

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## AUSTRALIAN PRODUCT INFORMATION

### JEMPERLI (Dostarlimab)

#### 1 NAME OF THE MEDICINE

Dostarlimab

#### 2 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).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

#### 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Dostarlimab is a clear to slightly opalescent colourless to yellow solution, free from visible particles.

#### 4 CLINICAL PARTICULARS

##### 4.1 THERAPEUTIC INDICATIONS

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

This medicine and indication have provisional approval, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

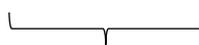
##### 4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose as monotherapy is 500 mg dostarlimab administered as an intravenous infusion over 30 minutes every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks for all cycles thereafter.

The dosage regimen is presented in Table 1.

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

<b>500 mg once every 3 weeks (1 Cycle = 3 weeks)</b>					<b>1,000 mg once every 6 weeks until disease progression or unacceptable toxicity (1 cycle = 6 weeks)</b>			
<b>Cycle</b>	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Continue dosing Q6W
<b>Week</b>	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.

*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.

**Table 2. Recommended dose modifications for dostarlimab**

Immune-related adverse reactions	Severity grade <sup>a</sup>	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 <sup>b</sup> or ALT <sup>c</sup> > 3 and up to 5 × ULN <sup>d</sup> 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). <sup>e</sup>
Type 1 diabetes mellitus (T1DM)	3 or 4 (hyperglycaemia)	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients.

**Table 2. Recommended dose modifications for dostarlimab**

<b>Immune-related adverse reactions</b>	<b>Severity grade<sup>a</sup></b>	<b>Dose modification</b>
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 involving a major organ	3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.

<b>Table 2. Recommended dose modifications for dostarlimab</b>		
<b>Immune-related adverse reactions</b>	<b>Severity grade<sup>a</sup></b>	<b>Dose modification</b>
Recurrence of immune-related adverse reactions after resolution to ≤ Grade 1	3 or 4	Permanently discontinue.
<b>Other adverse reactions</b>	<b>Severity grade<sup>a</sup></b>	<b>Dose modification</b>
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.

<sup>a</sup> Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

<sup>b</sup> AST = aspartate aminotransferase

<sup>c</sup> ALT = alanine aminotransferase

<sup>d</sup> ULN = upper limit of normal

<sup>e</sup> For patients with liver metastases who begin treatment with Grade 2 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.

## **Method of Administration**

### **Preparation**

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

### **Dilution**

For the 500-mg dose, withdraw 10 mL of dostarlimab 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 dostarlimab 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 dostarlimab would be withdrawn from the vial and transferred into the IV bag.

For the 1,000-mg dose, withdraw 10 mL of dostarlimab 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 and 10 mg/mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of dostarlimab into the IV bag.

- For example, if preparing a 1,000 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 dostarlimab 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.

### **Administration**

Dostarlimab is for intravenous infusion only. Dostarlimab should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes by a health care practitioner.

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

Dostarlimab 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. Infusion 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.

### **Children**

The safety and efficacy of dostarlimab 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 dostarlimab in patients aged 75 years or over (see section 5.1 PHARMACODYNAMIC PROPERTIES).

### **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 Section 5.2 PHARMACOKINETIC PROPERTIES).

## Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. There are limited data in patients with moderate or severe hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

### 4.3 CONTRAINDICATIONS

None

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### Traceability

In order to improve the traceability of biological medicinal products, the tradename 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 dostarlimab. 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, 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 DOSING AND ADMINISTRATION, 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.

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 ADVERSE 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 DOSING AND ADMINISTRATION).

### Immune-related colitis

Dostarlimab can cause immune-related colitis (see Section 4.8 ADVERSE EFFECTS). Monitor patients for signs and symptoms of colitis and manage with dostarlimab treatment modifications, anti-diarrhoeal agents and corticosteroids (see Section 4.2 DOSING AND ADMINISTRATION).

