ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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
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

Adverse reaction	Severity[1]	Treatment modification
Immune-related adverse reactions		
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.

When administered on the same day as chemotherapy, LOQTORZI should be administered prior to chemotherapy through a different intravenous line.

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.

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 ≥ 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 ≥ 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 Fertility, 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 national reporting system listed in Appendix V.

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.

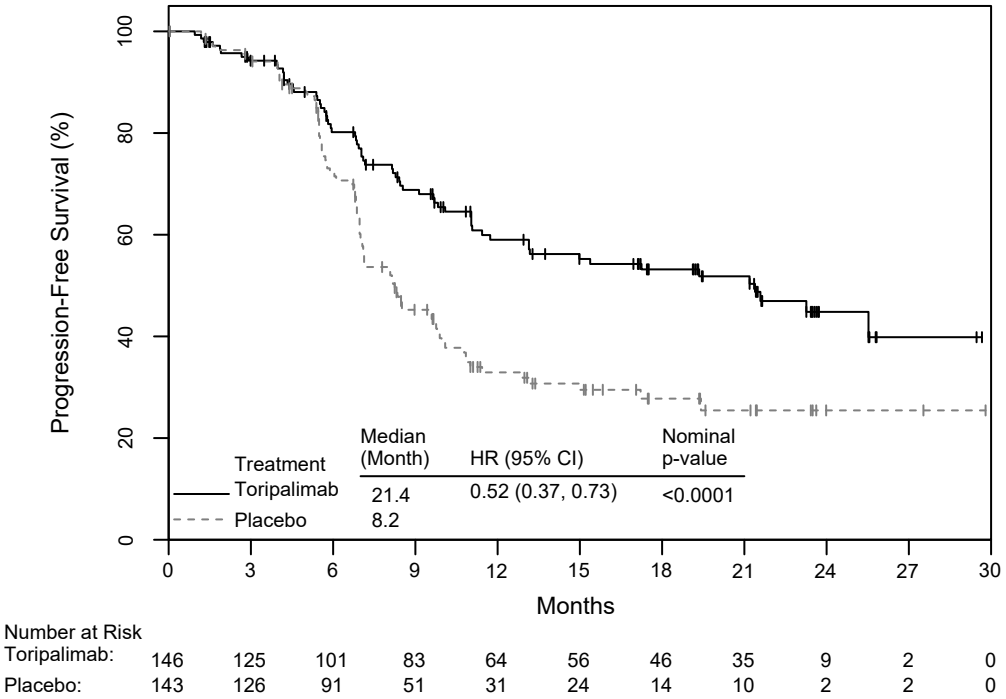
Efficacy results are summarised in Table 3, Figure 1 and Figure 2 below.

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)
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	

