# Summary Report of Benefit-Risk Assessment

## JEMPERLI CONCENTRATE FOR SOLUTION FOR INFUSION 500MG/10ML

## NEW DRUG APPLICATION

| | |
|---|---|
| **Active Ingredient(s)** | Dostarlimab |
| **Product Registrant** | GlaxoSmithKline Pte Ltd |
| **Product Registration Number** | SIN16623P |
| **Application Route** | Abridged evaluation |
| **Date of Approval** | 06 October 2022 |

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## A INTRODUCTION

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

The active substance, dostarlimab, is a humanised monoclonal antibody of the IgG4 subclass that binds with high affinity to programmed cell death protein-1 (PD-1) and blocks the interaction between PD-1 and its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2), releasing inhibition of PD-1 pathway-mediated immune response, including the anti-tumour immune response.

Jemperli is available as concentrate for solution for infusion containing 500mg/10mL of dostarlimab. Other ingredients in the vial are trisodium citrate dihydrate, citric acid monohydrate, L-arginine hydrochloride, sodium chloride, polysorbate 80 and water for injection.

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## B ASSESSMENT OF PRODUCT QUALITY

The drug substance, dostarlimab, is manufactured at WuXi Biologics Co., Ltd., WuXi, China. The drug product, Jemperli, is manufactured at Ajinomoto Althea Incorporated, San Diego, United States.

**Drug substance:**

Adequate controls have been presented for the cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice. Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at ≤ -35ºC and shelf-life of 36 months. The packaging is sterile, single-use containers with screwcap closures.

**Drug product:**

The manufacturing process involves homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered to be a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the shelf-life of 36 months when stored between 2ºC and 8ºC. The in-use period after dilution is no more than 6 hours at room temperature up to 25ºC or no more than 24 hours under refrigeration at 2ºC to 8ºC. The container closure system is a 10 mL Type I borosilicate clear glass vial with chlorobutyl stopper and an aluminium overseal with a flip-off cap.

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## C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of dostarlimab for the treatment of recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen was based on one pivotal study, GARNET (Study 4010-01-001). The GARNET study was a Phase 1/2, ongoing, open-label study of dostarlimab monotherapy in patients with solid tumours, including EC, non-small cell lung cancer, ovarian cancer, fallopian tube cancer and primary peritoneal cancer. The dMMR/MSI-H EC cohort (Cohort A1) provided the key evidence for clinical efficacy, where subjects with dMMR/MSI-H EC were treated with dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks, until disease progression or unacceptable toxicity.

The main inclusion criteria were patients aged 18 years and above with EC, who had progressed on or after platinum doublet therapy and received no more than two lines of anticancer therapy for recurrent or advanced disease. The identification of dMMR/MSI-H tumour status was prospectively determined based on testing using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS).

The primary efficacy endpoints were the objective response rate (ORR) and duration of response (DOR) assessed using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 based on blinded independent central review (BICR). ORR was defined as the proportion of patients achieving best overall response (BOR) of complete response (CR) or partial response (PR); DOR was defined as the time from first documentation of CR or PR until the time of first documentation of progressive disease (PD), or death due to any cause. Secondary efficacy endpoints included disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) as assessed using RECIST v1.1, as well as immune-related objective response rate (irORR), immune-related duration of response (irDOR), immune-related disease control rate (irDCR) and immune-related progression-free survival (irPFS) as assessed using immune-related Response Evaluation Criteria in Solid Tumours (irRECIST) based on Investigators' assessment.

For Cohort A1 with dMMR/MSI-H EC, the null hypothesis that the true response rate was ≤20% (H0: p≤0.2) was tested against a 1-sided alternative of ≥40% (Ha: p≥0.4). With 65 subjects treated, Cohort A1 has 92% power to rule out a ≤20% ORR (null hypothesis; expected ORR for conventional therapy) when the true ORR being 40% at the 2.5% type I error rate (1-sided).

Under protocol amendment 5, the sample size of Cohort A1 was increased to 100 subjects with the potential for up to 165 subjects, which allowed the lower-limit boundary of the exact 95% confidence interval (CI) excluding a response rate of 25% or less and assuming the observed ORR is 35%.

