|---|
| **Immune-related adverse reactions** | | |
| Exfoliative dermatologic conditions | Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug rash with eosinophilia and systemic symptoms (DRESS) | Withhold[2] |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue |
| Myocarditis | Grades 2, 3, or 4 | Permanently discontinue |
| Myositis | Grade 2-3 | Withhold or permanently discontinue depending on severity[2] |
| | Grade 4 | Permanently discontinue |
| Other adverse reactions (including but not limited to neurologic toxicities, pancreatitis, iritis, uveitis, immune-related cystitis, and immune-related inflammatory arthritis) | Grade 2-3 | Withhold or permanently discontinue depending on type and severity[2] |
| | Grade 4 | Permanently discontinue |
| **Infusion-related reactions** | | |
| Infusion-related reactions | Grade 1 or 2 | Interrupt or slow the rate of infusion |
| | Grade 3 or 4 | Stop infusion. Permanently discontinue |

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

[2] Resume LOQTORZI in patients with resolution to Grade 0-1 after corticosteroid taper. Permanently discontinue if not less than Grade 1 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 cannot be clinically stabilized on hormone replacement therapy.

*Patient card*
All prescribers of LOQTORZI should inform patients about the patient card, explaining what to do should they experience any symptom of immune-related adverse reactions. The physician will provide the patient card to each patient.

*Special populations*

*Elderly*
No dose adjustment is recommended for patients who are aged 65 years or over (see section 5.2).

*Renal impairment*
No dose adjustment is needed for patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment for dosing recommendations (see section 5.2).

*Hepatic impairment*
No dose adjustment is recommended for patients with mild hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations (see section 5.2).

*Paediatric population*
The safety and efficacy of LOQTORZI in children and adolescents aged under 18 years have not been established. No data are available.

Method of administration
LOQTORZI is for intravenous use only and must be administered by infusion. The first infusion should be administered over 60 minutes via an infusion pump through an in-line filter (0.2 micron or 0.22 micron pore size). If no infusion-related reactions occurred during the first infusion, subsequent infusions may be administered over 30 minutes.

Do not co-administer other medicinal products through the same infusion line.

When administered on the same day as chemotherapy, LOQTORZI should be administered prior to chemotherapy.

For instructions on dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-related adverse reactions
Immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including toripalimab. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-related adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. Important immune-related adverse reactions listed in this section are not inclusive of all possible severe and fatal immune-related reactions.

Early identification and management of immune-related adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Patients should be monitored closely for symptoms and signs of immune-related adverse reactions. Clinical chemistries including liver enzymes, creatinine, and thyroid function should be evaluated at baseline and periodically during treatment. In cases of suspected immune-related adverse reactions, appropriate workup should be initiated to exclude alternative aetiologies, including infection. Medical management should be instituted promptly, including specialty consultation as appropriate.

Toripalimab should be withheld or permanently discontinued depending on the type and severity of the adverse reaction (see section 4.2). If treatment with toripalimab should be withheld or permanently discontinued, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. If myocarditis is suspected, initiate high-dose steroids (e.g., methylprednisolone 1 g/day intravenously for 3–5 days). Upon improvement to Grade 1 or less, initiate corticosteroid taper. Consider administration of other systemic immunosuppressants in patients whose immune-related adverse reactions are not controlled with corticosteroid therapy. Hormone replacement therapy for endocrinopathies should be instituted as warranted.

Treatment with toripalimab may be restarted within 12 weeks after last dose of toripalimab if the adverse reaction recovers to Grade ≤1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Treatment with toripalimab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

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

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

*Immune-related pneumonitis*
Toripalimab can cause immune-related pneumonitis (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with toripalimab treatment modifications and corticosteroids, as clinically indicated (see section 4.2 and directions for corticosteroid treatment in section 4.4 above).

*Immune-related colitis*
Toripalimab can cause immune-related colitis, which may present with diarrhoea (see section 4.8). Patients should be monitored for signs and symptoms of colitis and managed with toripalimab treatment modifications, anti-diarrhoeal agents and corticosteroids, as clinically indicated (see section 4.2 and directions for corticosteroid treatment in section 4.4 above). In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative aetiologies. Cytomegalovirus (CMV) infection/reactivation has been reported in patients receiving other PD-1/PD-L1 blocking antibodies with corticosteroid-refractory immune-related colitis.

*Hepatotoxicity and immune-related hepatitis*
Toripalimab can cause immune-related hepatitis (see section 4.8). Patients should be monitored for changes in liver function periodically and as indicated, based on clinical evaluation. Patients should be managed with toripalimab treatment modifications (see sections 4.2) and corticosteroids, as clinically indicated (see directions for corticosteroid treatment in section 4.4 above).

*Immune-related endocrinopathies*

*Adrenal insufficiency*
Toripalimab can cause primary or secondary adrenal insufficiency (see section 4.8). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For Grade 2-4 adrenal insufficiency, toripalimab should be withheld until patient is clinically stable on physiologic hormone replacement therapy (see section 4.2).

*Hypophysitis*
Toripalimab can cause immune-related hypophysitis (see section 4.8). Hypophysitis can present with acute symptoms associated with mass effects such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Patients should be monitored for signs and symptoms of hypophysitis. For Grade 2-4 hypophysitis, toripalimab should be withheld until patient is clinically stable on physiologic hormone replacement therapy (see section 4.2).

*Thyroid disorders*
Toripalimab can cause immune-related thyroid disorders (see section 4.8). Patients should be monitored for signs and symptoms of thyroid disorders prior to and periodically during treatment, and as indicated based on clinical evaluation.

Hypothyroidism may be managed with replacement therapy without toripalimab interruption and without corticosteroids (see section 4.2). Thyroiditis can present with or without concomitant thyroid dysfunction. Thyroiditis and hyperthyroidism may be managed symptomatically which may include thyroid suppression and/or corticosteroid therapy for acute thyroiditis. Toripalimab should be withheld for Grade $\geq 3$ thyroiditis or hyperthyroidism until controlled with medical management and patient is clinically stable. Patients should be monitored for hypothyroidism that may follow hyperthyroidism or thyroiditis. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

*Type 1 diabetes mellitus, which can present with diabetic ketoacidosis*
Toripalimab can cause immune-related type I diabetes mellitus (see section 4.8). Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin treatment should be initiated for type I diabetes mellitus as clinically indicated and toripalimab should be withheld in patients with Grade $\geq 3$ hyperglycaemia. Treatment with toripalimab may be resumed when diabetes is controlled with medical management including insulin therapy and the patient is clinically stable (see section 4.2).

*Immune-related nephritis*
Toripalimab can cause immune-related nephritis (see section 4.8). Patients should be monitored for changes in renal function and other causes of renal dysfunction excluded. Toripalimab treatment should be modified (see section 4.2) and corticosteroids instituted, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 above).

