

JEMPERLI

1. GENERIC NAME

Dostarlimab concentrate for solution for infusion 500 mg/10 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab.

Each mL of concentrate for solution for infusion contains 50 mg of dostarlimab.

List of excipients

Trisodium citrate dihydrate

Citric acid monohydrate

L-arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection

3. DOSAGE FORM AND STRENGTH

Concentrate for solution for infusion (sterile concentrate).

500 mg/10 mL

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

4.2. Posology and Method of Administration

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

The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as IHC, PCR or NGS* (see section 5.2 for information on assays used in the studies).

*IHC=immunohistochemistry; PCR=polymerase chain reaction; NGS=next-generation sequencing.


Posology

The recommended dose as monotherapy is 500 mg dostarlimab every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter.

The dosage regimen is presented in Table 1.

Table 1. Dosage regimen for patients treated with *JEMPERLI*

	500 mg Once Every 3 Weeks (1 Cycle = 3 weeks)				1000 mg Once Every 6 Weeks until disease progression or unacceptable toxicity (1 cycle = 6 weeks)			
Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Continue dosing Q6W
Week	1	4	7	10	13	19	25	


3 weeks between cycle 4 and cycle 5

Administration of dostarlimab should continue according to the recommended dose and schedule until disease progression or unacceptable toxicity (*See section 5.2. Pharmacodynamic properties*).

Dose modifications

Dose reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 2.

Detailed guidelines for the management of immune-related adverse reactions and infusion-related reactions are described in *Section 4.4. Special Warnings and Precautions for Use*.

Table 2. Recommended dose modifications for *JEMPERLI*

Immune-related adverse reactions	Severity grade ^a	Dose modification
Colitis	2 or 3	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
	4	Permanently discontinue.
Hepatitis	Grade 2 with AST ^b or ALT ^c > 3 and up to 5 × ULN ^d or total bilirubin > 1.5 and up to 3 × ULN	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
	Grade ≥ 3 with AST or ALT > 5 × ULN or total bilirubin > 3 × ULN	Permanently discontinue (see exception below) ^e .
Type 1 diabetes mellitus (T1DM)	3 or 4 (hyperglycaemia)	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients.

Immune-related adverse reactions	Severity grade ^a	Dose modification
Hypophysitis or adrenal insufficiency	2, 3 or 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy.
Hypothyroidism or hyperthyroidism	3 or 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1. If grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Nephritis	2	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
	3 or 4	Permanently discontinue.
Exfoliative dermatologic conditions (e.g., SJS, TEN, DRESS)	Suspected	Withhold dose for any grade. Restart dosing if not confirmed and when toxicity resolves to grade 0 or 1.
	Confirmed	Permanently discontinue.
Myocarditis	2, 3 or 4	Permanently discontinue.
Severe neurological toxicities (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis)	2, 3 or 4	Permanently discontinue.
Other immune-related adverse reactions (including but not limited to myositis, sarcoidosis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, uveitis, diabetic ketoacidosis, arthralgia, solid organ transplant rejection, graft-versus-host disease)	3	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
	4	Permanently discontinue.

Immune-related adverse reactions	Severity grade ^a	Dose modification
Recurrence of immune-related adverse reactions after resolution to \leq grade 1 (except for pneumonitis, see above)	3 or 4	Permanently discontinue.
Other adverse reactions	Severity grade ^a	Dose modification
Infusion-related reactions	2	Withhold dose. If resolved within 1 hour of stopping, may be restarted at 50 % of the original infusion rate, or restart when symptoms resolve with pre-medication. If grade 2 recurs with adequate premedication, permanently discontinue.
	3 or 4	Permanently discontinue.

^a Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

^b AST = aspartate aminotransferase

^c ALT = alanine aminotransferase

^d ULN = upper limit of normal

^e For patients with liver metastases who begin treatment with grade 2 increase of AST or ALT, if AST or ALT increases by ≥ 50 % relative to baseline and lasts for at least 1 week, then treatment should be discontinued.

Special populations

Elderly

No dose adjustment is recommended for patients who are aged 65 years or over.

There is limited clinical data in with dostarlimab patients aged 75 years or over (see section 5.2. *Pharmacodynamic Properties*).

