# MODULE 1.8.2

# European Union Risk Management Plan (EU-RMP) for JEMPERLI (dostarlimab)

| **RMP version to be assessed as part of this application** | |
|---|---|
| RMP Version number | 4.2 |
| Data lock point for this RMP | GARNET (Monotherapy) 1 November 2021; RUBY Part 1 (Combination therapy) 28 September 2022; Post-marketing 20 October 2023 |
| Date of final sign off | |

**Rationale for submitting an updated RMP**

Post-authorisation efficacy study (RUBY Part 1; Study 213361) has been removed as a condition of market authorisation, having fulfilled the condition of the marketing authorisation. The indication statement has been revised to add 'first-line' treatment and remove the subpopulation of "mismatched repair deficient (dMMR)/microsatellite instability-high (MSI-H)" to/from the current indication statement for Jemperli in combination with carboplatin and paclitaxel, with similar changes throughout as appropriate. Additionally, data for the dMMR/MSI-H subpopulation for the combination with carboplatin and paclitaxel has been removed throughout.

| **Summary of significant changes in this RMP:** | | |
|---|---|---|
| **PART** | **MODULE** | **Changes made in EU-RMP** |
| RMP version to be assessed as part of this application | | Post-marketing data-cut off date included |
| I | | • Updated the indication statement for JEMPERLI in combination in the Product Overview |
| II | SI | S1.1 Indication statement updated |
| II | SII | RUBY study data related to dMMR/MSI-H population removed |
| II | SIII | RUBY study data related to dMMR/MSI-H population removed |
| II | SV | SV.1.2 Post-authorization exposure data updated |
| II | SVII | • SV11.3: RUBY data related to dMMR/MSI-H population removed |
| IV | | • Removed post-authorisation efficacy study RUBY Part 1 (213361) from Table 15 |
| VI | | • I: Updated indication statement<br>• II.B: Removed RUBY Study data related to dMMR/MSI-H population<br>• II.C.1 Removed RUBY Study as a condition of market authorisation |
| Annex 5 | | Deleted reference to RUBY Study and removed RUBY Protocol |
| Annex 8 | | Updated Summary Table of changes to the RMP over time |

| **Other RMP versions under evaluation**<br><br>Not applicable | | |
|---|---|---|
| **Details of the currently approved RMP** | | |
| **Version number** | **Approved with procedure** | **Date of approval (opinion date)** |
| 3.2 | EMEA/H/C/005204/II/0023 | 7 December 2023 |

| | |
|---|---|
| **QPPV Name** | Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV |
| **QPPV Signature** | |

## Abbreviations

| | |
|---|---|
| 1L | First-line |
| ADAs | Anti-drug antibodies |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| BICR | Blinded independent central review |
| BMI | Body mass index |
| CHO | Chinese hamster ovary |
| DCR | Disease control rate |
| dMMR | Mismatch repair deficient |
| DNA | Deoxyribonucleic acid |
| DOR | Duration of response |
| EAP | Expanded access program |
| EC | Endometrial cancer |
| EEA | European Economic Area |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EPAR | European public assessment report |
| EQ-5D-5L | European Quality of Life scale, 5-Dimensions, 5-Levels |
| ESMO | European Society for Medical Oncology |
| EU-RMP | European Union-Risk Management plan |
| FIGO | International Federation of Gynaecology and Obstetrics |
| HIV | Human immunodeficiency virus |
| IgE | Immunoglobulin type E |
| IgG | Immunoglobulin type G |
| INN | International nonproprietary name |
| irAR | Immune-related adverse reactions |
| IRR | Infusion-related reaction |
| MSI-H | Microsatellite instability-high |
| NAbs | Neutralising antibodies |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NPP | Named patient program |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Programmed cell death protein |
| PD-L | Programmed cell death ligand |
| PFS | Progression-free survival |
| PK | Pharmacokinetics |
| PL | Patient leaflet |
| PRO | Patient-reported outcomes |
| PSUR | Periodic safety update report |
| PT | Prothrombin time |
| PTT | Partial thromboplastin |
| Q3W | Every 3 weeks |
| Q6W | Every 6 weeks |
| QLQ-C30 | Quality of Life Questionnaires C30 |
| QLQ-EN24 | Quality of Life Questionnaires EN24 |
| QPPV | Qualified person for pharmacovigilance |

| | |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | Serious adverse events |
| SmPC | Summary of product characteristics |
| TEAE | Treatment-emergent adverse event |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| US | United States |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
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| JEMPERLI |
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| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| Keytruda |
| Opdivo |
| Tecentriq |
| Bavencio |
| Imfinzi |
| Libtayo |

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# PART I: PRODUCT(S) OVERVIEW

## Table 1 Product Overview

| | |
|---|---|
| Active substance(s) (International nonproprietary name (INN) or common name) | Dostarlimab |
| Pharmacotherapeutic group(s) (ATC Code**)** | L01FF07 |
| Marketing Authorisation Holder/ Applicant | GlaxoSmithKline (Ireland) Limited |
| Medicinal products to which this RMP refers | 1 |
| Invented name(s) in the European Economic Area (EEA) | JEMPERLI |
| Marketing authorisation procedure | Centralised |
| Brief description of the product | Chemical class:<br>Humanised monoclonal immunoglobulin type G (IgG) 4 antibody |
| | Summary of mode of action:<br>Binds with high affinity to programmed cell death protein (PD)-1, resulting in inhibition of binding to programmed cell death ligand (PD-L) 1 and PD-L2 releasing PD-1 pathway mediated inhibition of the immune response, including the anti-tumour immune response. |
| | Important information about its composition:<br>Produced by recombinant deoxyribonucleic acid (DNA) technology in mammalian Chinese hamster ovary (CHO) cells |
| Reference to the Product Information | Please refer to the product information (section 1.3.1 of the eCTD) |
| Indication(s) in the EEA | **Current:**<br>JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.<br><br>JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy. |

| | |
|---|---|
| | **Proposed :**<br><br>JEMPERLI is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.<br><br>JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy. |
| Dosage in the EEA | **Current :**<br><br>The recommended dose of dostarlimab as monotherapy is 500 mg as an intravenous infusion over 30 minutes every 3 weeks for 4 doses followed by 1000 mg every 6 weeks for all cycles thereafter.<br><br>The recommended dose as combination therapy is 500 mg dostarlimab as an intravenous infusion over 30 minutes every 3 weeks for 6 cycles followed by 1000 mg every 6 weeks for all cycles thereafter. |
| | **Proposed** :<br>Not Applicable |
| Pharmaceutical form(s) and strengths | **Current**:<br>Concentrate for solution for infusion.<br>One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab. |
| | **Proposed**:<br>Not Applicable |
| Is/will the product be subject to additional monitoring in the EU? | Yes |

# PART II: SAFETY SPECIFICATION

# PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

## SI.1 Indication

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

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

### Incidence

The majority (96%) of uterine cancers occur in the endometrium [Cancer Research UK, 2022]. Endometrial cancer (EC) accounted for 4.5% of all new cancer cases in women diagnosed in 2020, making it the second most common gynecological cancer after cervical cancer and the sixth most common type of malignancy diagnosed in women worldwide [Sung, 2021] . The age standardized (to the World standard population) incidence rate of uterine cancer was 8.7 per 100,000 population, with an estimated 417,367 new cases diagnosed in 2020 and 97,370 deaths [Sung, 2021].

In Europe, there were an estimated 130,051 newly diagnosed cases of uterine cancer in 2020 [Ferlay, 2018]. The age-standardised (to the World standard population) incidence rate of uterine cancer in 2020 was 16.6 per 100,000 and there were an estimated 29,963 deaths [Ferlay, 2018].

In the United States (US), there were an estimated 61,738 newly diagnosed cases of uterine cancer in 2020 [Ferlay, 2018]. The age-standardised (to the World standard population) incidence rate of uterine cancer in 2020 was 21.4 per 100,000 and there were an estimated 11,460 deaths [Ferlay, 2018].