*Immune-related skin adverse reactions*
Toripalimab can cause immune-related rash or dermatitis (see section 4.8). Exfoliative dermatitis, including Stevens-Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has been reported in patients receiving PD-1/PD-L1 blocking antibodies.
Patients should be monitored for skin adverse reactions and managed with toripalimab treatment modifications (see section 4.2) and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 above).

*Immune-related myocarditis*
Toripalimab can cause immune-related myocarditis (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. If myocarditis is suspected, high-dose steroids should be promptly initiated and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be started. Patients should be managed with toripalimab treatment modifications (see section 4.2) and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 above). Consider addition of immunosuppressants if the event does not improve within 48 hours after start of corticosteroid therapy.

*Immune-related myositis*
Toripalimab can cause immune-related myositis (see section 4.8). Patients should be monitored for signs and symptoms of myositis. For suspected myositis, monitor serial aldolase and creatine kinase and consider diagnostic workup according to current clinical guidelines. Patients should be managed with toripalimab treatment modifications (see section 4.2) and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 above).

*Other immune-related adverse reactions*
Given the mechanism of action of toripalimab, other potential immune-related adverse reactions may occur, including potentially serious events (e.g., encephalitis, demyelinating neuropathy [including Guillain Barré syndrome] myasthenic syndrome, sarcoidosis, vasculitis, rhabdomyolysis). Clinically significant immune-related adverse reactions reported in less than 1 % of patients treated with toripalimab in the clinical studies include pancreatitis, iritis, uveitis, immune-related inflammatory arthritis, and immune-related cystitis. Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with toripalimab treatment modifications (see section 4.2) and corticosteroids, as clinically indicated (see instructions for corticosteroid treatment in section 4.4 above).

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

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. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Infusion-related reactions
Toripalimab can cause severe and potentially life-threatening infusion-related reactions (see section 4.8). Patients should be monitored for signs and symptoms of infusion-related reactions. Patients should be managed with toripalimab treatment modifications and supportive care, as clinically indicated (see section 4.2). For patients with infusion related reactions, pre-medications with antipyretics and antihistamines to mitigate the risk of subsequent infusion reactions may be considered.

Patients excluded from clinical studies

Patients with active infections (active tuberculosis or hepatitis B or C or HIV infection), an immunocompromised state (systemic corticosteroids > 10 mg daily prednisone equivalents within 2 weeks of randomisation), active, systemic autoimmune diseases (except for controlled hypothyroidism or diabetes mellitus), active or untreated central nervous system metastases, eastern cooperative oncology group (ECOG) performance status (PS) ≥ 2, or a history of interstitial lung disease were not eligible for enrolment in clinical studies of toripalimab. There is limited information in patients with severe renal or moderate to severe hepatic impairment (see section 5.2).

In the absence of data, toripalimab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Excipient with known effect
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed. Since toripalimab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected. Toripalimab is not a substrate for cytochrome P450 or active substance transporters. Toripalimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of toripalimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies.

The use of systemic corticosteroids or immunosuppressants before starting toripalimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of toripalimab. However, systemic corticosteroids or other immunosuppressants can be used after starting toripalimab to treat immune-related adverse reactions (see section 4.4). Corticosteroids can also be used as premedication, when toripalimab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

## 4.6 Pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should use effective contraception during treatment with toripalimab and for at least 4 months after the last dose of toripalimab.

Pregnancy
There are no data on the use of toripalimab in pregnant women. Animal studies have not been conducted with toripalimab; however, animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-related rejection of the developing foetus and result in foetal death (see section 5.3). Human immunoglobulin G4 (IgG4) is known to cross the placental barrier; therefore, toripalimab can potentially be transmitted from the mother to the developing foetus. Toripalimab should not be used during pregnancy or in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Breast-feeding
It is unknown whether toripalimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; a risk to the breast-feeding newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from toripalimab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
If a woman chooses to be treated with toripalimab, she should be instructed not to breast-feed while receiving toripalimab and for at least 4 months after the last dose of toripalimab.

Fertility
Studies to evaluate the effect of toripalimab on fertility have not been performed (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Toripalimab has minor influence on the ability to drive and use machines. In some patients, dizziness and fatigue have been reported following administration of toripalimab (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

*Toripalimab in combination with platinum containing chemotherapy (see section 4.2)*

The safety of toripalimab in combination with platinum containing chemotherapy has been evaluated in 403 patients with NPC or oesophageal squamous cell carcinoma (OSCC) receiving 240 mg toripalimab every 3 weeks in JUPITER-02 or JUPITER-06. The median duration of treatment in these patients was 6.5 months (range 1 day-2.1 years). The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. In this patient population, the most frequent adverse reactions were anaemia (44.9%), leukopenia (41.7%), neutropenia (39.0%), thrombocytopenia (30.3%), nausea (29.8%), vomiting (27.3%), decreased appetite (23.8%), rash (23.8%), fatigue (23.6%), liver function test abnormal (22.3%), hypothyroidism (18.4%), constipation (16.6%), neuropathy (15.1%), colitis (14.1), pyrexia (13.6%), cough (11.4%), pruritus (11.4%), creatinine renal clearance decreased (11.2%), and hyponatraemia (10.2%). Incidences of grades 3-5 adverse reactions in patients with NPC were 81.5% for toripalimab combination therapy and 83.9% for chemotherapy alone and in patients with OSCC were 24.9% for toripalimab combination therapy and 13.6% for chemotherapy alone.

*Tabulated list of adverse reactions*

Adverse reactions observed in clinical studies of toripalimab as monotherapy or in combination with chemotherapy are listed in Table 2. Adverse reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 includes only treatment related adverse drug reactions. The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than the medicinal product such as the disease, other medicines or unrelated causes. Adverse reactions reported in clinical studies are listed by system organ class and by frequency.

The safety data is based on 1 514 patients exposed to toripalimab (of which 1 100 patients were exposed to toripalimab monotherapy and 514 patients in combination with chemotherapy) with a mean (range 0.03 months to 35.9 months) duration of exposure to toripalimab of 7.0 months and a median duration of exposure of 3.7 months (interquartile range 8.7 months) in 15 Phase 1, 2 or 3 clinical studies. See Section 5.1 for information on the demographics and baseline characteristics of participants in the main clinical studies.

When toripalimab is administered in combination with chemotherapy, refer to the SmPCs for the respective combination therapy components prior to initiation of treatment.