As of the data cut-off date of 01 March 2020, 129 subjects had been enrolled in Cohort A1 of the study. Of these, 105 subjects were included in the primary efficacy analysis set, which was defined as all subjects who had measurable disease at baseline by RECIST v1.1 per BICR and had the opportunity for at least 24 weeks of tumour assessment at the time of analysis. Most of the subjects were White (78.1%), and 3.8% were Asian. The median age was 64.0 years (range: 39 to 80 years). At baseline, 67.6% of the subjects had International Federation of Gynecology and Obstetrics (FIGO) Stage IV disease at the most recent assessment, 15.2% of the subjects were in FIGO Stage III and 15.2% of the subjects were in FIGO Stage I or II.

A total of 67.6% of subjects with dMMR/MSI-H EC had a histologic diagnosis of EC Type I, and the most common disease grade at diagnosis was Grade 2 (39.0%). Subjects had received a median of one prior line of anticancer therapy: 66 subjects (62.9%) had received one prior line, 27 subjects (25.7%) had received two prior lines, 9 subjects (8.6%) had received three prior lines, and 3 subjects (2.9%) had received at least four prior lines. Except for one subject who was enrolled in error and did not receive platinum-containing therapy, all subjects had received prior platinum-containing therapy. The study population was considered representative of the target patient population.

In subjects with dMMR/MSI-H EC, the ORR as assessed using RECIST v1.1 based on BICR was 44.8% (95% CI: 35.0, 54.8), with 11 subjects (10.5%) achieving CR and 36 subjects (34.3%) achieving PR. The results of subgroup analyses of ORR were generally consistent across subgroups defined by tumour MSI status (MSI-H based on NGS: 42.5%; dMMR based on IHC: 44.7%), number of prior anticancer therapy regimens (1 line: 50.0%; ≥2 lines: 35.9%), prior radiation therapy (received prior radiation: 47.3%; had not received prior radiation: 38.7%), BOR from last platinum-containing prior anticancer therapy (CR/PR: 47.7%; stable disease [SD]: 65.0%; progressive disease [PD]: 20.0%), and progression-free interval from last platinum-containing prior anticancer therapy (≥6 months: 46.9%; <6 months: 38.5%).

With a median follow-up duration of 16.3 months, the median DOR was not reached. A total of 78.7% of responders had a DOR of ≥6 months, and 89.4% of responders had an ongoing response. Dostarlimab treatment resulted in a DCR of 57.1% (60 of 105 subjects). The median PFS was 5.5 months (95% CI: 3.2, not reached), and the median OS was not reached (95% CI: 17.1, not reached). In the absence of a comparator in a single-arm study, meaningful conclusions could not be drawn from the PFS and OS results.

Results of the other secondary endpoints as assessed using irRECIST based on Investigators' assessment in the secondary efficacy analysis set were consistent with the results as assessed using RECIST based on BICR. Subjects with dMMR/MSI-H EC had an irORR of 46.0%, with 7.1% immune-related complete response (irCR) and 38.9% immune-related partial response (irPR). The median irDOR was not reached with 76.9% of responders had an irDOR of ≥6 months, and 82.7% of responders had an ongoing response. The irDCR was 63.7%, and the median irPFS was 10.3 months (95% CI: 5.2, 18.0).