The percentage of patients who are diagnosed with advanced disease (stage III/IV) varies across studies, ranging from 25% to 46.5% in studies conducted in Europe [Bricou, 2018; Lubrano 2021]. The endometroid histological subtype accounts for the majority (75%-80%) of all EC. The molecular phenotype MSI-H accounts for approximately 20%-30% of EC overall; 33%-40% of endometroid and 2% of serous subtypes of EC [Cancer Genome Atlas Research Network, 2013]. EC is one of the cancers with a high observed rate of dMMR/MSI-H (up to 33%), although the incidence varies depending on histology and tumour grade [Mittica, 2017]. The rate of dMMR/MSI-H is lower in low-grade endometrial tumours (28.6%) than in high-grade endometrial tumours (54.3%). Although data on MMR/MSI status in the metastatic setting are limited, the rate of dMMR/MSI-H in EC classified as Stage III or IV according to

the International Federation of Gynaecology and Obstetrics (FIGO) was shown to range from 6% to 17% [Basil, 2000].

### Prevalence

The 5-year prevalence of uterine cancer among women worldwide was 1,415,213 estimated cases in 2020. In Europe, there were an estimated 482,952 women alive within 5 years of uterine cancer diagnosis (5-year prevalence) in 2020 and 241,265 (5-year prevalence) in the US [Ferlay, 2018].

### SI.1.1 Demographics of the population in the proposed indication and risk factors for the disease:

EC incidence is strongly related to age, with the highest incidence rates in older, postmenopausal women. In women ages <65 years, the age-standardised uterine cancer incidence rates in 2020 were 11.4 per 100,000 women in Europe and 15.3 per 100,000 women in the US. The age-standardised uterine cancer incidence rates among women ≥65 years were 85.9 per 100,000 women in Europe and 103.1 per 100,000 women in the US [Ferlay, 2018].

### Risk factors for the disease:

There are several additional factors associated with increased risk of EC [Wright, 2011; Moore, 2017; Stewart, 2014; Makker, 2017; Torre, 2017; Esposito, 2014; Rosato, 2011; Barry, 2014; Ali, 2014; Zucchetto, 2009; Lancaster, 2015].

- Long-lasting endogenous or exogenous hyperestrogenism
- Polycystic ovarian syndrome
- Nulliparity and infertility
- Postmenopausal tamoxifen therapy
- Anovulation
- Menopausal hormone therapy
- Oestrogen therapy
- Oestrogen-producing tumours
- Early menarche/late menopause
- Metabolic syndrome
    - Overweight (BMI 25-30) or obesity (BMI>30)
    - Hypertension
    - Diabetes mellitus
    - Hyperinsulinemia

- Hyperglycaemia
- Lynch syndrome type II (hereditary non-polyposis colorectal carcinoma syndrome)

### SI.1.2 The main existing treatment options

The majority of patients with EC are diagnosed in early stages (Stage I or II) and receive surgery with curative intent; however, approximately 20% of patients are diagnosed with high- risk primary advanced or metastatic disease (Stage III or IV) for which a surgical cure is not possible [Siegel, 2021]**.** For these patients, there is no approved anticancer therapy and optimal therapy following surgical resection and staging remains an area of active investigation [NCCN, 2022; Oaknin, 2022]. Radiotherapy, chemoradiation, or adjuvant systemic platinum- based chemotherapy is recommended. The most common platinum-based chemotherapy administered to patients with primary advanced or metastatic disease is carboplatin-paclitaxel [NCCN, 2022; Colombo, 2016]. Although cisplatin-paclitaxel in combination with doxorubicin has a similar efficacy to carboplatin-paclitaxel, it is not commonly used due to the higher toxicity observed with this regimen [Miller, 2020; Sorbe 2008].

In the EU, first-line chemotherapy in the advanced disease setting is carboplatin and paclitaxel. These are recommended over cisplatin, doxorubicin and paclitaxel, based on similar efficacy and less toxicity [Colombo, 2016]. There is currently no standard of care for second-line chemotherapy. Findings from phase II clinical trials suggest that the addition of bevacizumab to the standard regimen may contribute to improved survival.

Given that approximately 25-30% of ECs are dMMR/MSI-H, ICIs have been investigated as potential options in EC. Thus far, dostarlimab and pembrolizumab have been approved by the FDA and EMA as monotherapy in second-line dMMR or dMMR/MSI-H EC. In the EU, dostarlimab received conditional marketing authorisation for the treatment of patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen, with an ORR of 43.5% in 108 patients with dMMR/MSI- H EC [JEMPERLI SmPC, 2022]. The PD-1 inhibitor pembrolizumab received approval in April 2022 in the EU, as second-line therapy for advanced dMMR or MSI-H EC after prior systemic therapy, with an ORR of 51% in 83 patients with dMMR/MSI-H EC [KEYTRUDA SmPC, 2022]. Dostarlimab also received accelerated approval in the US with subsequent conversion to full approval for the treatment of patients with dMMR recurrent or advanced EC, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation, with an ORR of 45.4% in 141 participants with dMMR EC [JEMPERLI USPI, 2023]. The PD-1 inhibitor pembrolizumab received full approval in March 2022 as second-line therapy for advanced dMMR or MSI-H EC after prior systemic therapy, with an ORR of 46% in 90 patients with dMMR/MSI-H EC [KEYTRUDA USPI, 2023].

The combination of pembrolizumab with lenvatinib, which was approved in the EU for both dMMR and MMRp EC patients and in the US for MMRp EC in second-line setting, demonstrated superior PFS and OS compared to conventional chemotherapy in patients with MMRp EC as well as in the subgroup of patients with dMMR EC [Makker 2022]. The combination, however, was accompanied by considerable toxicity; dose modifications (dose

reductions, interruptions or discontinuations) due to AEs occurred in 93.6% of patients receiving lenvatinib plus pembrolizumab and in 41.5% of those receiving chemotherapy.

The main risks associated with commonly utilised systemic treatments for advanced or recurrent EC include the following:

| Treatment | Main treatment-related risks |
|---|---|
| Carboplatin [CARBOPLATIN SmPC, 2022] | Myelosuppression<br>Allergic reactions<br>Renal toxicity<br>Hematologic toxicity, haemolytic-uremic syndrome<br>Neurologic toxicity<br>Reversible Posterior Leukoencephalopathy Syndrome |
| Paclitaxel [PACLITAXEL SmPC, 2022] | Hypersensitivity<br>Hematologic toxicity<br>Neurologic toxicity<br>Sepsis<br>Pneumonitis<br>Hepatic impairment<br>Cardiotoxicity<br>Gastrointestinal toxicity |

### SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Most endometrial carcinomas (75%) are diagnosed at an early stage (FIGO stages I or II) [Sorbe, 2014]. It is estimated 10%-15% of endometrial carcinomas recur after initial treatment and 80%-90% of recurrences occur within 3 years [Sohaib, 2007]. Globally, there were an estimated 97,370 EC (corpus uteri) deaths in 2020; 29,963 deaths occurred in Europe [Ferlay, 2018]. Five-year OS for Stage I-II is estimated between 74 to 92%, while outcomes in women with advanced or recurrent EC remain poor with 5-year OS rates of 20 to 25% [Koskas, 2021; Oaknin, 2022]. In the US (2012-2018), relative 5-year survival for uterine cancer is 81.2% overall; 5-year survival is 94.9% for patients with localised uterine cancer, 69.8% for patients with regional uterine cancer, and 18.4% for patients with distant uterine cancer [SEER, 2022] . In Europe (2000-2007), relative 5-year survival for uterine cancer is 76%; relative 5-year survival ranges from 70% in Bulgaria to 85% in Sweden [De Angelis, 2014].

Morbidities associated with treatment include risk of urinary incontinence and vaginal prolapse after the surgical intervention. Radiotherapy may result in painful urination, bladder spasms resulting in an urgent need to urinate, presence of blood in the urine, urinary tract obstruction, and ulceration or necrosis of the mucous membrane lining the bladder. Effects on the lower digestive tract include abdominal pain, rectal discomfort, diarrhoea, mucus and blood rectal discharge, intestinal obstruction and, rarely, perforation of the intestines. Chemotherapy can cause infections and other toxicities like stroke, myocardial infarction and damage to the function of the kidneys and liver [ESMO, 2012].

### SI.1.4 Important co-morbidities

Since EC typically occurs in older populations, patients often have several comorbidities. These conditions are predictive factors for survival; cardiovascular disease and other malignancies are among the leading causes of death in advanced EC patients [Felix, 2017; Ward, 2012; Morice, 2016]. Obesity, diabetes and hypertension have been associated with reduced survival among EC patients as well [Lindemann, 2015; Chia, 2007; Nicholas, 2014; Nagle 2018]. A retrospective cohort study reported prevalent (≥10% of patients) comorbidities in 23,227 uterine cancer patients at the time of hysterectomy, which included: hypertension (58.9%), obesity (34.4%), diabetes (26.0%), hypothyroidism (15.7%), chronic pulmonary disease (12.4%), depression (10.9%), and deficiency anaemias (8.7%). Compared to patients without uterine cancer who also underwent hysterectomy, uterine cancer patients had higher age-adjusted odds of hypertension, obesity, diabetes, congestive heart failure, pulmonary circulation disorders, renal failure, psychosis, hypothyroid, and depression [Kurnit, 2015].

# PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Dostarlimab has been evaluated in a range of non-clinical toxicology studies including 1-month (with a 4-week recovery period) and 3-month (with an 8-week recovery period) repeat dose studies conducted in cynomolgus monkeys. The main preclinical findings are listed in the table below.

## Key safety findings from non-clinical studies and relevance to human usage:

| Key Safety findings (from non-clinical studies) | Relevance to human usage |
|---|---|
| **Immunogenicity**<br>Anti-drug antibodies (ADAs) were observed in cynomolgus monkeys across studies. | In the GARNET study, based on a data cutoff of 1 March 2020, 384 out of the 549 patients treated with the recommended therapeutic dose were tested for ADAs. In these patients 2.1% developed ADAs during the study with approximately 1% developing neutralising antibodies (NAbs).<br><br>In the RUBY study, based on a data cutoff of 08 August 2022, 225 patients who were treated with dostarlimab in combination with carboplatin and paclitaxel and evaluable for the presence of ADAs, there was no incidence of dostarlimab treatment-emergent ADA or treatment-emergent neutralising antibodies. |
| **Immune-related toxicity**<br>Potential immune-mediated reactions in cynomolgus monkeys included increased incidence of liquid faeces and findings observed in the skin (dermatitis), liver (mild mixed cell inflammation), kidney and heart (mild to moderate mononuclear infiltrates with or without minimal degeneration). These findings could be pharmacological effects based on the mechanism of action. | In the dostarlimab GARNET monotherapy study cohort A1 patients with dMMR/MSI-H EC, 45 (34.9%) experienced potential immune-related adverse reactions (irARs), based on data cutoff of 1 March 2020.<br><br>In the dostarlimab combination study with carboplatin-paclitaxel (RUBY Part 1), 92 (38.2%) of the overall 1L EC patients (N=241) experienced dostarlimab related potential irAEs based on the data cutoff of 28 September 2022.<br><br>IrARs will be considered an **Important Identified Risk**. |
| **Reproductive toxicity**<br>No reproductive | It is not known if dostarlimab may have adverse effects on a foetus in utero in |

| | |
|---|---|
| toxicology studies were conducted. In general in the toxicology studies there were no adverse findings caused by dostarlimab in the reproductive system.<br>Murine models of allogeneic pregnancy showed that blockade of PD-L1 signalling can eliminate foetomaternal tolerance and cause spontaneous abortion as indicated by increase in embryo resorption and a reduction in litter size. | human. For the indicated patient population surgery is the first treatment for almost all women with EC**,** including removal of the uterus, fallopian tubes, and ovaries. Therefore, for the indicated population this is not considered an important potential risk. |
| **Developmental toxicity**<br>No developmental toxicology studies were conducted. | Not known. |

# PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

## GARNET MONOTHERAPY STUDY (4010-10-001; 213346)

As of the cutoff date of 1 November 2021 for dostarlimab as a single agent, the number of patients exposed to dostarlimab in Part 2B of the GARNET study was 605, including 153 patients with dMMR/MSI-H EC. Dostarlimab was administered at the recommended therapeutic dose (ie, 500 mg every 3 weeks (Q3W) for 4 doses followed by 1,000 mg every 6 weeks (Q6W).

The safety population includes 605 patients with advanced or recurrent solid tumours receiving dostarlimab as a single agent at the recommended therapeutic dose (GARNET; data cutoff 1 November 2021).

Patients in the indicated population with dMMR/MSI-H EC (Cohort A1, N=153) were enrolled in Study 4010-01-001 (GARNET), an ongoing Phase 1 dose escalation and cohort expansion (multicentre, open-label, first-in-human) study of dostarlimab as monotherapy in subjects with advanced solid tumours.

As of the data cutoff date, the overall median treatment duration for patients treated with dostarlimab as a single agent (GARNET, N=605) and patients with dMMR/MSI-H EC (Cohort A1, N=153) was 24.0 weeks (range: 1 to 229 weeks) and 34.0 weeks (range: 3 to 220 weeks), respectively. The median relative dose intensity during the first 12 weeks of treatment (100.0%) and from 13 weeks of treatment and beyond (100.0%) indicate that the majority of patients received doses as planned without delays or interruptions.

The data presented below describes exposure in the indicated population of female patients with dMMR/MSI-H EC (Study 4010-01-001 (GARNET) Part 2B, Cohort A1; N=153) and in the monotherapy pool of adult patients with advanced/recurrent solid tumors (Study 4010-01-001 (GARNET) Part 2B, Cohorts A1, A2, E, F, G; N=605).

**Table 2 Cumulative Duration of Dostarlimab Exposure in Study 4010-01-001 (Part 2B,Cohort A1 – dMMR/MSI-H Endometrial cancer and Monotherapy Pool) (Safety population)**

| | Number of patients exposed (N) | | Duration of Exposure (Patient-years) | |
|---|---|---|---|---|
| **Duration of Exposure** | **dMMR/MSI-H** | **Monotherapy** | **dMMR/MSI-H** | **Monotherapy** |
| **Week 1 - Week 3** | 5 | 37 | 0.29 | 1.89 |
| **Week 4 - Week 6** | 7 | 48 | 0.78 | 5.51 |
| **Week 7 - Week 9** | 8 | 49 | 1.46 | 8.61 |
| **Week 10 - Week 12** | 15 | 59 | 3.69 | 13.79 |
| **Week 13 - Week 18** | 24 | 87 | 8.43 | 29.04 |
| **Week 19 - Week 24** | 9 | 34 | 4.22 | 15.35 |
| **Week 25 - Week 30** | 8 | 25 | 4.62 | 14.38 |
| **Week 31 - Week 36** | 3 | 21 | 2.10 | 14.66 |
| **Week 37 - Week 42** | 4 | 20 | 3.12 | 15.99 |
| **Week 43 - Week 48** | 1 | 16 | 0.99 | 15.04 |
| **Week 49 - Week 54** | 6 | 15 | 6.16 | 15.64 |
| **>Week 54** | **63** | **194** | **157.17** | **450.09** |
| **Total** | **153** | **605** | **193.02** | **599.98** |

Source: RMP Table 2
Data cutoff 1 November 2021

**Table 3 Cumulative Patient Exposure by Dostarlimab Dose in Study 4010-01-001 (Part 2B, Cohort A1 - dMMR/MSI-H Endometrial cancer and Monotherapy Pool) (Safety population)**

| | Number of patients exposed (N) | | Duration of Exposure (Patient-years) | |
|---|---|---|---|---|
| **Dose of Exposure** | **dMMR/MSI-H** | **Monotherapy** | **dMMR/MSI-H** | **Monotherapy** |
| **500 mg** | 153 | 605 | 193.02 | 599.98 |
| **500 mg/1000 mg*** | 117 | 398 | 186.57 | 566.98 |
| **Total** | 153 | 605 | 193.02 | 599.98 |

*Initially dosed at 500 mg Q3W for 4 doses prior to 1000 mg Q6W thereafter.
Source: RMP Table 3
Data cutoff 1 November 2021

**Table 4 Cumulative Exposure by Age Group and Gender in Study 4010-01-001 (Part 2B, Cohort A1) - dMMR/MSI-H Endometrial cancer and Monotherapy Pool) (Safety population)**

| | Number of patients exposed (N) | | | Duration of Exposure (Patient-years) | | |
|---|---|---|---|---|---|---|
| **Age Range (years)** | **Male** | **Female** | **Overall** | **Male** | **Female** | **Overall** |
| **dMMR/MSI-H** | 0 | 0 | 0 | 0 | 0 | 0 |
| **<18 years** | 0 | 0 | 0 | 0 | 0 | 0 |
| **18-64 years** | 0 | 75 | 75 | 0 | 98.83 | 98.83 |
| **65-74 years** | 0 | 64 | 64 | 0 | 77.89 | 77.89 |
| **75-84 years** | 0 | 13 | 13 | 0 | 15.95 | 15.95 |
| **>=85 years** | 0 | 1 | 1 | 0 | 0.35 | 0.35 |
| **Total** | 0 | 153 | 153 | 0 | 193.02 | 193.02 |
| | | | | | | |
| **Monotherapy** | 0 | 0 | 0 | 0 | 0 | 0 |
| **<18 years** | 0 | 0 | 0 | 0 | 0 | 0 |
| **18-64 years** | 88 | 224 | 312 | 88.82 | 229.33 | 318.14 |
| **65-74 years** | 44 | 179 | 223 | 60.19 | 163.55 | 223.74 |
| **75-84 years** | 17 | 48 | 65 | 8.28 | 47.40 | 55.68 |
| **>=85 years** | 0 | 5 | 5 | 0 | 2.42 | 2.42 |
| **Total** | 149 | 456 | 605 | 157.28 | 442.70 | 599.98 |

