PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] JEMPERLI

dostarlimab for injection

Solution for infusion

500 mg/10 mL vial (50 mg/mL)

Anti-neoplastic agent, monoclonal antibody

JEMPERLI (dostarlimab for injection) is indicated as:

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

has been issued market authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for JEMPERLI please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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Date of Initial Authorization:
December 23, 2021

Submission Control Number: 251105

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JEMPERLI (dostarlimab for injection) is indicated as:

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

The marketing authorization with conditions is primarily based on tumour objective response rate and durability of response. An improvement in survival has not been established (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years).

There are limited clinical data with dostarlimab in patients aged 75 years or over (see 4.2 Recommended Dose and Dosage Adjustment-Geriatrics; 7.1.4 Warnings and Precautions-Geriatrics).

2 CONTRAINDICATIONS

- JEMPERLI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- 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 4.3 Reconstitution.
- Patients should be selected for treatment based on MSI-H or dMMR tumour status as determined by an accredited laboratory using validated testing methods (see 14.1 Trial Design and Study Demographics).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of JEMPERLI as monotherapy in adult patients is:

- Dose 1 through Dose 4: 500 mg every 3 weeks
- Subsequent dosing beginning 3 weeks after Dose 4 (Dose 5 onwards): 1,000 mg every 6 weeks

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

Administer JEMPERLI as an intravenous infusion over 30 minutes. Administration of dostarlimab could continue according to the recommended 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 dose modifications to manage adverse reactions are provided in Table 2.

Detailed guidelines for the management of immune-mediated adverse reactions and infusion-related reactions are described in 7 WARNINGS AND PRECAUTIONS, Immune.

Table 2 Recommended dose modifications for JEMPERLI

Immune-mediated 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.

Immune-mediated adverse reactions	Severity grade[a]	Dose modification
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or1. 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-mediated adverse reactions (including but not limited to rash, 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.
Recurrence of immune-mediated 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 pre-medication, 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.

Geriatrics
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.

Pediatrics
Health Canada has not authorized an indication for pediatric use.

Hepatic Insufficiency
No dose adjustment is recommended for patients with mild hepatic impairment. Data are not sufficient for drawing any conclusion on patients with moderate hepatic impairment and there are no data in patients with severe hepatic impairment (see 10.3 Pharmacokinetics).

Renal Insufficiency
No dose adjustment is recommended for patients with mild or moderate renal impairment. Data are not sufficient for drawing any conclusion on patients with severe renal impairment or end stage renal disease undergoing dialysis (see 10.3 Pharmacokinetics).

4.3 Reconstitution

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.

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.

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.

Mix diluted solution by gentle inversion. Do not shake the final infusion bag. Discard any unused portion left in the vial (see 11 STORAGE, STABILITY AND DISPOSAL).

4.4 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. Do not co-administer other drugs through the same infusion line.

For instructions on dilution of the medicinal product before administration, see 4.3 Reconstitution.

4.5 Missed Dose

It is very important to not miss a dose of this medicine. If a planned dose of JEMPERLI is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 OVERDOSAGE

There is no information on overdosage with JEMPERLI. The maximum tolerated dose of JEMPERLI has not been determined.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Solution for infusion 500 mg/10 mL vial (50 mg/mL)	Citric acid monohydrate; L-arginine hydrochloride; polysorbate 80; sodium chloride; tri-sodium citrate dihydrate; water for injection

JEMPERLI is packaged in a carton containing one 10mL single-use vial with clear to slightly opalescent colourless to yellow solution, essentially free from visible particles. Each mL of solution for infusion contains 50 mg of dostarlimab. The solution for infusion has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

7 WARNINGS AND PRECAUTIONS

The data described in this section reflect exposure to JEMPERLI as monotherapy in 515 patients with recurrent or advanced solid tumours (i.e. monotherapy pooled safety population) including patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial cancer (N=129) in an open-label, single-arm, multicohort GARNET study (see 8 ADVERSE REACTIONS; 14 CLINICAL TRIALS).

General

JEMPERLI should be administered under the supervision of physicians experienced in the treatment of cancer.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Immune

Immune-mediated adverse reactions, which may be severe or fatal, have occured 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-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-mediated adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. Important immune-mediated adverse reactions listed in this section are not inclusive of all possible severe and fatal immune-mediated reactions.

Early identification and management of immune-mediated 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-mediated adverse reactions. Clinical and haematological chemistries, including liver, kidney and thyroid function tests, should be evaluated at baseline and periodically during treatment. For suspected immune-mediated 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 4.2 Recommended Dose and Dosage Adjustment). Upon improvement to Grade 0 or 1, corticosteroid taper should be initiated and continued for at least 1 month or longer. Based on limited data from clinical studies in patients whose immune-mediated 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 JEMPERLI should be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones and unless otherwise specified in 4.2 Recommended Dose and Dose Adjustment.

- **Immune-mediated pneumonitis**

Immune-mediated pneumonitis has been reported in patients receiving JEMPERLI (see 8.2 Clinical Trial 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 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications and 8 ADVERSE REACTIONS).

