Date: 4 April 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

JEMPERLI

International non-proprietary name: dostarlimab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 500 mg/10 ml

Route(s) of administration: intravenous

Marketing Authorisation Holder: GlaxoSmithKline AG

Marketing Authorisation No.: 68023

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 17 February 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BICR	Blinded independent central review
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CT	Computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
dMMR	Mismatch repair-deficient
DOR	Duration of response
EC	Endometrial carcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
iRAE	Immune-related adverse event
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PARP	Poly(ADP-ribose) polymerase
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics

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PD-1	Programmed cell death protein 1
Ph. Eur.	European Pharmacopoeia
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
USP	United States Pharmacopeia

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance dostarlimab of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Dostarlimab 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 that has progressed on or following prior treatment with a platinum-containing regimen.

2.2.2 Approved Indication

Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced endometrial cancer (EC) with deficient DNA mismatch repair (dMMR) / high levels of microsatellite instability (MSI-H) that has progressed during or after prior treatment with a platinum-based treatment regimen (see "Clinical efficacy").

2.2.3 Requested Dosage

Summary of the applied standard dosage:
500 mg dostarlimab administered as an IV infusion over 30 minutes once every third week for four doses, followed by 1000 mg once every 6 weeks for all cycles thereafter until disease progression or inacceptable toxicity.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 January 2021
Formal control completed	28 January 2021
List of Questions (LoQ)	6 May 2021
Answers to LoQ	2 August 2021
Predecision	28 October 2021
Answers to Predecision	15 December 2021
Final Decision	17 February 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

The incidence of endometrial carcinoma (EC) has risen over the past few decades. While it is often diagnosed at an early stage when it is curable, once it has recurred or if it is locally advanced, EC remains a fatal disease. Standard first-line systemic therapy is platinum plus paclitaxel. However, there is no standard second-line treatment, and response rates to various chemotherapy agents are low and responses of short duration. Expected median overall survival (OS) of recurrent disease is 10-12 months. There is a medical need to improve treatment for patients with recurrent EC.

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4 Quality Aspects

4.1 Drug Substance

Dostarlimab is a humanised monoclonal antibody of the IgG_4 subclass. It 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).
The dostarlimab drug substance is produced from a mammalian cell line (Chinese hamster ovary, CHO) using a fed-batch production process in a production bioreactor. The cell broth is harvested and subsequently purified by several chromatographic steps. The drug substance is finally stored frozen.

The fermentation and purification processes were validated using four and three batches, respectively, and demonstrated a consistent manufacturing process and that process-related impurities are effectively reduced.

A few changes were implemented during the development of the dostarlimab drug substance manufacturing process, including changes to production scale and site, and drug substance concentration. However, all processes used the same manufacturing cell line and the analytical comparability studies, which considered clinical and commercial drug substance batches, demonstrated comparability between process changes. For this assessment release, characterisation and stability data were evaluated.

Characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. appearance, identity, pH, several purity tests (e.g. SE-HPLC, CE-SDS, cIEF), protein concentration and a cell-based bioassay. Specifications are based on clinical data and batch analysis (release and stability data), and conform to current compendial or regulatory guidelines.

Batch analysis data for development, clinical and process performance qualification batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are described and were fully validated.

The drug substance is stored frozen. During storage, no changes were observed under the proposed storage conditions.

4.2 Drug Product

The dostarlimab 50 mg/mL drug product is provided in a vial as a sterile liquid solution for infusion and therefore does not require reconstitution with a diluent. The vials are filled to a target fill volume of 10.7 mL to allow for a delivered volume of 10 mL. All excipients used comply with the European Pharmacopoeia.
Regarding the drug substance, a few changes were implemented for the drug product, e.g. a lower protein concentration was used for the early-phase clinical process and a drug product site change took place. A comparability assessment considering early- phase batches (20 mg/mL) and late-phase clinical batches (50 mg/mL) was performed, and all predefined comparability acceptance criteria were met.

As the drug substance and drug product formulation and composition are identical, the finished product manufacturing process consists only of thawing, pooling of drug substance bottles, pre-filtration, sterile filtration, filling/stoppering and visual inspection.
Validation for the drug manufacturing process was performed with three process performance qualification (PPQ) batches for each filling line covering the proposed batch size range.

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The release and stability specifications include relevant tests and limits, e.g. appearance, identity, pH, extractable volume, purity tests (e.g. SE-HPLC, CE-SDS, cIEF), protein concentration, a cell-based bioassay, visible and subvisible particles, sterility and bacterial endotoxins. All specific methods are described and validated.

Batch analysis data for development, clinical and process performance qualification batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.

The primary container for the 50 mg/mL presentation is a 10 mL Type I borosilicate clear glass vial with chlorobutyl elastomeric stopper laminated with fluoropolymer and a 20 mm aluminium overseal with a flip-off top. All components are USP and Ph. Eur. compliant.

The drug product shelf life acceptance criteria are fulfilled when the product is stored under the proposed long-term storage conditions at 2 – 8°C. However, a purity decrease by cIEF can be observed. A shelf-life of 30 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

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5 Nonclinical Aspects

Regarding the marketing authorisation application of Jemperli, the Nonclinical Assessment Division conducted an abridged evaluation, which adequately considered the Day 90 List of Questions, Day 180 CHMP *List of Outstanding Issues* as well as the EMA CHMP positive opinion of 25 February 2021.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Jemperli in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use as outlined in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

General aspects
The PK of dostarlimab are derived from one study (4010-01-001 (GARNET)) using a popPK approach. A total of 4804 PK observations from 546 patients were included in the model development.