**Summary of efficacy results**

| | **Primary efficacy analysis set (N=105)** |
|---|---|
| ***Primary efficacy endpoints*** | |
| ORR, n (%)<br>(95% CI) | 47 (44.8%)<br>(35.0, 54.8) |
| BOR, n (%)<br>CR<br>PR<br>Stable disease (SD)<br>PD<br>Not evaluable (NE)<br>Not done | <br>11 (10.5%)<br>36 (34.3%)<br>13 (12.4%)<br>39 (37.1%)<br>3 (2.9%)<br>3 (2.9%) |
| DOR (months)<br>Median<br>(95% CI) | <br>NR<br>(NR, NR) |
| ***Secondary efficacy endpoints*** | |
| DCR, n (%)<br>(95% CI) | 60 (57.1%)<br>(47.1, 66.8) |
| PFS (months)<br>Median<br>(95% CI) | <br>5.5<br>(3.2, NR) |
| OS (months)<br>Median<br>(95% CI) | <br>NR<br>(17.1, NR) |
| | **Secondary efficacy analysis set (N=113)** |
| ***Secondary efficacy endpoints*** | |
| Immune-related ORR (irORR), n (%)<br>(95% CI) | 52 (46.0%)<br>(36.6, 55.6) |
| Immune-related BOR (irBOR), n (%)<br>irCR<br>irPR<br>Immune-related stable disease (irSD)<br>Immune-related progressive disease (irPD)<br>NE<br>Not done | <br>8 (7.1%)<br>44 (38.9%)<br>20 (17.7%)<br>36 (31.9%)<br>2 (1.8%)<br>3 (2.7%) |
| Immune-related DOR (irDOR) (months)<br>Median<br>(95% CI) | <br>NR<br>(20.5, NR) |
| Immune-related DCR (irDCR), n (%)<br>(95% CI) | 72 (63.7%)<br>(54.1, 72.6) |
| Immune-related PFS (irPFS) (months)<br>Median<br>(95% CI) | <br>10.3<br>(5.2, 18.0) |

Data cut-off date: 01 March 2020
NR = not reached

Overall, the ORR observed with dostarlimab was considered clinically relevant and compared favourably with that of chemotherapy treatments (7% to 13.5%) in patients with recurrent or advanced EC after prior platinum-containing therapy. The ORR results observed for dostarlimab were also comparable to that previously reported for the combination of pembrolizumab and lenvatinib (40%) in a similar subgroup of patients with recurrent or advanced dMMR EC after prior platinum-containing therapy. Given the lack of the comparator and the early phase design of the study with small sample size, there was no conclusive evidence on the survival benefit. Nevertheless, the preliminary results which demonstrated clinically meaningful benefit in terms of durable response rates was considered supportive for the use of dostarlimab in the treatment of recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen.

In order to confirm the clinical benefits of dostarlimab, the registrant will be required to submit the final results of the GARNET study (Cohort A1) and the results from Study 4010-03-001 (RUBY), which is a Phase 3, randomised study of dostarlimab in combination with chemotherapy versus chemotherapy alone in patients with recurrent (first recurrence only) or primary advanced (Stage III or IV) EC.

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## D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of dostarlimab for the treatment of recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen was based primarily on 129 subjects with dMMR/MSI-H EC from Cohort A1 of the GARNET study who had received at least 1 dose of dostarlimab treatment as of the data cut-off date of 01 March 2020. Additional supportive safety data were available from subjects with various solid tumours who had received dostarlimab monotherapy at the recommended therapeutic dose (RTD) in the GARNET study (N=515).

The overall median treatment duration for subjects with dMMR/MSI-H EC was 26.0 weeks (range: 3 to 139 weeks). Sixty-three subjects (48.8%), 40 subjects (31.0%) and 23 subjects (17.8%) were exposed to dostarlimab monotherapy for at least 24 weeks, 48 weeks and 72 weeks, respectively. For subjects with various solid tumours who received dostarlimab monotherapy at the RTD, the overall median treatment duration was 20.0 weeks (range: 1 to 146 weeks). Two hundred fifteen subjects (41.7%), 132 subjects (25.6%) and 51 subjects (9.9%) were exposed to dostarlimab monotherapy for at least 24 weeks, 48 weeks and 72 weeks, respectively.

**Overview of safety profile of dostarlimab**

| | **dMMR/MSI-H EC (N=129)** | **Dostarlimab monotherapy at RTD (various solid tumours) (N=515)** |
|---|---|---|
| TEAE | 123 (95.3%) | 504 (97.9%) |
| Treatment-related TEAE | 82 (63.6%) | 346 (67.2%) |
| SAE | 44 (34.1%) | 203 (39.4%) |
| TEAE leading to study treatment discontinuation | 15 (11.6%) | 49 (9.5%) |
| TEAE leading to death | 5 (3.9%) | 14 (2.7%) |

Data cut-off date: 01 March 2020

Treatment-emergent adverse events (TEAEs) were reported for 123/129 subjects (95.3%) with dMMR/MSI-H EC. The most frequently reported TEAEs (≥20%) were nausea (32.6%), diarrhoea (27.9%), anaemia (27.1%), fatigue (24.8%) and asthenia (21.7%). Grade ≥3 TEAEs were reported in 62/129 subjects (48.1%) with the highest incidence (≥5%) observed with anaemia (14.7%) and abdominal pain (5.4%). Treatment-related Grade ≥3 TEAEs were experienced by 17/129 subjects (13.2%). The only treatment-related Grade ≥3 TEAEs reported in >2 subjects were anaemia (5/129 [3.9%]) and lipase increased (3/129 [2.3%]).