Source: RMP Table 4
Data cutoff 1 November 2021

**Table 5 Cumulative Exposure by Racial Group in Study 4010-01-001 (Part 2B, Cohort A1 - dMMR/MSI-H Endometrial cancer and Monotherapy Pool) (Safety population)**

| | Number of patients exposed (N) | | Duration of Exposure (Patient-years) | |
|---|---|---|---|---|
| **Racial Group** | **dMMR/MSI-H** | **Monotherapy** | **dMMR/MSI-H** | **Monotherapy** |
| **White** | 117 | 436 | 151.67 | 415.64 |
| **Black or African American** | 5 | 21 | 8.80 | 19.87 |
| **Other** | 25 | 130 | 25.88 | 149.16 |
| **Asian** | 5 | 14 | 4.68 | 12.16 |
| **Unknown** | 1 | 4 | 1.99 | 3.15 |
| **Total** | 153 | 605 | 193.02 | 599.98 |

Source: RMP Table 5
Data cutoff 1 November 2021

## RUBY Carboplatin and Paclitaxel Combination Study (Part 1) 4010-03-001; 213361

As of the cutoff date of 28 September 2022, the number of 1L EC patients exposed to dostarlimab plus carboplatin-paclitaxel in Part 1 of the RUBY study was 241. Dostarlimab was administered at 500 mg every 3 weeks (Q3W) for 6 doses followed by 1,000 mg every 6 weeks (Q6W).

As of the data cutoff date, the overall median treatment duration for patients treated with dostarlimab in combination with carboplatin and paclitaxel in adults with primary advanced or recurrent endometrial cancer (RUBY, N=241) was 43 weeks (range: 3 to 150.9 weeks). The median relative dose intensity was 97.96%, indicating that the majority of patients received doses as planned without delays of interruptions.

The RUBY Part 1 data below describes exposure to dostarlimab in combination with carboplatin-paclitaxel in primary advanced or recurrent EC patients (N=241).

**Table 6 Duration of Dostarlimab Exposure in Combination with Chemotherapy in RUBY Study Part 1: 1L EC Population**

**a. Number of Patients Exposed**

| Duration of Exposure (months) | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| <3 months | 28 | 29 |
| 3 to <6 months | 51 | 56 |
| 6 to <12 months | 61 | 90 |
| 12 to <24 months | 62 | 43 |
| 24 to <48 months | 39 | 28 |
| 48 to <96 months | 0 | 0 |
| TOTAL | 241 | 246 |

Data Source: RMP Table 2
Data cutoff 28 September 2022

**b. Patient Years of Exposure**

| Duration of Exposure (months) | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| <3 months | 3.84 | 4.55 |
| 3 to <6 months | 20.17 | 22.42 |
| 6 to <12 months | 45.45 | 65.92 |
| 12 to <24 months | 92.72 | 62.22 |
| 24 to <48 months | 92.91 | 66.63 |
| 48 to <96 months | 0 | 0 |
| TOTAL | 255.09 | 221.74 |

Data Source: RMP Table 2
Data cutoff 28 September 2022

## Table 7 Exposure of Dostarlimab by Dose in Combination with Chemotherapy in RUBY Study Part 1: 1L EC Population (Safety population)

**a. Number of Patients Exposed**

| Dose of Exposure | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| **500 mg** | 57 | 62 |
| **500 mg/1000 mg*** | 184 | 184 |
| **Total** | 241 | 246 |

*Initially dosed at 500 mg Q3W for 6 doses prior to 1000 mg Q6W thereafter.
Source: RMP Table 3
Data cutoff 28 September 2022

**b. Patient Years of Exposure**

| Dose of Exposure | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| 500 mg | 13.61 | 16.23 |
| 500 mg/1000 mg* | 241.48 | 205.51 |
| Total | 255.09 | 221.74 |

*Initially dosed at 500 mg Q3W for 6 doses prior to 1000 mg Q6W thereafter.
Source: RMP Table 3
Data cutoff 28 September 2022

## Table 8 Exposure of Dostarlimab by Age in Combination Chemotherapy in RUBY Study Part 1: 1L EC Population (Safety population)

**a. Number of Patients Exposed**

| Age Range (Years) | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| < 18 | 0 | 0 |
| 18 to 64 | 126 | 112 |
| 65 to 74 | 88 | 97 |
| 75 to 84 | 27 | 36 |
| 85+ | 0 | 1 |
| TOTAL | 241 | 246 |

Data Source: RMP Table 4
Data cutoff 28 September 2022

**b. Patient Years of Exposure**

| Duration of Exposure (months) | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| < 18 | 0 | 0 |
| 18 to 64 | 135.86 | 112.07 |
| 65 to 74 | 93.77 | 81.82 |
| 75 to 84 | 25.46 | 27.00 |
| 85+ | 0 | 0.84 |
| TOTAL | 255.09 | 221.74 |

Data Source: RMP Table 4
Data cutoff 28 September 2022

**Table 9 Exposure of Dostarlimab by Racial Group in Combination with Chemotherapy in RUBY Study Part 1: 1L EC Population (Safety population)**

**a. Number of Patients Exposed**

| Racial Group | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | All Patients | All Patients |
| **White** | 187 | 190 |
| **Black or African American** | 27 | 31 |
| **Other** | 2 | 9 |
| **Asian** | 7 | 8 |
| **Unknown** | 13 | 8 |
| **Not Reported** | 5 | 8 |
| **TOTAL** | 241 | 246 |

Data Source: RMP Table 5
Data cutoff 28 September 2022

**b. Patient Years of Exposure**

| Racial Group | Dostarlimab + Chemotherapy | Placebo + Chemotherapy |
|---|---|---|
| | **All Patients** | **All Patients** |
| **White** | 196.65 | 177.99 |
| **Black or African American** | 26.87 | 22.25 |
| **Other** | 4.68 | 2.17 |
| **Asian** | 7.54 | 7.05 |
| **Unknown** | 10.69 | 7.97 |
| **Not Reported** | 8.66 | 4.31 |
| **TOTAL** | 255.09 | 221.74 |

Data Source: RMP Table 5
Data cutoff 28 September 2022

# PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Exclusion from clinical trials have not resulted in a safety concern for the product. There is no missing information based on exclusion criteria that is relevant for the approved indication.

| Exclusion criterion | Reason for exclusion | Is it considered to be included as missing information (YES/NO) | Rationale |
|---|---|---|---|
| Patient has known uncontrolled central nervous system metastases and/or carcinomatous meningitis | To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments. | No | Use in this population is not predicted to be associated with additional risks of clinical significance. |
| Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer | To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments. | No | Use in this population is not predicted to be associated with additional risks of clinical significance. |
| Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active infection requiring systemic therapy. Specific examples include, but are not limited to, active, non-infectious pneumonitis; uncontrolled ventricular | To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments. | No | Use of dostarlimab in these patients is very unlikely, because use of dostarlimab can be postponed until the condition is successfully treated or patients are medically controlled and stabilised. |

| Exclusion criterion | Reason for exclusion | Is it considered to be included as missing information (YES/NO) | Rationale |
|---|---|---|---|
| arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent) | | | |
| Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 150 days after the last dose of study treatment | Standard clinical practice | No | **Surgery is the first treatment for almost all women with EC,** including removal of the uterus, fallopian tubes, and ovaries. |
| Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment | To avoid confounding evaluation of safety due to study treatment and reduce occurrence of complications of other treatments. | No | Use in this population is not predicted to be associated with additional risks of clinical significance; for most patients use of dostarlimab can be postponed until the condition is successfully treated, and toxicities can be appropriately managed. |
| Patient has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies) | To avoid confounding evaluation of safety due to study treatment and reduce occurrence of complications of other treatments. | No | Based on currently available information [Cook, 2019], use in this population is not predicted to be associated with additional risks of clinical significance. |