### Immune-related hepatitis

Dostarlimab can cause immune-related hepatitis. Monitor patients for changes in liver function periodically as indicated based on clinical evaluation and manage with dostarlimab treatment modifications and corticosteroids (see Section 4.2 DOSING AND 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 ADVERSE 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 in Section 4.2 DOSING AND 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 in Section 4.2 DOSING AND ADMINISTRATION.

### Immune-related nephritis

Dostarlimab can cause immune-related nephritis (see Section 4.8 ADVERSE EFFECTS). Monitor patients for changes in renal function and manage with dostarlimab treatment modifications and corticosteroids (see Section 4.2 DOSING AND ADMINISTRATION).

### Immune-related rash

Immune-related rash has been reported in patients receiving dostarlimab, including pemphigoid (see Section 4.8 ADVERSE EFFECTS). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended (see 4.2 DOSING AND ADMINISTRATION). Events of Stevens-Johnson

Syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS) 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.

#### Other immune-related adverse reactions

Given the mechanism of action of dostarlimab other potential immune-related adverse reactions may occur. Clinically significant immune-related adverse reactions reported in less than 1% of patients treated with dostarlimab as monotherapy in clinical trials include autoimmune haemolytic anaemia, uveitis, and iridocyclitis. Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed as described in Section 4.2 DOSING AND ADMINISTRATION.

#### Transplant-related adverse reactions

##### *Solid organ transplant rejection*

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

Dostarlimab can cause infusion-related reactions, which can be severe (see Section 4.8 ADVERSE EFFECTS). For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue Dostarlimab (see Section 4.2 DOSING AND ADMINISTRATION).

#### **Patient Card**

All prescribers of JEMPERLI 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.

### **Use in hepatic impairment**

There are limited data in patients with severe or moderate hepatic impairment (see section 5.2 PHARMACOKINETICS).

### **Use in renal impairment**

There are limited data in patients with severe renal impairment or end-stage renal disease undergoing dialysis (see section 5.2 PHARMACOKINETICS).

### **Use in the elderly**

There are limited clinical data with dostarlimab in patients aged 75 years or over (see section 5.1 PHARMACODYNAMIC PROPERTIES).

### **Paediatric use**

No data are available.

### **Effects on laboratory tests**

No data are available

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

No drug-drug interaction studies have been conducted with dostarlimab. Monoclonal antibodies (mAbs) such as dostarlimab are not substrates for cytochrome P450 or drug transporters. Additionally, pharmacokinetic (PK) drug-drug interaction of dostarlimab with small molecule drugs is not expected.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

Fertility studies have not been conducted with dostarlimab. No effects on male and female reproductive organs were observed in a 3-month repeat dose toxicity study in cynomolgus monkeys at  $\leq 100$  mg/kg/week IV, resulting in exposures (AUC) at least 28 times that expected in patients; however, these results may not be predictive of clinical risk because of the immaturity of the reproductive system of animals used in the study.

### **Use in pregnancy (Category D)**

There are no available data on the use of dostarlimab in pregnant women. Animal reproduction studies have not been conducted with dostarlimab to evaluate its effect on reproduction and fetal development. Based on its mechanism of action, dostarlimab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signalling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal 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 fetus. Advise women of the potential risk to a fetus.

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

## Use in 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 dostarlimab.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Clinical trial data

#### Summary of the safety profile

Adverse reactions observed in 601 patients with recurrent or advanced solid tumours, including 315 patients with endometrial cancer and 286 patients with other advanced solid tumours who received dostarlimab 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. Patients generally received dostarlimab doses of 500 mg every 3 weeks (Q3W) for 4 doses followed by 1,000 mg every 6 weeks (Q6W) for all cycles.