Dostarlimab's PK are well described by a two-compartment model with linear, time-dependent clearance from the central compartment. The typical decrease in clearance over time was estimated to be 14.9%, which is in line with other anti-PD1-monoclonal antibodies where similar time-dependent decreases in Cl were observed.

Overall, dostarlimab's PK are approximately dose-proportional over the dose range evaluated in study 4010-01-001 (GARNET) (1 mg/kg to 10 mg/kg and 500 mg vs 1000 mg). With the proposed dosing regimen, an approximate two-fold increase (based on AUC or C_{max}) is observed when comparing exposures at steady state vs single dose.

ADME
Bioavailability of dostarlimab is complete since it is administered by IV infusion. Maximum dostarlimab serum concentrations are generally observed at, or shortly after, the end of the infusion.

Dostarlimab has a small volume of distribution (geometric mean [CV%] 5.26 L [14.2]), consistent with distribution largely in the systemic circulation and interstitial spaces.

Dostarlimab is a therapeutic mAb IgG4, which is expected to be catabolised into small peptides, amino acids and small carbohydrates by lysosome through fluid-phase or receptor-mediated endocytosis. Therefore, the metabolic pathways are well understood, and conventional metabolism and elimination studies are not required for dostarlimab.

Dostarlimab has a baseline systemic clearance of 0.00745 L/hr for a typical patient. Over time, the clearance is reduced to 0.00682 L/hr with a terminal elimination half-life (T1/2) of 23.5 days.

Special populations
Dostarlimab's PK are similar between patients with normal (N=196) renal function and those with mild (N=223) or moderate (N=91) renal impairment. Similarly, mild (N=51) hepatic impairment did not appear to cause a significant change in the PK of dostarlimab when compared to patients with normal (N=456) hepatic function. Accordingly, no dose adjustments are recommended in these cases. For patients with severe renal impairment or moderate or severe hepatic impairment, no dose recommendations can be made. No dose adjustments are necessary based on age (up to 75 years), gender or race.

Pharmacodynamics
In Part 2B of study 4010-01-001 (GARNET), PD-1 receptor occupancy following the first dose of 500 mg dostarlimab, directly before the next dose at Day 22, was near complete.

Safety pharmacology
Monoclonal antibodies have a low likelihood of direct ion channel interactions. Based on the results of the concentration-ΔQTc modelling, summary statistics, incidence of ECG interval values and rhythm abnormalities, dostarlimab administered at 500 mg Q3W and 1000 mg Q6W does not cause a clinically significant QTcF prolongation that exceeds the threshold of regulatory concern based on ECG data collected during Part 2B of study 4010-01-001 (GARNET).

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Immunogenicity
The overall incidence of treatment-emergent ADAs was low (3.1%). Similarly, the incidence of neutralising antibodies was low with 1.7% overall. There was no obvious impact of ADAs and neutralising antibodies on the PK, efficacy and safety of dostarlimab.

6.2 Dose Finding and Dose Recommendation

Study 4010-01-001 (GARNET) part 1 and 2A is the pivotal study that was submitted for dose finding as well as for efficacy.

Part 1 of the GARNET study consisted of a classic 3+3 first-in-human dose-finding design with a body weight-based dosing regimen in patients with advanced solid tumours. Part 2A consisted of a fixed-dose safety run-in with a modified 6+6 design of 500 mg flat dose every 3 weeks (Q3W) or 1000 mg flat dose every 6 weeks (Q6W).

No dose-limiting toxicities were observed, and the recommended therapeutic dose was determined to be 500 mg Q3W for the first 4 cycles, followed by 1000 mg Q6W for all subsequent cycles. This dosing schedule was used in Part 2B (efficacy).

6.3 Efficacy

The applicant submitted one single-arm, multicentre, open-label dose-finding and extension cohort study, study 4010-01-001 (GARNET), in patients with advanced solid tumours. The current application concerns cohort A1, which enrolled patients with mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) tumours. The objective of the study was to evaluate the efficacy of the new active substance dostarlimab, an anti-PD1 IgG4 monoclonal antibody.

The study screened 479 patients, and 129 patients were enrolled in cohort A1. Patients were treated with the recommended phase 2 dose of dostarlimab 500 mg flat dose every 3 weeks for 4 cycles, followed by dostarlimab 1000 mg flat dose every 6 weeks until progression, toxicity or withdrawal of consent. The study planned treatment for a maximum of 2 years (105 weeks); however, treatment beyond 2 years was allowed if the investigator considered that the patient was still deriving benefit. The same is true for treatment beyond progression.

Patients were eligible if they presented mismatch repair -deficient endometrial carcinoma that was not amenable to curative treatment, i.e. the tumour was locally advanced and unresectable, metastatic or recurrent. Patients had to have received at least one prior line of systemic treatment including a platinum agent, but no more than two prior lines. Endocrine therapies did not count as a treatment line. Patients had to be progressive on or following their prior line of treatment as demonstrated by two CT scans. They were also required to have measurable disease. Patients with prior immunotherapy were excluded. All histologies of endometrial carcinoma were eligible except for sarcomas or carcinosarcomas.

The primary endpoints of the study were objective response rate (ORR) and duration of response (DOR) as assessed by blinded independent central review (BICR) according to RECIST1.1. The primary hypothesis was that the ORR would be ≥20%. However, there was no control for multiple testing regarding the three planned interim analyses given the exploratory nature of the study. Secondary endpoints were immune-related ORR, immune-related DOR and immune-related DCR as assessed by the investigators. In addition, PFS (assessed by BICR) and OS were also secondary endpoints.