- **Immune-mediated colitis**

JEMPERLI can cause immune-mediated colitis (see 8 ADVERSE REACTIONS). Monitor patients for signs and symptoms of colitis and manage with JEMPERLI treatment modifications, anti-diarrhoeal agents and corticosteroids (see 4.2 Recommended Dose and Dosage Adjustment and 8 ADVERSE REACTIONS).

- **Immune-mediated hepatitis**

JEMPERLI can cause immune-mediated hepatitis. Monitor patients for changes in liver function periodically as indicated based on clinical evaluation and manage with JEMPERLI treatment modifications and corticosteroids (see 4.2 Recommended Dose and Dosage Adjustment and 8 ADVERSE REACTIONS).

- **Immune-mediated endocrinopathies**

Immune-mediated endocrinopathies, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis and adrenal insufficiency (primary and secondary), have been reported in patients receiving JEMPERLI. Long-term hormone replacement therapy may be necessary in cases of immune-mediated endocrinopathies.

Adrenal insufficiency

Immune-mediated adrenal insufficiency (primary and secondary) 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 4.2 Recommended Dose and Dosage Adjustment (see 8 ADVERSE REACTIONS).

Hypophysitis

JEMPERLI can cause hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism). Administer corticosteroids and hormone replacement as clinically indicated (See 4.2 Recommended Dose and Dosage Adjustment).

Type 1 diabetes mellitus

JEMPERLI can cause type 1 diabetes mellitus, including diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes and withhold JEMPERLI in cases of severe hyperglycemia until metabolic control is achieved (See 4.2 Recommended Dose and Dosage Adjustment).

Thyroid disorders (Hypothyroidism and hyperthyroidism)

Immune-mediated thyroid disorders, including hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving JEMPERLI. Hypothyroidism may follow hyperthyroidism. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with hormone replacement therapy (if indicated). Initiate medical management for control of hyperthyroidism.

Immune-mediated hypothyroidism and hyperthyroidism (including thyroiditis) should be managed as recommended in 4.2 Recommended Dose and Dosage Adjustment. (see 8 ADVERSE REACTIONS)

- **Immune-mediated nephritis**

JEMPERLI can cause immune-mediated nephritis (see 8 ADVERSE REACTIONS). Monitor patients for changes in renal function and manage with JEMPERLI treatment modifications and corticosteroids (see 4.2 Recommended Dose and Dosage Adjustment).

- **Immune-mediated skin adverse reactions**

Immune-mediated skin reactions including rash, pruritus and pemphigoid been reported in patients receiving JEMPERLI (see 8.2 Clinical Trial Adverse Reactions). Patients should be monitored for signs and symptoms of severe skin reactions and exclude other causes. Immune-mediated severe skin reactions should be managed as recommended for other immune-mediated adverse reactions (see 4.2 Recommended Dose and Dosage Adjustment).

Cases of Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN), some with fatal outcomes, have been reported in patients treated with PD-1 inhibitors. Exfoliative dermatological conditions should be managed as recommended in 4.2 Recommended Dose and Dosage Adjustment. For signs and symptoms of SJS or TEN, withold treatment and refer the patient for specialized care for assessment and further treatment. If SJS or TEN is confirmed, permanently discontinue treament.

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-mediated adverse reactions**

Given the mechanism of action, JEMPERLI can cause other clinically important immune-mediated adverse reactions including potentially serious events [e.g. myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis].

Clinically significant immune-mediated adverse reactions reported in less than 1% of patients treated with JEMPERLI as monotherapy in clinical trials include autoimmune haemolytic anaemia, pancreatitis, uveitis, and iridocyclitis. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed as described in 4.2 Recommended Dose and Dosage Adjustment.

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

- **Complications of Allogeneic HSCT after PD-1/PD-L1–Blocking Antibody**

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, including hypersensitivity, which can be severe. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue JEMPERLI (see 4.2 Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed as described in 4.2 Recommended Dose and Dosage Adjustment.

For suspected immune-mediated adverse reactions, adequate evaluation including specialty consultation should be ensured (see 7 WARNINGS AND PRECAUTIONS, Immune).

Patients should be evaluated for clinical and haematological chemistries, including liver function tests (hepatic transaminase and bilirubin levels), serum electrolytes and renal and thyroid function tests, at baseline and periodically during treatment.

Reproductive Health: Female and Male Potential

- **Fertility**

Fertility studies have not been conducted with JEMPERLI (see 16 NON-CLINICAL TOXICOLOGY).

- **Embryo-fetal toxicity**

JEMPERLI can cause fetal harm. Pregnant women or women with reproductive potential should be advised of the potential risk associated with the administration of JEMPERLI to the fetus (see 7.1.1 Pregnant Women). Verify pregnancy status in females of reproductive potential prior to initiating JEMPERLI.

Women of childbearing potential should use effective contraception during treatment with JEMPERLI and until 4 months after the last dose of JEMPERLI.

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on the use of JEMPERLI in pregnant women. Animal reproduction and development studies have not been conducted with JEMPERLI; however, inhibition of the PD-1/PD-L1 pathway has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss (See 16 NON-CLINICAL TOXICOLOGY). These results indicate a potential risk, based on its mechanism of action, that administration of JEMPERLI during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 immunoglobulins (IgG4) are

known to cross the placental barrier; therefore, being an IgG4, JEMPERLI has the potential to be transmitted from the mother to the developing fetus.