**Table 2: Adverse reactions in patients treated with toripalimab**

| | |
|---|---|
| **Infections and infestations** | |
| Very common | upper respiratory tract infection |
| Common | pneumonia, urinary tract infection, infection (not specified by site or pathogen), ear infections[1], dental and oral soft tissue infections[2], herpes simplex/herpes zoster infection |
| Uncommon | conjunctivitis, gingivitis, skin and subcutaneous tissue infections[3], skin infections, bacteraemia, toe infection, paronychia/dermatophytosis of nail, osteomyelitis, pulmonary tuberculosis |
| Rare | diverticulitis, hepatitis B reactivation, muscle abscess, urosepsis |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | |
| Common | tumour pain |
| Uncommon | tumour haemorrhage, tumour rupture |
| Rare | myelodysplastic syndrome |
| **Blood and lymphatic system disorders** | |
| Very common | anaemia, leukopenia, neutropenia, thrombocytopenia |
| Common | leukocytosis, neutrophilia, lymphopenia |
| Uncommon | coagulopathy, bone marrow failure, myelosuppression |
| Rare | eosinopenia, pancytopenia |
| **Immune system disorders** | |
| Uncommon | hypersensitivity/serum sickness |
| **Endocrine disorders** | |
| Very common | hypothyroidism |
| Common | hyperthyroidism |
| Uncommon | thyroiditis, adrenal insufficiency/cortisol decreased, thyroid disorder (excluding hypothyroidism and hyperthyroidism), hypophysitis/empty sella syndrome |
| Rare | hyperparathyroidism, hypopituitarism |
| **Metabolism and nutrition disorders** | |
| Very common | decreased appetite, hyponatraemia, weight decreased, hypoproteinaemia, hyperglycaemia, hypokalaemia, hyperuricaemia/gout |
| Common | hypochloraemia, hypomagnesaemia, hypocalcaemia, hypophosphataemia, hyperkalaemia, hypercalcaemia, hypoglycaemia, dehydration |
| Uncommon | electrolyte imbalance, hyperphosphataemia, hypernatraemia, acid base disorder[4], diabetes mellitus, malnutrition, hypovolaemia |
| Rare | hypolipidaemia |
| **Psychiatric disorders** | |
| Common | hypersomnia/insomnia |
| Uncommon | depression/dysphoria, anxiety |

| | |
|---|---|
| Rare | mental disorder, tic |
| **Nervous system disorders** | |
| Very common | neuropathy[5] |
| Common | dizziness, headache, neurotoxicity, dysgeusia |
| Uncommon | somnolence, syncope, encephalopathy, epilepsy, tremor, memory impairment, dysarthria, nervous system disorder, speech disorder |
| Rare | disturbance in attention, haemorrhage intracranial, paraplegia |
| **Eye disorders** | |
| Common | vision blurred |
| Uncommon | eye inflammation[6], eye movement disorder, papilloedema |
| Rare | blepharochalasis, glaucomatocyclitic crises, hypermetropia, retinal haemorrhage |
| **Ear and labyrinth disorders** | |
| Common | ear disorder[7] |
| Uncommon | vertigo, deafness |
| **Cardiac disorders** | |
| Very common | arrhythmia[8] |
| Uncommon | pericardial effusion, cardiac failure/cardiac dysfunction, myocarditis/immune-mediated myocarditis, myocardial injury/myocardial ischaemia, cardiac discomfort |
| Rare | aortic valve disease, cardiac disorder |
| **Vascular disorders** | |
| Common | hypertension, hypotension/orthostatic hypotension, embolism and thrombosis |
| Uncommon | phlebitis |
| Rare | aortic aneurysm, flushing |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common | cough |
| Common | dyspnoea, pneumonitis/immune-mediated lung disease/interstitial lung disease, upper respiratory tract disorders[9], haemoptysis, epistaxis, pleural effusion, hiccups, dysphonia, rhinitis allergic |
| Uncommon | nasal congestion, respiratory failure, bronchospasm, sinus disorder, pneumonia aspiration, sputum increased, tracheo-esophageal fistula |
| Rare | hydrothorax, pleurisy, vocal cord thickening |
| **Gastrointestinal disorders** | |
| Very common | nausea/dyspepsia/eructation, vomiting, constipation/dyschezia, colitis/diarrhoea, abdominal pain |
| Common | stomatitis, abdominal distension/flatulence, dry mouth, dysphagia, toothache, gastrointestinal haemorrhage, gastrooesophageal reflux disease/hyperchlorhydria |

| | |
|---|---|
| Uncommon | intestinal obstruction/subileus, gastritis, gastroenteritis, oesophageal obstruction, pancreatitis, proctalgia, gastric disorder, gastric ulcer, gastrointestinal disorder, gastric dilatation, gastric fistula, hypoaesthesia oral |
| Rare | faecaloma, oesophageal ulcer, pancreatic disorder, pneumatosis intestinalis, swollen tongue, tongue discolouration |
| **Hepatobiliary disorders** | |
| Very common | Hyperbilirubinaemia/jaundice |
| Common | hepatitis[10], total bile acids increased |
| Uncommon | hepatic pain, cholecystitis, hepatic steatosis |
| **Skin and subcutaneous tissue disorders** | |
| Very common | rash[11], pruritus |
| Common | alopecia, vitiligo, pigmentation disorder |
| Uncommon | night sweats, skin disorder, skin exfoliation, hyperhidrosis, dry skin, skin ulcer, hair colour changes, psoriasis, photosensitivity reaction, skin hyperpigmentation |
| Rare | dermatomyositis, leukoderma, neurodermatitis, onychomadesis, pain of skin, panniculitis, pemphigus, purpura senile, telangiectasia |
| **Musculoskeletal and connective tissue disorders** | |
| Very common | musculoskeletal pain |
| Common | muscular weakness, arthritis/joint range of motion decreased/periarthritis |
| Uncommon | muscle spasms, intervertebral disc protrusion, myositis |
| Rare | limb mass |
| **Renal and urinary disorders** | |
| Very common | proteinuria, haematuria |
| Common | renal injury/nephropathy |
| Uncommon | pollakiuria, hydronephrosis, pyelocaliectasis, ureteric dilatation |
| Rare | cystitis noninfective, hydroureter, immune-mediated renal disorder |
| **Reproductive system and breast disorders** | |
| Uncommon | benign prostatic hyperplasia, breast pain, oedema genital, scrotal oedema |
| Rare | hypomenorrhoea, menorrhagia, menstrual disorder, menstruation irregular, prostatic calcification, vulvovaginal inflammation |
| **General disorders and administration site conditions** | |
| Very common | fatigue, pyrexia, pain[12] |
| Common | oedema, influenza like illness, face oedema, chills, eye disorder[13] |
| Uncommon | facial pain, swelling, temperature intolerance, thirst |
| Rare | administration site reactions, hyperplasia, medical device pain, secretion discharge |

| | |
|---|---|
| **Investigations** | |
| Very common | liver function test abnormal, thyroid function test abnormal, increased or decreased lipids, urine analysis abnormal[14] |
| Common | creatinine renal clearance decreased, blood creatine phosphokinase decreased/blood creatine phosphokinase increased, blood lactate dehydrogenase increased, amylase increased, lymphocyte count abnormal/monocyte count abnormal, blood alkaline phosphatase increased, blood urea increased, weight increased, lipase increased, electrocardiogram abnormal, C-reactive protein increased, occult blood positive, cardiac investigation abnormal[15] |
| Uncommon | platelet count increased, anti-thyroid antibody positive, eosinophil count abnormal, blood prolactin increased, blood testosterone decreased, blood follicle stimulating hormone increased, blood luteinising hormone increased, urine output decreased |
| **Injury, poisoning and procedural complications** | |
| Uncommon | infusion related reaction, contusion/muscle injury, rib fracture |

The following terms represent a group of related events that describe a medical condition rather than a single event.