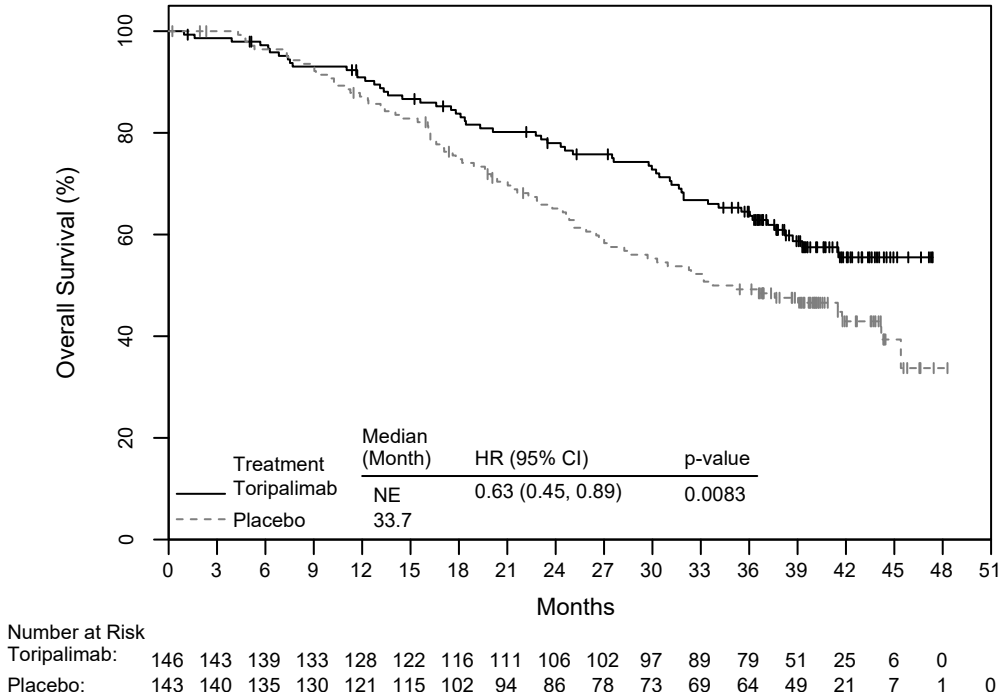
[1] The final analysis of PFS was based on the data with cut-off date of 08 Jun 2021 and the final analysis of OS was based on the data with cut-off date of 18 Nov 2022.
[2]The hazard ratio and its confidence interval were computed using a stratified Cox proportional-hazards model.
[3]Two-sided p-value, 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^2intravenously 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).

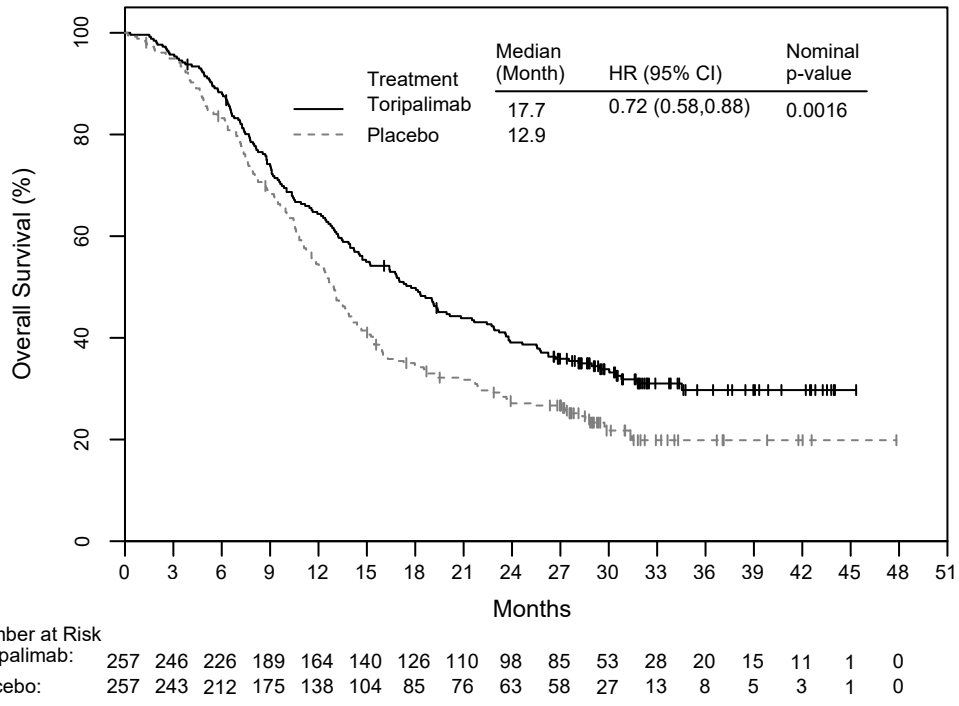
Efficacy results of OS and BIRC-determined PFS are summarised in Table 4, Figure 3 and Figure 4 below.

