swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

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 use

Marketing authorisation holder: GlaxoSmithKline AG

Marketing authorisation no.: 68023

Decision and decision date: extension of therapeutic indication approved on 22.12.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
dMMR	Deficient DNA mismatch repair
EC	Endometrial cancer
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
K_M	Michaelis-Menten constant
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MSI-H	Microsatellite instability-high
N/A	Not applicable
OS	Overall survival
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
RMP	Risk management plan
RTD	Recommended therapeutic dose
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)
Vc	Volume of distribution of the central compartment
Vp	Volume of distribution of the peripheral compartment

2 Background information on the procedure

2.1 Applicant's request(s)

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Jemperli is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) with deficient DNA mismatch repair (dMMR) / high microsatellite instability (MSI-H) who are candidates for systemic therapy.

2.2.2 Approved indication

Jemperli is indicated in combination with therapy containing carboplatin and paclitaxel for the treatment of adult patients with primary recurrent or advanced endometrial cancer (EC) with deficient DNA mismatch repair (dMMR) / high microsatellite instability (MSI-H) with a high risk of recurrence (see "Warnings and precautions" and "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The dosage recommendation for the requested first-line therapy remains as the one for the approved second-line therapy. The increase to 1000 mg, however, only takes place with Cycle 7 at Week 19 instead of Cycle 5 at Week 13.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20 April 2023
Formal control completed	28 April 2023
Preliminary decision	6 October 2023
Response to preliminary decision	5 December 2023
Final decision	22 December 2023
Decision	approval

3 Medical context

Worldwide, endometrial cancer (EC) ranks as the sixth most common cancer in women and is the 14th leading cause of cancer-related death. In 2020 alone, approximately 417,000 women across the world were diagnosed with EC, with an estimated 97,000 deaths due to the disease[1]. Most notably, there has been an increase in the incidence of EC for both pre- and post-menopausal women. Unfortunately, minimal progress has been made to improve survival for women with this increasingly common malignancy. In the United States, the 5-year overall survival for women diagnosed with EC in 1985 was 83% and remained stable at 83% through to 2009[2].

In Switzerland, approximately 930 women were diagnosed with cancer of the uterine corpus per year between 2013 and 2017, translating into an age-standardised incidence rate (ASR) of 15.6/100,000/year, while approximately 220 women died of the disease each year (ASR 2.9/100,000/year). Approximately 10% of all women with the diagnosis of EC die within 1 year of diagnosis[3].

While EC is often diagnosed at an early stage when it is curable, it is rarely accessible to cure if the disease recurs after initial treatment. In addition, locally advanced disease is difficult to cure and curative treatment has a high morbidity. Finally, metastatic disease is currently incurable. These patients have a high medical need for new and effective treatment options. Approximately 25% of patients suffering from EC present with deficient DNA mismatch repair/microsatellite instability-high (dMMR/MSI-H) tumours.

[1] Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* CA Cancer J Clin, 2021. **71**(3): p. 209-249.

[2] Connor, E.V. and P.G. Rose, *Management Strategies for Recurrent Endometrial Cancer.* Expert Rev Anticancer Ther, 2018. **18**(9): p. 873-885.

[3] 2020, Swiss National Agency for Cancer Registration.

4 Nonclinical aspects

No additional nonclinical investigations for the new indication were conducted and no new nonclinical documentation was submitted. This is acceptable, as the pharmacological and toxicological profiles of Jemperli are considered to have been adequately addressed in the initial application. The requested maximum dosage is covered by the nonclinical data with the initial application and respective safety margins are already included in the information for the healthcare professional under “Preclinical data”. There is no change in the route of application, target population (ICH S9 indication), and treatment duration. An updated ERA was not submitted which is acceptable considering the nature of the product. No safety concerns were identified that would preclude a label extension.

5 Clinical aspects

5.1 Clinical pharmacology

One popPK analysis was submitted based on dostarlimab concentration data from 2 studies: GARNET (data cutoff for PK: 1 November 2021) and RUBY Part 1 (data cutoff for PK: 8 August 2022). Thus, new concentration data from the RUBY Part 1 study were added to the existing database from the GARNET study. The previously established popPK model was a 2-compartment model with linear, time-dependent elimination, with body weight as a covariate on CL, volume of distribution of the central compartment (Vc), and volume of distribution of the peripheral compartment (Vp) with a proportional residual error model. Changes in CL over time were described by a non-linear, time-dependent CL function based on time since first treatment dose.

The final analysis population consisted of 156 males and 713 females in the age range from 24 to 86 years with body weights ranging from 34 to 182 kg. The majority of the patients were White (74.6%), 5.41% were Black or African American, and 2.3% were Asian. A total of 8,032 individual dostarlimab concentration values were included in the final database.