[1]Ear infections includes mastoiditis, myringitis, and otitis media

[2]Dental and oral soft tissue infections includes oral candidiasis, pericoronitis, and periodontitis.

[3]Skin and subcutaneous tissue infections includes cellulitis, folliculitis, and subcutaneous abscess.

[4]Acid base disorder includes metabolic acidosis, metabolic alkalosis, and metabolic disorder.

[5]Neuropathy includes anaesthesia, anosmia, formication, hypoaesthesia, Lhermitte's sign, nerve injury, neuropathy peripheral, paraesthesia, parosmia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, tongue paralysis, VIth nerve disorder, VIth nerve injury, and vocal cord paralysis.

[6]Eye inflammation includes eye inflammation, iritis, keratitis, and uveitis.

[7]Ear disorder includes ear pain, eustachian tube disorder, hypoacusis, middle ear inflammation, otorrhoea, and tinnitus.

[8]Based on a standard query including bradyarrhythmias and tachyarrhythmias.

[9]Upper respiratory tract disorders includes catarrh, dry throat, laryngeal oedema, laryngeal pain, nasal obstruction, rhinalgia, rhinorrhoea, and throat irritation.

[10]Hepatitis includes drug-induced liver injury, hepatic failure, hepatic function abnormal, and immune-mediated hepatitis.

[11]Rash includes dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, erythema, erythema multiforme, hand dermatitis, palmar-plantar erythrodysaesthesia syndrome, papule, rash, rash erythematous, rash generalised, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin plaque, and urticaria.

[12]Pain includes chest discomfort, chest pain, eye pain, lymph node pain, non-cardiac chest pain, and pain.

[13]Eye disorder includes cataract, diplopia, dry eye, eye pruritus, and eye swelling.

[14]Urine analysis abnormal includes bilirubin urine present, crystal urine present, glucose urine present, urea urine increased, urinary casts, urinary casts present, urinary sediment present, urine bilirubin increased, urine ketone body present, urobilinogen urine increased, and white blood cells urine positive.

[15]Cardiac investigation abnormal includes blood creatine phosphokinase MB increased, brain natriuretic peptide increased, and troponin increased.

Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on 403 patients who received toripalimab at a dose of 240 mg Q3W in combination with platinum and gemcitabine chemotherapy (n=146) or in combination with cisplatin and paclitaxel (n=257). The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

*Immune-related adverse reactions (see section 4.4)*

*Immune-related pneumonitis*
Immune-related pneumonitis occurred in 3.2% (13/403) patients receiving toripalimab in JUPITER-02 and JUPITER-06, including, 2 (0.5%) Grade 3, and 7 (1.7%) Grade 2 adverse reactions. The median time to onset of pneumonitis was 5.4 months (range 1.3 to16.6 months). The median duration was 2.8 months (range 0.8 to 20.9 months). Corticosteroids were administered to 69.2% (9/13) of patients. Permanent discontinuation occurred in 3 (0.7%) and withholding of toripalimab in 5 (1.2%) patients. Immune-related pneumonitis resolved in 31.0% (4/13) patients.

*Immune-related colitis*
Immune-related colitis occurred in 0.7% (3/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 2 (0.5%) Grade 3 and 1 (0.2%) Grade 2 adverse reactions. The median time to onset of colitis was 3.7 months (range 1.5 to 5.1 months). The median duration was 1.3 months (range 1.3 to 1.3 months). Corticosteroids were administered to 66.7% (2/3) of these patients. Permanent discontinuation occurred in 2 (0.5%) patients and withholding of toripalimab in 1 (0.2%) patient. Immune-related colitis resolved in 33% (1/3) of these patients.

*Hepatotoxicity and immune-related hepatitis*
Immune-related hepatitis occurred in 2.0% (8/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 2 (0.5%) Grade 4, 5 (1.2%) Grade 3, and 1 (0.2%) Grade 2 adverse reactions. The median time to onset of hepatitis was 4.0 months (range 0.7 to 22.7 months). The median duration was 0.6 months (range 0.4 to 3.2 months). Corticosteroids were administered to 7 of the 8 (87.5%) patients. Permanent discontinuation occurred in 5 (1.2%) and withholding of toripalimab in 2 (0.5%) patients. Immune-related hepatitis resolved in 87.5% (7/8) of these patients.

*Immune-related endocrinopathies*
Immune-related adrenal insufficiency occurred in 0.2% (1/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 1 (0.2%) Grade 3adverse reaction. The time to onset of the adverse reaction was 2.0 months. Corticosteroids were administered to this patient. Toripalimab was permanently discontinued.

Thyroiditis occurred in 2.0% (8/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 4 Grade 2 (1.0%) and 4 Grade 1 (1.0%) adverse reactions. The median time to onset of thyroiditis was 5.9 months (range 0.7 to 13.5 months). The median duration was 11.7 months (range 7.4 to 17.8 months). Corticosteroids were required in 1/8 (12.5%) of patients and hormone replacement in 5/8 (62.5%). Permanent discontinuation occurred in 1/403 (0.2%) and dose interruption in 1/403 (0.2%) patients. Thyroiditis resolved in 12.5% (1/8) of these patients.

In patients receiving toripalimab in JUPITER-02 and JUPITER-06, hyperthyroidism occurred in 2.0% (8/403) of patients, all of which were Grade

1 adverse reactions. The median time to onset of hyperthyroidism was 6.5 months (range 1.5 to 12.5 months). The median duration was 1.4 months (range 0.7 to 3.7 months).

Hypothyroidism occurred in 17.1% (69/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, with 46 Grade 2 (11.4%) and 23 Grade 1 (5.7%) adverse reactions. The median time to onset of hypothyroidism was 5.9 months (range 1.2 to 20.7 months). The median duration was 3.2 months (range 0.4 to 30.6 months). Thyroid hormone replacement therapy was required in 72.5% (50/69) of patients. Corticosteroids were administered to 1/69 (1.4%) patients. No patients permanently discontinued and 1.2% (5/403) of the patients interrupted toripalimab.

In patients receiving toripalimab in JUPITER-02 and JUPITER-06, diabetes mellitus occurred in 0.2% (1/403) of patients, including 1 (0.2%) Grade 3, and no Grade 2 adverse reactions. The time to onset of diabetes mellitus was 0.7 month. The patient did not receive corticosteroids but was treated with insulin. The patient did not permanently discontinue or interrupt toripalimab.

In patients receiving toripalimab in JUPITER-02 and JUPITER-06, hypophysitis occurred in 0.2% (1/403) of patients with 1 (0.2%) Grade 2 adverse reaction. The time to onset of hypophysitis was 23.7 month. Corticosteroids were administered and the patient did not permanently discontinue toripalimab or interrupt dosing.