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The first efficacy assessment was performed 12 weeks after baseline and every 6 weeks thereafter until 48 weeks. After 48 weeks, assessments were performed every 12 weeks or whenever judged clinically indicated.

Patient disposition at data cut-off (DCO) showed that 55% of patients in cohort A1 had discontinued study treatment. Discontinuation of treatment was primarily due to disease progression (38%). Discontinuation of the study was primarily due to death (28%). Discontinuation of the study treatment due to adverse events (AEs) occurred in 11% of patients. All-cause fatal AEs were observed in 3.9% of patients. Treatment beyond progression was administered in 21.7% of patients.

Most patients were white (78%), the median age was 64 years with 51% of patients being younger than 65 years of age and 11% being 75 years of age or older. The median body mass index was 28 kg/m^2. The ECOG performance status was 1 in 60% of patients and 0 in 40%.

Disease baseline characteristics showed endometrioid carcinoma type I in 68% of patients and type II in 31% of patients. Only 4 patients (3.8%) presented serous carcinoma, and 1 patient presented clear cell carcinoma. The most frequent histological grade was grade 2, with 30% grade 1 and 27% grade 3. Most patients were FIGO stage IV at the time of study enrolment (68%).

As defined by the inclusion criteria, all patients had received prior systemic anticancer treatment including a platinum agent. A vast majority of patients had also undergone surgery (>90%) as well as receiving prior radiotherapy (71%). The **median platinum-free interval** was **6.51 months** (Q1, Q3: 4.4, 12.5 months, range 0.2-123 months).

ORR in the primary efficacy analysis set of **cohort A1** (105 patients with baseline measurable disease and minimum of 24 weeks follow-up) was **44.8%**, with 10.5% complete responses (CR) and 34.3% partial responses (PR). The disease control rate (DCR) was 57.1% (secondary endpoint) with dostarlimab. Of 47 patients who showed a response, 42 (89.4%) had an ongoing response at the time of data cut-off.

After a median follow-up of 22.5 months, median DOR was 34.7 months with a range of 34.7 months to “not reached”.

Median PFS in the primary efficacy analysis set (105 patients with baseline measurable disease and min. of 24 weeks follow-up) **was 5.5 months (95% CI: 3.2 months to *not reached*)**. A sensitivity analysis not censoring patients who received a new anticancer treatment but instead counting them as events was consistent with the primary analysis with an identical median PFS.

Median OS was **not reached**. The probability of being alive at one year was 69% (compared to an estimated median OS on standard of care therapy of approximately 10-12 months).

6.4 Safety

The applicant provided data on the 129 patients in cohort A1, as well as on the 161 patients in cohort A2 in the submitted clinical study report for the GARNET study.

The applicant provided safety data on 568 patients treated with dostarlimab monotherapy in the GARNET study. In addition, the applicant provided separate safety data from combination studies with another immunotherapy, a PARP inhibitor and chemotherapy.

Median treatment exposure in cohort A1 of the GARNET study was 26 weeks, 27% received treatment for 54 weeks or more and the maximum exposure time was 139 weeks.

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In cohort A2 of the GARNET study (mismatch repair-proficient endometrial carcinoma), median treatment exposure was 17.9 weeks (versus 26 weeks in cohort A1), 8.7% of patients received treatment for 54 weeks or more (vs 27% in cohort A1) and the maximum exposure time was 146 weeks (vs 139 weeks in cohort A1).

Overall, infusion interruptions were rare. Infusion delays and missed infusions were infrequent in both cohorts during cycles 1-4. After cycle 5 until the end of treatment, more infusion delays were observed in cohort A1 (19.4%) compared to cohort A2 (9.9%). However, in cohort A2 there were more missed infusions (11.8% vs 5.4% in cohort A1). Overall, the median relative dose intensity was 100% in both cohorts.
Nearly all patients in cohort A1 presented treatment-emergent adverse events (TEAEs) with 48% of patients presenting with a grade 3 or higher AE. Only 13% of the grade ≥ 3 AEs were considered treatment-related.

TEAEs leading to treatment discontinuation were observed in 13.0% of patients in cohort A1, but only one third of these (3.9%) were considered treatment-related.

AEs leading to treatment interruption occurred in 24% of patients in cohort A1. In cohort A1, 35% of patients presented immune-related adverse events (irAEs). However, only 22% in cohort A1 of irAEs were considered treatment-related.

Few grade 4 AEs were observed. In cohort A1, one grade 4 hyponatraemia, one grade 4 pulmonary embolism and three grade 4 sepsis cases occurred.

The **most commonly observed AEs in all cohorts of the GARNET study** (N=515) were **anaemia** (26%), **fatigue** (25%), **nausea** (25%), **diarrhoea** (23%) and **asthenia** (19%).

Grade ≥3 TEAEs
The **most frequent grade 3 AE** was **anaemia** with 14.7% in cohort A1 and 9.9% in cohort A2, followed by **abdominal pain** with 5.4% in cohort A1 and **dyspnoea** with 6.2% in cohort A2.

In cohort A1, there were 16 patients with grade 3 AEs considered treatment-related (5 anaemia, 3 lipase increased, 2 ALT increased, 2 colitis, 2 diarrhoea, 2 transaminases increased, 1 amylase increased, 1 arthralgia, 1 asthenia, 1 constipation, 1 hypertension, 1 leukopenia, 1 neutropenia, 2 pancreatitis, 1 pulmonary embolism). There was one treatment-related grade 4 GGT increased and there were no treatment-related fatal AEs.