The concentration data added from the RUBY study were well described by the existing model based on the GARNET study.

All identified covariates (similarly to the previous popPK analysis: sex, age, ALT, and combination therapy) had limited impact on exposure (effect size within 0.8-1.25 fold for AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) at the 5th and 95th percentiles of the respective covariate distribution as compared to the reference patient (female, 70 kg, 64 years old, albumin of 39 g/L, and ALT of 17 U/L).

Similarly, the impact of body weight on exposure at steady state was modest: around 0.8 - 1.25 fold at the 5th and 95th percentiles of the covariate distribution as compared to the reference patient. AUC_{ss} values in reference patients with the 5th (49.7) kg and 95th (116 kg) percentiles of the covariate value were estimated to be 19.0% higher and 23.7% lower, respectively. The impact on $C_{min,ss}$ and $C_{max,ss}$ was of a similar magnitude.

Dostarlimab PK was similar between patients with normal renal function and those with mild or moderate renal impairment. Similarly, mild hepatic impairment did not appear to cause a significant change in the PK of dostarlimab when compared to patients with normal hepatic function.

ADA was not found to have a significant effect on dostarlimab CL.

Dostarlimab showed approximately a 2-fold accumulation (2.3- and 1.72-fold for area under the concentration versus time curve for a dosing interval (AUC_{0-tau}) and C_{max}, respectively) when comparing individual predicted exposure after the first 500 mg dose Q3W with steady state exposure following 500 mg Q3W (RUBY study).

5.2 Dose finding and dose recommendation

The dose of dostarlimab chosen for the RUBY study was based on data from the GARNET trial (study 213346), which established the recommended therapeutic dose (RTD) for dostarlimab monotherapy. Data for dostarlimab administration in combination with chemotherapy were provided in the IOLite trial (study 213351), which evaluated dostarlimab in combination with chemotherapy, including carboplatin-paclitaxel.

5.3 Efficacy

RUBY Part 1 is an international, multicentre, randomised, placebo-controlled Phase 3 study evaluating the efficacy and safety of carboplatin-paclitaxel chemotherapy in combination with the anti-

PD1 antibody dostarlimab followed by dostarlimab maintenance versus carboplatin-paclitaxel plus placebo followed by placebo maintenance in patients with primary advanced or recurrent endometrial carcinoma. Patients were randomised 1:1 and stratified according to dMMR/MSI-H versus DNA mismatch repair proficient/microsatellite stable (pMMR/MSS) status, disease status (recurrent versus primary stage III versus primary stage IV), and prior pelvic radiotherapy (yes or no).

In total, 494 patients were randomised in the RUBY Part 1 study. Of these, 118 were dMMR/MSI-H. Only this dMMR/MSI-H population was assessed, as the requested indication extension only concerns these patients with DNA mismatch repair-deficient tumours (dMMR/MSI-H).

The study design and statistical assumptions are acceptable, with the exception that overall survival (OS) in the dMMR/MSI-H population was not included among the alpha-controlled endpoints. The chosen chemotherapy treatment with carboplatin and paclitaxel is the standard of care and the study was double blinded. The primary endpoints were investigator-assessed progression-free survival (PFS) in the intention-to-treat (ITT) population and in the dMMR/MSI-H population as well as OS in the ITT population. Secondary endpoints were numerous but none were included in the type I error control. OS in the dMMR/MSI-H population was not a pre-defined endpoint.

Patients received 6 cycles of chemotherapy with carboplatin and paclitaxel every 3 weeks together with either dostarlimab or placebo. Starting with Cycle 7, dostarlimab or placebo were administered every 6 weeks until progression or a total duration of 3 years.

Baseline characteristics were reasonably balanced.

The combination of carboplatin-paclitaxel and dostarlimab showed a PFS benefit in the dMMR/MSI-H population with an HR of 0.29 (0.17, 0.50), with a median PFS for the dostarlimab arm of 30.3 months (11.8, NE) versus 7.7 months (5.6, 9.7) in the placebo arm. These results are statistically significant and clinically meaningful.

Although OS in the dMMR/MSI-H population is not an alpha controlled endpoint, a prespecified subgroup analysis of OS in this population was also performed. At 26% OS event rate, there was a separation of the KM curves in favour of the dostarlimab plus carboplatin-paclitaxel arm with a 71% reduction in the probability of death, corresponding to an HR of 0.29 (95% CI 0.13, 0.64; median OS not reached for either arm).

The main uncertainties regarding the beneficial effects of dostarlimab in combination with carboplatin and paclitaxel compared to carboplatin-paclitaxel and placebo are twofold.