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/Adverse Reaction	Frequency (all grades)	All Grades n (%)	Grades 3-4 n (%)
<b>Blood and lymphatic system disorders</b>			
Anaemia	Very common	163 (27.1)	54 (9.0)
Autoimmune haemolytic anaemia	Uncommon	1 (0.2)	1 (0.2)
<b>Endocrine disorders</b>			
Hypothyroidism	Very common	61 (10.1) <sup>a</sup>	
Hyperthyroidism	Common	29 (4.8)	1 (0.2)
Adrenal insufficiency	Common	8 (1.3)	4 (0.7)
Hypophysitis	Uncommon	3 (0.5) <sup>b</sup>	
Thyroiditis	Uncommon	4 (0.7) <sup>c</sup>	
<b>Metabolism and nutrition disorders</b>			
Type 1 diabetes mellitus	Uncommon	2 (0.3)	
Diabetic ketoacidosis	Uncommon	1 (0.2)	

<b>System Organ Class/Adverse Reaction</b>	<b>Frequency (all grades)</b>	<b>All Grades n (%)</b>	<b>Grades 3-4 n (%)</b>
<b>Nervous system disorders</b>			
Myasthenia gravis	Uncommon	1 (0.2)	
Myasthenic syndrome	Uncommon	1 (<1.0) <sup>d</sup>	1 (<1.0) <sup>d</sup>
<b>Eye disorders</b>			
Uveitis	Uncommon	2 (0.3) <sup>e</sup>	
<b>Cardiac disorders</b>			
Myocarditis	Uncommon	2 (0.4) <sup>d, f</sup>	2 (<1.0) <sup>d, f</sup>
<b>Respiratory, thoracic and mediastinal disorders</b>			
Pneumonitis	Common	19 (3.2%) <sup>g</sup>	4 (0.7) <sup>g</sup>
<b>Gastrointestinal disorders</b>			
Nausea	Very common	149 (24.8)	11 (1.8)
Diarrhoea	Very common	141 (23.5)	8 (1.3)
Vomiting	Very common	108 (18.0)	9 (1.5)
Colitis	Common	12 (2.0) <sup>h</sup>	4 (0.7) <sup>j</sup>
Pancreatitis	Common	7 (1.2) <sup>i</sup>	6 (<1.0) <sup>i</sup>
<b>Hepatobiliary disorders</b>			
Hepatitis	Uncommon	6 (<1.0) <sup>k</sup>	3 (0.5) <sup>k</sup>
<b>Skin and subcutaneous tissue disorders</b>			
Pruritus	Very common	75 (12.5)	2 (0.3)
Rash	Very common	118 (19.6) <sup>l</sup>	7 (1.2) <sup>m</sup>
<b>Musculoskeletal and connective tissue disorders</b>			
Myalgia	Common	37 (6.2)	
Immune-mediated arthritis	Uncommon	1 (0.2)	
Polymyalgia rheumatica	Uncommon	1 (0.2)	
Myositis	Uncommon	2 (0.4) <sup>n</sup>	1 (0.2) <sup>n</sup>
<b>Renal and urinary disorders</b>			
Nephritis	Uncommon	4 (0.7) <sup>o</sup>	
<b>General disorders and administration site conditions</b>			
Pyrexia	Very common	65 (10.8)	2 (0.3)
Chills	Common	21 (3.5)	1 (0.2)
Systemic inflammatory response syndrome	Uncommon	2 (0.4) <sup>n</sup>	2 (0.4) <sup>n</sup>

System Organ Class/Adverse Reaction	Frequency (all grades)	All Grades n (%)	Grades 3-4 n (%)
<b>Investigations</b> Transaminases increased	Very common	84 (14.0) <sup>p</sup>	18 (3.0) <sup>p</sup>
<b>Injury, poisoning and procedural complications</b> Infusion-related reaction	Common	7 (1.2) <sup>q</sup>	1 (0.2)

<sup>a</sup> Includes autoimmune hypothyroidism

<sup>b</sup> Includes lymphocytic hypophysitis

<sup>c</sup> Includes thyroiditis and autoimmune thyroiditis

<sup>d</sup> Adverse reaction reported from ongoing blinded trials of dostarlimab in combination with other anticancer agents; estimated frequency category. No events reported in monotherapy population.

