Medicines & Healthcare products Regulatory Agency

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:

http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and is to be used in combination with (an)other medicine(s) prescribed outside the licence. The information is provided to assist physicians in prescribing medicines used outside the licence. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:

https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the combination therapy in this new promising indication. As such, this is a scientific opinion and should not be regarded as an indication licensed by the MHRA or a future commitment by the MHRA to license such an indication, nor should it be regarded as an authorisation to sell or supply a medicine for such an indication. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated. For other updates of the safety information, please refer to the product information of the combination products on the electronic Medicines Compendium (eMC) website: https://www.medicines.org.uk/emc.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Dostarlimab 500 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab.

Each mL of concentrate for solution for infusion contains 50 mg of dostarlimab.

Dostarlimab is an anti-programmed cell death protein-1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb), produced by recombinant DNA technology in mammalian Chinese hamster ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent colourless to yellow solution, essentially free from visible particles.

The concentrate for solution for infusion has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Dostarlimab is indicated in combination with platinum-containing chemotherapy 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.

4.2 Posology and method of administration

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Patients are only eligible for treatment in this EAMS if their endometrial cancer is identified as being mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H).

The identification of dMMR/MSI-H tumour status should be determined for all patients using a validated testing method such as immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS).

Posology

The recommended dosage of dostarlimab as combination therapy is 500 mg given intravenously (IV) every 3 weeks for 6 cycles, followed by dostarlimab monotherapy 1000 mg IV every 6 weeks for all cycles thereafter (cycle 7 onwards).

When dostarlimab is administered in combination with platinum-containing chemotherapy, healthcare professionals are advised to consult the Summary of Product Characteristics (SmPC) of the combined product(s) for further information on administration, safety aspects, and pharmaceutical particulars (see also section 5.1). The dosage regimen for dostarlimab in combination with chemotherapy is presented in table 1.

Table 1: Dosage regimen for dostarlimab in combination with chemotherapy

	500 mg once every 3 weeks in combination with chemotherapy[a] (1 cycle = 3 weeks)						1000 mg once every 6 weeks until disease progression or unacceptable toxicity (1 cycle = 6 weeks)			
Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Continue dosing Q6W
Week	1	4	7	10	13	16	19	25	31	

3 weeks between cycle 6 and cycle 7

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

Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years (see section 5.1).

Combination therapy with carboplatin and paclitaxel

Carboplatin recommended dose is at an AUC of 5 mg/mL/min. by IV infusion every 3 weeks for 6 cycles and should be determined by the physician, taking into consideration the patient's pre-existing medical conditions. Paclitaxel recommended dose is 175 mg/m2 by IV infusion every 3 weeks for 6 cycles. Prior to receiving paclitaxel, all patients must be premedicated with corticosteroids, antihistamines, and H2 antagonists.

Dose modifications

Dostarlimab

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

Detailed guidelines for the management of immune-related adverse reactions and infusion-related reactions associated with dostarlimab are described in section 4.4.

Table 2: Recommended dose modifications for dostarlimab

Immune-related adverse reactions	Severity grade[a]	Dose modification
Colitis	2 or 3	Withhold dose. Restart dosing when toxicity resolves to grade 0 or1.
	4	Permanently discontinue.
Hepatitis	Grade 2 with AST[b] or ALT[c] >3 and up to 5 × ULN[d] or	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.

	total bilirubin >1.5 and up to 3 × ULN	
	Grade ≥3 with AST or ALT > 5 × ULN or total bilirubin > 3 × ULN	Permanently discontinue (see exception below)[e].

Table 2: Recommended dose modifications for dostarlimab (continued)

Immune-related adverse reactions	Severity grade[a]	Dose modification
Type 1 diabetes mellitus (T1DM)	3 or 4 (hyperglycaemia)	Withhold dose. Restart dosing in appropriately managed, clinically, and metabolically stable patients.
Hypophysitis or adrenal insufficiency	2, 3, or 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1. Permanently discontinue for recurrence or worsening while on adequate hormonal therapy.
Hypothyroidism or hyperthyroidism	3 or 4	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1. If grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Nephritis	2	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
	3 or 4	Permanently discontinue.
Exfoliative dermatologic conditions (e.g., SJS, TEN, DRESS)[f]	Suspected	Withhold dose for any grade. Restart dosing if not confirmed and when toxicity resolves to grade 0 or 1.
	Confirmed	Permanently discontinue.
Myocarditis	2, 3, or 4	Permanently discontinue.
Severe neurological toxicities (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, encephalitis, transverse myelitis)	2, 3, or 4	Permanently discontinue.