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

7.1.2 Breast-feeding

It is unknown if JEMPERLI is secreted in human milk. A risk to the newborns/infants cannot be excluded. Precaution should be exercised because many drugs can be secreted in human milk. Because of the potential for serious adverse reactions in breastfed children, **JEMPERLI should not be used during breast-feeding and breast-feeding should be avoided for at least 4 months after the last dose of JEMPERLI.**

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is recommended for patients who are aged 65 years or over.

There are limited clinical data with dostarlimab in patients aged 75 years or over (see 4.2 Recommended Dose and Dosage Adjustment-Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of JEMPERLI has been evaluated in 515 patients (i.e. monotherapy pooled safety population) with endometrial cancer or other advanced solid tumours who received dostarlimab monotherapy in the open-label, multi-cohort GARNET study, including 129 patients with dMMR/MSI-H recurrent or advanced endometrial cancer. Patients received doses of 500 mg every 3 weeks for 4 doses followed by 1000 mg every 6 weeks for all cycles thereafter (see 4.2 Recommended Dose and Dosage Adjustment) . The median treatment duration for the monotherapy pooled population was 20.0 weeks (range 1 to 146 weeks), including 42.7 % of patients treated for greater than six months and 25.6 % of patients treated for greater than one year.

Dostarlimab is most commonly associated with immune-mediated adverse reactions (see 8.2 Clinical Trial Adverse Reactions, Immune-mediated Adverse Reactions).

In patients with advanced or recurrent solid tumours (N = 515), the most common adverse reactions (≥ 10 %) were anemia (25.6 %), nausea (25.0 %), diarrhea (22.5 %), vomiting (18.4 %), arthralgia (13.8 %)

pruritus (11.5 %), rash (11.1 %), pyrexia (10.5 %) and hypothyroidism (10.1 %). Adverse reactions were serious in 9.5 % of patients; most serious adverse reactions were immune-mediated adverse reactions (see 8.2 Clinical Trial Adverse Reactions, Immune-mediated Adverse Reactions). Serious adverse reactions reported in ≥ 1 % of patients were pyrexia (1.6 %), vomiting (1.6 %) and nausea (1.4 %). JEMPERLI was permanently discontinued due to adverse reactions in 17 (3.3 %) patients, most of them were immune-mediated events. Adverse reactions leading to dose interruption were reported in 55 (10.7 %) patients.

The safety profile for patients with dMMR/MSI-H endometrial cancer in the GARNET study (N=129) was not different from that of the overall monotherapy population (i.e. monotherapy pooled safety population).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Immune-mediated Adverse Reactions

The selected adverse reactions described below are based on the safety of dostarlimab in a monotherapy pooled safety database of 515 patients in the GARNET study in patients with endometrial cancer or other advanced solid tumours. Immune-mediated adverse reactions were defined as events of grade 2 and above from a pre-specified list of terms; the frequencies below exclude grade 1 events. The management guidelines for these adverse reactions are described in section 4.2 Recommended Dose and Dosage Adjustment.

Immune-mediated pneumonitis
Immune-mediated pneumonitis occurred in 7 (1.4 %) of 515 patients, including grade 2 (1.2 %) and grade 3 (0.2 %) pneumonitis. Pneumonitis led to discontinuation of dostarlimab in 3 (0.6 %) patients.

Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in all 7 patients experiencing pneumonitis. Pneumonitis resolved in 6 (85.7 %) patients.

Immune-mediated colitis
Colitis occurred in 8 (1.6 %) patients, including grade 2 (1.0 %) and grade 3 (0.6 %) colitis. Colitis did not lead to discontinuation of dostarlimab in any patients.

Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 2 (28.6 %) patients. Colitis resolved in 6 (75.0 %) patients experiencing colitis.

Immune-mediated hepatitis
Hepatitis occurred in 1 (0.2 %) patient, which was grade 3. Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required. Hepatitis did not lead to discontinuation of dostarlimab and resolved.

Immune-mediated endocrinopathies

Hypothyroidism occurred in 37 (7.2 %) patients, all of which were grade 2. Hypothyroidism did not lead to discontinuation of dostarlimab and resolved in 13 (35.1 %) patients.

Hyperthyroidism occurred in 10 (1.9 %) patients, including grade 2 (1.7 %) and grade 3 (0.2 %). Hyperthyroidism did not lead to discontinuation of dostarlimab and resolved in 8 (80 %) patients.

Thyroiditis occurred in 2 (0.4 %) patients; both were grade 2. Neither event of thyroiditis resolved; there were no discontinuations of dostarlimab due to thyroiditis.

Adrenal insufficiency occurred in 7 (1.4 %) patients, including grade 2 (0.8 %), and grade 3 (0.6 %). Adrenal insufficiency resulted in discontinuation of dostarlimab in 1 (0.2 %) patient and resolved in 2 (28.6 %) patients.

Immune-mediated nephritis
Nephritis, including tubulointerstitial nephritis, occurred in 3 (0.6 %) patients; all were grade 2. Systemic corticosteroids (prednisone ≥ 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 2 of 3 (66.7 %) patients.