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is limited data in patients with severe renal impairment or end stage renal disease undergoing dialysis (see section 5.3. *Pharmacokinetic Properties*).

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. There is limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment (see section 5.3. *Pharmacokinetic Properties*).

Paediatric population

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

Method of administration

JEMPERLI is for intravenous infusion only. *JEMPERLI* should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes.

JEMPERLI must not be administered as an intravenous push or bolus injection.

For instructions on dilution of the medicinal product before administration, *see section 8.4. Storage and Handling Instructions*

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2. *Qualitative and Quantitative composition*

4.4. Special Warnings and Precautions for Use

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 *JEMPERLI*. 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 for symptoms and signs of immune related adverse reactions. Haematological and clinical chemistries, including liver, kidney and thyroid function tests, should be evaluated at baseline and periodically during treatment. For suspected immune related adverse reactions, adequate evaluation including specialty consultation should be ensured.

Based on the severity of the adverse reaction, treatment with dostarlimab should be withheld or permanently discontinued and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy administered (*see below and section 4.2 Posology and Method of Administration*). Upon improvement to Grade ≤ 1 , corticosteroid taper should be initiated and continued for 1 month or longer. Based on limited data from clinical studies in patients whose immune related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Hormone replacement therapy for endocrinopathies should be instituted as warranted.

Treatment with dostarlimab should 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 and unless otherwise specified in Table 2.

Immune-related pneumonitis

Pneumonitis has been reported in patients receiving dostarlimab (*see section 4.8 Undesirable effects*). 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

dostarlimab treatment modifications and corticosteroids (*see section 4.2 Posology and Method of Administration*).

Immune-related colitis

Dostarlimab can cause immune-related colitis (*see section 4.8 Undesirable Effects*). Patients should be monitored for signs and symptoms of colitis and managed with dostarlimab treatment modifications, anti diarrhoeal agents and corticosteroids (*see section 4.2 Posology and Method of Administration*).

Immune-related hepatitis

Dostarlimab can cause immune-related hepatitis (*see section 4.8 Undesirable Effects*). Patients should be monitored for changes in liver function periodically as indicated, based on clinical evaluation and managed with dostarlimab treatment modifications and corticosteroids (*See section 4.2 Posology and Method of Administration*).

Immune-related endocrinopathies

Immune-related endocrinopathies, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis and adrenal insufficiency, have been reported in patients receiving dostarlimab (*see section 4.8 Undesirable Effects*).

Hypothyroidism and hyperthyroidism

Immune related hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving dostarlimab, and hypothyroidism may follow hyperthyroidism. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) should be managed as recommended (*see section 4.2 Posology and Method of Administration*).

Adrenal insufficiency

Immune-related adrenal insufficiency occurred in patients receiving dostarlimab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended (*see section 4.2 Posology and Method of Administration*).

Immune-related nephritis

Dostarlimab can cause immune-related nephritis (*see section 4.8 Undesirable Effects*). Patients should be monitored for changes in renal function and manage with dostarlimab treatment modifications and corticosteroids (*see section 4.2 Posology and Method of Administration*).

Immune-related rash

Immune-related rash has been reported in patients receiving dostarlimab, including pemphigoid (*see section 4.8 Undesirable Effects*). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended (*see section 4.2 Posology and Method of Administration*). Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors.

Caution should be used when considering the use of dostarlimab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune stimulatory anticancer agents.

Immune related arthralgia

Immune-related arthralgia has been reported in patients receiving dostarlimab (*see section 4.8 Undesirable Effects*). Patients should be monitored for signs and symptoms of arthralgia. Suspected immune-related

arthralgia should be confirmed and other causes excluded. Patients should be managed with dostarlimab treatment modifications and corticosteroids (*see section 4.2 Posology and Method of Administration*).

Other immune related adverse reactions

Given the mechanism of action of dostarlimab other potential immune-related adverse reactions may occur, including potentially serious events [e.g. myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis]. Clinically significant immune related adverse reactions reported in less than 1 % of patients treated with dostarlimab as monotherapy in clinical studies include encephalitis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis and uveitis. Patients should be monitored for signs and symptoms of immune related adverse reactions and managed as described in *section 4.2 Posology and Method of Administration*. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with dostarlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with dostarlimab versus the risk of possible organ rejection should be considered in these patients.