Other immune-related adverse reactions (including but not limited to myositis, sarcoidosis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, uveitis, diabetic ketoacidosis, arthralgia, solid organ transplant rejection, graft-versus-host disease)	3	Withhold dose. Restart dosing when toxicity resolves to grade 0 or 1.
	4	Permanently discontinue.

Table 2: Recommended dose modifications for dostarlimab (continued)

Immune-related adverse reactions	Severity grade[a]	Dose modification
Recurrence of immune-related adverse reactions after resolution to ≤ grade 1 (except for pneumonitis, see above)	3 or 4	Permanently discontinue.
Infusion-related reactions	2	Withhold dose. If resolved within 1 hour of stopping, may be restarted at 50% of the original infusion rate, or restart when symptoms resolve with pre-medication. If grade 2 recurs with adequate premedication, permanently discontinue.
	3 or 4	Permanently discontinue.

[a]Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
[b]AST=aspartate aminotransferase
[c]ALT=alanine aminotransferase
[d]ULN=upper limit of normal
[e]For patients with liver metastasis who begin treatment with Grade 2 of AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then treatment should be discontinued.
[f]SJS = Stevens–Johnson syndrome; TEN = Toxic epidermal necrolysis; DRESS = Drug rash with eosinophilia and systemic symptoms.

Platinum-containing chemotherapy

For information on dose adjustments to the platinum-containing chemotherapy administered with dostarlimab, physicians should consult the relevant SmPC.

In the case of platinum-containing chemotherapy such as carboplatin and paclitaxel, dose reduction of one chemotherapy agent and not the other agent is appropriate if the toxicity is clearly related to one of the chemotherapy agents. If the toxicity is related to both agents, they should both be modified according to their recommended dose modification. If the toxicity is related to the combination of dostarlimab and both chemotherapy agents, the doses of the chemotherapy agents should be reduced, or the dose of all three drugs should be interrupted or discontinued. Patients may have chemotherapy discontinued and continue dostarlimab as monotherapy, in the same way patients may discontinue dostarlimab and continue chemotherapy alone.

Patient Card

All prescribers of dostarlimab should inform patients about the Patient Card, explaining what to do should they experience any symptom of immune-related adverse reactions. The physician will provide the Patient Card to each patient.

Special populations

Elderly

No dose adjustment of dostarlimab is recommended for patients who are aged 65 years or over. There are limited clinical data with dostarlimab in patients aged 75 years or over (see section 5.1).

Renal impairment

No dose adjustment of dostarlimab is recommended for patients with mild or moderate renal impairment. There are limited data in patients with severe renal impairment or end-stage renal disease undergoing dialysis (see section 5.2).

Hepatic impairment

No dose adjustment of dostarlimab is recommended for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment (see section 5.2).

Paediatric population

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

Method of administration

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

Dostarlimab must not be administered as an intravenous push or bolus injection. For instructions on dilution of this medicinal product before administration, see section 6.6.

For further information on the method of administration of platinum-containing chemotherapy see Section 4.2 of their respective Summary of Product Characteristics.

4.3 Contraindications

Hypersensitivity to the active substance (dostarlimab) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the EAMS and the batch number of the administered product should be clearly recorded.

Immune-related adverse reactions

Immune-related adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including dostarlimab. While immune-related adverse reactions usually occur during treatment with PD-1/PD-L1

blocking antibodies, symptoms can also manifest after discontinuation of treatment. Immune-related adverse reactions may occur in any organ or tissue and may affect more than one body system simultaneously. Important immune-related adverse reactions listed in this section are not inclusive of all possible severe and fatal immune-related reactions.

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

Based on the severity of the adverse reaction, treatment with dostarlimab should be withheld or permanently discontinued and corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy administered (see below and section 4.2). Upon improvement to Grade ≤1, corticosteroid taper should be initiated and continued for 1 month or longer. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Hormone replacement therapy for endocrinopathies should be instituted as warranted.

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

Immune-related pneumonitis

Pneumonitis has been reported in patients receiving dostarlimab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Patients should be managed with dostarlimab treatment modifications and corticosteroids (see section 4.2).

Immune-related colitis

Dostarlimab can cause immune-related colitis (see section 4.8). Patients should be monitored for signs and symptoms of colitis and managed with dostarlimab treatment modifications, anti-diarrhoeal agents, and corticosteroids (see section 4.2).

Immune-related hepatitis

Dostarlimab can cause immune-related hepatitis (see section 4.8). Patients should be monitored for changes in liver function periodically as indicated, based on clinical evaluation and managed with dostarlimab treatment modifications and corticosteroids (see section 4.2).