Immune-mediated skin adverse reactions
Immune-mediated rash (rash, rash maculo-papular, rash macular, rash pruritic, pemphigoid) occurred in 17 (3.3 %) patients, including Grade 3 in 6 (1.2 %) patients receiving dostarlimab. The median time to onset of rash was 41 days (range 2 days to 407 days). Systemic corticosteroids (prednisone ≥ 40 mg per day or equivalent) were required in 5 (29 %) patients experiencing rash. Rash did not lead to discontinuation of dostarlimab and resolved in 13 (76.5 %) patients.

Infusion-related reactions
Infusion-related reactions including hypersensitivity occurred in 7 (1.4 %) patients, including grade 2 (1.2 %) and grade 3 (0.2 %) infusion-related reactions. All patients recovered from the infusion-related reaction.

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial cancer (EC) patient population

In 129 patients with dMMR/MSI-H EC the most common adverse reactions (³ 10%) were nausea (32.6%), diarrhoea (27.9%), anaemia (27.1%), vomiting (18.6%), arthralgia (15.5%), pruritus (14.0%), myalgia (10.9%), pyrexia (10.9%), and rash (10.1%). Grade ≥ 3 adverse reactions were reported in 20.9% of patients receiving JEMPERLI. Grade ≥ 3 adverse reactions occurring in more than 1 patient were anaemia (14.7%), diarrhoea (2.3%), alanine transaminase increased (2.3%), transaminases increased (1.6%) and colitis (1.6%). There were no Grade 4 adverse reactions. Serious adverse reactions occurred in 13 (10.1%) patients; the only serious adverse reactions occurring in more than 1 patient were pyrexia (2.3%) and colitis (1.6%). None of the 129 patients treated with JEMPERLI experienced an adverse reaction which led to death. JEMPERLI was permanently discontinued due to adverse reactions in 7 (5.4 %) patients; the only adverse reactions resulting in permanent discontinuation in more than 1 patient were alanine transaminase increased and transaminases increased (1.6% each). No patients discontinued the study due to adverse reactions.

Table 4 summarises adverse reactions that occurred in ≥ 1% patients with dMMR/MSI-H endometrial cancer who received JEMPERLI (N=129) in the GARNET study.

Table 4 Adverse Reactions (incidence ≥1%) in dMMR/MSI-H EC Patients who Received JEMPERLI in GARNET study

Adverse Reaction	JEMPERLI (N = 129)	
	All Grades n (%)	Grade 3 or 4 n (%)
Blood and Lymphatic System		
Anemia	35 (27.1)	19 (14.7)
Endocrine disorders		
Hypothyroidism	10 (7.8)	0
Hyperthyroidism	4 (3.1)	0
Gastrointestinal		
Nausea	42 (32.6)	0
Diarrhea	36 (27.9)	3 (2.3)
Vomiting	24 (18.6)	0
Colitis	3 (2.3)	2 (1.6)
General and Administration Site		
Pyrexia	14 (10.9)	0
Chills	6 (4.7)	0
Investigations		
Alanine aminotransferase increased	9 (7.0)	3 (2.3)
Aspartate aminotransferase increased	9 (7.0)	1 (0.8)
Transaminases increased	3 (2.3)	2 (1.6)
Musculoskeletal and Connective Tissue		
Arthralgia	20 (15.5)	1 (0.8)
Myalgia	14 (10.9)	0
Respiratory, Thoracic, and Mediastinal		
Pneumonitis	2 (1.6)	0
Skin and Subcutaneous Tissue		
Pruritus	18 (14.0)	1 (0.8)
Rash	13 (10.1)	0
Erythema	2 (1.6)	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions were reported in <1% of patients with recurrent or advanced dMMR/MSI-H endometrial cancer, treated with JEMPERLI in the GARNET study (N=129). Adverse reactions presented elsewhere in this section are excluded.

Endocrine disorders: adrenal insufficiency, hypophysitis
Eye disorders: iridocyclitis, uveitis
Gastrointestinal: enterocolitis haemorrhagic, pancreatitis, pancreatitis acute
Hepatobiliary disorders: hypertransaminasemia
Renal and urinary: nephritis, tubulointerstitial nephritis
Respiratory, thoracic and mediastinal: interstitial lung disease

Skin and subcutaneous: pemphigoid, rash maculo-papular

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 5 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR/MSI-H EC on JEMPERLI in GARNET study.

Table 5. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR/MSI-H Endometrial Cancer Receiving JEMPERLI in GARNET Study

Laboratory Test	JEMPERLI N=129	
	All Grades[a] n (%)	Grades 3 or 4 n (%)
Hematology		
Decreased lymphocytes	50 (38.8)	13 (10.1)
Decreased leukocytes	24 (18.6)	3 (2.3)
Chemistry		
Decreased albumin	40 (31.0)	4 (3.1)
Increased creatinine	37 (28.7)	3 (2.3)
Increased alkaline phosphatase	32 (24.8)	3 (2.3)
Increased aspartate aminotransferase	26 (20.2)	2 (1.6)
Increased alanine aminotransferase	24 (18.6)	4 (3.1)
Electrolytes		
Decreased sodium	29 (22.5)	6 (4.7)
Increased calcium	8 (6.2)	2 (1.6)
Decreased potassium	22 (17.1)	2 (1.6)

[a] Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug-drug interaction studies have been conducted with dostarlimab. Dostarlimab is considered to have low potential to affect pharmacokinetics of other drugs based on the lack of effect on cytokines, cytochrome P450, and active substance transporters.

