

JEMPERLI

Dostarlimab

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 50 mg of dostarlimab.
One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab (50 mg/mL).

Clear to slightly opalescent colourless to yellow solution in a single-dose vial.

CLINICAL INFORMATION

Indications

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

Dosage and Administration

Pharmaceutical Form

Concentrate for solution for infusion.

Posology

The recommended dose as monotherapy is 500 mg *JEMPERLI* administered as an intravenous infusion over 30 minutes every 3 weeks for 4 doses 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
Week	1	4	7	10	13	19	25	Q6W

3 weeks between Cycle 4 and Cycle 5

Administration of *JEMPERLI* should continue according to the recommended dose and schedule until disease progression or unacceptable toxicity.

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 *Warnings and Precautions*.

Table 2. Recommended dose modifications for <i>JEMPERLI</i>		
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 (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 (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.
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.

Table 2. Recommended dose modifications for JEMPERLI

Immune-related adverse reactions	Severity grade^a	Dose modification
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 involving a major organ	3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Recurrence of immune-related adverse reactions after resolution to ≤ 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 AST or ALT, if AST or ALT increases by $\geq 50\%$ relative to baseline and lasts for at least 1 week, then treatment should be discontinued.

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 *Use and Handling*.

Children

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

Elderly

No dose adjustment is recommended for patients who are aged 65 years of age or over. There are limited clinical data with *JEMPERLI* in patients aged 75 years or over.

Renal impairment

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

Hepatic impairment

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients (*see List of Excipients*).

Warnings and Precautions

The data described in this section reflect exposure to *JEMPERLI* as monotherapy in patients with recurrent or advanced solid tumours in an open-label, single-arm, multicohort study (GARNET).

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. Monitor for symptoms and signs of immune-related adverse reactions. Evaluate haematological and clinical chemistries, including liver, kidney and thyroid function tests, 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, *JEMPERLI* 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 Posology, Dose modification*). Upon improvement to Grade 0 or 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. Institute hormone replacement therapy for endocrinopathies as warranted.

JEMPERLI 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 *JEMPERLI* (see *Adverse Reactions*). 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 *JEMPERLI* treatment modifications and corticosteroids (see *Posology*).

Immune-related colitis

JEMPERLI can cause immune-related colitis (see *Adverse Reactions*). Monitor patients for signs and symptoms of colitis and manage with *JEMPERLI* treatment modifications, anti-diarrhoeal agents and corticosteroids (see *Posology*).

Immune-related hepatitis

JEMPERLI can cause immune-related hepatitis. Monitor patients for changes in liver function periodically as indicated based on clinical evaluation and manage with *JEMPERLI* treatment modifications and corticosteroids (see *Posology*).

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 *JEMPERLI* (see *Adverse Reactions*).

Hypothyroidism and hyperthyroidism

Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving *JEMPERLI*, 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 in *Posology*.

Adrenal insufficiency

Immune-related adrenal insufficiency occurred in patients receiving *JEMPERLI*. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in *Posology*.

Immune-related nephritis

JEMPERLI can cause immune-related nephritis (see *Adverse Reactions*). Monitor patients for changes in renal function and manage with *JEMPERLI* treatment modifications and corticosteroids (see *Posology*).

Immune-related rash

Immune-related rash has been reported in patients receiving *JEMPERLI*, including pemphigoid (see *Adverse Reactions*). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended (see *Posology*). 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 *JEMPERLI* in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions

Given the mechanism of action of *JEMPERLI* other potential immune-related adverse reactions may occur. Clinically significant immune-related adverse reactions reported in less than 1% of patients treated with *JEMPERLI* as monotherapy in clinical trials include encephalitis, autoimmune haemolytic anaemia, uveitis and iridocyclitis. Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed as described in *Posology*.

Transplant-related adverse reaction

Solid organ transplant

Solid organ transplant rejection has been reported in the postmarketing 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.