Fatal and other serious complications can occur in patients who receive 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 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

Dostarlimab can cause infusion-related reactions, which can be severe (*see section 4.8 Undesirable Effects*) For severe (grade 3) or life threatening (grade 4) infusion-related reactions, the infusion should be stopped and treatment should be permanently discontinued (*see section 4.2 Posology and Method of Administration*).

Patients excluded from clinical studies

Patients with the following status were excluded from the GARNET study: ECOG baseline performance score ≥ 2 ; uncontrolled central nervous system metastases or carcinomatous meningitis; other malignancies within the last 2 years; immunodeficiency or receiving immunosuppressive therapy within 7 days; active HIV, hepatitis B or hepatitis C infection; active autoimmune disease requiring systemic treatment in the past 2 years excluding replacement therapy; history of interstitial lung disease; or receiving live vaccine within 14 days.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e. essentially “sodium-free”.

4.5. Drug Interactions

No interaction studies have been performed. Monoclonal antibodies (mAb) such as dostarlimab are not substrates for cytochrome P450 or active substance transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of dostarlimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies.

4.6. Use in Special Populations

Women of childbearing potential/Contraception

There is a risk associated with the administration of dostarlimab to women of childbearing potential. Women of childbearing potential must use effective contraception during treatment with dostarlimab and until 4 months after the last dose of dostarlimab.

Pregnancy

There are no or limited amount of data on the use of dostarlimab in pregnant women. Based on its mechanism of action, dostarlimab can cause foetal harmful pharmacological effects when administered during pregnancy.

Animal reproduction and development studies have not been conducted with dostarlimab; however, inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune mediated rejection of the developing foetus resulting in foetal death (*see section 6. Nonclinical Properties*). Human immunoglobulins (IgG4) are known to cross the placental barrier, and therefore, being an IgG4, dostarlimab has the potential to be transmitted from the mother to the developing foetus. The potential for harm to a human fetus is unknown.

JEMPERLI is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether dostarlimab/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

JEMPERLI should not be used during breast feeding and breast feeding should be avoided for at least 4 months after the last dose of dostarlimab.

Fertility

Fertility studies have not been conducted with dostarlimab (*see section 6. Nonclinical Properties*).

4.7. Effects on Ability to Drive and Use Machines

JEMPERLI has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable Effects

Summary of the safety profile

The safety of dostarlimab has been evaluated in 605 patients with endometrial cancer or other advanced solid tumours who received dostarlimab monotherapy in the GARNET study, including 153 patients with advanced or recurrent dMMR/MSI-H endometrial cancer. Patients received doses of 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter. Dostarlimab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of dostarlimab (*see "Description of selected adverse reactions" below*).

In patients with advanced or recurrent solid tumours (N = 605), most common adverse reactions (> 10 %) were anaemia (28.6 %), diarrhoea (26.0 %), nausea (25.8 %), vomiting (19.0 %), arthralgia (17.0 %), pruritus (14.2 %), rash (13.2 %), pyrexia (12.4 %), aspartate aminotransferase increased (11.2 %) and hypothyroidism (11.2 %). *JEMPERLI* was permanently discontinued due to adverse reactions in 38 (6.3 %) patients; most of them were immune related events. Adverse reactions were serious in 11.2 % of patients; most serious adverse reactions were immune-related adverse reactions (*See section 4.4 Special Warnings and Precautions for Use*).

The safety profile for patients with dMMR/MSI-H endometrial cancer in the GARNET study (N=153) was not different from that of the overall monotherapy population presented in Table 3.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials are listed by system organ class and by frequency. Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequency identified in 605 patients with advanced or recurrent solid tumours from the GARNET study exposed to dostarlimab monotherapy for a median duration of treatment of 24 weeks (range: 1 week to 229 weeks).

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available data).