9.4 Drug-Drug Interactions

Immunosuppression

The use of systemic corticosteroids or immunosuppressants before starting JEMPERLI should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of JEMPERLI. However, systemic corticosteroids or other immunosuppressants can be used after starting JEMPERLI to treat immune-mediated adverse reactions (See 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 binds to PD-1 and blocks its interaction with 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.

10.2 Pharmacodynamics

Dostarlimab provides sustained target engagement as measured by direct PD-1 binding and IL-2 production throughout the dosing interval at the recommended therapeutic dosing regimen.

Cardiac Electrophysiology
In a phase 1, open-label, single-arm study of JEMPERLI administered to patients with multiple tumour types, no large mean increase from baseline in QTc interval (i.e. >10 ms) was detected following treatment with JEMPERLI at the recommended therapeutic dose, when assessed at 0.5 hours postdose.

10.3 Pharmacokinetics

Dostarlimab pharmacokinetics (PK) was assessed using non-compartmental analysis (NCA) and population PK (n=546) based approach for single agent JEMPERLI. The pharmacokinetics of dostarlimab is linear in the dose range of 1 to 10 mg/kg. NCA PK parameters corresponding to the 500 mg (single dose) is summarized in Table 6. 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.

Table 6 - Summary of Dostarlimab Non-Compartmental Pharmacokinetic Parameters in Patients with Solid Tumours

	C_{max} (µg/mL)[a]	C_{min} (µg/mL)[a]	T_{max} (h)[b]	$t_{½}$ (h)[a]	$AUC_{0-\infty}$ (µg.h/mL)[a]	CL (mL/h)[a]	Vd (mL)[a]
Single dose mean (500 mg Q3W) [N=6]	171.1 (20.0)	39.17 (26.7)	0.96 (0.5-3.02)	346.8 (12.3)	55510 (24.2)	9.007 (24.2)	4506 (20.5)

[a] Geometric mean and geometric coefficient of variation (%), when applicable

[b] Median (range), when applicable

C_{max}: maximum drug concentration, C_{min}: minimum drug concentration, T_{max}: time when maximum drug concentration is attained, $t_{1/2}$: drug half life, $AUC_{0-\infty}$:area under the concentration-time curve between times zero and infinity, CL: systemic drug clearance, Vd : volume of distribution after single dose

Absorption

JEMPERLI is administered via the intravenous route and therefore is immediately and expected to be completely bioavailable.

Distribution

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

Metabolism

The metabolic pathway of dostarlimab has not been characterized. As a humanized IgG4 monoclonal antibody, dostarlimab is expected to be degraded into small peptides and amino acids via catabolic non-specific pathways in the same manner as endogenous IgG.

Elimination

The geometric mean clearance (CL) parameter at steady state and terminal half-life are 6.82 mL/h (30.2% CV) and 23.5 days (22.4% CV), respectively.

Special Populations and Conditions

Based on population pharmacokinetic analysis, age (24-86 years), sex, race, ethnicity, and tumour type did not have an effect on pharmacokinetic parameters of dostarlimab.

- **Hepatic Insufficiency:** No dose adjustment is needed in patients with mild hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) based on a population PK analysis. Data are not sufficient for drawing any conclusion on patients with moderate hepatic impairment (TB > 1.5 to 3 x ULN and any AST) and no data in patients with severe hepatic impairment (TB > 3 x ULN and any AST).

- **Renal Insufficiency:** No dose adjustment is needed in patients with mild (estimated Glomerular Filtration Rate (eGFR) < 90 and ≥ 60 mL/min/1.73 m^2) or moderate (eGFR < 60 and ≥ 30 mL/min/1.73 m^2) renal impairment based on a population PK analysis. Data are not sufficient for

drawing a conclusion on patients with severe (eGFR < 30 and ≥ 15 mL/min/1.73 m^2) renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator 2°C to 8°C. Do not freeze. Store in the original package until time of preparation in order to protect from light. Do not shake. Keep out of the reach and sight of children.

For storage conditions after dilution of the medicinal product, see 12 SPECIAL HANDLING INSTRUCTIONS, Storage.

12 SPECIAL HANDLING INSTRUCTIONS

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 25ºC 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.
- Do not freeze

Administration
JEMPERLI should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes by a health professional.

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: dostarlimab

Chemical name: Immunoglobulin G4-kappa, anti-[Homo sapiens PDCD1(programmed cell death 1, PD1, PD1 CD279)], humanized monoclonal antibody

Molecular formula and molecular mass: $C_{6420}H_{9832}N_{1680}O_{2014}S_{44}$ (non-glycosylated form with C-terminal lysine residues) and 143.9 kDa.

Structural formula: Dostarlimab is a humanized IgG4 monoclonal antibody. It is a glycosylated homodimer consisting of two identical heavy chains and two identical light chains, with 12 intra-chain disulfide bonds and 4 inter-chain disulfide bonds.