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 section 4.8).

Hypothyroidism and hyperthyroidism

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

Immune-related hypothyroidism and hyperthyroidism (including thyroiditis) should be managed as recommended in section 4.2.

Adrenal insufficiency

Immune-related adrenal insufficiency occurred in patients receiving dostarlimab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in section 4.2.

Immune-related nephritis

Dostarlimab can cause immune-related nephritis (see section 4.8). Patients should be monitored for changes in renal function and manage with dostarlimab treatment modifications and corticosteroids (see section 4.2).

Immune-related rash

Immune-related rash has been reported in patients receiving dostarlimab, including pemphigoid (see section 4.8). Patients should be monitored for signs and symptoms of rash. Exfoliative dermatologic conditions should be managed as recommended in section 4.2. Events of Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN) have been reported in patients treated with PD-1 inhibitors.

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

Immune-related arthralgia

Immune-related arthralgia has been reported in patients receiving dostarlimab (see section 4.8). Patients should be monitored for signs and symptoms of arthralgia. Suspected immune-related arthralgia should be confirmed and other causes excluded. Patients should be managed with dostarlimab treatment modifications and corticosteroids (see section 4.2).

Other immune-related adverse reactions

Given the mechanism of action of dostarlimab other potential immune-related adverse reactions may occur, including potentially serious events [e.g., myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis]. Clinically significant immune-related adverse reactions reported in less than 1% of patients treated with dostarlimab as monotherapy in clinical studies include encephalitis, autoimmune haemolytic anaemia, pancreatitis, iridocyclitis, and uveitis. Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed as described in section 4.2. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with dostarlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with dostarlimab versus the risk of possible organ rejection should be considered in these patients.

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

Infusion-related reactions

Dostarlimab can cause infusion-related reactions, which can be severe (see section 4.8). For severe (grade 3) or life-threatening (grade 4) infusion-related reactions, the infusion should be stopped and treatment should be permanently discontinued (see section 4.2).

Patients excluded from clinical studies

Patients with the following status were excluded from the RUBY study: ECOG baseline performance score ≥2, uncontrolled central nervous system metastases, carcinomatous meningitis or both; other malignancies within the last 3 years; history of HIV; active hepatitis B or hepatitis C infection; active autoimmune disease requiring systemic treatment in the past 2 years excluding replacement therapy; immunodeficiency or receiving systemic steroid or immunosuppressive therapy within last 7 days; or receiving live vaccine within 30 days.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 500 mg dose, i.e., essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Monoclonal antibodies (mAb) such as dostarlimab are not substrates for cytochrome P450 or active substance transporters. Dostarlimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, pharmacokinetic (PK) interaction of dostarlimab with small molecule active substances is not expected. There is no evidence of interaction mediated by non-specific clearance of lysosome degradation for antibodies.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential/Contraception

There is a risk associated with the administration of dostarlimab to women of childbearing potential. Women of childbearing potential must use effective contraception during treatment with dostarlimab and until 4 months after the last dose of dostarlimab.

Pregnancy

There are no or limited amount of data on the use of dostarlimab in pregnant women. Based on its mechanism of action, dostarlimab can cause foetal harmful pharmacological effects when administered during pregnancy.

Animal reproduction and development studies have not been conducted with dostarlimab; however, inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing foetus resulting in foetal death (see section 5.3). Human immunoglobulins (IgG4) are known to cross the placental barrier, and therefore, being an IgG4, dostarlimab has the potential to be transmitted from the mother to the developing foetus.

Dostarlimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether dostarlimab/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Dostarlimab should not be used during breast-feeding and breast-feeding should be avoided for at least 4 months after the last dose of dostarlimab.

Fertility

Fertility studies have not been conducted with dostarlimab (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Dostarlimab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy and/or withdrawal of dostarlimab (see "Description of selected adverse reactions" below).

Dostarlimab in combination with chemotherapy

The safety of dostarlimab has been evaluated in 241 patients with primary advanced or recurrent EC who received dostarlimab in combination with paclitaxel and carboplatin in the RUBY study. Patients received doses of 500 mg dostarlimab every 3 weeks for 6 cycles in combination with chemotherapy followed by 1000 mg every 6 weeks as monotherapy for all cycles thereafter.

In patients with primary advanced or recurrent EC (N = 241), the most common adverse reactions (>10%) were rash (22.8%), rash maculopapular (14.1%), hypothyroidism (14.1%), alanine aminotransferase increased (12.9%), aspartate aminotransferase increased (12.0%), pyrexia (12.0%) and dry skin (10.4%). Dostarlimab was permanently discontinued due to adverse reactions in 12 (5.0%) patients; most were immune-related events. Adverse reactions were serious in 5.8% of patients; most serious adverse reactions were immune-related adverse reactions (see section 4.4).