<sup>e</sup> Includes uveitis and iridocyclitis

<sup>f</sup> Includes myocarditis and immune-mediated myocarditis

<sup>g</sup> Includes pneumonitis and interstitial lung disease

<sup>h</sup> Includes colitis, enterocolitis and enterocolitis haemorrhagic

<sup>i</sup> Includes pancreatitis and pancreatitis acute

<sup>j</sup> Includes colitis and enterocolitis haemorrhagic

<sup>k</sup> Includes hepatitis, autoimmune hepatitis and hepatocellular injury

<sup>l</sup> 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

<sup>m</sup> Includes rash, rash maculopapular and drug eruption

<sup>n</sup> Reported from pooled data from studies of dostarlimab in combination with various types of anticancer therapies. No events reported in monotherapy population.

<sup>o</sup> Includes nephritis and tubulointerstitial nephritis

<sup>p</sup> Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased and hypertransaminasaemia

<sup>q</sup> Includes infusion-related reaction and hypersensitivity.

### **Other adverse events**

Table 4 summarises other adverse events that occurred in 10% or more of patients with solid tumours treated with dostarlimab monotherapy in the GARNET study. Fatigue is the only adverse event reported in at least 20% of patients. Grade 4 events included asthenia (N=1 patient, 0.2%) and dyspnoea (N=2 patients, 0.3%).

**Table 4: Other adverse events in ≥10% of patients with solid tumours treated with dostarlimab monotherapy**

System Organ Class/Adverse Reaction	All Grades n (%)	Grades 3-4 n (%)
<b>Gastrointestinal disorders</b>		
Constipation	101 (16.8)	4 (0.7)
Abdominal pain	91 (15.1)	20 (3.3)
<b>General disorders and administration site conditions</b>		
Fatigue	153 (25.5)	17 (2.8)
Asthenia	116 (19.3)	9 (1.5)

<b>System Organ Class/Adverse Reaction</b>	<b>All Grades n (%)</b>	<b>Grades 3-4 n (%)</b>
<b>Infections and infestations</b> Urinary tract infection	81 (13.5)	10 (1.7)
<b>Musculoskeletal and connective tissue disorders</b> Arthralgia Back pain	100 (16.6) 74 (12.3)	4 (0.7) 11 (1.8)
<b>Metabolism and nutrition disorders</b> Decreased appetite	104 (17.3)	5 (0.8)
<b>Respiratory, thoracic and mediastinal disorders</b> Cough Dyspnoea	92 (15.3) 75 (12.5)	1 (0.2) 21 (3.5)

### 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 dostarlimab 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 dostarlimab. Because of the small number of patients who developed ADAs, the impact of immunogenicity on the efficacy and safety of dostarlimab is inconclusive.

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **4.9 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-neoplastic agents, monoclonal antibodies.

#### ATC code

L01XC40

#### 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 signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Dostarlimab is a humanised mAb of 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 within the exposure range attained under the recommended therapeutic dosing regimen (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks thereafter). 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.

#### Clinical trials

##### *Mismatch repair deficient 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 (EC) that has 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) EC that has progressed on or after a platinum-containing regimen.

Patients received dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1,000 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.

At the time of the first interim analysis (data cut-off 08 July 2019), a total of 70 patients with dMMR EC were evaluated for efficacy in the GARNET study. Among these 70 patients, the baseline characteristics were: median age 64.5 years (50% age 65 or older); 82.9% White, 1% Asian, 1% Black; and Eastern Cooperative Oncology Group (ECOG) PS 0 (32.9%) or 1 (67.1%). The median number of prior therapies for recurrent or advanced endometrial cancer was one and all had received treatment with a platinum-containing regimen. Forty-one 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.

A second interim analysis was performed (data cut-off 01 March 2020). A total of 103 patients with dMMR EC were evaluated for efficacy at the second interim analysis. In addition, efficacy data for the 70 patients with dMMR previously evaluated in the first interim analysis were updated at the time of the second interim analysis.

#### *Interim analysis 1 population (70 patients)*

Median follow-up at time of data cut-off (01 March 2020) was 17.5 months for N=70. The DCR in patients with dMMR EC, including complete response (n=10), partial response (n=22), and stable disease (n=9), was 58.6%.