Physicochemical properties: Formulated drug substance: dostarlimab is a clear to slightly opalescent, colorless to yellow solution, essentially free from visible particles.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Mismatch repair deficient (dMMR) / or microsatellite instability-high (MSI-H) endometrial cancer (EC)

The efficacy and safety of JEMPERLI were investigated in the GARNET study, a multicentre, uncontrolled, multiple parallel cohort, open-label phase-1 study. The GARNET study included expansion cohorts in subjects with recurrent or advanced solid tumours who have limited available treatment options.

GARNET study Cohort A1 enrolled 129 patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer who have progressed on or after a platinum containing regimen. 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 status in tumour material. Most of the sites used IHC as it was the most common assay available.

Patients with the following status were excluded from the GARNET study: ECOG baseline performance score $\geq$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 JEMPERLI 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. The

median duration of treatment was 26 weeks, with a minimum of 3 weeks and a maximum of 139 weeks.

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 Tumors (RECIST v1.1). 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.

Demographic and baseline characteristics are summarized in Table 7.

Table 7 Demographic and baseline characteristics of patients with dMMR/MSI-H endometrial cancer in GARNET study

Demographic Characteristics	
Characteristic	**Total (N=108)**
Race, n (%)	
White	84 (77.8)
Black	2 (1.9)
Asian	5 (4.6)
American Indian or Alaska Native	3 (2.9)
Not Reported	14 (13.0)
Age (years)	
n	108
Median	64.5
Min, max	39, 80
Age group, n (%)	
<65 years	54 (50.0)
≥65 years to <75 years	43 (39.8)
≥75 years	11 (10.2)
ECOG performance status	
0	42 (38.9)
1	66 (61.1)
Primary Cancer History	
Variable, n (%)	**Total (N=108)**
Grade of disease at diagnosis	
Grade 1	31 (28.7)
Grade 2	42 (38.9)

Demographic Characteristics	
Grade 3	30 (27.8)
Not assessable	5 (4.6)
FIGO stage at diagnosis	
Stage I	41(38.0)
Stage II	9 (8.3)
Stage III	38 (35.2)
Stage IV	20 (18.5)
Prior Anticancer Treatment	
Variable, n (%)	**Total (N=108)**
Any prior anticancer treatment	108 (100)
Prior surgery for study indication	98 (90.7)
Any prior anticancer radiotherapy	74 (71.3)
Prior bevacizumab use	5 (4.6)
Any prior adjuvant/neo-adjuvant anticancer treatment	59 (54.6)
Number of prior anticancer regimens	
1	69 (63.9)
2	27 (25.0)
3	9 (8.3)
≥4	3 (2.8)
Number of prior regimens for metastatic disease[a]	
0	49 (45.4)
1	48 (44.4)
2	10 (9.3)
3	1 (0.9)

Abbreviations: BMI=body mass index; dMMR=mismatch repair-deficient; EC=endometrial cancer; FIGO=International Federation of Gynecology and Obstetrics; ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; MMR-unk=unknown mismatch repair tumour status; MSI-H=microsatellite instability high.

[a] Excluding neo-adjuvant, adjuvant regimens, and hormonal agents.

14.2 Study Results

A total of 108 patients (18 years or older) with dMMR/MSI-H EC were evaluated for efficacy in the GARNET study. A total of twenty-one patients were excluded from primary efficacy analysis including 12 patients with measureable disease at baseline who had not discontinued either from treatment or from the study at the time of analysis but had insufficient follow-up at the time of the data cut-off, and 9 patients who had no measurable disease at baseline by RECIST 1.1 per BICR. At the time of analysis,

63% of subjects and 41% of subjects had discontinued treatment and discontinued from the study respectively.

The efficacy results of GARNET study for mismatch-repair deficient /MSI-H endometrial cancer patients are shown in Table 8.

Table 8 Efficacy results in GARNET study for patients with dMMR/MSI-H endometrial cancer

Endpoint	JEMPERLI (N=108)
Objective response rate (ORR)	
ORR n (%) (95% CI)	47 (43.5%)[1] (34.0, 53.4)
Complete response rate n (%)	11 (10.2%)
Partial response rate n (%)	36 (33.3%)
Duration of response (DOR)	
Median in months (range)	Not reached (2.6, 28.1+)
Patients with duration ≥6 months n (%)	37 (78.7%)

[1] At time of data cut-off (01 March 2020)
+ = ongoing at last assessment

Median follow up at the time of data cut off was 16.3 months (range 0.0+, 30.6+ months).

14.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Anti-drug antibodies (ADA) were tested in 384 patients who received 500 mg Q3W for the first 4 cycles followed by 1000 mg Q6W dostarlimab and the incidence of dostarlimab treatment-emergent ADAs was 2.1%. Neutralising antibodies were detected in 1.0% of patients. Due to the limited number of patients who tested positive for anti-drug antibody, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Dostarlimab was administrated by IV to cynomolgus monkeys in a single dose study and two repeat-dose studies: 4-weeks and 13-weeks. Dostarlimab was generally well tolerated in cynomolgus monkeys in the single- and 4-weeks repeat-dose toxicity studies and the no observed adverse effect level (NOAEL) in both studies was considered to be 100 mg/kg, the top dose. The NOAEL could not be determined in the 13-weeks repeat-dose study.