The safety profile for patients with dMMR/MSI-H EC in the RUBY study (N=52) was not different from that of the overall combination therapy population presented in Table 3.

Dostarlimab in monotherapy

The safety of dostarlimab has been evaluated in 605 patients with EC or other advanced solid tumours who received dostarlimab monotherapy in the GARNET study, including 153 patients with advanced or recurrent dMMR/MSI-H EC. Patients received doses of 500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter.

In patients with advanced or recurrent solid tumours (N = 605), the most common adverse reactions (>10%) were anaemia (28.6%), diarrhoea (26.0%), nausea (25.8%), vomiting (19.0%), arthralgia (17.0%), pruritus (14.2%), rash (13.2%), pyrexia (12.4%), aspartate aminotransferase increased (11.2%) and hypothyroidism (11.2%). Dostarlimab was permanently discontinued due to adverse reactions in 38 (6.3%) patients; most of them were immune-related events. Adverse reactions were serious in 11.2% of patients; most serious adverse reactions were immune-related adverse reactions (see section 4.4).

The safety profile for patients with dMMR/MSI-H EC in the GARNET study (N=153) was not different from that of the overall monotherapy population presented in Table 3.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials of dostarlimab as a monotherapy or in combination with chemotherapy are listed in Table 3 by system organ class and by frequency. The frequencies of adverse reactions listed in the dostarlimab monotherapy column are based on all-cause adverse event frequency identified in 605 patients with advanced or recurrent solid tumours from the GARNET study exposed to dostarlimab monotherapy for a median duration of treatment of 24 weeks (range: 1 week to 229 weeks). Unless otherwise stated, the frequencies of adverse reactions listed in the dostarlimab in combination therapy column are based on all-cause adverse event frequency identified in 241 patients with primary advanced or recurrent EC from the RUBY study exposed to dostarlimab in combination with chemotherapy for a median duration of treatment of 43 weeks (range: 3 to 151 weeks).

For additional safety information when dostarlimab is administered in combination with platinum-containing regimens (i.e., carboplatin and paclitaxel), refer to the respective Prescribing Information for the combination products.

Adverse reactions known to occur with dostarlimab as monotherapy or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); and not known (cannot be estimated from the available data).

Table 3: Adverse reactions in patients treated with dostarlimab

System Organ Class	Dostarlimab monotherapy	Dostarlimab in combination therapy
Blood and lymphatic system disorders	**Very common** Anaemia[a]	
Endocrine disorders	**Very common** Hypothyroidism*[b] **Common** Hyperthyroidism*, adrenal insufficiency* **Uncommon** Thyroiditis*[c], hypophysitis[d],	**Very common** Hypothyroidism[e] **Common** Hyperthyroidism, adrenal insufficiency **Uncommon** Thyroiditis
Metabolism and nutrition disorders	**Uncommon** Type 1 diabetes mellitus, diabetic ketoacidosis	**Uncommon** Type 1 diabetes mellitus
Nervous system disorders	**Uncommon** Encephalitis, myasthenia gravis	**Uncommon** Myasthenic syndrome[f]
Eye disorders	**Uncommon** Uveitis[g]	**Uncommon** Uveitis
Cardiac disorders		**Uncommon** Myocarditis[h]
Respiratory, thoracic, and mediastinal disorders	**Common** Pneumonitis*[i]	**Common** Pneumonitis
Gastrointestinal disorders	**Very common** Diarrhoea, nausea, vomiting **Common**	**Common** Colitis[l] **Uncommon**

	Colitis*[j], pancreatitis[k], gastritis **Uncommon** Oesophagitis	Pancreatitis, immune mediated gastritis[f], vasculitis gastrointestinal[f]
Hepatobiliary disorders	**Common** Hepatitis*[m]	

Table 3: Adverse reactions in patients treated with dostarlimab (continued)

System Organ Class	Dostarlimab monotherapy	Dostarlimab in combination therapy
Skin and subcutaneous tissue disorders	**Very common** Rash*[n], pruritus,	**Very common** Rash[o], dry skin
Musculoskeletal and connective tissue disorders	**Very common** Arthralgia* **Common** Myalgia **Uncommon** Immune-mediated arthritis, polymyalgia rheumatica, immune-mediated myositis	**Uncommon** Immune-mediated arthritis, myositis[p]
Renal and urinary disorders	**Uncommon** Nephritis*[q]	
General disorders and administration site conditions	**Very common** Pyrexia **Common** Chills	**Very common** Pyrexia **Uncommon** Systemic inflammatory response syndrome[p]
Investigations	**Very common** Transaminases increased[r]	**Very common** Alanine aminotransferase increased, aspartate aminotransferase increased
Injury, poisoning and procedural complications	**Common** Infusion-related reaction*[s]	