Table 3: Adverse reactions in patients treated with dostarlimab

System Organ Class	Frequency of all grades	Frequency of grades 3-4
Blood and lymphatic system disorders	Very common Anaemia ^a	Common Anaemia ^a
Endocrine disorders	Very common Hypothyroidism ^{*b} Common Hyperthyroidism [*] , adrenal insufficiency Uncommon Thyroiditis ^c , hypophysitis ^d	Uncommon Adrenal insufficiency, hyperthyroidism
Metabolism and nutrition disorders	Uncommon Type 1 diabetes mellitus, diabetic ketoacidosis	Uncommon Type 1 diabetes mellitus, diabetic ketoacidosis
Nervous system disorders	Uncommon Encephalitis, myasthenia gravis, myasthenic syndrome ^e	Uncommon Encephalitis, myasthenic syndrome ^e
Eye disorders	Uncommon Uveitis ^f	
Cardiac disorders	Uncommon Myocarditis ^{e, g}	Uncommon Myocarditis ^{e, g}
Respiratory, thoracic and mediastinal disorders	Common Pneumonitis ^{*h}	Common Pneumonitis ⁱ
Gastrointestinal disorders	Very common Diarrhoea, nausea, vomiting Common Colitis ^{*j} , pancreatitis ^k , gastritis ^l Uncommon Oesophagitis	Common Nausea, vomiting, diarrhoea Uncommon Pancreatitis ^k , colitis ^m , gastritis ^l , oesophagitis
Hepatobiliary disorders	Common	Uncommon

System Organ Class	Frequency of all grades	Frequency of grades 3-4
	Hepatitis ⁿ	Hepatitis ⁿ
Skin and subcutaneous tissue disorders	Very common Rash ^o , pruritus	Common Rash ^p Uncommon Pruritus
Musculoskeletal and connective tissue disorders	Very common Arthralgia Common Myalgia Uncommon Immune-mediated arthritis, polymyalgia rheumatica, myositis ^q	Uncommon Arthralgia, immune-mediated arthritis, myositis ^q
Renal and urinary disorders	Uncommon Nephritis ^{*r}	
General disorders and administration site conditions	Very common Pyrexia Common Chills Uncommon Systemic inflammatory response syndrome ^s	Uncommon Pyrexia, chills, Systemic inflammatory response syndrome ^s
Investigations	Very common Transaminases increased ^t	Common Transaminases increased ^u
Injury, poisoning and procedural complications	Common Infusion-related reaction ^v	Uncommon Infusion-related reaction

* See section 'Description of selected adverse reactions.'

^a Includes anaemia and autoimmune haemolytic anaemia

^b Includes hypothyroidism and autoimmune hypothyroidism

^c Includes thyroiditis and autoimmune thyroiditis

^d Includes hypophysitis and lymphocytic hypophysitis

^e Reported from ongoing blinded trials of dostarlimab in combination, estimated frequency category

^f Includes uveitis and iridocyclitis

^g Includes myocarditis and immune-mediated myocarditis

^h Includes pneumonitis, interstitial lung disease and immune-mediated lung disease

ⁱ Includes pneumonitis and interstitial lung disease

^j Includes colitis, enterocolitis and immune-mediated enterocolitis (monotherapy pool), and enteritis reported from ongoing blinded trial of dostarlimab in combination, estimated frequency category

^k Includes pancreatitis and pancreatitis acute

^l Includes gastritis (monotherapy pool), and immune-mediated gastritis and vasculitis gastrointestinal reported from ongoing blinded trial of dostarlimab in combination, estimated frequency category.

^m Includes colitis and immune-mediated enterocolitis (monotherapy pool), and enteritis reported from ongoing blinded trial of dostarlimab in combination, estimated frequency category

ⁿ Includes hepatitis, autoimmune hepatitis and hepatic cytolysis

^o Includes rash, rash maculo-papular, erythema, rash macular, rash pruritic, rash erythematous, rash papular, erythema multiforme, skin toxicity, drug eruption, toxic skin eruption, exfoliative rash and pemphigoid

^p Includes rash, rash maculo-papular and drug eruption

^q Includes myositis reported in an ongoing trial of dostarlimab in combination, and immune-mediated myositis (monotherapy pool); estimated frequency category

^r Includes nephritis and tubulointerstitial nephritis

^s Reported from an ongoing trial of dostarlimab in combination, estimated frequency category

^t Includes transaminases increased, alanine aminotransferases increased, aspartate aminotransferases increased and hypertransaminasaemia

^u Includes alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased

^v Includes infusion-related reaction and hypersensitivity.

Description of selected adverse reaction

The selected adverse reactions described below are based on the safety of dostarlimab in a combined monotherapy safety database of 605 patients in the GARNET study in patients with endometrial cancer or other advanced solid tumours. Immune related adverse reactions were defined as events of grade 2 and above; the frequencies below exclude grade 1 events. The management guidelines for these adverse reactions are described in *section 4.2 Posology and Method of Administration*.