In patients with primary stage III EC, the number of patients is too small to draw any conclusion in the dMMR/MSI-H population. The applicant explains this finding by a longer time to progression and therefore a longer time needed to demonstrate such a benefit. The applicant argues that there is no biological rationale as to why participants with stage III EC would respond differently to treatment than patients with stage IV or recurrent EC. Swissmedic Clinical Assessment does not entirely agree that there is no biological rationale that the treatment should not work. In other tumours, it has been demonstrated that immune checkpoint inhibitors work better in the presence of disease such as, for example, in the neo-adjuvant setting compared to an adjuvant setting where no more macroscopic tumour is present. Therefore, it could be argued that stage III patients do not have sufficient tumour present to provide stimulation for the immune system. In addition, based on PORTEC-3 data approximately 30% of stage III patients relapse irrespective of their molecular subtype[4,5]. This indicates that approximately 70% of patients would receive potentially toxic treatment who may not have needed it. In addition, with the current data available, it remains unclear whether any relapses

[4] Leon-Castillo, A., et al., *Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy.* J Clin Oncol, 2020. **38**(29): p. 3388-3397.

[5] de Boer, S.M., et al., *Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial.* Lancet Oncol, 2019. **20**(9): p. 1273-1285.

for stage III patients were prevented. The question also remains as to whether these patients may have benefitted the same from the treatment at relapse. Only two thirds of patients in the placebo arm who relapsed and received further treatment received an immune checkpoint inhibitor.

The second uncertainty regarding the OS benefit of patients with dMMR/MSI-H disease is the post-progression treatment. For these patients, immune checkpoint inhibitors are authorised and patients in the placebo arm who progressed in particular should have received this treatment. As mentioned above, approximately two thirds of patients who relapsed in the placebo arm and who received further treatment received immunotherapy at relapse. In the dostarlimab arm, 7/13 patients who relapsed and received further treatment received an immune checkpoint inhibitor. The question of whether treatment at relapse could be as effective therefore remains unanswered. Nevertheless, the HR of 0.30 for OS is convincing and suggests that first-line treatment does benefit the patients.

5.4 Safety

The safety profile of carboplatin-paclitaxel and dostarlimab is in line with what would be expected of the chemotherapy combination and the single agent dostarlimab. Overall, toxicity was higher in the dostarlimab arm compared to the placebo arm and in particular, there were TEAEs resulting in death, all in the dostarlimab arm. However, there is no clear indication that the deaths were directly related to the treatment.

Safety data from the RUBY Part 1 study are consistent with the pooled safety data from all exposed patients. The only notable difference between the RUBY Part 1 safety data and the overall pooled safety was a higher proportion of fatal TEAEs in the overall safety pool of 5.7% compared to 2.1% in RUBY Part1.

In addition, the applicant provided upon request a safety analysis according to age for patients 65 years and older. This analysis showed a higher rate of TEAEs leading to treatment discontinuation in patients 65 years and older compared to patients < 65 years of age (29.5% for patients ≥ 65 versus 19.6% for patients < 65 years).

5.5 Final clinical benefit-risk assessment

Advanced and recurrent endometrial carcinoma remains a disease with a high medical need. While some patients with advanced primary endometrial cancer can be cured, the disease is nearly universally fatal in case of recurrence or if metastases are present.

Given the significant and clinically meaningful benefit on PFS and OS of the combination of dostarlimab with carboplatin and paclitaxel in patients with dMMR/MSI-H EC without a prohibitive safety signal, the benefit-risk evaluation is positive for patients with primary advanced or recurrent endometrial carcinoma with a high risk of relapse.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for 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 valid and relevant reference document 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. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 has been granted temporary authorisation for certain indications; see the “*Indications/Uses*” 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

Temporarily authorised indications

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”).

This/these indication(s) has/have been granted temporary authorisation as the clinical data were incomplete at the time that the authorisation application was assessed (Art. 9a, Therapeutic Products

Act). The temporary authorisation is contingent upon the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into a regular authorisation.

Indication authorised in standard procedure

Jemperli is indicated in combination with therapy containing carboplatin and paclitaxel for the treatment of adult patients with primary recurrent or advanced endometrial cancer (EC) with deficient DNA mismatch repair (dMMR) / high microsatellite instability (MSI-H) with a high risk of recurrence (see “Warnings and precautions” and “Clinical efficacy”).

Dosage/Administration

Usual dosage

Jemperli in combination with chemotherapy

If Jemperli is administered in combination with chemotherapy, please read the full product information for each combination product (see “Clinical efficacy”).