*See section 'Description of selected adverse reactions.'
[a]Includes anaemia and autoimmune haemolytic anaemia
[b]Includes hypothyroidism and autoimmune hypothyroidism
[c]Includes thyroiditis and autoimmune thyroiditis
[d]Includes hypophysitis and lymphocytic hypophysitis
[e]Includes hypothyroidism and immune-mediated hypothyroidism
[f]Reported from ongoing blinded trial of dostarlimab in combination; estimated frequency category
[g]Includes uveitis and iridocyclitis
[h]Includes myocarditis (combination with chemotherapy) and immune-mediated myocarditis from ongoing blinded trial of dostarlimab in combination; estimated frequency category
[i]Includes pneumonitis, interstitial lung disease and immune-mediated lung disease
[j]Includes colitis, enterocolitis, and immune-mediated enterocolitis
[k]Includes pancreatitis and pancreatitis acute
[l]Includes colitis (combination with chemotherapy) and enteritis reported from ongoing trial of dostarlimab in combination
[m]Includes hepatitis, autoimmune hepatitis, and hepatic cytolysis

[n]Includes rash, rash maculo-papular, erythema, rash macular, rash pruritic, rash erythematous, rash papular, erythema multiforme, skin toxicity, drug eruption, toxic skin eruption, exfoliative rash, and pemphigoid
[o]Includes rash and rash maculo-papular
[p]Reported in ongoing trial of dostarlimab in combination
[q]Includes nephritis and tubulointerstitial nephritis
[r] Includes transaminases increased, alanine aminotransferases increased, aspartate aminotransferases increased, and hypertransaminasaemia
[s]Includes infusion-related reaction and hypersensitivity.

Description of selected adverse reactions based on dostarlimab in combination with chemotherapy

In the RUBY study, immune-related adverse events (irAEs) were identified as any ≥Grade 2 AEs based on a prespecified search list of preferred terms and MedDRA Version 25.0.

In the overall population, 92 of 241 participants (38.2%) in the dostarlimab plus carboplatin-paclitaxel arm and 38 of 246 participants (15.4%) in the placebo plus carboplatin-paclitaxel arm had dostarlimab or placebo-related irAEs. The most frequently reported dostarlimab or placebo-related irAEs were hypothyroidism in the dostarlimab plus carboplatin-paclitaxel arm and arthralgia in the placebo plus carboplatin-paclitaxel arm (Table 4).

In the dostarlimab plus carboplatin-paclitaxel arm, potential irAEs which were Grade ≥3, SAEs, or leading to discontinuation were reported in 1 or 2 participants each with the exception of potential irAEs Grade ≥3 of rash (4.1%) and rash maculo-papular, alanine aminotransferase increased and aspartate aminotransferase increased (2.1% each), and potential irAEs leading to discontinuation of rash and infusion-related reactions (1.2% each). There were no reported potential irAEs leading to death.

Table 4. Immune related adverse reactions in patients treated with dostarlimab in combination with chemotherapy

Category (n%) **Preferred term (n%)**	**Dostar + carbo/pac (N=241)**			
	All events	**Dostarlimab related**		
Any immune-related AE	137 (56.8%)	92 (38.2%)		
Arthralgia	32 (13.3%)	14 (5.8%)		
Infusion-related reaction	31 (12.9%)	4 (1.7%)		
Hypothyroidism	27 (11.2%)	27 (11.2%)		
Hypersensitivity/ Drug hypersensitivity	6 (2.5%)/7 (2.9%)	0/0		
Rash	21 (8.7%)	16 (6.6%)		
Rash maculo-papular	16 (6.6%)	11 (4.6%)		
Pruritus	15 (6.2%)	8 (3.3%)		
ALT increased	15 (6.2%)	14 (5.8%)		
AST increased	12 (5.0%)	10 (4.1%)		
Hyperthyroidism	8 (3.3%)	8 (3.3%)		

Abbreviations: AE=adverse event; carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel.

Note: AEs were coded using MedDRA version 25.0. AE severity coded using NCI CTCAE v4.03. Immune-related AEs are identified as any ≥Grade 2 AEs based on a prespecified preferred terms list.