| Exclusion criterion | Reason for exclusion | Is it considered to be included as missing information (YES/NO) | Rationale |
|---|---|---|---|
| Patient has known active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative] is detected) | To avoid confounding evaluation of safety due to study treatment and reduce occurrence of complications of other treatments. | No | Based on currently available information, use in this population is not predicted to be associated with additional risks of clinical significance, which may require appropriate supportive treatment [Pandey, 2018]. |
| Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops are allowed | To avoid confounding evaluation of safety due to study treatment and reduce occurrence of complications of other treatments. | No | Use in this population is not predicted to be associated with unexpected risks or risks of clinical significance that would not be manageable with appropriate intervention [Garret, 2018; Johnson, 2017]. |
| Patient has a history of interstitial lung disease | To avoid confounding evaluation of safety due to study treatment. | No | Pneumonitis/interstitial lung disease is an important identified immune-related risk for dostarlimab. Although this event may recur while on treatment, given the life-threatening nature of advanced/recurrent dMMR/MSI-H EC, and that pneumonitis/interstitial lung disease may be reversible with dose interruption or |

| Exclusion criterion | Reason for exclusion | Is it considered to be included as missing information (YES/NO) | Rationale |
|---|---|---|---|
| | | | discontinuation, the benefit of treatment may outweigh the associated risks and the option of treatment with dostarlimab should be available to patients. |
| Patient has not recovered (i.e., to ≤ Grade 1 or to baseline) from radiation- and chemotherapy-induced adverse events (AEs) or received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte-colony stimulating factor, granulocyte macrophage colony-stimulating factor or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug | To avoid confounding evaluation of safety due to study treatment and reduce occurrence of complications of other treatments. | No | Use of dostarlimab in these patients is very unlikely, because use of dostarlimab can be postponed until the condition is successfully treated or patients are medically controlled and stabilised. |
| Patient has received prior anti-cancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 21 days, or less than 5 times the half-life of the most recent therapy prior to study Day 1, whichever is shorter. Note: palliative radiation therapy to a small field > 1 week prior to Day 1 of study treatment may be allowed | To avoid confounding evaluation of safety and efficacy due to study treatment. | No | In patients with prior anti-cancer therapy/interventions, the treating physician is best positioned to determine the appropriate time to initiate therapy with dostarlimab, taking into account the specific prior therapy and the clinical condition of the patient. |
| Patient has not recovered adequately (≤ Grade 1) from | To avoid confounding | No | Use of dostarlimab in these patients is very unlikely, because |

| Exclusion criterion | Reason for exclusion | Is it considered to be included as missing information (YES/NO) | Rationale |
|---|---|---|---|
| AEs and/or complications from any major surgery prior to starting therapy | evaluation of safety due to study treatment and reduce occurrence of complications of other treatments. | | use of dostarlimab can be postponed until the condition is successfully treated or patients are medically controlled and stabilised. |
| Patient has received a live vaccine within 14 days of planned start of study therapy | To avoid confounding evaluation of safety due to study treatment and reduced vaccine efficacy | No | Use of dostarlimab in these patients is very unlikely because use of dostarlimab can be postponed. |
| Patient has a known hypersensitivity to the active substance or to any of the components or excipients | To minimize risk to patients. | No | Contraindication; thus, use in this population in the post-marketing period is not anticipated. |

| Subjects not meeting these Inclusion criteria were excluded from participation | Reason for exclusion | Is it considered to be included as missing information (YES/NO) | Rationale |
|---|---|---|---|
| Patient has adequate organ function, defined as:<br>1. Absolute neutrophil count ≥ 1,500 cells/µL<br>2. Platelets ≥ 100,000 cells/µL<br>3. Haemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L<br>4. Serum creatinine ≤ 1.5X upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5X institutional ULN<br>5. Total bilirubin ≤ 1.5X ULN and direct bilirubin ≤ 1X ULN<br>6. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5X ULN unless liver metastases are present, in which case they must be ≤ 5X ULN<br>7. International normalized ratio or prothrombin time (PT) ≤1.5X ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin (PTT) is within therapeutic range of intended use of anticoagulants. Activated PTT ≤1.5X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants | To avoid confounding evaluation of safety and efficacy due to study treatment and reduce occurrence of complications of other treatments. | No | In patients with prior anti-cancer therapy/interventions, the treating physician is best positioned to determine the appropriate time to initiate therapy with dostarlimab, taking into account the specific prior therapy and the clinical condition of the patient. |

## SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

## SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

**Table 10 Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development programme |
| Breastfeeding women | Not included in the clinical development programme |
| Patients with relevant comorbidities:<br>• Patients with hepatic impairment<br>• Patients with renal impairment<br>• Patients with cardiovascular impairment<br>• Immunocompromised patients<br>• Patients with a disease severity different from inclusion criteria in clinical trials | Patients with the following conditions were excluded from the clinical trials; active CNS metastases; HIV, hepatitis B, hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; serious uncontrolled medical disorder, non-malignant systemic disease or active infection requiring systemic therapy – specific examples include, non-infectious pneumonitis; uncontrolled ventricular arrhythmia, recent myocardial infarction; a history of severe hypersensitivity to another monoclonal antibody; history of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy prior to start of therapy; adequate organ function at baseline including renal and hepatic function defined as:<br>• Serum creatinine ≤ 1.5X upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5X institutional ULN<br>• Total bilirubin ≤ 1.5X ULN and direct bilirubin ≤ 1X ULN<br>• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5X ULN unless liver metastases are present, in which case they must be ≤ 5X ULN<br>Therefore, information is limited in patients with severe renal and moderate to severe hepatic function.<br>These criteria were applied to ensure the population under study had adequate organ function to avoid potential confounding |

| | |
|---|---|
| | variables in the interpretation of safety data from the studies. |
| Population with relevant different ethnic origin | Clinical trials by race are presented in Part II: Module SIII |
| Subpopulations carrying relevant genetic polymorphisms | The monotherapy indication is limited to advanced or recurrent dMMR/MSI-H EC |

# PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

## SV.1 Post-authorisation exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for dostarlimab.

### SV.1.1 Method used to calculate exposure

The algorithm used to derive post-approval exposure data from IQVIA is total sales units ÷ 18, where 18 equals vials per patient per year (averaging 1.5 vials per month). The estimate assumes an annual average use by patient of 18 vials, each containing 500 mg of dostarlimab: 500 mg administered for the first 4 cycles (1 vial per cycle every 3 weeks, weeks 1-12) and 1000 mg administered for the remaining seven cycles (2 vials per cycle every 6 weeks, weeks 13-52). There are no assumptions regarding compliance, persistence and drop-out rates.

### SV.1.2 Exposure

As of the most recent post-marketing cut-off date (DCO) of 20 October 2023, the cumulative post- marketing experience is estimated to be 528.9 patient-years of treatment (IQVIA data can be up to six months in arrears from the cut-off date).

Three patient access programs with dostarlimab, described below, have been opened in a total of 24 countries as of the DCO, with participants in 20 of these countries approved to receive dostarlimab. In addition, individual compassionate use requests have been approved from 11 of these 24 countries with a total of approximately 906 patients approved to receive dostarlimab in all these programs combined.

- EAP 214159*: dostarlimab in adult patients with recurrent or advanced dMMR/ MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen. *Includes Expanded Access Program 219058 being conducted in South Korea in the same indication.
- EAP 220718**: dostarlimab in adult patients with primary advanced or recurrent EC. **Includes UK EAMS program.
- NPP 214166: dostarlimab as 2L treatment in patients with advanced or recurrent dMMR EC.
- Individual Compassionate Use requests for dostarlimab in patients with dMMR rectal CA.

# PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## Potential for misuse for illegal purposes

Given the pharmacological class of dostarlimab, there is no expected potential for drug abuse or misuse.

# PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Identification of safety concerns in the initial RMP submission

## SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

| System Organ Class | Frequency of all grades* | Grades 3-4* | Seriousness |
|---|---|---|---|
| Blood and lymphatic system disorders | Very common<br>Anaemia | Very common<br>Anaemia | None were serious |
| Gastrointestinal disorders | Very common<br>Nausea, vomiting | None | None were serious |
| Musculoskeletal and connective tissue disorders | Very common<br>Myalgia | None | There was one case of serious myalgia |
| General disorders and administration site conditions | Common<br>Pyrexia, chills | None | There were 3 cases (2.3%) of serious pyrexia. None of the cases of chills were serious. |

*AE severity was graded using NCI CTCAE v4.03.

## SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

### Important Identified Risk #1: IrARs (such as immune-related pneumonitis, colitis, endocrinopathies, immune-related skin adverse reactions, nephritis, systemic inflammatory response syndrome, myositis and other irARs)

**Scientific evidence for risk to be added in the safety specification**: IrARs are considered to be an important identified risk based on non-clinical observations in cynomolgus monkeys, clinical observations and class effect. In subjects with dMMR/MSI-H EC (N=129), 47 (36.4%) subjects experienced potential irARs and 29 (22.5%) subjects reported treatment-related irARs. Grade ≥3 irARs were reported in 17 (13.2%) subjects, serious adverse events (SAEs) were reported in 10 (7.8%) subjects, and irARs leading to permanent treatment discontinuation were reported in 6 (4.7%) subjects.

IrARs are important risks (identified and potential risks) in the EU-RMP for all drugs in the PD-1/PD-L1 class (i.e, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and cemiplimab).

**Risk benefit impact**: The benefit of dostarlimab is its being an effective treatment for dMMR/MSI-H EC. While the identified risk of irARs includes events that could be serious or fatal, irARs can be managed in clinical practice through drug interruption or discontinuation, with appropriate supportive measures including treatment with steroids.

### Important Identified Risk #2: Infusion-related reactions

**Scientific evidence for risk to be added in the safety specification**: 'Infusion-related reactions' is considered to be an important identified risk based on class effect for PD-1/PD-L1 inhibitors, and clinical observations in the broader dostarlimab monotherapy treated population (N=515) in which 1.4% (N=7) of the patients experienced infusion-related reactions. Infusion-related reactions were not experienced by any of the patients in GARNET Cohort A1 (N=129).

'Infusion-related reactions' is an identified risk for all drugs in the class in the EU-RMP (i.e, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and cemiplimab).

**Risk benefit impact**: The benefit of dostarlimab is an effective treatment for EC. The identified risk of infusion-related reactions includes events that could be serious or fatal, however, the rate of infusion-related reactions is very low (1.4%) and these events are manageable with careful monitoring of symptoms and discontinuation of treatment if severe or life-threatening infusion-related reactions occur.

### Missing Information #1: Long-term safety

**Scientific evidence for risk to be added in the safety specification**: The long-term effect of dostarlimab cannot be defined based on available evidence. In the clinical development programme, 35 patients were exposed for 54 weeks or longer. Longer term exposure data is available for other PD-1 inhibitors [Yamazaki, 2019; Garon, 2019].

**Risk benefit impact**: Additional toxicity may occur after long-term treatment with dostarlimab. However, in patients with life-threatening advanced or recurrent dMMR/MSI-H EC, potential new toxicities are unlikely to outweigh the benefit of dostarlimab therapy as evidenced by global experience with marketed drugs of the same class.

## SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

## SVII.3 Details of important identified risks, important potential risks, and missing information

### SVII.3.1 Presentation of important identified risks and important potential risks

### Table 11 Important Identified Risk: Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs)

| | |
|---|---|
| Potential mechanism(s) | PD-1 is an immune inhibitory checkpoint expressed on the surface of activated T cells. When PD-1 engages its ligands, PD-L1 and PD-L2, T cells become functionally exhausted. This interaction is particularly important in the peripheral tissues and at sites of ongoing inflammation, including the tumour microenvironment. Anti-PD-1/PD-L1 agents block the PD-1/ligand interaction and reinvigorate these quiescent T cells. The resulting T cell response may cause an autoimmune or inflammatory response in normal tissue resulting in irARs [Wang, 2018]. |
| Evidence source(s) and strength of evidence | **Non-clinical**:<br>Non-clinical observations in cynomolgus monkeys included increased incidence of liquid faeces, dermatitis, mild mixed cell inflammation in the liver, mild to moderate mononuclear infiltrates with or without minimal degeneration in the kidney and heart.<br><br>**Clinical**<br>**GARNET: Dostarlimab monotherapy study for 2L EC (dMMR/MSI-H EC patients N=153)**<br>In subjects with dMMR/MSI-H EC, 59 (38.6%) subjects experienced potential irARs and 42 (27.5%) subjects reported treatment-related irARs. Grade ≥3 irARs were reported in 20 (13.1%) subjects, SAEs were reported in 16 (10.5%) subjects, and irARs leading to permanent treatment discontinuation were reported in 14 (9.2%) subjects.<br><br>**RUBY: Dostarlimab combination therapy for 1L EC (Part 1; All EC patients)**<br>In all EC subjects (N=241) receiving dostarlimab plus carboplatin and paclitaxel, 137 (56.8%) experienced irARs and 92 (38.2%) reported treatment-related irARs. Grade ≥3 irARs were reported in 40 (16.6%) , SAEs were reported in 14 (5.8%) subjects, and irARs leading to permanent treatment discontinuation were reported in 19 (7.9%) subjects. |

**Class effect**: 'IrARs' is a risk for all drugs in the class: Keytruda (pembrolizumab), Opdivo (Nivolumab), Tecentriq (Atezolizumab), Bavencio (Avelumab), Imfinzi (Durvalumab), and Libtayo (cemiplimab) [KEYTRUDA SmPC, 2022; TECENTRIQ SmPC, 2022; BAVENCIO SmPC, 2022; IMFINZI SmPC, 2022; LIBTAYO SmPC, 2022].

Characterisation of the risk

**Clinical:**

**GARNET: Dostarlimab monotherapy study for 2L EC (Part 2B; All EC patients N=605 and dMMR/MSI-H EC patients N=153)**

**Frequency, Seriousness and Severity of irARs* ≥2% of All EC patients in Study 4010-01-001 Part 2B (N=605)**

| Category/ Preferred Term | Treatment-emergent adverse events (TEAEs) | SAEs | Severity Leading to ≥Grade 3 | Treatment Discontinuation |
|---|---|---|---|---|
| Hypothyroidism | 46 (7.6) | 0 | 0 | 0 |
| Arthralgia | 34 (5.6) | 1 (0.2) | 5 (0.8) | 1 (0.2) |
| ALT increased | 26 (4.3) | 0 | 13 (2.1) | 8 (1.3) |
| AST increased | 24 (4.0) | 1 (0.2) | 11 (1.8) | 4 (0.7) |
| Rash | 19 (3.1) | 0 | 6 (1.0) | 0 |
| Pneumonitis | 14 (2.3) | 8 (1.3) | 6 (1.0) | 8 (1.3) |
| Hyperthyroidism | 14 (2.3) | 1 (0.2) | 1 (0.2) | 0 |
| Pruritis | 13 (2.1) | 0 | 2 (0.3) | 1 (0.2) |

Source: RMP Table 6
Data cut-off 1 November 2021

**Frequency, Seriousness and Severity of irARs* in ≥2% of dMMR/MSI-H EC patients (Study 4010-01-001 Part 2B Cohort A1 (N=153))**

| Category/ Preferred Term | TEAEs | SAEs | Severity Leading to ≥Grade 3 | Treatment Discontinuation |
|---|---|---|---|---|
| Hypothyroidism | 14 (9.2) | 0 | 0 | 0 |
| Arthralgia | 10 (6.5) | 0 | 3 (2.0) | 1 (0.7) |
| Pruritis | 7 (4.6) | 0 | 2 (1.3) | 1 (0.7) |
| ALT increased | 6 (3.9) | 0 | 4 (2.6) | 3 (2.0) |
| Hyperthyroidism | 6 (3.9) | 0 | 0 | 0 |
| Pneumonitis | 5 (3.3) | 3 (2.0) | 2 (1.3) | 3 (2.0) |
| AST increased | 4 (2.6) | 1 (0.7) | 1 (0.7) | 1 (0.7) |
| Rash | 4 (2.6) | 0 | 0 | 0 |
| Colitis | 3 (2.0) | 2 (1.3) | 2 (1.3) | 0 |
| Gastritis | 3 (2.0) | 1 (0.7) | 1 (0.7) | 0 |
| Transaminases increased | 3 (2.0) | 1 (0.7) | 2 (1.3) | 2 (1.3) |

* Potential irARs were defined as Grade 2 or above events from a pre-specified list (Integrated safety summary statistical analysis plan)
Source: RMP Table 7
Data cut-off 1 November 2021

Additional clinically significant immune-mediated adverse reactions reported in less than 1% of patients treated with dostarlimab as a single agent (N=605) include encephalitis, myasthenia gravis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, pemphigoid, type 1 diabetes mellitus, and myositis. Of these, encephalitis, acute pancreatitis, pancreatitis, iridocyclitis, and pemphigoid occurred in 1 patient each in the indicated population (N=153).