The recommended dose as combination therapy is 500 mg dostarlimab every 3 weeks for 6 cycles, followed by 1,000 mg every 6 weeks for all subsequent cycles.

The dosage schedule in combination with chemotherapy is summarised in Table 1.

Table 1. Dosage schedule for Jemperli in combination with chemotherapy

	500 mg once every 3 weeks in combination with chemotherapy[a] (1 cycle = 3 weeks)						**1,000 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	Cycle 8	Cycle 9	Continue treatment every 6 weeks
Week	1	4	7	10	13	16	19	25	31	

3 weeks between Cycle 6 and Cycle 7

[a] Administer dostarlimab on the same day prior to chemotherapy.

Jemperli should be continued according to the recommended regimen until disease progression or unacceptable toxicity or for up to 3 years (see “Clinical efficacy”).

Jemperli as monotherapy

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 for the use of Jemperli as monotherapy is presented in Table 2.

Table 2. Dosage schedule for Jemperli as monotherapy

	500 mg once every three weeks (1 cycle = 3 weeks)				**1,000 mg once every six weeks until progression or unacceptable toxicity (1 cycle = 6 weeks)**			
Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Continue treatment every six weeks
Week	1	4	7	10	13	19	25	

Three weeks between Cycle 4 and Cycle 5

The administration of Jemperli should be continued according to the recommended dose and 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 administration based on the individual safety and tolerability of each patient. Recommended adjustments to the treatment of adverse reactions are presented in Table 3.

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

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

	Grade ≥3 (AST[b] or ALT[c] >5 × ULN or total bilirubin >3 × ULN[d])	Permanently discontinue (see exception below)[e]
Type 1 diabetes mellitus (T1DM)	3 or 4 (hyperglycaemia)	Withhold administration. Restart dosing in appropriately treated, clinically and metabolically stable patients.
Hypophysitis or adrenal insufficiency	2, 3 or 4	Withhold administration. Restart dosing when toxicity resolves to Grade 0 or 1. Permanently discontinue in the event of recurrence or deterioration under adequate hormonal therapy.
Hypothyroidism or hyperthyroidism	3 or 4	Withhold administration. Restart dosing when toxicity has improved to Grade 0 or 1 or the patient is otherwise clinically stable.
Pneumonitis	2	Withhold administration. Restart dosing when toxicity resolves to Grade 0 or 1.
	3 or 4, or recurrent Grade 2	Permanently discontinue.
Nephritis	2	Withhold administration. Restart dosing when toxicity resolves to Grade 0 or 1.
	3 or 4	Permanently discontinue.
Exfoliative dermatological conditions (e.g. SJS, TEN, DRESS)	Suspected	Withhold administration 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.
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis	2, 3 or 4	Permanently discontinue.
Transverse myelitis	all degrees	Permanently discontinue.

Other immune-related adverse reactions involving a major organ	3	Withhold administration. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Recurrence of immune-related adverse reactions after resolution to ≤ Grade 1 (excluding pneumonitis, see above)	3 or 4	Permanently discontinue.
Other undesirable effects	**Degree of severity[a]**	**Dose adjustment**
Infusion-related reactions	2	Withhold administration. If symptoms resolve within one hour of halting administration, administration 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 or 4	Permanently discontinue.

[a]Toxicity graded in accordance with the National Cancer Institute's 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 hepatic disorders

No dose adjustment is recommended for patients with mildly impaired hepatic function. Only limited data are available concerning patients with moderately to severely impaired hepatic function (see "Pharmacokinetics").

Patients with renal disorders

No dose adjustment is recommended for patients with mildly to moderately impaired renal function. Only limited data are available concerning patients with severely impaired renal function or end-stage renal disease undergoing dialysis (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is recommended for patients aged 65 or over. Only 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 investigated. 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

There are currently no data available on the efficacy or safety of Jemperli in patients previously treated with immunotherapy.

Due to the small subgroup and low data maturity at the time of the primary analysis for PFS in the RUBY study, efficacy information in the subgroup of patients with stage III disease does not currently confirm a benefit for progression-free or overall survival (For exact inclusion criteria for patients in primary stage III, see "Clinical efficacy").

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 these 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. Patients should therefore be monitored for signs and symptoms of immune-related adverse reactions. Haematological and 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, is 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 3”, 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. If indicated based on clinical criteria, patients must be monitored regularly for changes in liver function and treated with an adjusted dostarlimab treatment and corticosteroids (see “Dosage/Administration”).

Immune-related endocrinopathies

Immune-related endocrinopathies (including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis and adrenal insufficiency) have been reported in patients receiving dostarlimab (see “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 hyperthyroidism 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, including pemphigoid, has been observed in patients receiving dostarlimab (see “Undesirable effects”). Patients should therefore be monitored for signs and symptoms of a rash. Exfoliative dermatological conditions are 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.