For the dMMR/MSI-H population, the most frequently reported dostarlimab or placebo related irAE was hypothyroidism (15.4%) in the dostarlimab plus carboplatin-paclitaxel arm, and hypothyroidism and arthralgia (4.6% each) in the placebo plus carboplatin-paclitaxel arm.

Description of selected adverse reactions based on dostarlimab monotherapy

The selected adverse reactions described below are based on the safety of dostarlimab in a combined monotherapy safety database of 605 patients in the GARNET study in patients with EC or other advanced solid tumours. Immune-related adverse reactions were defined as events of grade 2 and above; the frequencies below exclude grade 1 events. The management guidelines for these adverse reactions are described in section 4.2.

Immune-related adverse reactions (see section 4.4)

Immune-related pneumonitis

Immune-related pneumonitis occurred in 14 (2.3%) patients, including grade 2 (1.3%), grade 3 (0.8%), and grade 4 (0.2%) pneumonitis. Pneumonitis led to discontinuation of dostarlimab in 8 (1.3%) patients.

Systemic corticosteroids (prednisone ≥40 mg per day or equivalent) were required in 11 (78.6%) patients experiencing pneumonitis. Pneumonitis resolved in 11 (78.6%) patients.

Immune-related colitis

Colitis occurred in 8 (1.3%) patients, including grade 2 (0.7%) and grade 3 (0.7%) colitis. Colitis did not lead to discontinuation of dostarlimab in any patients.

Systemic corticosteroids (prednisone ≥40 mg per day or equivalent) were required in 5 (62.5%) patients. Colitis resolved in 5 (62.5%) patients experiencing colitis.

Immune-related hepatitis

Hepatitis occurred in 3 (0.5%) patients, all of which were grade 3. Systemic corticosteroids (prednisone ≥40 mg per day or equivalent) were required in 2 (66.7%) patients. Hepatitis lead to discontinuation of dostarlimab in 1 (0.2%) patient and resolved in 2 of the 3 patients.

Immune-mediated endocrinopathies

Hypothyroidism occurred in 46 (7.6%) patients, all of which were grade 2. Hypothyroidism did not lead to discontinuation of dostarlimab and resolved in 17 (37.0%) patients.

Hyperthyroidism occurred in 14 (2.3%) patients, including grade 2 (2.1%) and grade 3 (0.2%). Hyperthyroidism did not lead to discontinuation of dostarlimab and resolved in 10 (71.4%) patients.

Thyroiditis occurred in 3 (0.5%) patients; all were grade 2. None of the events of thyroiditis resolved; there were no discontinuations of dostarlimab due to thyroiditis.

Adrenal insufficiency occurred in 7 (1.2%) patients, including grade 2 (0.5%), and grade 3 (0.7%). Adrenal insufficiency resulted in discontinuation of dostarlimab in 1 (0.2%) patient and resolved in 4 (57.1%) patients.

Immune-mediated nephritis

Nephritis, including tubulointerstitial nephritis, occurred in 3 (0.5%) patients; all were grade 2. Systemic corticosteroids (prednisone ≥40 mg per day or equivalent) were required in 2 (66.7%) patients experiencing nephritis. Nephritis led to discontinuation of dostarlimab in 1 (0.2%) patient and resolved in all 3 patients.

Immune-related rash

Immune-related rash (rash, rash maculo-papular, rash macular, rash pruritic, pemphigoid, drug eruption, skin toxicity, toxic skin eruption) occurred in 31 (5.1%) patients, including Grade 3 in 9 (1.5%) patients receiving dostarlimab. The median time to onset of rash was 57 days (range 2 days to 1485 days). Systemic corticosteroids (prednisone ≥40 mg per day or equivalent) were required in 9 (29.0%) patients experiencing rash. Rash lead to discontinuation of dostarlimab in 1 (0.2%) patient and resolved in 24 (77.4%) patients.

Immune-related arthralgia

Immune-related arthralgia occurred in 34 (5.6%) patients. Grade 3 immune-related arthralgia was reported in 5 (0.8%) patients receiving dostarlimab. The median time to onset of arthralgia was 94.5 days (range 1 day to 840 days). Systemic corticosteroids (prednisone ≥40 mg per day or equivalent) were required in 3 (8.8%) patients experiencing arthralgia. Arthralgia led to discontinuation of dostarlimab in 1 (0.2%) patient and resolved in 19 (55.9%) patients experiencing arthralgia.

Infusion-related reactions

Infusion-related reactions including hypersensitivity occurred in 6 (1.0%) patients, including grade 2 (0.3%) and grade 3 (0.2%) infusion-related reactions. All patients recovered from the infusion-related reaction.