Immune-related adverse reactions (see section 4.4 Special Warnings and Precautions for Use)

Immune-related pneumonitis

Immune-related pneumonitis occurred in 14 (2.3 %) patients, including grade 2 (1.3 %), grade 3 (0.8 %) and grade 4 (0.2 %) pneumonitis. Pneumonitis led to discontinuation of dostarlimab in 8 (1.3 %) patients.

Systemic corticosteroids (prednisone \geq 40 mg per day or equivalent) were required in 11 (78.6 %) patients experiencing pneumonitis. Pneumonitis resolved in 11 (78.6 %) patients.

Immune-related colitis

Colitis occurred in 8 (1.3 %) patients, including grade 2 (0.7 %) and grade 3 (0.7 %) colitis. Colitis did not lead to discontinuation of dostarlimab in any patients.

Systemic corticosteroids (prednisone \geq 40 mg per day or equivalent) were required in 5 (62.5 %) patients. Colitis resolved in 5 (62.5 %) patients experiencing colitis.

Immune-related hepatitis

Hepatitis occurred in 3 (0.5 %) patients, all of which were grade 3. Systemic corticosteroids (prednisone \geq 40 mg per day or equivalent) were required in 2 (66.7 %) patients. Hepatitis led to discontinuation of dostarlimab in 1 (0.2%) patient and resolved in 2 of the 3 patients.

Immune-mediated endocrinopathies

Hypothyroidism occurred in 46 (7.6 %) patients, all of which were grade 2. Hypothyroidism did not lead to discontinuation of dostarlimab and resolved in 17 (37.0 %) patients.

Hyperthyroidism occurred in 14 (2.3 %) patients, including grade 2 (2.1 %) and grade 3 (0.2 %). Hyperthyroidism did not lead to discontinuation of dostarlimab and resolved in 10 (71.4 %) patients.

Thyroiditis occurred in 3 (0.5 %) patients; all were grade 2. None of the events of thyroiditis resolved; there were no discontinuations of dostarlimab due to thyroiditis.

Adrenal insufficiency occurred in 7 (1.2 %) patients, including grade 2 (0.5 %), and grade 3 (0.7 %). Adrenal insufficiency resulted in discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 4 (57.1 %) patients.

Immune-mediated nephritis

Nephritis, including tubulointerstitial nephritis, occurred in 3 (0.5 %) patients; all were grade 2. Systemic corticosteroids (prednisone \geq 40 mg per day or equivalent) were required in 2 (66.7 %) patients experiencing nephritis. Nephritis led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in all 3 patients.

Immune-related rash

Immune-related rash (rash, rash maculo-papular, rash macular, rash pruritic, pemphigoid, drug eruption, skin toxicity, toxic skin eruption) occurred in 31 (5.1 %) patients, including Grade 3 in 9 (1.5 %) patients receiving dostarlimab. The median time to onset of rash was 57 days (range 2 days to 1485 days). Systemic corticosteroids (prednisone \geq 40 mg per day or equivalent) were required in 9 (29.0 %) patients experiencing rash. Rash led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 24 (77.4 %) patients.

Immune-related arthralgia

Immune related arthralgia occurred in 34 (5.6 %) patients. Grade 3 immune related arthralgia was reported in 5 (0.8 %) patients receiving dostarlimab. The median time to onset of arthralgia was 94.5 days (range 1 day to 840 days). Systemic corticosteroids (prednisone \geq 40 mg per day or equivalent) were required in 3 (8.8 %) patients experiencing arthralgia. Arthralgia led to discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 19 (55.9 %) patients experiencing arthralgia.

Infusion-related reactions

Infusion related reactions including hypersensitivity occurred in 6 (1.0 %) patients, including grade 2 (0.3 %) and grade 3 (0.2 %) infusion related reactions. All patients recovered from the infusion related reaction.

Immunogenicity

Anti-drug antibodies (ADA) were tested in 315 patients who received dostarlimab and the incidence of dostarlimab treatment emergent ADAs was 2.5 %. Neutralising antibodies were detected in 1.3 % of patients. In the patients who developed anti-dostarlimab antibodies, there was no evidence of altered efficacy or safety of dostarlimab.