Serious adverse events (SAEs) were reported in 44/129 subjects (34.1%). The most frequently reported SAEs (>2%) were abdominal pain (3.1%), acute kidney injury (3.1%), sepsis (3.1%), pulmonary embolism (2.3%), pyrexia (2.3%), and urinary tract infection (2.3%). TEAEs leading to study treatment discontinuation were reported for 15/129 subjects (11.6%). The most commonly (≥1%) reported TEAEs leading to study treatment discontinuation were alanine aminotransferase increased (1.6%) and transaminases increased (1.6%). Five subjects (3.9%)

experienced TEAEs leading to death, none of which were assessed by the investigator as related to dostarlimab.

The most notable safety concerns with dostarlimab were immune-related adverse events and infusion-related reactions. In subjects with dMMR/MSI-H EC, 47/129 subjects (36.4%) reported immune-related adverse events. The most frequently reported immune-related adverse events (>5%) were diarrhoea (8.5%) and hypothyroidism (7.0%). Almost half of the subjects required treatment with immune modulatory medication to manage the immune-related adverse events and most of them were resolved at the time of the data cut-off date. No infusion-related reactions were reported in dMMR/MSI-H EC subjects, while 7/515 subjects (1.4%) with various solid tumours reported infusion-related reactions. Of these 7 subjects, 1 experienced a Grade ≥3 infusion-related reaction and was treated with an immune modulatory medication. All patients recovered from the infusion-related reactions. The package insert had included adequate information for clinical management of the immune-related adverse events and infusion-related reactions, including monitoring and dose modifications.

In terms of immunogenicity, the incidence of dostarlimab treatment emergent anti-drug antibodies (ADA) was 2.1% and neutralising antibodies were detected in 1.0% of patients. In the patients who developed ADA, there was no evidence of altered efficacy or safety of dostarlimab.

Overall, the safety profile of dostarlimab was generally in line with the known safety profile of other PD-1/PD-L1 inhibitors and was considered acceptable for the intended population in the context of recurrent or advanced EC with limited treatment options in the second-line setting. The identified safety risks have been adequately described in the package insert. The size of the safety database is currently limited. The lack of a comparator arm and long-term data did not allow a full characterisation of the safety profile of dostarlimab. Additional safety data will be available from the final results of the GARNET study (Cohort A1) and the RUBY study.

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## E ASSESSMENT OF BENEFIT-RISK PROFILE

EC is the fourth most common cancer in females and the most common gynaecological cancer in Singapore. EC is also one of the cancers which has a high rate of dMMR/MSI-H. For patients with recurrent or advanced EC, including dMMR/MSI-H EC, who have progressed on or following treatment with a platinum-containing regimen, there is currently no established standard of care. Current available therapy options generally provide limited clinical benefits, hence there is a medical need for more effective therapies in this patient population.

The efficacy of dostarlimab for the treatment of recurrent or advanced dMMR/MSI-H EC that had progressed on or following prior treatment with a platinum-containing regimen was based on the ORR of 44.8% (95% CI: 35.0, 54.8) from Cohort A1 of the GARNET study. While the median DOR was not reached; 78.7% of responders had a DOR of ≥6 months, and 89.4% of responders had an ongoing response. The ORR results compared favourably with that of chemotherapy treatments and comparable to other PD-1 inhibitor regimens. The magnitude and durability of the observed response was considered clinically meaningful in the context of the patient population who had received prior treatment with a platinum-containing regimen, and who have limited treatment options.

With respect to the survival endpoints, the median PFS was 5.5 months and the median OS was not reached. The current available data based on these time-to-event endpoints did not allow any meaningful conclusions to be drawn without a comparator in a single-arm study.