*Immune-related skin adverse reactions*
Immune-related skin adverse reactions occurred in 9.4% (38/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 12 Grade 3 (3.0%) and 8 Grade 2 (2.0%) adverse reactions. The median time to onset of immune-related skin adverse reactions was 1.0 month (range 0.1 to 23.1 months). The median duration was 1.2 months (range 0.1 to 13.1 months). Systemic corticosteroids were required in 18.4% (7/38) of the patients with immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation or interruption of toripalimab in 1.5% (6) of patients. Immune-related skin adverse reactions resolved in 73.7% (28/38) of these patients.

*Immune-related myocarditis*
Immune-related myocarditis occurred in 0.7% (3/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 2 (0.5%) Grade 4 and 1 (0.2%) Grade 3adverse reactions. The median time to onset of immune-related myocarditis was 1.7 months (range 1.4 to 4.1 months). The median duration was 1.3 months (range 1.0 to 1.6 months). All three patients with immune-related myocarditis received corticosteroids. Two patients permanently discontinued toripalimab and no patients interrupted dosing. Immune-related myocarditis resolved in 33.3% (1/ 3) of these patients.

*Immune-related myositis*
Immune-related myositis occurred in 0.5% (2/403) of patients receiving toripalimab in in JUPITER-02 and JUPITER-06, including 2 (0.5%) Grade 3

and no Grade 2 adverse events. The median time to onset of immune-related myositis was 2.5 month (range 1.2 to 3.9 months). The two patients with immune-related myositis received corticosteroids and both permanently discontinued toripalimab.

*Immune-related nephritis*
Immune-related nephritis occurred in 0.2% (1/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06. The time to onset of immune-related nephritis was 18.2 months and the duration was 3.3 months. The patient with immune-related nephritis (Grade 4) required systemic corticosteroids and nephritis led to discontinuation of toripalimab. Nephritis resolved in this patient.

*Other immune-related adverse reactions*
Immune-related cystitis occurred in 0.5% (2/403) of patients receiving toripalimab in JUPITER-02 and JUPITER-06, including 1 Grade 3 (0.2%) and 1 Grade 1 (0.2%) adverse reactions. The median time to onset of immune-related cystitis was 5.0 months (range 3.4 to 6.6 months). Corticosteroid therapy was required in the one patient with Grade 3 cystitis who also permanently discontinued toripalimab. The other patient did not interrupted dosing. Immune-related cystitis resolved in the single patient with a Grade 3 cystitis who received corticosteroid treatment.

*Infusion related reactions*
Of the 403 patients who received toripalimab in combination with platinum containing chemotherapy in JUPITER-02 or JUPITER-06, infusion-related reactions occurred in 11 patients (2.7%), including Grade 4 (0.2%), Grade 3 (0.2%) and Grade 2 (0.5%) adverse reactions.

Overall, infusion related reactions occurred in 28 (1.8%) of 1514 patients treated with toripalimab, including Grade 4 (0.07%) and Grade 3 (0.13%) reactions. Infusion-related reaction led to permanent discontinuation of toripalimab in 3 (0.2%) patients. Common symptoms of infusion-related reaction include fever, chills, rash, pruritus, nausea and hypotension.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. In patients who received toripalimab, treatment-emergent antibodies to toripalimab were detected in 8.7% (128/1479) of the evaluable patients tested. There was no evidence of any clinically relevant effect of anti-toripalimab antibody development on its pharmacokinetics. Across all studies, the median time to onset of ADA was 46 days (range to 14 to 506 days). There are insufficient numbers of patients to adequately assess the effect of ADA on efficacy.

Elderly
Of the 403 patients treated with toripalimab in combination with platinum-based chemotherapy in clinical studies, 73.2% (295/403) were less than 65 years and 26.8% (108/403) were 65 years or older.

No overall differences in safety were observed between patients ≥ 65 years of age and younger patients receiving toripalimab.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 4.9 Overdose

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01FF13

Mechanism of action
Toripalimab is a humanised 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-tumour immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation, cytokine production, and cytotoxic activity.

Clinical efficacy and safety

*Nasopharyngeal carcinoma*
The efficacy of toripalimab in combination with cisplatin and gemcitabine was investigated in JUPITER-02, a randomised, multi-centre, double-blind, placebo-controlled study in 289 patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma (NPC) not amenable to curative therapy 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.

Randomisation was stratified according to ECOG PS (0 versus 1) and disease stage (recurrent versus metastatic) at study entry. Patients were randomised (1:1) to receive one of the following treatments:

- Toripalimab 240 mg intravenously on Day 1 in combination with cisplatin 80 mg/m$^2$ on Day 1 and gemcitabine 1 000 mg/m$^2$ on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by toripalimab 240 mg once every 3 weeks, or
- Placebo intravenously on Day 1 in combination with cisplatin 80 mg/m$^2$ on Day 1 and gemcitabine 1 000 mg/m$^2$ on Days 1 and 8 every 3 weeks for up to 6 cycles, followed by placebo once every 3 weeks.

Treatment with toripalimab or placebo continued until disease progression per response
evaluation criteria in solid tumours (RECIST) v1.1 (with the exception noted below), unacceptable toxicity, or a maximum of 2 years. Administration of toripalimab 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.

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%). Approximately 86% of the study population had metastatic disease at randomisation, with histological subtypes of NPC including 98% non-keratinizing, 1% keratinizing squamous cell carcinoma, and 1% unclassified NPC/other. The majority (63%) of patients had serum Epstein-Barr virus (EBV) titres ≥ 2000 U/mL.

The study showed statistically significant improvements in BIRC-assessed PFS and OS for patients randomised to toripalimab in combination with cisplatin/gemcitabine compared to cisplatin and gemcitabine with placebo.

Efficacy results are summarised in Table 3, Figure 1 and Figure 2 below.