Elderly population

Of the 605 patients treated with dostarlimab monotherapy, 51.6 % were under 65 years, 36.9 % were 65 to less than 75 years, and 11.5 % were 75 years or older. No overall differences in safety were reported between elderly (\geq 65 years) and younger patients ($<$ 65 years).

4.9. Overdose

If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Anti neoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FF07

5.1. Mechanism of Action

Dostarlimab is a humanised mAb of the IgG4 isotype that binds to PD-1 receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway mediated immune response results in inhibition of T cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti tumour immuno responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

5.2. Pharmacodynamic Properties

Clinical efficacy and safety

The efficacy and safety of *JEMPERLI* were investigated in the GARNET study, a multicentre, uncontrolled, multiple parallel cohorts, open-label study. The GARNET study included expansion cohorts in subjects with recurrent or advanced solid tumours who have limited available treatment options. Cohort A1 enrolled patients with mismatch repair deficient (dMMR)/microsatellite instability- high (MSI-H) EC who have progressed on or after a platinum-containing regimen.

Patients received 500 mg dostarlimab every 3 weeks for 4 cycles followed by 1000 mg dostarlimab every 6 weeks. Treatment continued until unacceptable toxicity or disease progression for up to two years.

The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by blinded independent central radiologists' (BICR) review according to response evaluation criteria in solid tumours (RECIST) v 1.1. The efficacy population was defined as patients who had measurable disease by BICR at baseline and had minimum of 24 weeks follow-up or had less than 24 weeks of follow-up and discontinued due to adverse events or disease progression.

A total of 143 patients with dMMR/MSI-H EC were evaluated for efficacy in the GARNET study.

Among these 143 patients, the baseline characteristics were: median age of 65 years (52 .0 % aged 65 years or older); 77 % white, 3.5 % Asian, 2.8 % black; and eastern cooperative oncology group (ECOG) performance status (PS) 0 (39 %) or 1 (61 %). At the time of diagnosis, 21 % of the patients with dMMR/MSI-H EC were International Federation of Gynecology and Obstetrics (FIGO) Stage IV. At study entry (the most recent FIGO stage), 67 % of the patients were FIGO Stage IV. The median number of prior lines of therapy was one: 63 % of patients had one prior line, 37 % had two or more prior lines. Forty-nine patients (34 %) received treatment only in the neoadjuvant or adjuvant setting before participating in the study.

The identification of dMMR/MSI-H tumour status was prospectively determined based on local testing.

Local diagnostic assays (IHC, PCR or NGS) available at the sites were used for the detection of the dMMR/MSI-H expression in tumour material. Most of the sites used IHC as it was the most common assay available.

Table 4 includes the efficacy data for the 143 patients . The overall median treatment duration in weeks was 34 (range 2 to 220). Twenty four percent of subjects who received any amount of dostarlimab received treatment >102 weeks (2 years).

Table 4: Efficacy results in GARNET for patients with dMMR/MSI-H endometrial cancer

Endpoint	Results (N=143) ^a
Objective response rate (ORR)	
ORR n (%) (95 % CI)	65 (45.5) (37.1, 54.0)
Complete response rate, n (%)	23 (16.1)
Partial response rate, n (%)	42 (29.4)
Duration of response (DOR)^b	
Median in months	Not reached
Patients with duration \geq 12 months, n (%)	52 (80.0)
Patients with duration \geq 24 months, n (%)	29 (44.6)

Disease control rate (DCR)^c	
DCR n (%)	86 (60.1)
(95 % CI)	(51.6, 68.2)

CI: Confidence interval

^a Efficacy data with a median follow-up of 27.6 months (cut-off date 01 Nov 2021)

^b For patients with a partial or complete response.

^c includes patient with complete response, partial response and stable disease for at least 12 weeks.

Efficacy and PD-L1 status

Clinical activity was observed regardless of tumour PD-L1 combined positive score (CPS) by IHC. The relationship between PD-L1 status and efficacy was analysed post-hoc in patients with available tissue samples (N = 81) among the efficacy population from Cohort A1 using a data cut-off date of 01 March 2020. Among 23 patients with PD-L1 CPS < 1 %, ORR was 30.4 % (7/23, 95 % CI 13.2, 52.9) and among 58 patients with PD-L1 CPS ≥ 1 %, ORR was 55.2 % (32/58, 95 % CI 41.5, 68.3).