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	

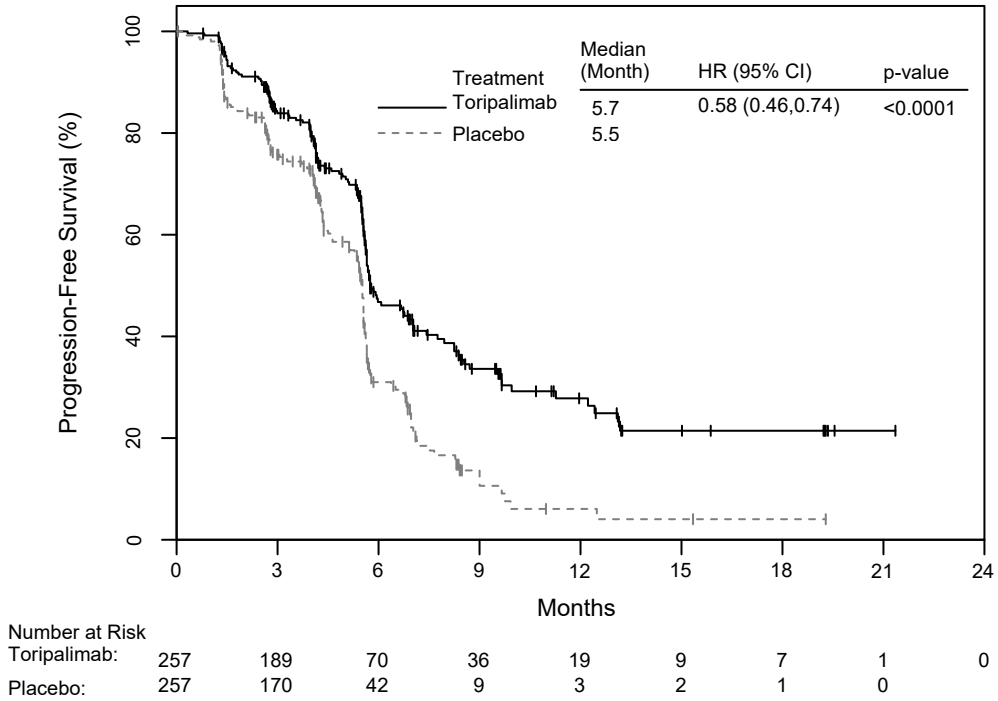
[1]The data cut-off for the final analysis of OS was 23 Feb 2023.
[2]The hazard ratio and its confidence interval were computed using the stratified Cox proportional-hazards model.
[3]Two-sided p-value, based on the stratified log-rank test.
[4]The data cut-off for the final analysis of PFS was 22 Mar 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 European Medicines 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.

After dilution

Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at 2°C to 8°C or at 20°C to 25°C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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 and other handling

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)

EU/1/24/1853/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19-09-2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Suzhou Union Biopharm Co., Ltd.
999 Longqiao Rd
Wujiang
Suzhou, Jiangsu, 215299
China

Name and address of the manufacturer responsible for batch release

Eurofins PHAST GmbH
Kardinal-Wendel-Strasse 16
Homburg
Saarland
66424
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where LOQTORZI is marketed, all healthcare professionals who are expected to prescribe and use LOQTORZI have access to/are provided with the patient alert card.

The Patient Alert Card shall contain the following key messages:

- That LOQTORZI treatment may increase the risk of:
    - Immune-related pneumonitis
    - Immune-related colitis
    - Immune-related hepatitis
    - Immune-related nephritis
    - Immune-related endocrinopathies
    - Immune-related skin adverse reactions
    - Other immune-related adverse reactions

- Signs or symptoms of the safety concern and when to seek attention from a healthcare provider (HCP).