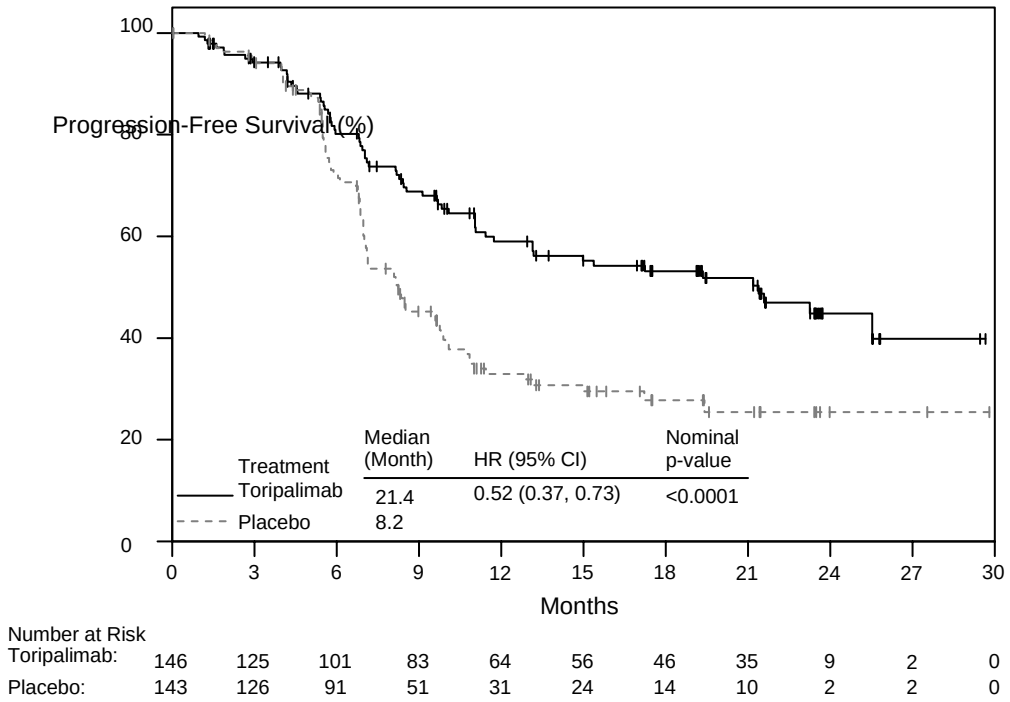
**Table 3: Efficacy results in JUPITER-02**

| **Endpoints**[1] | **Toripalimab + cisplatin/ gemcitabine N =146** | **Placebo + cisplatin/ gemcitabine N =143** |
|---|---|---|
| **BIRC-assessed progression-free survival (PFS)** | | |
| Number of PFS events (%) | 63 (43.2) | 87 (60.8) |

| **Endpoints**[1] | **Toripalimab + cisplatin/ gemcitabine N =146** | **Placebo + cisplatin/ gemcitabine N =143** |
|---|---|---|
| Median PFS, months (95% CI) | 21.4 (11.7, NE) | 8.2 (7.0, 9.8) |
| Hazard ratio (95% CI)[2] | 0.52 (0.37, 0.73) | |
| Nominal p-value[3] | < 0.0001 | |
| **Overall survival (OS)** | | |
| Number of deaths (%) | 57 (39.0) | 76 (53.1) |
| Median OS, in 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 | |

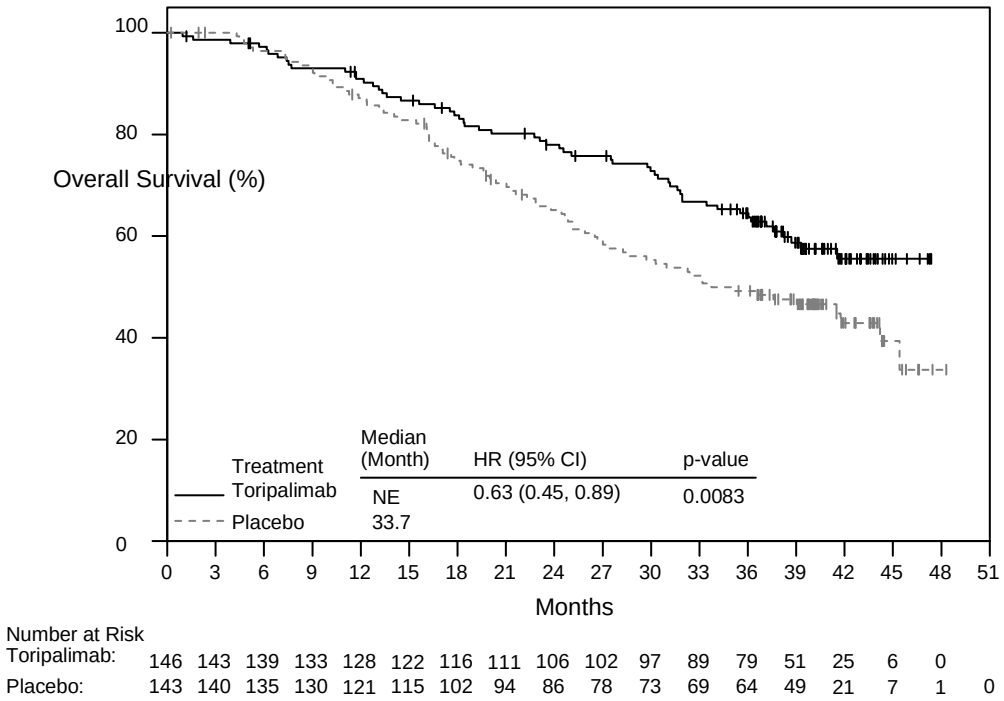
[1] The final analysis of PFS was based on the data with cut-off date of 08 Jun 2021 and the final analysis of OS was based on the data with cut-off date of 18 Nov 2022.
[2]The hazard ratio and its confidence interval were computed using a stratified Cox proportional-hazards model.
[3]Two-sided p-value, based on stratified log-rank test.
BIRC=blinded independent review committee; CI= confidence interval; NE=Not estimable

**Figure 1: Kaplan-Meier curves for BIRC-assessed PFS in JUPITER-02**




data cut-off date: 08 Jun 2021

**Figure 2: Kaplan-Meier curves for overall survival in JUPITER-02**




data cut-off date: 18 Nov 2022

In exploratory subgroup analyses of PFS and OS, the magnitude of the treatment effects appeared similar across patient subgroups based on PD-L1 expression or EBV titres.

*Elderly population*
A minority of patients (4.8%; 14/289) were age ≥ 65 years. Data are too limited to draw conclusions on this population.

*Oesophageal squamous cell carcinoma*
The efficacy of toripalimab in combination with paclitaxel and cisplatin was investigated in JUPITER-06, a randomised, multi-centre, single region, double-blind, placebo-controlled study in 514 patients with metastatic or recurrent, locally advanced oesophageal squamous cell carcinoma (OSCC) who had not received previous systemic chemotherapy for recurrent or metastatic disease. Patients with recurrent OSCC after treatment with curative intent were required to have an interval of at least 6 months between the last dose of adjuvant, neoadjuvant chemotherapy, radiation, or chemoradiotherapy and recurrence or at least 12 months between the last dose of adjuvant chemotherapy/chemoradiotherapy with paclitaxel and cisplatin. Patients with autoimmune disease, other than stable hypothyroidism or Type I diabetes, and patients who required systemic immunosuppression were ineligible.

Randomisation was stratified according to ECOG PS (0 versus 1) and previous radiotherapy (yes versus no). Patients were randomized (1:1) to receive one of the following treatments:

- Toripalimab 240 mg intravenously in combination with paclitaxel 175 mg/m$^2$ intravenously and cisplatin 75 mg/m$^2$intravenously on Day 1 every 3 weeks for 4 to 6 cycles, followed by toripalimab 240 mg once every 3 weeks, or

- Placebo intravenously in combination with paclitaxel 175 mg/ m$^2$ intravenously and cisplatin 75 mg/m$^2$ intravenously on Day 1 every 3 weeks for 4 to 6 cycles, followed by placebo once every 3 weeks.