Haemophagocytic lymphohistiocytosis (HLH)

HLH has occurred in patients treated with Jemperli in combination with another immune checkpoint inhibitor. HLH is a potentially life-threatening syndrome with pathological activation of the immune system. If HLH is not recognised and treated early, it is often fatal. The disease is characterised by clinical signs and symptoms of severe systemic inflammation such as fever, skin rash, hepatosplenomegaly, cytopaenia (especially anaemia and thrombocytopaenia), lymphadenopathy, neurological symptoms, high serum ferritin, hypertriglyceridaemia as well as liver function and coagulation disorders. Patients with such signs and symptoms must be examined immediately and evaluated for a possible diagnosis of HLH. The administration of Jemperli should be suspended until an alternative aetiology can be established.

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 encephalitis, autoimmune haemolytic anaemia, uveitis and iridocyclitis. Cases of transverse myelitis have been observed in patients treated with PD1/PD-L1 inhibitors. Patients are to be monitored for signs and symptoms of immune-related adverse reactions and treated as described under “Dosage/Administration”.

Cases of solid organ transplant rejection were reported after market launch in patients treated with PD-1 inhibitors. Treatment with dostarlimab may increase the risk of rejection among recipients of solid organ transplants. In these patients, the benefit of treatment with dostarlimab should be weighed up against the risk of potential organ rejection.

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 venous 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 weighed up against 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, the infusion is to be stopped and Jemperli is to be permanently discontinued (see “Dosage/Administration”).

Sodium

This medicinal product contains 22.78 mg of sodium per vial, which 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 interactions 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 also 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, highly effective contraceptive methods 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 must not be administered during pregnancy unless treatment with dostarlimab is necessary due to the clinical condition of the woman. Women are to be informed of the potential risk to the foetus.

Lactation

There is no information regarding the transmission of dostarlimab into human breast 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

Tabulated list of undesirable effects

The GARNET trial evaluated the safety of dostarlimab as monotherapy in more than 600 patients with recurrent or advanced endometrial cancer or other solid tumours. Patients initially received dostarlimab at doses of 500 mg in 3-week intervals for 4 cycles, followed by 1,000 mg every 6 weeks in all subsequent cycles.

The RUBY trial evaluated the safety of dostarlimab in combination with chemotherapy in 241 patients with primary advanced or recurrent endometrial cancer. Patients initially received dostarlimab at doses of 500 mg in 3-week intervals for 6 cycles, followed by 1,000 mg every 6 weeks in all subsequent cycles.

The undesirable effects observed in over 800 patients with solid tumours treated with dostarlimab as monotherapy or in combination with carboplatin and paclitaxel or other anti-cancer agents are listed in Table 4.

When dostarlimab is administered in combination, refer to the local prescribing information for the respective combination therapy components prior to initiation of treatment.

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 (frequency cannot be estimated from the available data).

Table 4: Adverse reactions in patients with advanced/recurrent solid tumours treated with dostarlimab

System organ class	Frequency
Blood and lymphatic system disorders	**Very common** Anaemia[a] (32.3%)
Endocrine disorders	**Very common** Hypothyroidism[b] (12.2%) **Common** Hyperthyroidism, adrenal insufficiency **Uncommon** Thyroiditis[c], hypophysitis[d]

Metabolic and nutritional disorders	**Very common** Decreased appetite (18.9%) **Common** Hypoalbuminaemia, hypocalcaemia **Uncommon** Type 1 diabetes mellitus, diabetic ketoacidosis
Nervous system disorders	**Uncommon** Encephalopathy, encephalitis, myasthenia gravis, myasthenic syndrome[e]
Eye disorders	**Uncommon** Uveitis[f], keratitis
Cardiac disorders	**Common** Hypertension, tachycardia, palpitations **Uncommon** Myocarditis[g]
Respiratory, thoracic and mediastinal disorders	**Very common** Cough (15.1%) **Common** Pneumonitis[h]
Gastrointestinal tract disorders	**Very common** Nausea (33.8%), diarrhoea (27.4%), constipation (22.7%), vomiting (19.3%) **Common** Colitis [i], pancreatitis [j], gastritis[k] **Uncommon** Oesophagitis
Hepatobiliary disorders	**Very common** Transaminases increased[l] (15.1%) **Uncommon** Hepatitis[m]
Skin and subcutaneous tissue disorders	**Very common** Skin rash[n] (25.8%), itching (15.7%) **Common** Dry skin
Musculoskeletal, connective tissue and bone disorders	**Very Common** Arthralgia (22.3%), myalgia (12.9%) **Uncommon**