In Study 4010-09-003, dostarlimab was administrated by IV to cynomolgus monkeys (4 animals/ sex/group) at dose levels of 10, 30, and 100 mg/kg once weekly over 13 weeks (14 doses in total). After

completion of dosing, 2 animals/sex/group from the control and high-dose groups were assigned to an 8-week treatment-free recovery period. One male receiving 10 mg/kg dostarlimab was euthanized on Day 89 due to chronic, unresolved, generalized skin findings (first recorded on Day 5) and secondary swollen and firm inguinal lymph nodes. The skin findings were indicative of an immune reaction and they could be exaggerated pharmacological effects of dostarlimab based on the mechanism of action. Additionally, liquid feces observed in all groups, including control, was considered a possible drug-related effect at ≥30 mg/kg/week dose given the increased incidence over concurrent controls and timing relative to dosing. However, there were no correlated changes in body weight and food consumption, or associated pathology findings, thus, it was not considered adverse. Also, sporadic and dose-unrelated macroscopic and/or microscopic findings of an immune-mediated nature were observed in the skin, kidney, liver, or heart of 1-2 animals per group, dosed with dostarlimab. These findings could be the anticipated pharmacological effects or drug-related exacerbation of background findings.

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

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

Reproductive and Developmental 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 fetus throughout pregnancy. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that the administration of JEMPERLI during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

Animal fertility studies have not been conducted with dostarlimab. In 1-month and 3-month repeat-dose toxicology studies in cynomolgus monkeys, there were no notable effects in the male and female reproductive organs; however, these results may not be representative at all of the potential clinical risks because of the immaturity of the reproductive system of animals used in the studies. Therefore, fertility toxicity remains unknown.

Special Toxicology: No immunotoxicity or local tolerance studies have been performed with dostarlimab. Tissue cross-reactivity studies were performed in human and cynomolgus monkey tissues in two JEMPERLI doses, 0.5 or 5.0 µg/mL. Dostarlimab-specific binding was observed at 0.5 or 5.0 µg/mL in both human and cynomolgus monkey tissues. Binding in cynomolgus monkey tissues was similar to that of human tissues; however, a greater amount of staining was present in the human tissue panel. In both the human and cynomolgus monkey studies, there was no unexpected binding, and hence no tissue cross-reactivity was observed.

Juvenile Toxicity: No studies have been performed to assess the potential of JEMPERLI for juvenile animal toxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]JEMPERLI (jem-PER-lee)

dostarlimab for injection

Read this carefully before you start taking **JEMPERLI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JEMPERLI**.

What is JEMPERLI used for?

For the following indication(s), JEMPERLI has been **approved with conditions (NOC/c).** This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

JEMPERLI is a prescription medicine used in adults to treat:

- a kind of cancer called endometrial cancer (cancer of the lining of the womb) in adults that is shown by a laboratory test to be mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) that has progressed on or following prior treatment with a platinum containing regimen.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada. Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments. Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does JEMPERLI work?

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

JEMPERLI works by helping your immune system fight your cancer.

It is given when endometrial cancer (cancer of the lining of the womb) has spread, or cannot be taken out by surgery, and has progressed on or following prior treatment.

What are the ingredients in JEMPERLI?

Medicinal ingredients: dostarlimab

Non-medicinal ingredients: trisodium citrate, dihydrate; citric acid, monohydrate; L-arginine hydrochloride; sodium chloride; polysorbate 80; and water for injection (see "Do not use JEMPERLI if").

JEMPERLI comes in the following dosage forms:

Solution for infusion, 500 mg dostarlimab per vial

Do not use JEMPERLI if:

- if you are allergic to dostarlimab or any of the other ingredients of this medicine (listed in "What are the ingredients in JEMPERLI?"). Talk to your doctor before you are given JEMPERLI if you are not sure

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JEMPERLI. Talk about any health conditions or problems you may have, including if you:

- have immune system problems
- have lung or breathing problems
- have liver or kidney problems
- have serious skin problems
- have any other medical problems including but not limited to:
  - had an allergic reaction to other monoclonal antibody therapies;
  - have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
  - have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS);
  - have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic); or
  - take other medicines that make your immune system weak. Examples of these may include steroids, such as prednisone.

Pregnancy

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

Breast-feeding

- **You must not breast-feed during treatment and for at least 4 months after your last dose of JEMPERLI.**
- A risk to the newborns/infants cannot be excluded.
- If you are breast-feeding, ask your doctor for advice before you are given this medicine.
- The active ingredient of JEMPERLI may pass into your breast milk.
- You and your doctor should decide if you will take JEMPERLI or breast-feed, you should not do both.

Children:

- It is not known if JEMPERLI is safe and effective in children less than 18 years of age. Therefore, **Health Canada has not authorized an indication for children less than 18 years of age**.

Elderly

- No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is recommended for patients who are aged 65 years or over. There are limited clinical data with dostarlimab in patients aged 75 years or over.

Other warnings you should know about:

There are possible side effects of JEMPERLI treatment in people who have received a transplant

- **Rejection of a transplanted organ**. People who have had an organ transplant may have an increased risk of organ transplant rejection. Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.
- **JEMPERLI can cause complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic)**. These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with JEMPERLI. Your healthcare professional will monitor you for these complications.