- Contact details of the LOQTORZI prescriber

- The importance of carrying the patient alert card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g., emergency healthcare professionals).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LOQTORZI 240 mg concentrate for solution for infusion
toripalimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of concentrate contains 40 mg of toripalimab.
One vial of 6 mL contains 240 mg of toripalimab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, mannitol, polysorbate 80, sodium chloride, sodium citrate dihydrate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

240 mg/6 mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Read the leaflet for the shelf life of the diluted medicine.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE 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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1853/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LOQTORZI 240 mg concentrate for solution for infusion
toripalimab
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP Refer to container labelling for expiry date. Record date and time of vial opening for dilution.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

240 mg/6 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

LOQTORZI 240 mg concentrate for solution for infusion
toripalimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the patient alert card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LOQTORZI is and what it is used for

LOQTORZI contains the active substance toripalimab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

LOQTORZI is used in adults to treat:
- a type of head and neck cancer called nasopharyngeal cancer that starts at the upper part of the throat behind the nose and near the base of the skull. It is used when the cancer has spread to other parts of the body, or has come back after previous treatment and cannot be removed by surgery.
- a type of oesophageal (gullet) cancer called oesophageal squamous cell cancer. It is used when the cancer cannot be removed by surgery, has come back after previous treatment or has spread to other parts of the body.

LOQTORZI is given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these medicines. If you have any questions about LOQTORZI or these other medicines, please ask your doctor.

The active substance in LOQTORZI, toripalimab, works by attaching to a target protein called programmed death-1 receptor (PD-1). PD-1 can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences), which prevents your immune system from fighting the cancer. By attaching to PD-1, toripalimab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the cancer.

2. What you need to know before you are given LOQTORZI

You must not be given LOQTORZI

- if you are allergic to toripalimab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before receiving LOQTORZI if you:
- have an autoimmune disease (an illness where the body attacks its own cells)
- have lung problems or breathing problems (called pneumonitis)
- have been told that your cancer has spread to your brain
- have active viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have active tuberculosis (TB)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have liver damage
- have kidney damage
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)
- are currently taking medicines to suppress your immune system. Examples of these may include corticosteroids, such as prednisone.

If any of the above apply to you (or you are not sure), talk to your doctor before you are given LOQTORZI.

When you get LOQTORZI, you may develop some serious side effects. These side effects can be life-threatening and may happen anytime during treatment or even after your treatment has ended. You may experience more than one side effect at the same time.

If you have any of the following conditions, call or see your doctor immediately:

- inflammation of the lungs (pneumonitis), which may include symptoms of shortness of breath, chest pain or coughing.
- Inflammation of the large bowel (colitis), which may include symptoms of diarrhoea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness.
- inflammation of the liver (hepatitis), which may include symptoms of nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal.
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include symptoms of rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache.
- type 1 diabetes, including diabetic ketoacidosis (acid in the blood produced from diabetes), which may include symptoms of feeling more hungry or thirsty than usual, need to urinate more often or weight loss, feeling tired or feeling sick, stomach pain, fast and deep breathing, confusion, unusual sleepiness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat.
- inflammation of the kidneys (nephritis), which may include symptoms of changes in the amount or colour of your urine.
- inflammation of the skin, which may include symptoms of rash, itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area
- inflammation of the heart muscle (myocarditis), which may include symptoms of shortness of breath, irregular heartbeat, feeling tired, or chest pain.
- inflammation in the muscles (myositis), which may include symptoms of muscle pain or weakness.
- inflammation of the uvea, the layer beneath the white of the eyeball (uveitis), which may include change in eyesight.

- inflammation of the pancreas (pancreatitis), which may include symptoms of abdominal pain, nausea and vomiting.
- inflammation of bladder (cystitis), which may include symptoms of painful urination and blood in the urine.
- inflammation of the joints (arthritis/arthralgia), which may include symptoms of painful, red, or swollen joints or permanent damage to the joints
- infusion reactions, which may include symptoms of fever, chills, itching or rash, nausea and low blood pressure.
- problems in other parts of the body (see section 4 'Possible side effects')

Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms, withhold the next dose of LOQTORZI or stop your treatment with LOQTORZI. Please note that these signs and symptoms are sometimes delayed, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have blood tests during your treatment.