	Immune-mediated arthritis, polymyalgia rheumatica, myositis[o]
Renal and urinary tract disorders	**Common** Blood creatinine increased, acute kidney injury **Uncommon** Nephritis[p]
General disorders and administration site conditions	**Very common** Fatigue[q] (48.1%), fever (12.3%) **Common** Chills **Uncommon** Systemic inflammatory response syndrome[r]
Infections and infestations	**Common** Sepsis
Injury, poisoning and procedural complications	**Common** Infusion-related reactions[s]

[a] Includes anaemia, haemoglobin decreased, iron deficiency, iron deficiency anaemia, and autoimmune haemolytic anaemia

[b] Includes hypothyroidism, autoimmune hypothyroidism, and immune-mediated hypothyroidism

[c] Includes thyroiditis and autoimmune thyroiditis

[d] Includes hypophysitis and lymphoytic hypophysitis

[e] Reported from ongoing blinded study, estimated frequency category

[f] Includes uveitis and iridocyclitis

[g] Includes myocarditis, and immune-mediated myocarditis from an ongoing blinded study, estimated frequency category

[h] Includes pneumonitis, interstitial lung disease and immune-mediated lung disease

[i] Includes colitis, enterocolitis, and immune-mediated enterocolitis, and enteritis from another ongoing study

[j] Includes pancreatitis and acute pancreatitis

[k] Includes gastritis, and immune-mediated gastritis and vasculitis gastrointestinal from an ongoing blinded study, estimated frequency category

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

[m] Includes hepatitis, autoimmune hepatitis and hepatic cytolysis

[n] Includes rash, rash maculopapular, erythema, rash macular, skin toxicity, palmar-plantar erythrodysaesthesia syndrome, rash pruritic, drug eruption, rash papular, rash pustular, rash

erythematous, toxic skin eruption, erythema multiforme, exfoliative rash, pemphigoid, skin exfoliation, vulvovaginal rash

[o] Includes myositis from an ongoing blinded study (estimated frequency) and immune-mediated myositis

[p] Includes nephritis and tubulointerstitial nephritis

[q] Includes fatigue and asthenia

[r] Reported from another ongoing study

[s] Includes infusion-related reaction and hypersensitivity

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, such as 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.
In the GARNET trial, 384 patients who received the recommended therapeutic dose of dostarlimab were tested for anti-drug antibodies (ADAs). 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.

Co- administration with chemotherapy did not affect dostarlimab immunogenicity. In the RUBY trial, of the 225 patients who were treated with dostarlimab in combination with chemotherapy and evaluable for the presence of ADAs, there was no incidence of dostarlimab treatment-emergent ADA or treatment-emergent neutralising antibodies.

In the patients who developed ADA, 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-PD-1 (programmed cell death protein-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 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 functional IL-2 production assay, was maintained throughout the dosing interval for the recommended therapeutic dosage schedule.

Clinical efficacy

The efficacy and safety of dostarlimab in combination with carboplatin-paclitaxel was investigated in a phase 3 multicentre, randomised, double-blind, placebo-controlled study in patients with primary advanced or recurrent EC.

Patients were randomised (1:1) to receive either dostarlimab 500 mg plus carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles, followed by dostarlimab 1,000 mg every 6 weeks (n = 245) or to receive placebo plus carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles, followed by placebo every 6 weeks (n = 249). Randomisation was stratified by MMR/MSI status, prior external pelvic radiation therapy and disease status (recurrent, primary advanced stage III or primary advanced stage IV).

The patients who were eligible for the RUBY study had a high risk of EC recurrence. The key eligibility criteria for the study were International Federation of Gynaecology and Obstetrics (FIGO) or a redivergent disease including. In particular, patients with stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1, stage IIIC1 patients with carcinosarcoma, clear

cell, serous, or mixed histology (containing ≥10% carcinosarcoma, clear cell, or serous histology) regardless of presence of evaluable or measurable disease on imaging, stage IIIC2 or stage IV disease regardless of presence of evaluable or measurable disease.

The study also included patients with first recurrent EC with a low potential for cure by radiation therapy or surgery alone or in combination. This also included patients with a first recurrence of the disease and were naïve to systemic anticancer therapy or who had received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or progressive disease ≥6 months after completing treatment (first recurrence).

Excluded from the study were patients who had previously been treated with an anti-PD-1, anti-PD-L1 or anti-PD-L2 active substance, patients who had received prior cancer therapy (chemotherapy, targeted therapies, hormone therapy, radiation therapy or immune therapy) within 21 days or within the quintuple half-life of the last treatment before the first study day (whichever period is shorter), patients with uterine sarcoma, patients with known uncontrolled metastases of the central nervous system, carcinomatous meningitis or both.