In terms of safety, the most commonly reported TEAEs with dostarlimab included nausea (32.6%), diarrhoea (27.9%), anaemia (27.1%), fatigue (24.8%) and asthenia (21.7%). The main safety risks identified with dostarlimab were immune-related adverse events and infusion-related reactions which are consistent with that known for PD-1/PDL-1 inhibitors. These safety concerns have been adequately described in the package insert, which included recommendations for dose modifications for adverse reactions.

Given the limited treatment options for patients with recurrent or advanced EC who have received prior treatment with a platinum-containing regimen, the observed ORR supplemented by the durability of the responses demonstrated with dostarlimab were considered clinically meaningful and the safety profile was considered acceptable. Taken together, the benefit-risk profile of dostarlimab in the treatment of adults with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen was deemed favourable. Nonetheless, the treatment benefits of dostarlimab in this patient population will need to be further confirmed with the final data from the GARNET study (Cohort A1) and the Phase 3 study, RUBY.

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## F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Jemperli for the treatment of adult patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen was deemed favourable and approval of the product registration was granted on 06 October 2022. The approval of this application is subject to the submission of the final results of the GARNET study (Cohort A1) and the RUBY study to confirm the efficacy and safety of dostarlimab in the treatment of patients with dMMR/MSI-H EC.

## APPROVED PACKAGE INSERT AT REGISTRATION

# JEMPERLI

**Dostarlimab**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

## CLINICAL INFORMATION

### Indications

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

### Dosage and Administration

Pharmaceutical Form

Concentrate for solution for infusion.

### Posology

The recommended dose as monotherapy is 500 mg *JEMPERLI* administered as an intravenous infusion over 30 minutes every 3 weeks for 4 doses followed by 1000 mg every 6 weeks for all cycles thereafter.

The dosage regimen is presented in Table 1.

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

| **500 mg once every 3 weeks (1 Cycle = 3 weeks)** | | | | | **1000 mg once every 6 weeks until disease progression or unacceptable toxicity (1 cycle = 6 weeks)** | | | |
|---|---|---|---|---|---|---|---|---|
| **Cycle** | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Cycle 7 | Continue dosing Q6W |
| **Week** | 1 | 4 | 7 | 10 | 13 | 19 | 25 | |

**3 weeks between Cycle 4 and Cycle 5**

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

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

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

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

| **Immune-related adverse reactions** | **Severity grade[a]** | **Dose modification** |
|---|---|---|
| Colitis | 2 or 3 | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. |
| | 4 | Permanently discontinue. |
| Hepatitis | Grade 2 (AST[b] or ALT[c] > 3 and up to 5 × ULN[d] or total bilirubin > 1.5 and up to 3 × ULN) | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. |
| | Grade ≥3 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN) | Permanently discontinue (see exception below).[e] |
| Type 1 diabetes mellitus (T1DM) | 3 or 4 (hyperglycaemia) | Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients. |
| Hypophysitis or adrenal insufficiency | 2, 3 or 4 | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy. |
| Hypothyroidism or hyperthyroidism | 3 or 4 | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. |

| **Table 2. Recommended dose modifications for JEMPERLI** | | |
|---|---|---|
| **Immune-related adverse reactions** | **Severity grade[a]** | **Dose modification** |
| Pneumonitis | 2 | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. If Grade 2 recurs, permanently discontinue. |
| | 3 or 4 | Permanently discontinue. |
| Nephritis | 2 | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. |
| | 3 or 4 | Permanently discontinue. |
| Exfoliative dermatologic conditions (e.g. SJS, TEN, DRESS) | Suspected | Withhold dose for any grade. Restart dosing if not confirmed and when toxicity resolves to Grade 0 or 1. |
| | Confirmed | Permanently discontinue. |
| Myocarditis | 2, 3 or 4 | Permanently discontinue. |
| Severe neurological toxicities (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis) | 2, 3 or 4 | Permanently discontinue. |
| Other immune-related adverse reactions involving a major organ | 3 | Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. |
| | 4 | Permanently discontinue. |
| Recurrence of immune-related adverse reactions after resolution to ≤ Grade 1(except for pneumonitis, see above) | 3 or 4 | Permanently discontinue. |

| Other adverse reactions | Severity grade[a] | Dose modification |
|---|---|---|
| Infusion-related reactions | 2 | Withhold dose. If resolved within 1 hour of stopping, may be restarted at 50% of the original infusion rate, or restart when symptoms resolve with pre-medication. If Grade 2 recurs with adequate premedication, permanently discontinue. |
| | 3 or 4 | Permanently discontinue. |

[a] Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
[b] AST = aspartate aminotransferase
[c] ALT = alanine aminotransferase
[d] ULN = upper limit of normal
[e] For patients with liver metastases who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then treatment should be discontinued.