At the time of the data-cut (n=70), the median PFS in patients with dMMR was 8.1 months. Just under half the patients (45.7%) were censored at the time, and a total of 38 events were observed. The median overall survival (OS) for patients with dMMR (n=70, data cut 01 March 2020) had not been reached and 26 OS events had been observed. Due to the single arm nature of the study and limited events, PFS and OS must be interpreted with caution.

#### *Interim analysis 2 population (103 patients)*

Median follow-up at time of data cut-off (01 March 2020) was 16.3 months. The DCR in patients with dMMR EC, including complete response (n=11), partial response (n=35), and stable disease (n=13), was 57.3%.

Efficacy results are shown in Table 5.

<b>Table 5: Efficacy results in GARNET for patients with dMMR endometrial cancer</b>		
<b>Endpoint</b>	<b>Dostarlimab IA1 population (N=70)</b>	<b>Dostarlimab IA2 population (N=103)*</b>
<b>Objective response rate (ORR)</b>		
ORR (95% CI)	45.7% <sup>1</sup> (33.7, 58.1)	44.7% <sup>1</sup> (34.9, 54.8)
Complete response rate	14.3%	10.7%
Partial response rate	31.4%	34.0%
<b>Duration of response (DOR)</b>		
Median in months (range)	Not reached (2.6, 28.1+)	Not reached (2.6, 28.1+)
Probability of maintaining response at 6 months by K-M (95% CI)	96.9% (79.8, 99.6)	97.8% (85.6, 99.7)
Probability of maintaining response at 12 months by K-M (95% CI)	89.7% (71.3, 96.6)	90.6% (72.9, 97.0)

\* Interim analysis per prespecified endpoints; includes N=70 patients from the initial interim analysis (IA1).

<sup>1</sup> At time of the second interim analysis (IA2) data cut-off (01 March 2020)

K-M: Kaplan-Meier curve estimate

#### 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 effectiveness were observed between patients under 65 years and in patients 65 years and older.

#### Paediatric population

The safety and efficacy of dostarlimab in children and adolescents below 18 years of age have not been established.

## **5.2 PHARMACOKINETIC PROPERTIES**

Dostarlimab pharmacokinetic (PK) properties were characterised using population PK analysis from 546 patients with various solid tumours, including 267 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.

## **Excretion**

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%).

## **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), sex or race, ethnicity, or tumour type on the clearance of dostarlimab. This population PK model also indicates that alterations in renal function (normal to moderate) and hepatic function (normal to mild impairment) do not alter the disposition of dostarlimab.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

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

### **Carcinogenicity**

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Sodium citrate dihydrate

Citric acid monohydrate

Arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store in a refrigerator 2°C to 8°C.

Do not freeze.

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.

#### After preparation of infusion

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. 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.

Product is for single use in one patient only, discard any residue.

### **6.5 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 dostarlimab.

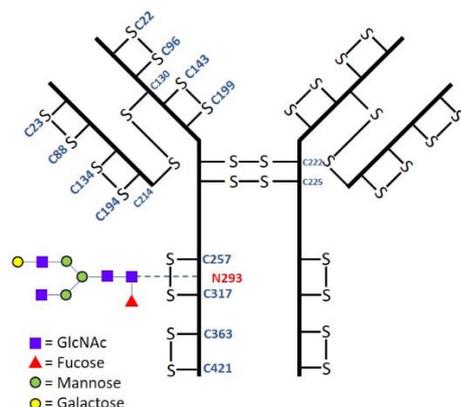
Each carton contains one vial.

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure



### CAS number

2022215-59-2

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

GlaxoSmithKline Australia Pty Ltd  
Level 4, 436 Johnston Street,  
Abbotsford, Victoria, 3067

## 9 DATE OF FIRST APPROVAL

17 February 2022

## 10 DATE OF REVISION

Not applicable.

### SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New Product Information

Version 1.0

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