Treatment with toripalimab or placebo continued until disease progression per RECIST v1.1, unacceptable toxicity (with the exception noted below), or a maximum of 2 years. Tumour assessments were performed every 6 weeks for the first 12 months and every 9 weeks thereafter. The co-primary endpoints were Blinded Independent Review Committee (BIRC)-assessed progression-free survival (PFS) according to RECIST v1.1 and OS.

The study population characteristics were: median age of 63 years (range: 20 to 75), 38% age 65 or older, 85% male, 100% Asian, and ECOG PS of 0 (26%) or 1 (74%). Seventy-nine percent of patients had metastatic disease at study entry.

The results of the final analysis of BIRC-determined PFS showed a statistically significant improvement in PFS. At the final analysis of OS (data cut-off 23 Feb 2023), the study showed consistent improvement in OS (HR 0.72; 95% CI 0.58-0.88).

Efficacy results of OS and BIRC-determined PFS are summarised in Table 4, Figure 3 and Figure 4 below.

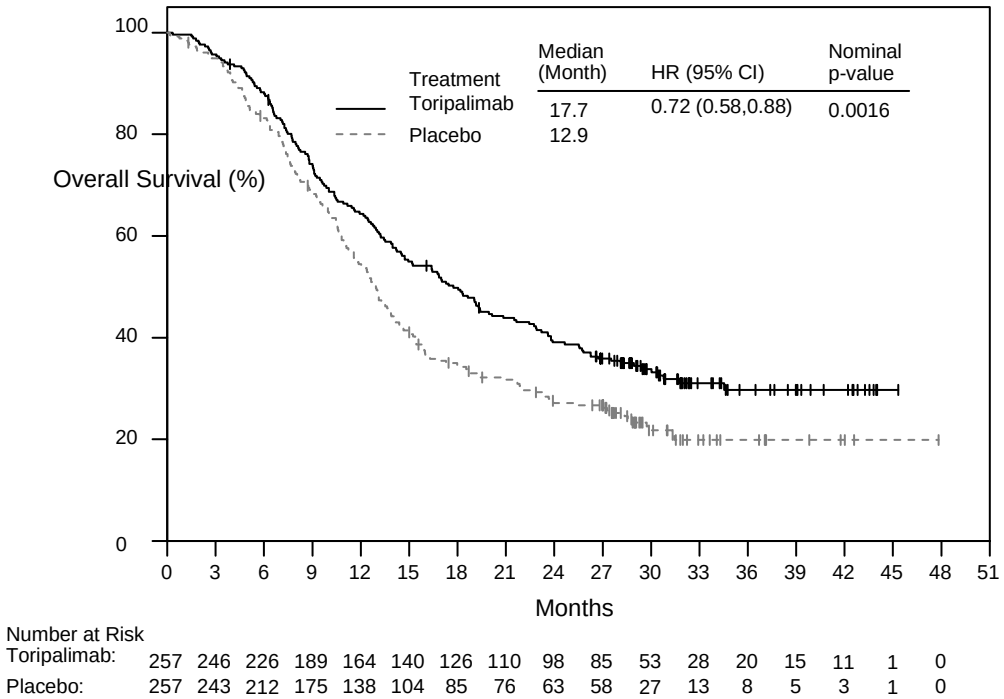
**Table 4: Efficacy results in JUPITER-06**

| | **Toripalimab + paclitaxel/cisplatin N = 257** | **Placebo + paclitaxel/cisplatin N = 257** |
|---|---|---|
| **Overall survival (OS)**[1] | | |
| Number of OS events (%) | 172 (66.9) | 195 (75.9) |
| Median OS, months (95% CI) | 17.7 (14.6, 20.8) | 12.9 (11.6, 14.1) |
| Hazard ratio (95% CI)[2] | 0.72 (0.58, 0.88) | |
| p-value[3] | 0.0016 | |
| **BIRC-assessed progression-free survival (PFS)**[4] | | |
| Number of PFS event (%) | 132 (51.4) | 164 (63.8) |
| Median PFS, months (95% CI) | 5.7 (5.6, 7.0) | 5.5 (5.2, 5.6) |
| Hazard ratio[2] (95% CI) | 0.58 (0.46, 0.74) | |
| p-value[3] | < 0.0001 | |

[1]The data cut-off for the final analysis of OS was 23 Feb 2023.
[2]The hazard ratio and its confidence interval were computed using the stratified Cox proportional-hazards model.

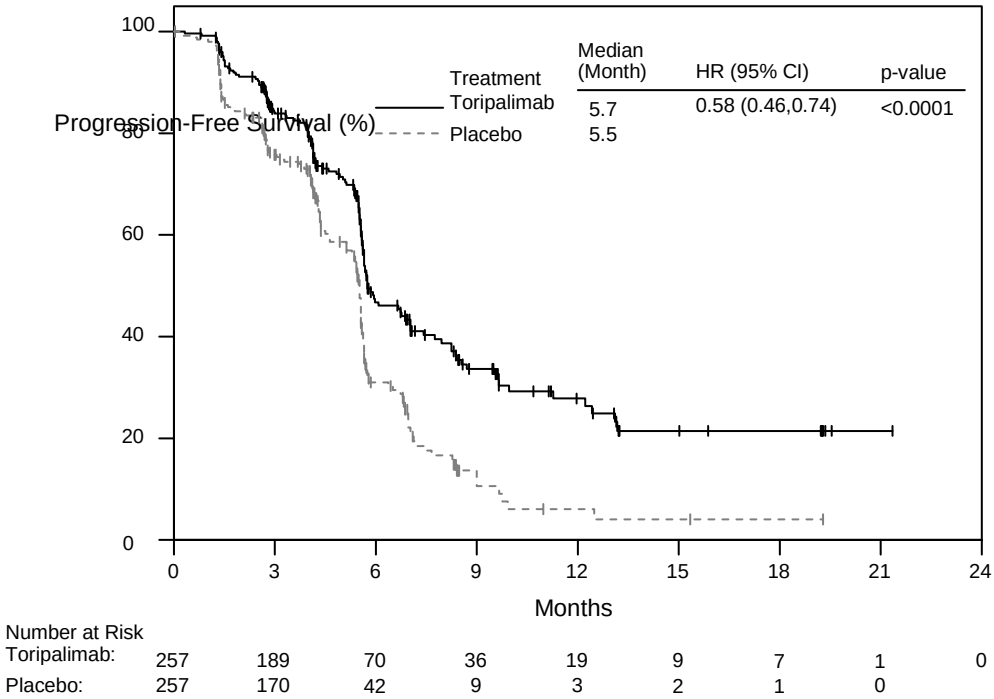
[3]Two-sided p-value, based on the stratified log-rank test.
[4]The data cut-off for the final analysis of PFS was 22 Mar 2021.
BIRC=blinded independent review committee; CI=confidence interval

**Figure 3: Kaplan-Meier curves for overall survival in JUPITER-06**




data cutoff date: 23 Feb 2023

**Figure 4: Kaplan-Meier curves for BIRC-assessed PFS in JUPITER-06**




data cutoff date: 22 Mar 2021

*Efficacy and PD-L1 status*
In exploratory subgroup analyses of PFS and OS, the magnitude of the treatment effects appeared similar across patient subgroups based on PD-L1 expression.