Rejection of solid organ transplants (such as kidney, lung, heart or liver transplants) in patients who received such transplants or complications, including graft-versus-host-disease (GVHD), in people with bone marrow (stem cell) transplant that uses donor stem cells (allogeneic) may occur with use of LOQTORZI. These complications can be severe and can lead to death. They may occur if you had this kind of transplant in the past or if you get it in the future. Your doctor will monitor you for signs and symptoms of these complications, which may include skin rash, liver inflammation, abdominal pain, or diarrhoea.

Children and adolescents
LOQTORZI should not be used in children and adolescents below 18 years of age because it was not studied in patients less than 18 years of age.

Other medicines and LOQTORZI
Tell your doctor or nurse
- If you are taking medicines that suppress your immune system, such as corticosteroids (like prednisone). These medicines may interfere with the effect of LOQTORZI.
  However, once you are treated with LOQTORZI, your doctor may give you corticosteroids to reduce the side-effects that you may have with LOQTORZI. Corticosteroids may also be given to you before receiving LOQTORZI in combination with chemotherapy to prevent and/or treat nausea, vomiting, and other side effects caused by chemotherapy.
- If you are taking, have recently taken or might take any other medicines. Do not take any other medicines during your treatment without talking to your doctor first.

Pregnancy
- You must not be given LOQTORZI if you are pregnant unless your doctor specifically recommends it.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.
- LOQTORZI can cause harmful effects or death to your unborn baby.
- If you are a woman who could become pregnant, you must use effective contraception while you are being treated with LOQTORZI and for at least 4 months after your last dose.

Breast-feeding
- If you are breast-feeding, ask your doctor for advice before you are given this medicine.
- You must not breast-feed during treatment and for at least 4 months after your last dose of LOQTORZI.
- It is not known if LOQTORZI passes into your breast milk.

Driving and using machines

LOQTORZI may have a minor effect on your ability to drive or use machines, as feeling dizzy or tired are possible side effects. Do not drive or use machines unless you are sure you are feeling well.

LOQTORZI contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before LOQTORZI is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

3. How LOQTORZI is given

LOQTORZI will be given to you in a hospital or clinic under the supervision of a doctor experienced in cancer treatment.

The recommended dose is 240 mg every 3 weeks. This will be given to you by your doctor as an infusion (drip) into a vein. The infusion will take about 60 minutes the first time. This may be lowered to about 30 minutes for subsequent doses.

Your doctor will decide how many treatments you need.

LOQTORZI is given in combination with other anti-cancer medicines. You will be given LOQTORZI first, followed by the other medicines.

If you forget an appointment to receive LOQTORZI
Contact your doctor or hospital immediately to reschedule your appointment. It is very important that you do not miss a dose of this medicine.

If you stop receiving LOQTORZI
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with LOQTORZI unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

Patient alert card
Important information from this package leaflet can be found in the patient alert card you have been given by your doctor. It is important that you keep this patient alert card and show it to your partner or caregivers.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects that can result in hospitalization or death are listed below by frequency.

Uncommon (may affect up to 1 in 100 people)
- Inflammation of lungs (pneumonitis)
- Inflammation of the skin (immune-related skin reactions)
- Inflammation of the liver (hepatitis)
- Inflammation of the heart muscle (myocarditis)
- Inflammation in the muscles (myositis)
- Inflammation of the large bowel (colitis)
- Inflammation of adrenal glands (adrenal insufficiency)
- Inflammation of the kidneys (nephritis)
- Decreased in number of platelet (immune mediated thrombocytopenia)
- Inflammation of thyroid (hyperthyroidism/thyroiditis)

- Inflammation of thyroid gland (hypothyroidism)
- Inflammation of insulin-producing cells (diabetes mellitus/ hyperglycaemia)
- Inflammation of pituitary gland (hypophysitis)
- Infusion reactions

Rare (may affect up to 1 in 1 000 people)
- Inflammation of the pancreas (pancreatitis)
- Inflammation of bladder (cystitis)
- Inflammation of the joints (arthritis/arthralgia)

Problems in other parts of the body/Other immune-related side effects (frequency cannot be estimated from the available toripalimab data but have been reported with this class of medicines)
- Inflammation of the brain (encephalitis) which may include symptoms of confusion, fever, memory problems or seizure.
- Myasthenic syndrome, a condition in which the muscles become weak and there is a rapid fatigue of the muscles
- Inflammation of the nerves, including Guillain Barré syndrome: symptoms may include weakness in the arm and leg muscles, or face muscles, double vision, and tingling in hands and feet
- Rhabdomyolysis, symptoms may include stiffness in muscles and joints, muscle spasm.
- Organ transplant rejection
- Inflammation of the uvea (uveitis)

If you experience any of these serious side effects, seek urgent medical attention or contact your healthcare provider immediately.