Complications of allogeneic Haematopoietic Stem Cell transplant (HSCT)

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

JEMPERLI can cause infusion-related reactions, which can be severe (*see Adverse Reactions*). For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue *JEMPERLI* (*see Posology*).

Interactions

No drug-drug interaction studies have been conducted with *JEMPERLI*. Monoclonal antibodies (mAbs) such as *JEMPERLI* are not substrates for cytochrome P450 or drug transporters. *JEMPERLI* is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) drug-drug interaction of *JEMPERLI* with small molecule drugs is not expected. There is no evidence of drug-drug interaction mediated by non-specific clearance of lysosome degradation for antibodies.

Pregnancy and Lactation

Fertility

Fertility studies have not been conducted with dostarlimab.

Pregnancy

There are no available data on the use of *JEMPERLI* in pregnant women. Animal reproduction studies have not been conducted with dostarlimab to evaluate its effect on reproduction and foetal development. Based on its mechanism of action, *JEMPERLI* can cause foetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to foetal tissue. Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, dostarlimab has the potential to be transmitted from the mother to the developing foetus. Advise women of the potential risk to a foetus.

JEMPERLI is not recommended during pregnancy. Women of childbearing potential should use highly effective contraception during treatment with *JEMPERLI* and for 4 months after the last dose.

Lactation

There is no information regarding the presence of dostarlimab in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose of *JEMPERLI*.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical trial data

Adverse reactions observed in patients with recurrent or advanced solid tumours who received *JEMPERLI* monotherapy in the open-label, multicohort GARNET study are listed in Table 3. Additional immune-related adverse reactions identified based on pooled data generated from other clinical trials in patients with solid tumors receiving dostarlimab in combination with various types of anticancer therapies are also shown in Table 3.

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 with solid tumours treated with dostarlimab

System Organ Class	Frequency of all grades	Frequency of grades 3-4
Blood and lymphatic system disorders	Very common Anaemia Uncommon Autoimmune haemolytic anaemia	Common Anaemia Uncommon Autoimmune haemolytic anaemia
Endocrine disorders	Very common Hypothyroidism ^a Common Hyperthyroidism, adrenal insufficiency Uncommon Thyroiditis ^b , hypophysitis ^c	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 ^d	Uncommon Encephalitis, myasthenic syndrome ^d
Eye disorders	Uncommon Uveitis ^e	
Cardiac disorders	Uncommon Myocarditis ^{d, f}	Uncommon Myocarditis ^{d, f}
Respiratory, thoracic and mediastinal disorders	Common Pneumonitis ^g	Common Pneumonitis ^h
Gastrointestinal disorders	Very common Diarrhoea, nausea, vomiting Common Colitis ⁱ , pancreatitis ^j , gastritis ^k Uncommon Oesophagitis	Common Nausea, vomiting, diarrhoea Uncommon Pancreatitis ^j , colitis ^l , gastritis ^k , oesophagitis
Hepatobiliary disorders	Common Hepatitis ^m	Uncommon Hepatitis ^m
Skin and subcutaneous tissue disorders	Very common Rash ⁿ , pruritus	Common Rash ^o

		Uncommon Pruritus
Musculoskeletal and connective tissue disorders	Very Common Arthralgia Common Myalgia Uncommon Immune-mediated arthritis, polymyalgia rheumatica, myositis ^p	Uncommon Arthralgia, immune-mediated arthritis, myositis ^p
Renal and urinary disorders	Uncommon Nephritis ^q	
General disorders and administration site conditions	Very common Pyrexia Common Chills Uncommon Systemic inflammatory response syndrome ^r	Uncommon Pyrexia, chills, systemic inflammatory response syndrome ^r
Investigations	Very common Transaminases increased ^s	Common Transaminases increased ^t
Injury, poisoning and procedural complications	Common Infusion-related reaction ^u	Uncommon Infusion-related reaction