### Method of Administration

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

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

For instructions on dilution of the medicinal product before administration, *see Use and Handling*.

### Children

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

### Elderly

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

### Renal impairment

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

### Hepatic impairment

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

## Contraindications

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

## Warnings and Precautions

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

Immune-related adverse reactions

Immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including *JEMPERLI*. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-related adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. Important immune-related adverse reactions listed in this section are not inclusive of all possible severe and fatal immune-related reactions.

Early identification and management of immune-related adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs of immune-related adverse reactions. Evaluate haematological and clinical chemistries, including liver, kidney and thyroid function tests, at baseline and periodically during treatment. For suspected immune-related adverse reactions, adequate evaluation including specialty consultation should be ensured.

Based on the severity of the adverse reaction, *JEMPERLI* should be withheld or permanently discontinued and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy administered (*see below and Posology, Dose modification*). Upon improvement to Grade 0 or 1, corticosteroid taper should be initiated and continued for 1 month or longer. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Institute hormone replacement therapy for endocrinopathies as warranted.

*JEMPERLI* should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones and unless otherwise specified in Table 2.

*Immune-related pneumonitis*
Pneumonitis has been reported in patients receiving *JEMPERLI* (*see Adverse Reactions*). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with *JEMPERLI* treatment modifications and corticosteroids (*see Posology*).

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

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

*Immune-related endocrinopathies*
Immune-related endocrinopathies, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis and adrenal insufficiency, have been reported in patients receiving *JEMPERLI* (*see Adverse Reactions*).

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

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

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

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

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

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

*Transplant-related adverse reaction*

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

*Complications of allogeneic Haematopoietic Stem Cell transplant (HSCT)*
Fatal and other serious complications can occur in patients who receive allogeneic haematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.
Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

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

## Interactions

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

## Pregnancy and Lactation

### Fertility

Fertility studies have not been conducted with dostarlimab.

### Pregnancy

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

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

### Lactation

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

## Effects on Ability to Drive and Use Machines

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

## Adverse Reactions

### Clinical trial data

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

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

**Table 3: Adverse reactions in patients with solid tumours treated with dostarlimab**

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

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

[a] Includes hypothyroidism and autoimmune hypothyroidism
[b] Includes thyroiditis and autoimmune thyroiditis
[c] Includes hypophysitis and lymphocytic hypophysitis
[d] Reported from ongoing blinded trials of dostarlimab in combination; estimated frequency category
[e] Includes uveitis and iridocyclitis
[f] Includes myocarditis and immune-mediated myocarditis
[g] Includes pneumonitis, interstitial lung disease and immune-mediated lung disease
[h] Includes pneumonitis and interstitial lung disease
[i] Includes colitis, enterocolitis and immune-mediated enterocolitis (monotherapy pool), and enteritis reported from ongoing blinded trial of dostarlimab in combination; estimated frequency category
[j] Includes pancreatitis and pancreatitis acute
[k] Includes gastritis (monotherapy pool), and immune-mediated gastritis and vasculitis gastrointestinal reported from ongoing blinded trial of dostarlimab in combination; estimated frequency category
[l] Includes colitis and immune-mediated enterocolitis (monotherapy pool), and enteritis reported from ongoing blinded trial of dostarlimab in combination; estimated frequency category
[m] Includes hepatitis, autoimmune hepatitis and hepatic cytolysis
[n] Includes rash, rash maculopapular, erythema, rash macular, rash pruritic, rash erythematous, rash papular, erythema multiforme, skin toxicity, drug eruption, toxic skin eruption, exfoliative rash and pemphigoid
[o] Includes rash, rash maculo-papular and drug eruption
[p] Includes myositis reported in an ongoing trial of dostarlimab in combination, and immune-mediated myositis (monotherapy pool); estimated frequency category
[q] Includes nephritis and tubulointerstitial nephritis
[r] Reported from an ongoing trial of dostarlimab in combination; estimated frequency category
[s] Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased and hypertransaminasaemia
[t] Includes alanine aminotransferase increased, aspartate aminotransferase increased and transaminases increased
[u] Includes infusion-related reaction and hypersensitivity.