The following side effects have been reported in clinical studies with toripalimab:

Very common (may affect more than 1 in 10 people)
- decreased appetite;
- weight loss
- fatigue (feeling tired);
- pyrexia (fever);
- cough
- abdominal pain (pain in the belly)
- pain
- nausea (feeling sick)
- vomiting
- diarrhoea/ colitis (inflammation in the large bowel)
- constipation
- neuropathy (nerve damage)
- anaemia (low levels of red blood cells)
- thrombocytopenia (low levels of blood platelets, components which help the blood to clot)
- leucopenia (low levels of white blood cells)
- neutropenia (low levels of neutrophils, a type of white blood cell)
- upper respiratory tract infection (nose and throat infection)
- hyponatraemia (low blood sodium levels)
- hypoproteinaemia (low blood protein levels)
- hypokalaemia (low blood potassium levels which can cause weakness, muscle cramps, tingling and heart rhythm disturbance)
- hyperglycaemia (high blood glucose levels)
- hyperuricaemia (high blood levels of uric acid, a byproduct of metabolism)
- hyperbilirubinaemia (high blood levels of bilirubin, a breakdown product of red blood cells, which can cause yellowing of the skin and eyes)

- proteinuria (excess protein in the urine)
- haematuria (blood in the urine)
- rash including skin inflammation, itching, skin blistering, peeling or sores, acne-like skin problem
- pruritis (itching)
- pain
- musculoskeletal (muscle and bone) pain
- hypothyroidism (an underactive thyroid gland with tiredness, weight gain, and skin and hair changes)
- arrhythmia (abnormal or irregular heartbeat)
- abnormal results for tests of liver function
- abnormal results for tests of thyroid function
- abnormal results for tests of blood levels of lipids
- abnormal results for tests of urine analysis

Common (may affect up to 1 in 10 people)
- vomiting; bloating and distended belly; acid reflux; blood in the stool;
- decrease in flow of bowel content or bowel occlusion
- sores or burning sensation in the mouth, gums, throat or oesophagus; dry mouth; toothache
- overactive thyroid gland activity;
- chills; influenza like illness
- pain (in muscle, bones, lymph nodes, chest)
- eye disorder (dry or itchy eye, cataract)
- kidney damage
- shortness of breath; inflammation of the lungs, fluid around the lungs; nose bleeding, coughing up blood, upper respiratory tract congestion or irritation
- decrease in the number of platelets (bruising or bleeding more easily)
- trouble sleeping; change in mood
- night sweats; increased sweating
- inflammation of the nerves causing numbness, weakness, tingling or burning pain; headache; dizziness
- lung infection, urinary infection, infection, ear infections, fungal infection of the mouth, herpes virus infection
- skin colour change in patches (including loss of pigmentation, vitiligo), hair loss, dry skin, hair colour changes, increased sensitivity to sunlight, skin peeling or sores
- muscle weakness
- inflammation of the liver
- high or low blood pressure; blood clots; cancer pain
- ear disorder, ear pain, ringing; hearing loss; blurred vision
- lung infection, upper respiratory tract infection, urinary infection

Uncommon (may affect up to 1 in 100 people)
- inflammation of the stomach
- inflammation of the pancreas
- type 1 diabetes, including diabetic ketoacidosis
- muscle pain
- temperature intolerance, thirst
- breathing difficulties, wheezing, hoarseness
- sinus congestion, abnormal speaking sound
- reactions related to the infusion of the medicine
- change in your sense of taste; drowsiness; speech disorder
- conjunctivitis, gingivitis, infections of skin and subcutaneous tissue
- inflammation of the joints; bulging disc; muscle spasms
- liver pain, gallbladder inflammation