^a Includes hypothyroidism and autoimmune hypothyroidism

^b Includes thyroiditis and autoimmune thyroiditis

^c Includes hypophysitis and lymphocytic hypophysitis

^d Reported from ongoing blinded trials of dostarlimab in combination; estimated frequency category

^e Includes uveitis and iridocyclitis

^f Includes myocarditis and immune-mediated myocarditis

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

^h Includes pneumonitis and interstitial lung disease

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

^j Includes pancreatitis and pancreatitis acute

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

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

^m Includes hepatitis, autoimmune hepatitis and hepatic cytolysis

ⁿ Includes rash, rash maculopapular, erythema, rash macular, rash pruritic, rash erythematous, rash papular, erythema multiforme, skin toxicity, drug eruption, toxic skin eruption, exfoliative rash and pemphigoid

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

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

^q Includes nephritis and tubulointerstitial nephritis

^r Reported from an ongoing trial of dostarlimab in combination; estimated frequency category

^s Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased and hypertransaminasaemia

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

^u Includes infusion-related reaction and hypersensitivity.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dostarlimab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the GARNET study, anti-drug antibodies (ADA) were tested in 384 patients who received *JEMPERLI* and the incidence of dostarlimab treatment-emergent ADAs was 2.1%. Neutralising antibodies were detected in 1.0% of patients. In the patients who developed anti-dostarlimab antibodies, there was no evidence of altered pharmacokinetics, efficacy or safety of *JEMPERLI*.

Overdose

If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate standard of care measures should be instituted immediately.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Anti-neoplastic agents, monoclonal antibodies and antibody drug conjugates.

ATC code

L01FF07

Mechanism of action

Dostarlimab is an anti-programmed cell death protein-1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb), derived from a stable Chinese hamster ovary (CHO) cell line.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Dostarlimab is a humanised mAb of the

IgG4 isotype that binds to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2, releasing inhibition of PD-1 pathway-mediated immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Pharmacodynamic effects

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 IL-2 production functional assay was maintained throughout the dosing interval at the recommended therapeutic dosing regimen.

Pharmacokinetics

Dostarlimab PK were characterised using population PK analysis from 546 patients with various solid tumours, including 288 patients with EC. The PK of dostarlimab is approximately dose proportional. 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.

Absorption

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

Distribution

The geometric mean volume of distribution of dostarlimab at steady state is approximately 5.26 L (CV% of 14.2%).

Metabolism

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 geometric mean clearance is 0.00682 L/h (CV% of 30.2%) at steady state. The geometric mean terminal half-life ($t_{1/2}$) at steady state is 23.5 days (CV% of 22.4%).

Linearity/non-linearity

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

Special patient populations

Renal impairment was evaluated based on the estimated creatinine clearance [CLCR mL/min] (normal: CLCR \geq 90 mL/min, n = 173; mild: CLCR = 60-89 mL/min, n = 210; moderate: CLCR = 30-59 mL/min, n = 90; severe: CLCR = 15-29 mL/min, n = 3 and ESRD: CLCR < 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 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.

Clinical Studies

Mismatch repair deficient/MSI-H endometrial cancer

The efficacy and safety of dostarlimab were investigated in GARNET, a multicentre, open-label, Phase 1 dose escalation study conducted in patients with recurrent or advanced endometrial cancer who have progressed on or after treatment with a platinum-containing regimen.

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 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.

Patients received dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1000 mg 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 RECIST v1.1.

All patients included in both the primary and secondary efficacy analysis set had a minimum follow-up period of 24 weeks from first dose, regardless of whether they had a post-treatment scan.

A total of 105 patients with dMMR/MSI-H EC were evaluated for efficacy in the GARNET study (data cut-off 01 March 2020). Among these 105 patients, the baseline characteristics were: median age 64 years (50% age 65 or older); 78% White, 4% Asian, 2% Black; and Eastern Cooperative Oncology Group (ECOG) PS 0 (40%) or 1 (60%). The median number of prior therapies for recurrent or advanced endometrial cancer was one and all had received treatment with a platinum-containing regimen. Thirty-seven percent of patients received two or more prior lines of therapy.