JEMPERLI can have serious side effects, which can sometimes become life-threatening and can lead to death. These side effects may happen at any time during treatment, or even after your treatment has ended. You may get more than one side effect at the same time.

You need to be aware of possible symptoms, so your doctor can give you treatment for side effects if necessary.

Driving and using machines:

If you experience side effects that affect your ability to concentrate and react, do not drive or use machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JEMPERLI:

- *Some medicines may interfere with the effect of JEMPERLI, especially medicines that make your immune system weak-for example corticosteroids, such as prednisone.*

Once you are treated with JEMPERLI, your doctor may give you corticosteroids to reduce any side effects that you may have.

How to take JEMPERLI:

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

Your doctor will give you JEMPERLI as a drip into a vein *(intravenous infusion)* for about 30 minutes.

Your doctor will decide how many treatments you need.

Usual dose:

The recommended dose of JEMPERLI is 500 mg every 3 weeks for first 4 doses, followed by 1000 mg every 6 weeks for all cycles thereafter.

Overdose:

If you think you, or a person you are caring for, have taken too much JEMPERLI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment to receive JEMPERLI

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

What are possible side effects from using JEMPERLI?

When you get JEMPERLI, you can have some serious side effects. These side effects can sometimes become life-threatening and can lead to death. These side effects may happen anytime during treatment or even after your treatment has ended. You may experience more than one side effect at the same time. The following lists do not include all the possible side effects you may feel when taking JEMPERLI. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported with dostarlimab alone:

Very Common

- diarrhea; feeling sick *(nausea)*; being sick *(vomiting)*
- skin redness or rash; blistering of the skin or mucous membranes; itchy skin
- high temperature; fever

Common
- muscle or joint pain
- chills

If you are being treated with JEMPERLI and have any of the following serious side effects, call or see your doctor or nurse right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of JEMPERLI or stop your treatment with JEMPERLI.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Low red blood cells count *(anaemia)*		X	
Increased liver enzyme levels in the blood: feeling tired or weak		X	
Inflammation of the skin: rash, itching, peeling or skin sores; ulcers in the mouth, nose, throat or genital area		X	
COMMON			
Overactive or underactive thyroid gland: rapid heartbeat, weight loss or weight gain, increased sweating, hair loss, feeling cold, constipation, abdominal pain, deeper voice, muscle aches, dizziness or fainting, headache that will not go away or unusual headache		X	
Inflammation of the lungs (*pneumonitis*): shortness of breath, chest pain, new or worse cough		X	
Inflammation of the lining of the bowel *(colon)*: diarrhea, or more bowel movements than usual; black, tarry, sticky stools, blood or mucus in stools; severe stomach pain or tenderness; feeling sick (*nausea*), being sick (*vomiting*)		X	
UNCOMMON			
Decreased secretion of adrenal hormones: Feeling tired, muscle weakness, loss of appetite, weight loss, abdominal pain		X	
Inflammation of the eye: changes in the coloured part of the eye (the iris) and the area around the iris, changes to eyesight		X	
Inflammation of the kidneys: changes in amount or colour of urine, swelling of the ankles, loss of appetite, blood in the urine		X	
Inflammation of the pancreas: rapid heartbeat, weight loss or weight gain, increased sweating, hair loss, feeling cold, constipation, abdominal pain, deeper voice, muscle aches,		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
dizziness or fainting, headache that will not go away or unusual headache			
Inflammation of the pituitary gland, in the base of the brain: rapid heartbeat, weight loss or weight gain, increased sweating, hair loss, feeling cold, constipation, abdominal pain, deeper voice, muscle aches, dizziness or fainting, headache that will not go away or unusual headache		X	
FREQUENCY UNKNOWN			
Brain and nervous system *(myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis):* neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, weakness of eye muscles, drooping eyelids, dry eyes and blurred vision, difficulty swallowing, dry mouth, impaired speech, confusion and sleepiness, dizziness, pricking or pins and needles sensations in the hands and feet, aching muscles, difficulty walking or lifting objects, abnormal heart beat/rate or blood pressure		X	
Heart muscle *(myocarditis)*: trouble breathing, dizziness or fainting, fever, chest pain and chest tightness, flu-like symptoms		X	
Inflammation of the liver (*hepatitis*): feeling sick *(nausea)*, being sick *(vomiting)*; loss of appetite; pain on the right side of the abdomen (stomach); yellowing of the skin or the whites of the eyes; dark-coloured urine**;** bleeding or bruising more easily than normal		X	
Inflammation of other organs: severe or persistent muscle or joint pains, severe muscle weakness, swollen or cold hands or feet, feeling tired		X	
Infusion-related reactions: shortness of breath or wheezing, itching or rash, flushing, dizziness, chills or shaking, fever, drop in blood pressure (feeling like passing out)		X	
Spinal cord *(myelitis)*: pain, numbness, tingling or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation		X	
Type 1 diabetes or diabetic complications (*diabetic ketoacidosis)*		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

It is unlikely that you will be asked to store JEMPERLI yourself. It will be stored in the hospital or clinic where it is given to you.

Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light. Keep out of reach and sight of children.

If you want more information about JEMPERLI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.gsk.ca, or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.

Last Revised: December 23, 2021