Elderly patients

Of the 108 patients treated with dostarlimab in the efficacy population, 50.0 % were older than 65 years.

Consistent results were observed in the elderly population, where the ORR by BICR (95% CI) was 42.6 % (29.2 %, 56.8 %) in patients ≥ 65 years.

Paediatric population

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

5.3. Pharmacokinetic Properties

Dostarlimab was characterized using population PK analysis from 477 patients with various solid tumours, including 267 patients with EC. When dosed at the recommended therapeutic dose (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks), dostarlimab shows an approximate two-fold accumulation (C_{min}) starting cycle 4 through cycle 12, consistent with the terminal half-life ($t_{1/2}$).

Absorption

Dostarlimab is administered via the intravenous route and therefore estimates of absorption are not applicable.

Distribution

The mean volume of distribution of dostarlimab at steady state is approximately 5.3 L (CV % of 12.3 %).

Biotransformation

Dostarlimab is a therapeutic mAb IgG4 that is expected to be catabolised into small peptides, amino acids, and small carbohydrates by lysosome through fluid phase or receptor mediated endocytosis. The degradation products are eliminated by renal excretion or returned to the nutrient pool without biological effects.

Elimination

The mean clearance is 0.007 L/h (CV % of 31.3 %) at steady state. The $t_{1/2}$ at steady state is 25.4 days (CV % of 24.0 %).

Linearity/non-linearity

Exposure (both maximum concentration [C_{max}] and the area under the concentration time curve, [$AUC_{0-\tau}$] and [AUC_{0-inf}]) was approximately dose proportional.

Pharmacokinetic/pharmacodynamic relationship

Based on exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety when doubling the exposure of dostarlimab. Full receptor occupancy as measured by both the direct PD-1 binding and interleukin 2 (IL-2) production functional assay was maintained throughout the dosing interval at the recommended therapeutic dosing regimen.

Special populations

A population PK analysis of the patient data indicates that there are no clinically important effects of age (range: 24 to 86 years), gender or race, ethnicity, or tumour type on the clearance of dostarlimab.

Renal impairment

Renal impairment was evaluated based on the estimated creatinine clearance [CL_{CR} mL/min] (normal: $CL_{CR} \geq 90$ mL/min, $n = 173$; mild: $CL_{CR} = 60-89$ mL/min, $n = 210$; moderate: $CL_{CR} = 30-59$ mL/min, $n = 90$; severe: $CL_{CR} = 15-29$ mL/min, $n = 3$ and ESRD: $CL_{CR} < 15$ mL/min, $n = 1$). The effect of renal impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of dostarlimab were found between patients with mild or moderate renal impairment and patients with normal renal function. There are limited data in patients with severe renal impairment.

Hepatic impairment

Hepatic impairment was evaluated as defined using the US National Cancer Institute criteria of hepatic dysfunction by total bilirubin and AST (Normal: total bilirubin (TB) & AST \leq upper limit of normal (ULN), $n = 425$; mild: TB $>$ ULN to 1.5 ULN or AST $>$ ULN, $n = 48$; and moderate: TB $>$ 1.5-3 ULN, any AST, $n = 4$). The effect of hepatic impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment compared to patients with normal hepatic function. No clinically important differences in the clearance of dostarlimab were found between patients with mild hepatic impairment and normal hepatic function. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

Nonclinical data reveal no special hazard for humans based on repeat-dose toxicity studies of duration up to 3 months in the cynomolgus monkey. No studies have been performed to assess the potential of

dostarlimab for carcinogenicity or genotoxicity. Animal reproduction and development toxicity studies have not been conducted with dostarlimab. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of dostarlimab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

No notable effects on the male and female reproductive organs were observed in monkeys in the 1-month and 3-month repeat-dose toxicology studies; however, these results may not be representative at all of the potential clinical risk because of the immaturity of the reproductive system of animals used in the studies. Therefore, fertility toxicity remains unknown.

7. DESCRIPTION

One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab. Each mL of concentrate for solution for infusion contains 50 mg of dostarlimab. *See section 2. Qualitative and Quantitative composition.*

Clear to slightly opalescent colourless to yellow solution, essentially free from visible particles.