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.

Efficacy results are shown in Table 4.

Table 4: Efficacy results in GARNET for patients with dMMR/MSI-H endometrial cancer	
Endpoint	Dostarlimab (N=105)¹
Objective response rate (ORR)	
ORR (95% CI)	44.8% ¹ (35.0, 54.8)
Complete response rate	10.5%
Partial response rate	34.3%
Duration of response (DOR)	
Median in months (range)	Not reached (2.6, 28.1+)
Probability of maintaining response at 6 months by K-M (95% CI)	97.9% (85.8, 99.7)
Probability of maintaining response at 12 months by K-M (95% CI)	90.9% (73.7, 97.1)

¹ Data cut-off (01 March 2020)

K-M: Kaplan-Meier curve estimate

Median follow-up at time of data cut-off (01 March 2020) was 16.3 months. The DCR in patients with dMMR/MSI-H EC, including complete response (n=11), partial response (n=36), and stable disease (n=13), was 57.1%.

Elderly patients

Of the 515 patients treated with dostarlimab monotherapy (IA1 GARNET population at time of data cut-off 01 March 2020), 51% were under 65 years, 38% were 65-75 years, and 12% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years).

In the 105 patients with dMMR/MSI-H EC in the efficacy analysis, the ORR by BICR (95% CI) was 45.3 % (31.6%, 59.6%) in patients under 65 years and 44.2% (30.5%, 58.7%) in patients 65 years and older.

Non-Clinical Information

Carcinogenesis/mutagenesis

No studies have been performed to assess the potential of dostarlimab for carcinogenicity or genotoxicity.

Reproductive Toxicology

Animal reproduction studies have not been conducted with dostarlimab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. 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.

Fertility

Animal fertility studies have not been conducted with dostarlimab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

Animal toxicology and/or pharmacology

The nonclinical safety of dostarlimab was evaluated in 1-month and 3-month repeat-dose toxicity studies in Cynomolgus monkeys administered intravenous doses of 10, 30 or 100 mg/kg/week. No findings of toxicological significance were observed in both studies except that one male monkey dosed at 10 mg/kg/week was euthanized due to chronic, unresolved generalised skin findings in the 3-month study. The no observed adverse effect level (NOAEL) was ≥ 100 mg/kg in the 1-month study, corresponding to exposure multiples of 35 and 28 times the exposure in humans at doses of 500 and 1000 mg, respectively. The NOAEL was not determined in the 3-month study as the relationship of the premature euthanasia of the animal to dostarlimab could not be ruled out.

PHARMACEUTICAL INFORMATION

List of Excipients

Trisodium citrate dihydrate

Citric acid monohydrate

L arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection.

Shelf Life

Unopened vial

The expiry date is indicated on the packaging.

After preparation of infusion

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

Due to the lack of preservative, the product must not be used beyond these storage times.

Storage

The storage conditions are detailed on the packaging.

Do not freeze. Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see *Use and Handling*.

Nature and Contents of Container

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 *JEMPERLI*.

Each carton contains one vial.

Incompatibilities

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

Use and Handling

Parenteral medicinal products 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 (IV) 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 IV bag.

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

For the 1,000-mg dose, withdraw 10 mL of *JEMPERLI* from each of two vials (withdraw 20 mL total) and transfer into an IV 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 to 10 mg/mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of *JEMPERLI* into the IV bag.

- For example, if preparing a 1000 mg dose in a 500 mL diluent IV bag, to achieve a 2 mg/mL concentration would require withdrawing 20 mL of diluent from the 500 mL IV bag. Then, 10 mL of *JEMPERLI* would be withdrawn from each of two vials, totaling 20 mL, and transferred into the IV 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 polyethersulfone (PES) filter must be used during administration of dostarlimab.

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.

Not all presentations are available in every country.

Product Registrant

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