Deaths
In cohort A1, 6 patients died on treatment. Five of these six patients died of progressive disease (PD). One patient died of an AE of aspiration (narrative could not be found, it is unclear whether it was pneumonia due to aspiration, or asphyxia). The 5 TEAEs with fatal outcomes were due to aspiration, pleural effusion, pneumonia, sepsis and shock (one patient each). Although none of these events were considered treatment-related, the narrative of the patient who died of shock is compatible with adrenal insufficiency. It remains unclear whether the patient was still on treatment or not.

Serious Adverse Events
In cohort A1, treatment-related SAEs occurred in 9.3% of patients and comprised well-known AEs of immune checkpoint inhibitors such as colitis, iridocyclitis, pancreatitis, pemphigoid, pneumonitis, increased transaminases, tubulointerstitial nephritis, as well as other AEs such as pulmonary embolism or myalgia.

In cohort A2, treatment-related SAEs occurred in 8.1% of patients and also comprised known AEs of checkpoint inhibitors, such as adrenal insufficiency, autoimmune haemolytic anaemia, hepatitis and rash.

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AEs leading to treatment discontinuation occurred in 9.9% of patients.

The data found in the EMA Assessment Report (EMA/176464/2021) on pooled safety data from all exposed patient, are consistent with the findings from the GARNET study.

Dostarlimab has a safety profile consistent with the known safety profiles of other immune checkpoint inhibitors. No unexpected safety signals were observed. The safety database currently consists of 719 patients and a median duration of exposure of 17 weeks (from EMA Assessment Report EMA/176464/2021).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

In patients with mismatch repair deficiency, dostarlimab has shown an ORR of 44.8% in the primary analysis set, which is higher than expected from traditional palliative chemotherapy. Patients who respond to the treatment have a long duration of response. Median duration of response in responders of the primary analysis population with a median follow-up of 22.5 months was reached at 34.7 months (range: 34.7 months to “not reached”). Nearly 3 years of response is clinically meaningful.

The submitted data are based on a single-arm trial and there is no comparator arm. In addition, the trial is still ongoing, so the data are not mature.

The safety profile of dostarlimab is manageable and comparable to other immune checkpoint inhibitors. There have been no treatment-related deaths on the GARNET study.

The safety pool comprises 568 patients on dostarlimab monotherapy and 295 patients on combination therapy with niraparib, TSR022 (anti-TIM3 antibody) or chemotherapy. Median treatment exposure was 17 weeks. With the current submission, there is no comparator arm based on the design of the study.

The ORR of 44.8% and a DOR of 34.7 months with a range of 34.7 months to “not reached” compare favourably to historic data with the known limitations of cross-trial comparisons. In particular, the single-arm trial design does not allow for comparative time-to-event endpoints. The immaturity of the data available and the limited safety dataset do not support a regular marketing authorisation. Nevertheless, the risk-benefit evaluation is positive for a temporary authorisation. Phase 3 comparative data are expected in Q3 2022 in a first-line setting in combination with platinum-based chemotherapy to confirm the currently available limited data.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Jemperli was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

JEMPERLI is temporarily approved; see the “Properties/Effects” section.

JEMPERLI

Composition

Active substances

Dostarlimab.

Excipients

Citric acid monohydrate, L-arginine hydrochloride, polysorbate 80, sodium chloride 18.11 mg, trisodium citrate dihydrate 66.8 mg, water for injection.
Total sodium content: 22.78 mg/vial.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.
One vial of 10 mL concentrate contains 500 mg dostarlimab (50 mg/mL).
Clear to slightly opalescent colourless to yellow solution in vials.

Indications/Uses

Jemperli is indicated as monotherapy for the treatment of adult patients with recurrent or advanced endometrial cancer (EC) with deficient DNA mismatch repair (dMMR)/high levels of microsatellite instability (MSI-H) that has progressed during or after prior treatment with a platinum-based treatment regimen (see “Clinical efficacy”).

Dosage/Administration

Usual dosage

The recommended dose as monotherapy is 500 mg of dostarlimab as an intravenous infusion over 30 minutes every three weeks for 4 doses, followed by 1,000 mg every six weeks for all cycles thereafter. The dosage schedule is presented in Table 1.

Table 1. Dosage schedule for patients treated with Jemperli

	500 mg once every three weeks (1 cycle = 3 weeks)				**1,000 mg once every six 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
Week	1	4	7	10	13	19	25	treatment every six weeks

Three weeks between Cycle 4 and Cycle 5

The administration of Jemperli should be continued according to the recommended schedule until disease progression or unacceptable toxicity or up to a maximum of two years.

In order to ensure the traceability of biotechnological medicinal products, it is recommended that the trade name and batch number be documented for each treatment.

Dose adjustment following undesirable effects

A dose reduction is not recommended. It may be necessary to delay or discontinue dosing based on the individual safety and tolerability of each patient. Recommended adjustments to the treatment of adverse reactions are presented in Table 2.

Detailed guidelines for the treatment of immune-related adverse reactions and infusion-related reactions are described under “Warnings and precautions”.