In the monotherapy population (N=605), immune-related hypothyroidism (7.6%) and arthralgia (5.6%) were the most frequently reported irARs. Similarly, in the indicated patient population (N=153) hypothyroidism (9.2%) and arthralgia (6.5%) were the most frequent of the significant irARs,; all events of hypothyroidism were Grade 2. Hypothyroidism was resolved/ resolving in 2 subjects and had not been resolved in 12 subjects at the time of data cut-off; dose was interrupted in 1 subject. Arthralgia resolved/resolved with sequelae in 7 subjects and had not been resolved in 3 subjects at the time of data cut-off; dose was interrupted in 1 subject.

Pneumonitis was the most frequent serious irAR, experienced by 8 subjects (1.3%) subjects in the monotherapy population and by 3 subjects in the indicated population. Five subjects experienced Grade ≥3 SAEs of pneumonitis which resolved.

**RUBY Study Part 1: Dostarlimab in combination with Chemotherapy; All EC patients (N= 241)**

**Clinical**:

**95% Confidence Interval for the Relative Risk (%) of Overall Incidence of Dostarlimab Related irARs* for Dostarlimab in Combination with Chemotherapy Treated 1L EC Patients in RUBY Study Part 1**

| Category | All Patients | | |
|---|---|---|---|
| | Dostar + Chemo (N=241) | Placebo + Chemo (N=246) | Relative Risk (95% CI) |
| Patients with any irAE* | 92 (38.2) | 38 (15.4) | 2.47 (1.77,3.45) |

* Potential irARs were defined as Grade 2 or above events from a pre-specified list (Integrated safety summary statistical analysis plan)
Source: RMP Table 6a
Data cut-off 28 September 2022

**Frequency, Seriousness, and Severity of Dostarlimab Related irARs* (> 1%) in All 1L EC Patients Treated with Dostarlimab in Combination with Chemotherapy in RUBY Study (Part 1)**

| Category/ Preferred Term | TEAE^ | | SAE^ | | Severity ≥Grade 3 | | Leading to Treatment Discontinuation | |
|---|---|---|---|---|---|---|---|---|
| | Dostar + Chemo (N=241) | Placebo + Chemo (N=246) | Dostar + Chemo (N=241) | Placebo + Chemo (N=246) | Dostar + Chemo (N=241) | Placebo + Chemo (N=246) | Dostar + Chemo (N=241) | Placebo + Chemo (N=246) |
| **Patients with any irAE*** | 92 (38.2) | 38 (15.4) | 7 (2.9) | 3 (1.2) | 30 (12.4) | 8 (3.3) | 13 (5.4) | 6 (2.4) |
| **Hypothyroidism** | 27 (11.2) | 7 (2.8) | 0 | 1 (0.4) | 0 | 1 (0.4) | 1 (0.4) | 0 |
| **Rash** | 16 (6.6) | 5 (2.0) | 1 (0.4) | 0 | 9 (3.7) | 3 (1.2) | 0 | 1 (0.4) |
| **Alanine aminotransferase increased** | 14 (5.8) | 2 (0.8) | 0 | 0 | 5 (2.1) | 0 | 2 (0.8) | 1 (0.4) |
| **Arthralgia** | 14 (5.8) | 16 (6.5) | 0 | 0 | 0 | 1 (0.4) | 1 (0.4) | 0 |
| **Rash maculo-papular** | 11 (4.6) | 0 | 0 | 0 | 5 (2.1) | 0 | 3 (1.2) | 0 |
| **Aspartate aminotransferase increased** | 10 (4.1) | 1 (0.4) | 0 | 0 | 5 (2.1) | 1 (0.4) | 2 (0.8) | 0 |
| **Hyperthyroidism** | 8 (3.3) | 1 (0.4) | 0 | 0 | 1 (0.4) | 0 | 0 | 0 |
| **Pruritus** | 8 (3.3) | 3 (1.2) | 0 | 0 | 1 (0.4) | 0 | 1 (0.4) | 0 |
| **Infusion related reaction** | 4 (1.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Pneumonitis** | 4 (1.7) | 0 | 0 | 0 | 1 (0.4) | 0 | 2 (0.8) | 0 |

* Potential irARs were defined as Grade 2 or above events from a pre-specified list (Integrated safety summary statistical analysis plan)
Source: RMP Table 8a with data cut-off of 28 September 2022
^TEAE = treatment emergent adverse event; SAE = serious adverse event

Additional clinically significant dostarlimab related irARs reported in <1 % of all 1L EC patients treated with dostarlimab in combination with carboplatin-paclitaxel (N=241) include adrenal insufficiency, colitis, pancreatitis, which occurred in 2 patients each (0.8%) and myocarditis, myositis, type 1 diabetes mellitus and uveitis all of which occurred in 1 patient each (0.4%) in the indicated population (N=1).

In the overall 1L EC patients treated with dostarlimab in combination with carboplatin and paclitaxel (N=241), hypothyroidism (11.2%) and rash (6.6%) were the most frequently reported dostarlimab related irARs. Of the patients that experienced hypothyroidism, none of the events were serious or $\geq$ Grade 3 and one patient discontinued treatment due to the event. Nine subjects (3.7%) experienced Grade $\geq$3 events of rash, with one patient having a serious event and no patients discontinuing treatment. Hypothyroidism resolved in 6 subjects and had not resolved in 18 subjects at the time of data cut-off. Rash resolved (N=14) or resolved with sequela (N=2) in all subjects.

**Reversibility**: Most irARs occurring during treatment with dostarlimab

| | |
|---|---|
| | monotherapy or in combination with carboplatin and paclitaxel were reversible and, when necessary, managed with interruptions/discontinuations of dostarlimab, along with appropriate treatment and supportive care.<br>**Long-term outcomes**: Since these events are generally reversible and manageable, long-term effects are not anticipated; however long-term safety is considered missing information.<br>**Impact on quality of life**: Since these events are generally reversible and manageable, the impact on quality life is limited. |
| Risk factors and risk groups | A retrospective medical record review showed that a higher body mass index (BMI) and multiple cycles of pembrolizumab were associated with higher risk of irARs. A derived neutrophil-lymphocyte ratio greater than 3 at baseline was correlated with low risk of irARs [Eun, 2019].<br>Patients with pre-existing autoimmune disease may be at increased risk of exacerbation of their autoimmune condition and for *de novo* irARs, however, use in this population is not predicted to be associated with unexpected risks or risks of clinical significance that would not be manageable with appropriate intervention [Garret, 2018; Johnson, 2017]. |
| Preventability | Patients should be monitored for signs and symptoms of irARs. Clinical chemistries, including liver tests and thyroid function tests, should be evaluated at baseline and periodically during treatment. For suspected immune-mediated adverse reactions, adequate evaluation to include specialty consultation should be ensured. Adverse reactions should be managed as described in the summary of product characteristics (SmPC). |
| Impact on the risk-benefit balance of the product | IrARs may be severe or fatal, can occur in any organ or tissue and may affect more than one body system simultaneously. While immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, symptoms can also manifest after discontinuation of treatment which may impact individual patients. However, irARs are generally manageable in patients with advanced or recurrent solid tumours. |
| Public health impact | Minimal due to the limited number of patients with the specific indication and the ability to manage the risk via routine risk minimisation activities. |

### SVII.3.2 Presentation of the missing information

### Table 12 Missing information: Long-term safety

| | |
|---|---|
| Evidence source: | The effect of long-term use in not known. |
| Population in need of further characterisation | The risks of long-term use cannot be defined based on available data and thus the safety profile in this population will be derived from routine pharmacovigilance activities. |

# PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

## Table 13 Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | ▪ Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other IrARs) |
| Important potential risks | None |
| Missing information | ▪ Long-term safety |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

## III.1 Routine pharmacovigilance activities

No routine PV activities beyond adverse reaction reporting and signal detection activities are required.

## III.2 Additional pharmacovigilance activities

Not proposed.