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

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

## Overdose

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

# PHARMACOLOGICAL PROPERTIES

## Pharmacodynamics

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

### ATC code

L01FF07

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

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

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

### Pharmacodynamic effects

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

## Pharmacokinetics

Dostarlimab PK were characterised using population PK analysis from 546 patients with various solid tumours, including 288 patients with EC. The PK of dostarlimab is approximately dose proportional. When dosed at the recommended therapeutic dose (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks), Dostarlimab shows an approximate two-fold accumulation ($C_{min}$) starting cycle 4 through cycle 12, consistent with the terminal half-life.

### Absorption

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

### Distribution

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

### Metabolism

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

### Elimination

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

### Linearity/non-linearity

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

### Special patient populations

Renal impairment was evaluated based on the estimated creatinine clearance [CLCR mL/min] (normal: CLCR ≥ 90 mL/min, n = 173; mild: CLCR = 60-89 mL/min, n = 210; moderate: CLCR = 30-59 mL/min, n = 90; severe: CLCR = 15-29 mL/min, n = 3 and ESRD: CLCR < 15 mL/min, n = 1). The effect of renal impairment on the clearance of

dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of dostarlimab were found between patients with mild or moderate renal impairment and patients with normal renal function. There are limited data in patients with severe renal impairment.

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

## Clinical Studies

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

The GARNET study included expansion cohorts in subjects with recurrent or advanced solid tumours who have limited available treatment options. Cohort A1 enrolled patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) EC who have progressed on or after a platinum-containing regimen.

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

Patients received dostarlimab 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks. Treatment continued until unacceptable toxicity or disease progression for up to two years. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by blinded independent central radiologists' (BICR) review according to RECIST v1.1.

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

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

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

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

Efficacy results are shown in Table 4.

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

| **Endpoint** | **Dostarlimab (N=105)[1]** |
|---|---|
| **Objective response rate (ORR)** | |
| ORR (95% CI) | 44.8%[1] (35.0, 54.8) |
| Complete response rate | 10.5% |
| Partial response rate | 34.3% |
| **Duration of response (DOR)** | |
| Median in months (range) | Not reached (2.6, 28.1+) |
| Probability of maintaining response at 6 months by K-M (95% CI) | 97.9% (85.8, 99.7) |
| Probability of maintaining response at 12 months by K-M (95% CI) | 90.9% (73.7, 97.1) |

[1] Data cut-off (01 March 2020)
K-M: Kaplan-Meier curve estimate

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

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

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

## Non-Clinical Information

### Carcinogenesis/mutagenesis

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

### Reproductive Toxicology

Animal reproduction studies have not been conducted with dostarlimab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of dostarlimab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

### Fertility

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

### Animal toxicology and/or pharmacology

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

# PHARMACEUTICAL INFORMATION

## List of Excipients

Trisodium citrate dihydrate

Citric acid monohydrate

L arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection.

## Shelf Life

Unopened vial
The expiry date is indicated on the packaging.

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

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

## Storage

The storage conditions are detailed on the packaging.

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

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

## Nature and Contents of Container

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

Each carton contains one vial.

## Incompatibilities

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

## Use and Handling

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

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

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

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

For the 1,000-mg dose, withdraw 10 mL of *JEMPERLI* from each of two vials (withdraw 20 mL total) and transfer into an IV bag containing sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. The final concentration of the diluted solution should be between 2 mg/mL to 10 mg/mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of *JEMPERLI* into the IV bag.

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

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

Storage

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

- At room temperature up to 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.

Administration

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

*JEMPERLI* must not be administered as an intravenous push or bolus injection. Do not co-administer other medicinal products through the same infusion line.

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

Not all presentations are available in every country.

## Product Registrant

GlaxoSmithKline Pte Ltd

23 Rochester Park, Singapore 139234

## Version number: GDS04/IPI03(SI)

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