Treatment continued for up to 3 years or until unacceptable toxicity, disease progression or investigator decision. Treatment could continue beyond 3 years or beyond disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed every 6 weeks until week 25, every 9 weeks until week 52 and every 12 weeks thereafter.

The primary efficacy endpoints were progression-free survival (PFS) as assessed by the investigator according to RECIST v1.1 in subjects with primary advanced or recurrent dMMR/MSI-H-EC and in all subjects (overall ITT population) with primary advanced or recurrent EC, and overall survival (OS) in all patients (overall ITT population) with primary or recurrent EC. The secondary endpoints included objective response rate (ORR) and duration of response (DOR) as assessed by a panel of blinded, independent, central review (BICR) and by the investigator according to RECIST v1.1 as well as PFS2, defined as the time from randomisation to treatment until the date of assessment of progression in the first anticancer therapy following the study treatment or death due to any cause, depending on which occurs first.

A total of 118 patients with dMMR/MSI-H-EC were evaluated for efficacy in the RUBY trial. Baseline demographics and characteristics of the overall study population were: median age 64 years (49% aged 65 years or older); 85% White, 9% Black, 2% Asian; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 (57%) or 1 (43%); and primary stage III 20%; primary stage IV 30%; recurrent EC 50%.

The identification of dMMR/MSI-H tumour status was prospectively determined based on local testing assays (IHC, PCR or NGS), or central testing (IHC) when no local result was available.

Efficacy results are presented in Table 5 and Figure 1. The RUBY trial demonstrated a statistically significant improvement in PFS in patients randomised to dostarlimab plus carboplatin-paclitaxel as compared with patients randomised to placebo plus carboplatin-paclitaxel.

Table 5: Efficacy results in the RUBY trial in patients with EC

Endpoint	**dMMR/MSI-H population[a]**	
	Dostarlimab + carboplatin-paclitaxel (n = 60)	**Placebo + carboplatin-paclitaxel (n = 62)**
Progression-free survival (PFS)		
Median months (95% CI)[b]	30.3 (11.8, NR)	7.7 (5.6, 9.7)
Number (%) patients with event	23 (38.3)	47 (75.8)
Hazard ratio (95% CI)[c]	0.29 (0.17, 0.50)	
p-value[b]	<0.0001	
Overall survival (OS) [d, e]		
Median months	Not reached	Not reached (20.3, NR)
Number (%) of patients with event	8 (13.3)	25 (40.3)
Hazard ratio (95% CI)[c]	0.29 (0.13, 0.64)	

CI: Confidence interval, NR = not reached.

[a] Efficacy data with a median follow-up of 25 months (cut-off date: 28 Sept. 2022).

[b] One-sided p-value based on stratified log-rank test.

[c] Based on stratified Cox regression model.

[d] Statistically not significant, as no hypothesis test for overall survival was carried out in the dMMR/MSI-H population.

[e] Assessed by investigator per RECIST v1.1.

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 treatment 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 had progressed during or after prior treatment with a platinum-containing treatment regimen. Patients with previous treatment with PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy were excluded from the study.

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. Treatment with dostarlimab lasted 220 weeks (51 months) and 24% of patients who received any amount of dostarlimab were treated for >102 weeks (2 years). The primary 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 analyses, regardless of whether they had a post-treatment imaging scan.

A total of 143 patients with dMMR/MSI-H EC were evaluated for efficacy in the GARNET study. Among these 143 patients, the baseline characteristics were: median age 65 years (52% age 65 or older); 77% White, 3% Asian, 3% Black; and Eastern Cooperative Oncology Group (ECOG) PS 0 (39%) or 1 (61%). The median number of prior lines of therapy was one: 63% of patients had one prior line, 37% had two or more prior lines. Forty-nine patients (34%) received treatment only in the neoadjuvant or adjuvant setting before participating in the study.

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 shown in Table 6.

Table 6: Efficacy results in the GARNET trial for patients with dMMR/MSI-H EC

Endpoint	**Dostarlimab (N=143)**[a]
Primary endpoints	
Objective response rate (ORR)	
ORR n (%) (95% CI)	45.5% (37.1, 54.0)
Complete response rate, n (%)	16.1%

Partial response rate, n (%)	29.4%
Duration of response (DOR)[b]	
Median in months	Not reached (1,2+; 47,2+)
Patients with duration ≥ 12 months, n (%)	52 (80.0)
Patients with duration ≥ 24 months, n (%)	29 (44.6)
Probability of maintenance of response at 6 months after K.-M.[c] (95% CI)	96.8% (87,7; 99,2)
Probability of maintenance of response at 12 months after K.-M.[c] (95% CI)	93.3% (83,0; 97,4)
Probability of maintenance of response at 24 months after K.-M.[c] (95% CI)	83.7% (70,8; 91,2)

CI: Confidence interval

[a] Efficacy data with a median follow-up of 27.6 months (cut-off date 01 Nov 2021).