## III.3 Summary Table of additional Pharmacovigilance activities

### Table 14 On-going and planned additional pharmacovigilance activities

| **Study**<br><br>**Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances | | | | |
| None | | | | |
| **Category 3**- Required additional pharmacovigilance activities | | | | |
| None | | | | |

# PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

**Table 15 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.**

| Study Status | Summary of objectives | Efficacy uncertainties addressed | Milestones | Due Date |
|---|---|---|---|---|
| Efficacy studies which are conditions of the marketing authorisation | | | | |
| None | | | | |
| Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| None | | | | |

# PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## Risk Minimisation Plan

## V.1. Routine Risk Minimisation Measures

### Table 16 Description of routine risk minimisation measures by safety concern

| Safety concern | Routine risk minimisation activities |
|---|---|
| Important identified risk:<br>Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other IrARs) | **Routine risk communication**:<br><br>SmPC Sections:<br>4.2: Posology and method of administration<br>4.4: Special warnings and precautions for use<br>4.8: Undesirable effects<br><br>Patient leaflet (PL) Sections:<br>2. What you need to know before you take Dostarlimab<br>4. Possible side effects<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk**:<br>Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4.<br><br>**Other routine risk minimisation measures beyond the Product Information**:<br>- Prescription only medicine<br>- Use restricted to physicians experienced in the use of anticancer medicinal products |
| Long-term safety | **Routine risk communication**:<br>None proposed.<br><br>**Other routine risk minimisation measures beyond the Product Information**:<br>- Prescription only medicine<br>- Use restricted to physicians experienced in the use of anticancer medicinal products |

## V.2. Additional Risk Minimisation Measures

### Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs)

The key messages from the educational materials are provided in ANNEX 6.

### Patient card

**Objectives**: To inform patients about the important identified risk of immune-related adverse reactions.

**Rationale for the additional risk minimisation activity:** A Patient Card will be included for dostarlimab to inform patients about signs and symptoms of the most common immune-related events with dostarlimab, and the main required actions to be taken if they experience any signs or symptoms of immune-related adverse reactions. The patient will be instructed to carry the card with them at all times and may be used to inform the patients' other HCPs on the risk of immune-related adverse reactions and the prescriber's contact information, if needed.

**Target audience and planned distribution path:** The Patient Card will be dispensed to the patient by the treating physician prior to the first administration. Following approval of the EU RMP, the Applicant will follow and oversee submission to local authorities at the national level according to local requirements.

**Plans to evaluate the effectiveness of the interventions and criteria for success:** Assessment of the effectiveness of the Patient Card will be performed by routine pharmacovigilance activities with a brief analysis included in Section 16.5 of each PSUR, as clarified by the PRAC Rapporteur (dated 10 July 2020).

Routine pharmacovigilance will include ongoing monitoring of immune-related adverse events from all sources (spontaneous, clinical trials, post-marketing surveillance) with special attention to compliance with labelling recommendations.

## V.3 Summary of risk minimisation measures

**Table 17 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, | **Routine risk minimisation measures**:<br>SmPC Sections: 4.2, 4.4, 4.8<br>PL Sections: 2, 4<br>Recommended treatment modifications are provided in SmPC section 4.2.<br>Instruction regarding symptom evaluation, | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| immune-related skin adverse reactions, nephritis and other irARs) | treatment modifications and interventions are provided in SmPC section 4.4.<br><br>Prescription only medicine<br>Use restricted to physicians experienced in the use of anticancer medicinal products<br><br>**Additional risk minimisation measures**:<br>Patient Card | **Additional pharmacovigilance activities:**<br>None |
| Long-term safety | **Routine risk minimisation measures**:<br>None<br><br>**Additional risk minimisation measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>None |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of risk management plan for JEMPERLI (dostarlimab)

This is a summary of the risk management plan (RMP) for JEMPERLI. The RMP details important risks of JEMPERLI, how these risks can be minimised, and how more information will be obtained about JEMPERLIs risks and uncertainties (missing information).

JEMPERLI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how JEMPERLI should be used.

This summary of the RMP for JEMPERLI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of JEMPERLI's RMP.

## I. The medicine and what it is used for

JEMPERLI is indicated as monotherapy for the treatment of patients with mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) recurrent or advanced endometrial cancer (EC) who have progressed on or after treatment with a platinum-containing regimen (see SmPC for the full indication). It contains dostarlimab as the active substance and it is given by infusion.

JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.

Further information about the evaluation of JEMPERLI's benefits can be found in JEMPERLI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

*https://www.ema.europa.eu/en/medicines/human/EPAR/jemperli*

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of JEMPERLI, together with measures to minimise such risks and the proposed studies for learning more about JEMPERLI's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of JEMPERLI is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of JEMPERLI are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of JEMPERLI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | ▪ Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) |
| Important potential risks | None |
| Missing information | ▪ Long-term safety |

## II.B Summary of important risks

| |
|---|
| **Important identified risk:** Immune-related adverse reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) |

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Non-clinical**: Non-clinical observations in cynomolgus monkeys included increased incidence of liquid faeces, dermatitis, mild mixed cell inflammation in the liver, mild to moderate mononuclear infiltrates with or without minimal degeneration in the kidney and heart.<br><br>**Clinical**:<br>**GARNET: Dostarlimab monotherapy study for 2L EC (dMMR/MSI-H EC patients N=153)**<br>In subjects with dMMR/MSI-H EC, 59 (38.6%) subjects experienced potential irARs and 42 (27.5%) subjects reported treatment-related irARs. Grade ≥3 irARs were reported in 20 (13.1%) subjects, SAEs were reported in 16 (10.5%) subjects, and irARs leading to permanent treatment discontinuation were reported in 14 (9.2%) subjects.<br><br>**RUBY: Dostarlimab combination therapy for 1L EC (Part 1; All EC patients N= 241**<br>In all EC patients receiving dostarlimab plus carboplatin and paclitaxel, 137 (56.8%) experienced irARs and 92 (38.2%) reported treatment-related irARs. Grade ≥3 irARs were reported in 40 (16.6%) patients, SAEs were reported in 14 (5.8%) patients, and irARs leading to permanent treatment discontinuation were reported in 19 (7.9%) subjects.<br><br>**Class effect**: 'IrARs' is a risk for all drugs in the class: Keytruda (pembrolizumab), Opdivo (Nivolumab), Tecentriq (Atezolizumab), Bavencio (Avelumab), Imfinzi (Durvalumab), and Libtayo (cemiplimab). |
| Risk factors and risk groups | A retrospective medical record review showed that a higher BMI and multiple cycles of pembrolizumab were associated with higher risk of irARs. A derived neutrophil-lymphocyte ratio greater than 3 at baseline was correlated with low risk of irARs.<br>Patients with pre-existing autoimmune disease may be at increased risk of exacerbation of their autoimmune condition and for *de novo* irARs, however, use in this population is not predicted to be associated with unexpected risks or risks of clinical significance that would not be manageable with appropriate intervention. |
| Risk minimisation measures | **Routine risk minimisation measures**:<br>SmPC Sections: 4.2, 4.4, 4.8<br>PL Sections: 2, 4<br>Recommended treatment modifications are provided in SmPC section 4.2. |

| | |
|---|---|
| | Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4.<br><br>Prescription only medicine<br>Use restricted to physicians experienced in the use of anticancer medicinal products<br><br>**Additional risk minimisation measures**:<br>Patient Card |

| **Missing information: Long-term safety** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures**:<br>None<br><br>**Additional risk minimisation measures**:<br>No risk minimisation measures |

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorization or specific obligations of JEMPERLI.

### II.C.2 Other studies in post-authorisation development plan

There are no studies required for JEMPERLI.

# ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

# ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

## Key messages of the additional risk minimisation measures

*Patient card*
The **patient card** includes the following key messages:

- Description of the main signs or symptoms of the immune-related adverse reactions.
- The importance of notifying their treating physician/nurse immediately if symptoms occur or worsen, and the importance of not attempting to treat themselves.
- The importance of carrying the patient alert card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
- Includes contact details of the prescriber and a warning message for healthcare professionals at any time, including in conditions of emergency, that the patient is using JEMPERLI

Prior to the launch of JEMPERLI in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme in the form of a Patient Card, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at informing patients about the important identified risk of immune-related adverse reactions associated with dostarlimab treatment and the actions to be taken should they experience symptoms.

The MAH shall ensure that in each Member State where JEMPERLI is marketed, all healthcare professionals who are expected to prescribe JEMPERLI are provided with the following educational package:

- Patient Card

*The Patient Card will include the following key messages:*

- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using JEMPERLI.
- That JEMPERLI treatment may increase the risk of irARs (including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs)
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional.
- Contact details of the JEMPERLI prescriber.