Table 2. Recommended dose adjustments for Jemperli		
Immune-related adverse reactions	**Degree of severity[a]**	**Dose adjustment**
Colitis	2 to 3	Withhold dose. Restart dosing when toxicity resolves to Grade 0–1.
	4	Permanently discontinue.
Hepatitis	Grade 2 (AST[b] or ALT[c] >3 and up to 5x ULN[d] or total bilirubin >1.5 and up to 3 ULN[d])	Withhold dose. Restart dosing when toxicity resolves to Grade 0–1.
	Grade ≥3 (AST [b] or ALT [c] >5x ULN or total bilirubin >3 x ULN [d])	Permanently discontinue (see exception below)[e]

Type 1 diabetes mellitus (T1DM)	3 to 4 (hyperglycaemia)	Withhold dose. Restart dosing in appropriately treated, clinically and metabolically stable patients.
Hypophysitis or adrenal insufficiency	2 to 3	Withhold dose. Restart dosing when toxicity resolves to Grade 0–1. Permanently discontinue in the event of recurrence or deterioration under adequate hormonal therapy.
	4	Permanently discontinue.
Hypothyroidism or hyperthyroidism	3 to 4	Withhold dose. Restart dosing when toxicity has improved to Grade 0–1 or is otherwise clinically stable.
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0–1.
	3 to 4, or recurrent Grade 2	Permanently discontinue.
Nephritis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0–1.
	3 to 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 0–1.
	Confirmed	Permanently discontinue.
Other immune-related adverse reactions involving a major organ	3	Withhold dose. Restart dosing when toxicity resolves to Grade 0–1.
	4	Permanently discontinue.
Recurrence of immune-related adverse reactions after resolution to ≤ Grade 1	3 to 4	Permanently discontinue.
Other adverse reactions	**Degree of severity[a]**	**Dose adjustment**
Infusion-related reactions	2	Withhold dose. If symptoms resolve within one hour of halting administration, dosing may be restarted at 50% of the original infusion rate or if symptoms subside following premedication. If Grade 2 recurs despite adequate

		premedication, permanently discontinue.
	3 to 4	Permanently discontinue.

[a]Toxicity graded in accordance with the 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 at Grade 2 AST or ALT, treatment should be discontinued if AST or ALT increases by ≥ 50% relative to the baseline value at the start of treatment and this increase persists for at least one week.

Special dosage instructions

Patients with impaired hepatic function

No dose adjustment is recommended for patients with mild hepatic impairment. Limited data are available concerning patients with moderate to severe hepatic impairment (see “Pharmacokinetics”).

Patients with renal disorders

No dose adjustment is recommended for patients with mild to moderate renal impairment. Limited data are available concerning patients with severe renal impairment or end-stage renal disease undergoing dialysis (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is recommended for patients aged 65 or over. Limited clinical data are available concerning the administration of Jemperli in patients aged 75 or over (see “Clinical efficacy”).

Children and adolescents

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

Mode of administration

Jemperli is intended for intravenous infusion only. Jemperli should be administered by intravenous infusion using a suitable intravenous infusion pump over 30 minutes.

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

For advice on the dilution of the medicinal product before administration, see “Other information: Instructions for handling”.

Contraindications

Hypersensitivity to the active substance or one of the excipients as per composition.

Warnings and precautions

The data described in this section refer to 568 patients with recurrent or advanced solid tumours who received Jemperli as monotherapy as part of an open-label, single-arm, multicohort study (GARNET).

Immune-related adverse reactions

Immune-related adverse reactions, which may be severe or even fatal, can occur in patients treated with antibodies, such as dostarlimab, which block the programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) pathway. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1-blocking antibodies, symptoms can also develop after treatment has ended. Immune-related adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. The major immune-related adverse reactions listed in this section are not inclusive of all possible severe and fatal immune-related reactions.

Early detection and treatment of immune-related adverse reactions is essential in order to ensure the safe application of PD-1/PD-L1-blocking antibodies. Patient should therefore be monitored for signs and symptoms of immune-related adverse reactions. Clinical laboratory parameters, including liver, kidney and thyroid function values, are to be evaluated both at the beginning of treatment and at regular intervals throughout. In the event of suspected immune-related adverse reactions, an adequate evaluation of the patient, including a specialist consultation, are to be ensured.

Depending on the severity of the adverse reaction, Jemperli is to be discontinued temporarily or permanently and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or another appropriate therapy are to be administered (see the information below and the information given under “Dosage/Administration” – “Dose adjustments”). In the event of improvement to Grade ≤1, the corticosteroids may be reduced gradually over a period of one month or longer. Based on limited data from clinical studies involving patients whose immune-related adverse reactions could not be controlled with corticosteroid use, the administration of other systemic immunosuppressants may be considered. Hormone replacement therapy is indicated in the case of endocrinopathies.

Unless otherwise specified under “Dosage/Administration; Table 1”, Jemperli should be permanently discontinued in the case of any recurring Grade 3 immune-related adverse reaction and any Grade 4

immune-related adverse reaction toxicity, with the exception of endocrinopathies, which are controlled via hormone replacement therapy.

Immune-related pneumonitis

Pneumonitis has been reported in patients receiving dostarlimab (see “Undesirable effects”). Patients should therefore be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis is to be confirmed with radiological imaging and other causes are to be ruled out. Patients are to be treated with an adjusted dostarlimab treatment and corticosteroids (see “Dosage/Administration”).

Immune-related colitis

Jemperli can cause immune-related colitis (see “Undesirable effects”). Patients are to be monitored for signs and symptoms of colitis and treated with an adjusted dostarlimab treatment, antidiarrhoeal agents and corticosteroids (See “Dosage/Administration”).

Immune-related hepatitis

Dostarlimab can cause immune-related hepatitis. Patients must be monitored regularly for changes in liver function if indicated based on clinical criteria and treated with an adjusted dostarlimab treatment and corticosteroids (see “Dosage/Administration”).

Immune-related endocrinopathies

Immune-related endocrinopathies (including hypothyroidism, hyperthyroidism, thyroiditis and adrenal insufficiency) have been reported in patients receiving dostarlimab (see “Undesirable effects”).

Hypothyroidism and hyperthyroidism

Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving Jemperli. Hypothyroidism may follow hyperthyroidism. Patients are to be monitored for abnormalities in thyroid function tests prior to and at regular intervals throughout treatment and if indicated based on clinical criteria. Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) are to be treated in accordance with the recommendations given under “Dosage/Administration”. Hormone replacement therapy for hypothyroidism or medical treatment for hypothyroidism should be initiated if this is clinically indicated.