***Elderly population***
There were 195 patients (38%) who were age 65 years or older. No overall differences in efficacy were observed between patients ≥ 65 years of age and younger patients receiving toripalimab in combination with paclitaxel/cisplatin.

Paediatric population
The Medicines and Healthcare Product Regulatory Agency has waived the obligation to submit the results of studies with LOQTORZI in all subsets of the paediatric population in the treatment of all conditions in the category of malignant neoplasms (except CNS, haematopoietic and lymphoid tissue and melanoma) (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Toripalimab pharmacokinetics were characterised using population PK analyses that included data from 574 patients across 5 clinical studies with

various solid tumours who received fixed (80 to 480 mg Q2W or Q3W) or weight-based (range: 1 to 10 mg/kg Q2W) dosing, including 92 patients with NPC and 236 patients with OSCC who received toripalimab at doses of 240 mg every 3 weeks in JUPITER-02 and JUPITER-06, respectively.

Toripalimab pharmacokinetic parameters are presented as geometric mean (coefficient of variation [CV]%) unless otherwise noted.

Absorption
Toripalimab is administered via the intravenous route; therefore, it is completely bioavailable.

Distribution
Toripalimab is primarily distributed in the plasma with a geometric mean volume of distribution at steady state of approximately 3.8 L (CV=27.4%).

Biotransformation
Dedicated metabolism studies were not performed. As a monoclonal antibody, toripalimab is expected to be metabolized into small peptides, amino acids, and small carbohydrates by catabolic pathways or by receptor-mediated endocytosis. The degradation products are eliminated by renal excretion or returned to the nutrient pool without biological effects.

Elimination
Toripalimab pharmacokinetics followed a 2-compartment model with time-varying clearance (CL). The mean CL was 12.01 mL/h (CV = 27%) after the first dose and 8.49 mL/h (CV = 24.4%) at steady state. The geometric mean value (CV%) for the terminal half-life is 14 days (32.5%) at steady-state with toripalimab administered at 240 mg Q3W.

Linearity/non-linearity
Exposure to toripalimab, as expressed by peak concentrations ($C_{max}$), increased dose proportionally over the dose range of 80 to 480 mg Q2W. The geometric mean trough concentrations ($C_{min}$) at steady state were estimated in the population PK model to be 26.3 μg/mL in patients receiving 240 mg every 3 weeks. The mean accumulation of $C_{min}$ at steady state is 2.7-fold compared to the $C_{min}$ after the first dose.

Pharmacokinetic/pharmacodynamic relationship(s)
Toripalimab exposure-response relationships for efficacy are essentially flat over the range of exposures achieved for nasopharyngeal carcinoma in JUPITER-02 and for OSCC in JUPITER-06. The toripalimab exposure-response relationships for safety showed negative (inverse) relationships over the range of exposures achieved; however, this is likely an artifact reflecting toripalimab accumulation.

Anticipated full receptor occupancy of PD-1 in immune cells was achieved at exposures below mean trough concentrations after the first dose and steady state at dose of 240 mg Q3W.

Special populations
No clinically significant differences in the pharmacokinetics of toripalimab were observed based on age (range: 19 to 85 years), body weight (range: 39 to 164 kg), sex, concomitant chemotherapy, mild or moderate renal impairment, mild hepatic impairment, tumour burden and primary cancer.

*Renal impairment*
The effect of renal impairment based on the estimated creatinine clearance on the clearance and volume of distribution of toripalimab were evaluated using population pharmacokinetic analyses. No differences in clearance or volume of distribution were found between patients with mild (CLcr 60 to 89 mL/min; n=483) or moderate (CLcr 30 to 59 mL/min; n=114) renal impairment and patients with normal renal function. The effect of severe (CLcr 15 to 29 mL/min) renal impairment on the pharmacokinetics of toripalimab has not been studied.

*Hepatic impairment*
The effects of hepatic impairment using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading system for hepatic dysfunction on the clearance and volume of distribution of toripalimab were evaluated using population pharmacokinetic analyses. No differences in clearance or volume of distribution were found between patients with mild (Grade 1, n=166) hepatic impairment (total bilirubin up to 1.5 times the upper limit of normal (ULN) or total bilirubin within normal limits and aspartate transaminase (AST) or alanine transaminase (ALT) > 1 and ≤ 3 ULN) compared to patients with normal liver function. There was a limited number of patients with moderate (Grade 2, n=1; total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment and no patients with severe (Grade 3; total bilirubin > 3 times ULN and any AST) hepatic impairment enrolled in clinical studies of toripalimab.

## 5.3 Preclinical safety data

No studies have been performed to test the potential of toripalimab for carcinogenicity or genotoxicity.

Animal reproduction studies have not been conducted with toripalimab to evaluate its effect on reproduction and foetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the foetus. In murine models of pregnancy, blockade of PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in an increase in foetal loss.

Fertility studies have not been conducted with toripalimab. In 4-week and 26-week repeat-dose toxicology studies in cynomolgus monkeys, there were

no adverse or notable effects in the male and female reproductive organs. However, those animals were unlikely sexually mature.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Citric acid monohydrate
Mannitol
Polysorbate 80
Sodium chloride
Sodium citrate dihydrate
Water for injections

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

Unopened Vial
3 years

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Type 1 neutral borosilicate glass vial capped sealed with a chlorobutyl rubber stopper and sealed with a 20 mm flip-off seal (aluminium), containing 6 mL of concentrate for solution for infusion.

Each carton contains one vial

## 6.6 Special precautions for disposal

Preparation

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colourless 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 sodium chloride 9 mg/mL (0.9%) solution for injection. Mix the 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.

Administration

- Administer the diluted solution intravenously via an infusion pump using a sterile in-line filter (0.2 micron or 0.22 micron pore size).
- 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.
- Do not co-administer other medicinal products through the same intravenous line.
- When administered on the same day as chemotherapy, LOQTORZI should be administered prior to chemotherapy.

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

# 7 MARKETING AUTHORISATION HOLDER

Topalliance Biosciences Europe Limited
Ground Floor
Two Dockland Central
Guild Street
I.f.s.c.
Dublin 1
Co. Dublin
D01 K2C5
Ireland

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 60874/0001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2024

## 10 DATE OF REVISION OF THE TEXT

17/04/2026