[b] For patients with a partial or complete response.

[c] By K.-M. (Kaplan-Meier method)

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 investigated.

Temporary authorisation

The medicinal product Jemperli has been granted temporary authorisation as the clinical data were incomplete at the time that the authorisation application was assessed (Art. 9a, Therapeutic Products Act). The temporary authorisation is contingent upon the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into a regular authorisation.

Pharmacokinetics

The pharmacokinetics of dostarlimab were assessed as monotherapy and when administered in combination with chemotherapy.

The pharmacokinetics of dostarlimab as monotherapy or in combination with chemotherapy were characterised using a population pharmacokinetic analysis of 869 patients with various solid tumours, including 546 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 for monotherapy (500 mg intravenously every three weeks for four doses, followed by 1,000 mg every six weeks) or in the recommended therapeutic dose for combination with chemotherapy (500 mg intravenously every 3 weeks in the case of the first 6 doses, followed by 1000 mg every 6 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. Exposure to dostarlimab as monotherapy and/or in combination with chemotherapy was similar.

Absorption

Dostarlimab is administered intravenously, which is why estimates of absorption are not applicable.

Distribution

The geometric mean volume of distribution of dostarlimab at steady state is approximately 5.8 L (CV% of 14.9%).

Metabolism

Dostarlimab is a therapeutic IgG4 mAb that is expected to be broken down into small peptides, amino acids and small 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 30.2%) at steady state. The geometric mean terminal half-life ($t_{1/2}$) at steady state is 23.2 days (CV% of 20.5%).

The clearance of dostarlimab was estimated to be 7.8% lower when dostarlimab was administered in combination with chemotherapy. There was no significant effect on dostarlimab exposure.

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 toxicity studies in long-tail macaques administered repeated 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 a 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 repeat dose toxicity studies in monkeys, there were no notable effects on the male and female reproductive organs. However, these results may not be representative of the potential clinical risk because of the immaturity of the reproductive organs of the 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 refrigerator at between 2 °C and 8 °C.

Do not freeze.

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

Keep out of the reach of children.

Instructions for handling

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

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

For the 500 mg dose, withdraw 10 mL of dostarlimab from a vial and transfer into an infusion bag containing 0.9% (9 mg/mL) sodium chloride solution for injection or 5% (50 mg/mL) glucose solution for injection. The final concentration of the diluted solution should be between 2 mg/mL and 10 mg/mL. To achieve this, it may be necessary to remove a volume of diluent from the infusion bag before adding a volume of dostarlimab to the infusion bag.

- If, for example, a dose of 500 mg is prepared in a 250 mL bag containing diluent, 10 mL of diluent would have to be removed from the 250 mL bag to achieve a concentration of 2 mg/mL.

10 mL of dostarlimab would then be withdrawn from the vial and transferred into the infusion bag.

For the 1,000 mg dose, withdraw 10 mL of dostarlimab from each of two vials (20 mL in total) and transfer into an infusion bag containing 0.9% (9 mg/mL) sodium chloride solution for injection or 5% (50 mg/mL) glucose solution for injection. The final concentration of the diluted solution should be between 2 mg/mL and 10 mg/mL. To achieve this, it may be necessary to remove a volume of diluent from the infusion bag before adding a volume of dostarlimab to the infusion bag.

- If, for example, a dose of 1,000 mg is prepared in a 500 mL bag containing diluent, 20 mL of diluent would have to be removed from the 500 mL bag to achieve a concentration of 2 mg/mL. 10 mL of dostarlimab would then be withdrawn from each of the two vials (20 mL in total) and transferred into the infusion bag.

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

Dostarlimab is to be administered by a healthcare professional via intravenous infusion using a suitable infusion pump over 30 minutes. The tubes should be made of PVC, platinum-cured silicone or PP, the fittings should be made of PVC or polycarbonate, and the needles should be made of stainless steel. A 0.2- or 0.22-micron inline polyethersulfone (PES) filter must be used when administering dostarlimab.

Dostarlimab must not be administered as an intravenous push or bolus injection. Other medicinal products must not be administered 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 (Swissmedic)

Packs

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

Marketing authorisation holder

GlaxoSmithKline AG, CH-3053 Münchenbuchsee.

Date of revision of the text

December 2023