Adrenal insufficiency

Immune-related adrenal insufficiency occurred in patients receiving Jemperli. Patients should therefore be monitored for clinical signs and symptoms of adrenal insufficiency. In the case of symptomatic adrenal insufficiency, patients are to be treated in accordance with the recommendations given under “Dosage/Administration”.

Immune-related nephritis

Dostarlimab can cause immune-related nephritis (see “Undesirable effects”). Patients are to be monitored for changes in renal function and treated with an adjusted dostarlimab treatment and corticosteroids (see “Dosage/Administration”).

Immune-related skin rash

An immune-related skin rash has been observed in patients receiving dostarlimab (see “Undesirable effects”). Patients should therefore be monitored for signs and symptoms of a rash. An immune-related rash is to be treated as recommended (see "Dosage/Administration"). Cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors.

Caution is to be exercised when considering the use of Jemperli in a patient who has previously experienced a severe or life-threatening skin intolerance under prior treatment with other immunostimulating anti-cancer agents.

Other immune-related adverse reactions

Due to the mechanism of action of dostarlimab, other potential immune-related adverse reactions may occur. The clinically relevant immune-related adverse reactions reported in less than 1% of patients treated with Jemperli as monotherapy in clinical trials include autoimmune haemolytic anaemia, uveitis, iridocyclitis, pemphigoid, hypophysitis, and type 1 diabetes mellitus. Patients are to be monitored for signs and symptoms of immune-related adverse reactions and treated as described under “Dosage/Administration”.

Fatal and other serious complications may occur in patients who receive an allogeneic haematopoietic stem cell transplant (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 febrile syndrome requiring treatment with steroids (without an identified infectious cause). These complications may occur despite interventional therapy between PD-1/PD-L1-blocking antibodies and allogeneic HSCT.

Patients are to be monitored closely for indications of transplant-related complications in order for immediate intervention to be provided if necessary. The benefit of treatment with a PD-1/PD-L1-blocking antibody prior to or after an allogeneic HSCT is to be considered in relation to the risks.

Infusion-related reactions

Jemperli may cause infusion-related reactions, which can be severe (see “Undesirable effects”). In the event that severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions do occur, stop infusion and permanently discontinue Jemperli (see “Dosage/Administration”).

Sodium

This medicinal product contains 22.78 of sodium in each vial. This corresponds to 1.14% of the maximum daily dietary sodium intake of 2 g recommended by the WHO for an adult.

Interactions

No studies on the interaction of dostarlimab with other medicinal products have been conducted. Monoclonal antibodies (mAbs) such as dostarlimab are not substrates for cytochrome P450 or active substance transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Furthermore, the pharmacokinetic interaction of dostarlimab with small molecule active substances is not expected. There is no evidence of drug interactions mediated by non-specific clearance due to the lysosomal degradation of antibodies.

Pregnancy, lactation

Women of childbearing age

Women of childbearing age should use reliable contraception from the beginning of treatment with Jemperli and for four months after the last dose.

Pregnancy

There are no available data on the use of dostarlimab in pregnant women. No experimental animal studies on reproductive toxicity have been conducted with dostarlimab to evaluate its effect on reproduction and foetal development. Due to its mechanism of action, dostarlimab may harm the foetus when administered during pregnancy (see “Preclinical data”). Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier, which indicates that dostarlimab has the potential to be transmitted from the mother to the developing foetus. Jemperli should only be used during pregnancy if treatment with dostarlimab is necessary due to the clinical condition of the woman. Women are to be informed of the potential risk to a foetus.

Lactation

There is no information regarding the transmission of dostarlimab into human milk or its effects on the breastfed child or milk production. Due to the potential for serious adverse reactions in breastfed children, women are to be advised not to breastfeed during treatment with Jemperli and for four months after the last dose.

Fertility

Fertility studies have not been conducted with dostarlimab.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The safety of dostarlimab has been evaluated in 568 patients with recurrent or advanced solid tumours, including 307 patients with endometrial cancer and 261 patients with other advanced solid tumours, who received dostarlimab as monotherapy in the open-label, multicohort GARNET trial. Patients received doses of 500 mg every three weeks for four doses followed by 1,000 mg every six weeks for all cycles thereafter.

Tabulated list of adverse reactions

The adverse reactions observed in 568 patients with recurrent or advanced solid tumours treated with dostarlimab in the GARNET trial are listed in Table 3.

These undesirable effects are presented by system organ class and frequency. Frequencies are defined as follows: 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). Within each frequency grouping, adverse reactions are presented in descending degree of severity.

Table 3: Adverse reactions in patients with advanced/recurrent solid tumours treated with dostarlimab as monotherapy

System organ class	Frequency of all degrees of severity	Grade 3–4
Blood and lymphatic system disorders	**Very common** Anaemia[a] (28.0%)	**Common** Anaemia
Endocrine disorders	**Very common** Hypothyroidism[b] (10.6%) Common Hyperthyroidism, adrenal insufficiency **Uncommon** Hypophysitis[c], thyroiditis[d]	**Uncommon** Adrenal insufficiency, hyperthyroidism
Metabolism and nutrition disorders	**Very common** Decreased appetite (17.8%) **Uncommon** Type 1 diabetes mellitus, diabetic ketoacidosis	**Uncommon** Decreased appetite
Eye disorders	**Uncommon**	