Immunogenicity

In the GARNET study, anti-drug antibodies (ADA) were tested in 315 patients who received dostarlimab and the incidence of dostarlimab treatment-emergent ADAs was 2.5%. Neutralising antibodies were detected in 1.3% of patients. Co administration with chemotherapy did not affect dostarlimab immunogenicity. In the RUBY study, 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 ADAs, there was no evidence of altered efficacy or safety of dostarlimab.

Elderly population

Of the 605 patients treated with dostarlimab monotherapy in the GARNET study, 51.6% were under 65 years, 36.9% were 65 to less than 75 years, and 11.5% were 75 years or older. No overall differences in safety were reported between elderly (≥65 years) and younger patients (<65 years).

4.9 Overdose

If dostarlimab overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agents, monoclonal antibodies, and antibody drug conjugates, ATC code: L01FF07

Mechanism of action

Dostarlimab is a humanised mAb of the IgG4 isotype that binds to PD-1 receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in inhibition of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immuno responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Clinical efficacy and safety

RUBY: Randomised controlled study of combination therapy in treatment of adult patients with primary advanced or recurrent EC.

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

Patients were randomised (1:1) to receive 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 1000 mg every 6 weeks (n = 245) or 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 radiotherapy, and disease status (recurrent, primary Stage III, or primary Stage IV).

The key eligibility criteria for the study were International Federation of Gynaecology and Obstetrics (FIGO) primary Stage III or Stage IV disease, including 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, including patients who had first recurrent 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). 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 through week 25, every 9 weeks through week 52, and every 12 weeks thereafter.

The primary efficacy outcome measures were progression-free survival (PFS) assessed by the investigator according to RECIST v1.1 in subjects with dMMR/MSI-H primary advanced or recurrent EC and in all subjects (overall ITT population) with primary advanced or recurrent EC, and overall survival (OS) in all subjects (overall ITT population) with primary advanced or recurrent EC. Secondary endpoints included objective response rate (ORR), disease control rate (DCR) and duration of response (DOR) as assessed by blinded independent central radiologists' (BICR) review and investigator assessment according to RECIST v1.1 and PFS2, defined as the time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following study treatment or death by any cause, whichever was earlier.

A total of 118 patients with dMMR/MSI-H EC were evaluated for efficacy in the RUBY study. Baseline demographics and characteristics of the overall study population (n = 494) were: median age 65 years (51% age 65 years or older); 77% White, 12% Black, 3% Asian; and Eastern Cooperative Oncology Group (ECOG) PS 0 (63%) or 1 (37%); and primary stage III 19%; primary stage IV 34%; recurrent EC 48%.

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.

Histology was balanced across treatment arms. The most frequent histology type at diagnosis was endometrioid histology (54.7% of total participants), followed by serous carcinoma (20.6%), and carcinosarcoma (8.9%). The most common grade was Grade 3 tumours (50%). In the overall population, 90.7% of participants had received prior anticancer surgical interventions for EC and 28.3% of participants had received previous radiotherapy. No noteworthy differences were observed in prior surgical intervention or radiotherapy treatment for EC between the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm.

Efficacy results for the dMMR/MSI-H population based on the first interim analysis of the RUBY study are shown in Table 5 and Figure 1. The median duration of follow up in this population was 24.8 months and the median duration of treatment in the dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel arms were 76.5 and 31.8 weeks respectively. In the dMMR/MSI-H and overall study population, the RUBY study demonstrated a statistically significant improvement in PFS in patients randomised to dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel.