The concentrate for solution for infusion has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2. Shelf Life

Unopened vial

36 months

After Dilution

If not used immediately, in-use chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C –8 °C and 6 hours at room temperature (up to 25 °C) from the time of preparation/dilution until the end of administration.

The expiry date is indicated on the label and packaging.

8.3. Packaging Information

10 mL type I borosilicate clear glass vial, with a grey chlorobutyl elastomer stopper laminated with fluoropolymer, sealed with an aluminium flip off cap containing 500 mg dostarlimab.

Each carton contains one vial.

8.4. Storage and Handling Instructions

Store in a refrigerator (+2°C to +8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, *see section 8.2 Shelf Life*.

Preparation/dilution

JEMPERLI should be inspected visually for particulate matter and discolouration prior to administration. *JEMPERLI* is a slightly opalescent colourless to yellow solution. Discard the vial if visible particles are observed.

JEMPERLI is compatible with an IV bag made of polyvinyl chloride (PVC) with or without di(2-ethylhexyl) phthalate (DEHP), ethylene vinyl acetate, polyethylene (PE), polypropylene (PP) or polyolefin blend (PP+PE), and a syringe made from PP.

For the 500 mg dose, withdraw 10 mL of *JEMPERLI* from a vial and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection, or glucose 50 mg/mL (5 %) solution for injection. The final concentration of the diluted solution should be between 2 mg/mL and 10 mg/mL. This may require withdrawing a volume of diluent from the intravenous bag prior to adding a volume of *JEMPERLI* into the IV bag.

- For-example, if preparing a 500 mg dose in a 250 mL diluent intravenous bag, to achieve a 2 mg/mL concentration would require withdrawing 10 mL of diluent from the 250 mL intravenous bag. Then, 10 mL of *JEMPERLI* would be withdrawn from the vial and transferred into the intravenous bag.

For the 1000 mg dose, withdraw 10 mL of *JEMPERLI* from each of two vials (withdraw 20 mL total) and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection, or glucose 50 mg/mL (5 %) solution for injection. The final concentration of the diluted solution should be between 2 mg/mL and 10 mg/mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of *JEMPERLI* into the intravenous bag.

- For-example, if preparing a 1000 mg dose in a 500 mL diluent intravenous bag, to achieve a 2 mg/mL concentration would require withdrawing 20 mL of diluent from the 500 mL intravenous bag. Then, 10 mL of *JEMPERLI* would be withdrawn from each of two vials, totaling 20 mL, and transferred into the intravenous bag.

Mix diluted solution by gentle inversion. Do not shake the final infusion bag. Discard any unused portion left in the vial.

Storage

Store in the original carton until time of preparation in order to protect from light. The prepared dose may be stored either:

- At room temperature up to 25 °C for no more than 6 hours from the time of dilution until the end of infusion.
- Under refrigeration at 2 °C to 8 °C for no more than 24 hours from time of dilution until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Administration

JEMPERLI should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes by a health care practitioner. Tubing should be made of PVC, platinum cured silicon or PP; fittings made from PVC or polycarbonate and needles made from stainless steel. A 0.2 or 0.22 micron in-line polyether sulfone (PES) filter must be used during administration of *JEMPERLI*.

JEMPERLI must not be administered as an intravenous push or bolus injection.

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

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

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *JEMPERLI*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

M/s. Ajinomoto Althea, Inc. (dba Ajinomoto Bio-Pharma Services), 11040 Roselle Street, San Diego, CA 92121, United States

OR

M/s. Glaxo Operations UK Limited, (Trading as Glaxo Wellcome Operations), Harmire Road, Barnard Castle, DL12 8DT United Kingdom

For further information please contact:

GSK Pharma India Private Limited

Registered Office

01, Battery House,
Bhulabhai Desai Road, Mumbai, Maharashtra 400026
India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Marketing Authorization Holder: GSK Pharma India Private Limited, 01, Battery House, Bhulabhai Desai Road, Mumbai, Maharashtra 400026 India.

Marketing Authorization Details: IMP/BIO/23/000048 dated 01-May-2023

12. DATE OF REVISION

04-MAR-2024

Trade marks are owned by or licensed to the GSK group of companies.

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