	Uveitis[e]	
Respiratory, thoracic and mediastinal disorders	**Common** Pneumonitis[f]	**Uncommon** Pneumonitis[f]
Gastrointestinal disorders	**Very common** Nausea (25.0%), diarrhoea (23.9%), vomiting (18.5%) **Common** Colitis[g], pancreatitis[h]	**Common** Nausea, vomiting, diarrhoea, pancreatitis[h] **Uncommon** Colitis[i]
Hepatobiliary disorders	**Very common** Transaminases increased[j] (14.1%) **Uncommon** Hepatitis[k]	**Common** Transaminases increased[l] **Uncommon** Hepatitis[m]
Skin and subcutaneous tissue disorders	**Very common** Itching (12.5%), skin rash[n] (19.5%)	**Common** Skin rash[o] **Uncommon** Itching
Musculoskeletal and connective tissue disorders	**Common** Myalgia **Uncommon** Immune-mediated arthritis, polymyalgia rheumatica	
Renal and urinary disorders	**Uncommon** Nephritis[p]	
General disorders and administration site conditions	**Very common** Fatigue[q] (44.9%), fever (11.3%) **Common** Chills	**Uncommon** Fever, chills, fatigue[q]
Injury, poisoning and procedural complications	**Common** Infusion-related reactions	**Uncommon** Infusion-related reactions

[a] Includes anaemia and autoimmune haemolytic anaemia

[b] Includes hypothyroidism and autoimmune hypothyroidism

[c] Includes hypophysitis and lymphocytic hypophysitis

[d] Includes thyroiditis and autoimmune thyroiditis

[e] Includes uveitis and iridocyclitis

[f] Includes pneumonitis and interstitial lung disease

[g] Includes colitis, enterocolitis and haemorrhagic enterocolitis

[h] Includes pancreatitis and acute pancreatitis

[i] Includes colitis and haemorrhagic enterocolitis

[j] Includes increased transaminases, increased alanine aminotransferases, increased aspartate aminotransferases and hypertransaminasaemia

[k] Includes hepatitis, autoimmune hepatitis and hepatocellular damage

[l] Includes increased transaminases, increased alanine aminotransferases and increased aspartate aminotransferases

[m] Includes hepatitis and autoimmune hepatitis

[n] Includes skin rash, maculopapular skin rash, erythema, macular skin rash, pruritogenic skin rash, erythematous skin rash, papular skin rash, toxic skin rash, exfoliative skin rash, skin toxicity, drug rash and pemphigoid.

[o] Includes skin rash, drug rash and maculopapular skin rash

[p] Includes nephritis and tubulointerstitial nephritis

[q] Includes fatigue and asthenia

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Furthermore, the observed incidence of antibody positivity (including neutralising antibody) 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 the formation of antibodies to dostarlimab in the studies described below with the incidence of the formation of antibodies in other studies or to other products may be misleading. Anti-drug antibodies (ADAs) were tested in 384 patients who received the recommended therapeutic dose of dostarlimab. The incidence of ADA formation under treatment with the recommended therapeutic dose of dostarlimab was 2.1%. Neutralising antibodies were detected in 1.0% of patients who received the recommended therapeutic dose of dostarlimab. In the patients who developed anti-dostarlimab antibodies, there was no evidence of a change to the efficacy or safety of dostarlimab.

Reporting suspected adverse reactions after authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

If overdose is suspected, the patient is to be monitored for signs or symptoms of adverse reactions or effects and an appropriate standard treatment is to be initiated without delay.

Properties/Effects

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. The upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Dostarlimab is a humanised monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype that binds to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2, which in turn triggers the inhibition of a PD-1 pathway-mediated immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, the blocking of PD-1 activity resulted in decreased tumour growth.

Phamacodynamics

Based on the links between exposure efficacy and safety, there are no clinically relevant differences in terms of the efficacy and safety of dostarlimab when exposure thereto is doubled. The full receptor occupancy, as measured on the basis of the direct PD-1 binding and the IL-2 production functional assay, was maintained throughout the dosing interval for the recommended therapeutic dosage schedule.

Clinical efficacy

The efficacy and safety of Jemperli were investigated in the GARNET trial, a multicentre, open-label, phase I dose-finding study conducted in patients with recurrent or advanced endometrial cancer which has progressed during or after treatment with a platinum-containing regimen.

The GARNET trial included expansion cohorts with patients with recurrent or advanced solid tumours who have only limited treatment options available to them. Cohort A1 enrolled patients with dMMR/MSI-H endometrial cancer which has progressed during or after prior treatment with a platinum-containing treatment regimen.

Patients received dostarlimab 500 mg every three weeks for four cycles followed by 1,000 mg every six weeks. Treatment was continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required emergency measures to be taken or occurred with a deterioration in performance status. The treatment with dostarlimab was continued for a maximum of 105 weeks (24 months) according to the protocol. In the study, 10 (7.8%) patients received

dostarlimab for longer than 105 weeks and up to a maximum of 139 weeks (32 months). The major efficacy endpoints were objective response rate (ORR) and duration of response (DOR), as assessed by a blinded, independent central review (BICR) by radiologists according to RECIST v1.1.

A minimum follow up period of 24 weeks from first dose was established for all patients included in both the primary and secondary efficacy analysis, regardless of whether they had a post-treatment imaging scan. The primary efficacy population was defined as patients who, at the beginning of the trial, had a measurable disease at baseline by BICR, received the trialled drug in any quantity and had the opportunity for at least 24 weeks of follow-up from the time of the first dose.

The identification of the 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 and reflected local practice. Most of the sites used IHC as it was the assay most broadly available.

The efficacy results are presented in Table 4.