- decreased secretion of hormones produced by the adrenal glands; inflammation of the pituitary
- gland situated at the base of the brain; inflammation of the thyroid
- accumulation of fluid around the heart; inflammation of the heart muscle; heart muscle damage
- tumour bleeding, tumour rupture
- oedema genital, scrotal oedema
- inflammation of the eye (which causes eye pain and redness), problems with coordinated eye movement; swelling of the optic nerve
- allergic reaction

Rare (may affect up to 1 in 1 000 people)
- gas in the intestinal wall, loss of sensation in the mouth, swollen or discoloured tongue
- inflammation of the layers that cover the lungs; increased amount of sputum
- vocal cord thickening
- diverticulitis
- inflammation of the skin (thickened, sometimes scaly skin growth; chronic itching or scaling; pain of skin)
- inflammation of the muscles which may include muscle pain or weakness (myositis) and could be associated with a rash (dermatomyositis)
- inflammation of subcutaneous fat, skin bruises
- overactive parathyroid gland activity; reduced pituitary gland activity
- paralysis in the extremities, disturbance in attention
- bulge in the aorta
- abnormal menstruation
- vaginal discharge or itching or pain of the skin outside vagina
- hearing loss; feeling off balance
- swelling, itching eyelid; farsightedness
- infection

Contact your healthcare providers if you experience any of these side effects listed immediately above.

Changes in test results
LOQTORZI alone or in combination may cause changes in the results of tests carried out by your doctor. These include:
- abnormal liver function tests (including increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, or alkaline phosphatase in your blood)
- abnormal kidney function tests (increased amounts of creatinine or other waste products, uric acid, urea in your blood; increase in the number of cells or amount of protein in urine, abnormal amount of waste products in urine)
- an increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- decreased amount of potassium, calcium, sodium, magnesium, chloride, phosphate, and protein in the blood
- increased amount of calcium, potassium, magnesium, sodium, or phosphate in the blood
- increased blood level of muscle enzymes
- abnormal thyroid function tests; anti-thyroid antibody positive; weight increased
- abnormal lipids and protein in the blood
- changes to the acid base balance in blood
- decreased in more than one type of blood cells (white blood cells, red blood cells, platelets)
- increased white blood cells, neutrophils; eosinophil count abnormal, platelet count increased;
- increase or decrease blood levels of endocrine gland hormones
- heart test abnormal

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LOQTORZI

LOQTORZI will be given to you in a hospital or clinic and the healthcare professionals will be responsible for its storage.

If you are given a carton of LOQTORZI, this is how it should be stored:
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and vial label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store in the original carton in order to protect from light.
- If the diluted solution is not used immediately, it may be stored at room temperature (up to 25 °C) for up to 8 hours or at 2 °C to 8 °C for up to 24 hours from the time of dilution to the end of administration.
- Do not use if this medicine contains visible particles.
- Do not store any unused medicine for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

6. Contents of the pack and other information

What LOQTORZI contains
- The active substance is toripalimab.

One vial of 6 mL concentrate for solution for infusion contains 240 mg of toripalimab.

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

- The other ingredients are citric acid monohydrate, mannitol, polysorbate 80, sodium chloride, sodium citrate dihydrate (Section 2 “LOQTORZI contains sodium”) and water for injections.

What LOQTORZI looks like and contents of the pack
LOQTORZI is supplied as a clear to slightly opalescent, colourless to slightly yellow solution, essentially free from visible particles.

It is available in cartons containing one glass vial containing 6 mL of concentrate for solution for infusion.

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

Manufacturer
Eurofins PHAST GmbH
Kardinal-Wendel-Strasse 16
Homburg
Saarland
66424
Germany

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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 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 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 medicines 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.