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

Endpoint	**Dostarlimab** **Second interim evaluation** **(N = 105)***
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 achieved (2.6, 28.1+)
Probability of maintaining response after six months by K-M (95% CI)	97.9% (85.8, 99.7)

Probability of maintaining response after twelve months by K-M (95% CI)	90.9% (73.7, 97.1)

*Interim analysis according to predefined endpoints

[1] on the day of data collection (1 March 2020).

K-M: estimated value based on the Kaplan-Meier curve

The median observation period on the day of data collection for the n=105 population (day of data collection 1 March 2020) was 16.3 months.

The key secondary efficacy endpoints were disease control rate (DCR) and progression free survival (PFS).

Elderly patients

Of the 568 patients treated with dostarlimab as monotherapy, 51% were under 65 years of age, 38% were between 65 and 75 years of age and 11% were 75 years or older. Safety risks were not observed to be higher in elderly patients than in younger ones.

Children and adolescents

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

Temporary authorisation

The medicinal product Jemperli has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

The pharmacokinetics of dostarlimab were characterised using a population pharmacokinetic analysis of 546 patients with various solid tumours, including 150 patients with endometrial cancer. The pharmacokinetics of dostarlimab behave approximately proportionally to the dose in the dose range of 1 mg/kg to 10 mg/kg. When administered at the recommended therapeutic dose (500 mg intravenously every three weeks for four doses, followed by 1,000 mg every six weeks), dostarlimab shows an approximate two-fold accumulation ($AUC_{0\text{-}tau}$ and C_{max}) when comparing the exposure after the first 500 mg dose (Cycle 1) with the steady-state exposure, which was achieved either after the two doses of 500 mg every three weeks or one dose of 1,000 mg every six weeks.

Absorption

Dostarlimab is administered intravenously and estimates of absorption are therefore not applicable.

Distribution

The geometric mean volume of distribution of dostarlimab at steady state is approximately 5.3 L (CV% of 14.2%)

Metabolism

Dostarlimab is a therapeutic IgG4 mAb that is expected to be broken down into small peptides, amino acids and carbohydrates by lysosomes 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 0.07 L/h (CV% of 30%) at steady state. The geometric mean terminal half-life ($t_{1/2}$) at steady state is 25.4 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 [$AUC_{0\text{-}inf}$]) were approximately proportional to the dose.

Kinetics in specific patient groups

A population pharmacokinetic analysis of the patient data indicates that age (range: 24 to 86 years), sex (77% female) or race, ethnicity (75% white, 2% Asian, 4% black, 19% other) or tumour type have no clinically relevant effect on the clearance of dostarlimab. This population pharmacokinetic model also indicates that changes in renal function (normal to moderate) and hepatic function (normal to mild impairment) do not alter the disposition of dostarlimab.

Preclinical data

Repeat dose toxicity

The preclinical safety of dostarlimab was evaluated in one- and three-month repeated dose toxicity studies in long-tail macaques administered intravenous doses of 10, 30 or 100 mg/kg/week. No findings of toxicological relevance were observed in either study, with the exception that one male monkey in the three-month study dosed at 10 mg/kg/week was euthanised due to a chronic, unresolved generalised skin condition. The "no observed adverse effect level" (NOAEL) was ≥ 100 mg/kg in the one-month study, corresponding to exposure of 35 and 28 times that observed in humans at doses of 500 and 1,000 mg respectively. The NOAEL was not determined in the three-

month study as the link between the premature euthanasia of the animal and dostarlimab could not be ruled out.

Mutagenicity/carcinogenicity

No studies have been performed to date to assess the carcinogenic or genotoxic potential of dostarlimab.

Reproductive toxicity

No experimental animal studies on reproductive toxicity have been conducted with dostarlimab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. The blocking of the PD-L1 pathway has been shown to disrupt tolerance to the foetus and result in an increase in foetal loss in murine pregnancy models.

Fertility

No experimental animal studies on fertility have been conducted with dostarlimab. In one- and three-month repeated dose toxicity studies in monkeys, there were no notable effects on the male and female reproductive organs. However, these results may not be representative at all of the potential clinical risk because of the immaturity of the reproductive system of animals used in the studies. Therefore, fertility toxicity remains unknown.

Other information

Incompatibilities

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

Shelf life

Do not use this medicinal product after the expiry date (“EXP”) stated on the container.

Shelf life after opening

Store in the original packaging until preparation in order to protect the contents from light.

The prepared solution for infusion may be stored either:

- At room temperature up to 25 ºC for no more than six hours from the time of dilution until the end of infusion.

- Refrigerated at 2 °C to 8 °C for no more than 24 hours from time of dilution until the end of infusion. If refrigerated, allow the diluted solution to reach room temperature prior to administration.

Due to the lack of a preservative, the medicinal product must not be used beyond this expiry date.

Special precautions for storage

Store vials in the fridge at between 2 °C and 8 °C.

Do not freeze.

Store in the original packaging in order to protect the contents from light.

Store out of the reach of children.

Instructions for handling

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

For the 500 mg dose, withdraw 10 mL of dostarlimab from a vial and transfer into an infusion 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 dostarlimab from each of the two vials (20 mL in total) and transfer into an infusion 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 4 mg/mL and 10 mg/mL.

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

Jemperli is to be administered by a healthcare professional via intravenous infusion using a suitable infusion pump over 30 minutes.

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

Any unused medicinal product or waste material is to be disposed of in accordance with national requirements.

Authorisation number

68023

Packs

Jemperli vial containing 500 mg/10 mL: 1 [A]

Marketing authorisation holder

GlaxoSmithKline AG, CH-3053 Münchenbuchsee.

Date of revision of the text

February 2022