Table 5: Efficacy results in RUBY for patients with EC

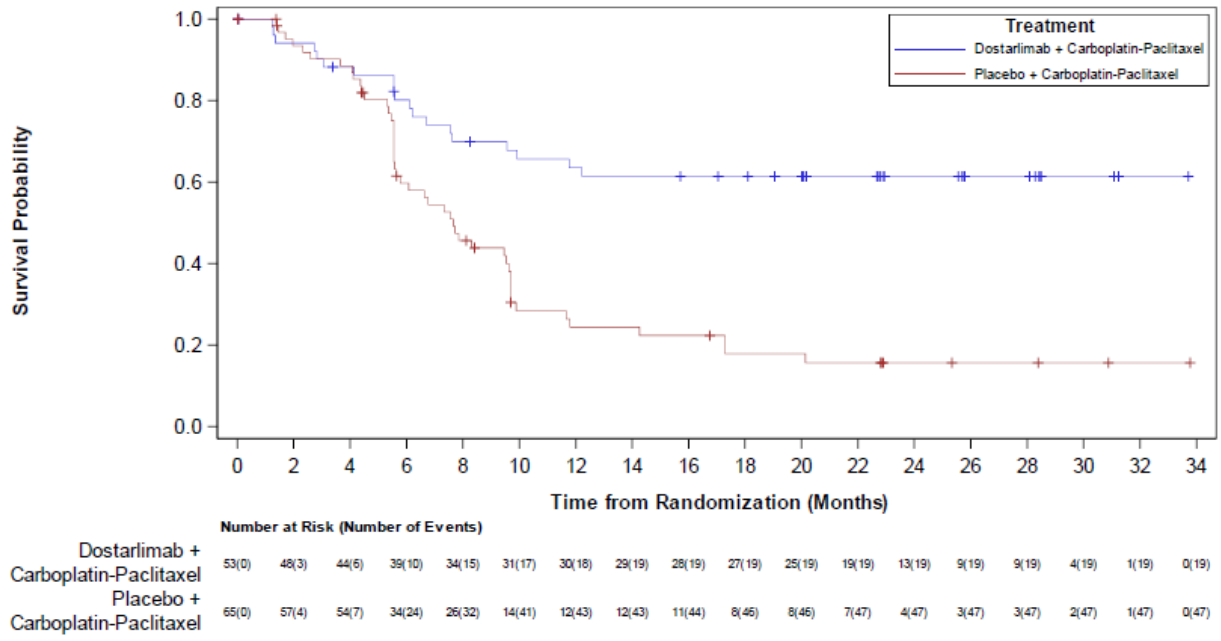
Endpoint	**dMMR/MSI-H population[a]**	
	Dostarlimab + carboplatin-paclitaxel (N = 53)	Placebo + carboplatin-paclitaxel (N = 65)
Progression free Survival (PFS)		
Median in months (95% CI)[b]	Not reached	7.7 (5.6, 9.7)
Number (%) of patients with event	19 (35.8%)	47 (72.3%)
Hazard ratio (95% CI)[c]	0.28 (0.16, 0.50)	
p-value[b]	<0.0001	
Probability of PFS at 12 months, (95% CI)[d]	63.5 (48.5, 75.3)	24.4 (13.9, 36.4)
Probability of PFS at 24 months, (95% CI)[d]	61.4 (46.3, 73.4)	15.7 (7.2, 27.0)
Overall Survival (OS)		
Median in months (95% CI)	Not reached	Not reached
Number (%) of patients with event	7 (13.2%)	24 (36.9%)
Hazard ratio (95% CI)[c]	0.30 (0.13, 0.70)	
Probability of OS at 12 months, (95% CI)[d]	90.1 (77.8, 95.7)	79.6 (67.5, 87.6)
Probability of OS at 24 months, (95% CI)[d]	83.3 (66.8, 92.0)	58.7 (43.4, 71.2)
Objective response rate (ORR)[e]		
Number of participants with evaluable disease at baseline (n)	49	58
ORR n (%) (95% CI)	38 (77.6) (63.4, 88.2)	40 (69.0) (55.5, 80.5)
Complete response rate, n (%)	15 (28.3)	12 (18.5)
Partial response rate, n (%)	23 (43.4)	28 (43.1)
Disease control rate (DCR)		
DCR n (%) (95% CI)	48 (90.6) (79.3, 96.9)	58 (89.2) (79.1, 95.6)

Table 5: Efficacy results in RUBY for patients with EC (continuation)

Endpoint	dMMR/MSI-H population[a]	
	Dostarlimab + carboplatin-paclitaxel (N = 53)	Placebo + carboplatin-paclitaxel (N = 65)
Duration of response (DOR)[e, f]		
Number of responder (n)	38	40
Median in months (95% CI)[g]	Not reached	5.4 (3.9, 8.1)
Patients with duration ≥6 months, n (%)	28 (73.7)	18 (45.0)
Patients with duration ≥12 months, n (%)	22 (57.9)	7 (17.5)
PFS 2		
Median in months (95% CI)[g]	NE	22.0 (13.4, NE)
Hazard ratio (95% CI)[c]	0.37 (0.19, 0.73)	
Probability of PFS2 at 24 months (95% CI)[d]	76.6 (61.4, 86.5)	48.3 (34.7, 60.6)

CI: Confidence interval; NA = not applicable; NE = not estimable
[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] By Kaplan-Meier method.
[e] Assessed by investigator according to RECIST v1.1.
[f] For patients with a partial or complete response.
[g] By Brookmeyer and Crowley method.

Figure 1: Kaplan-Meier curve of progression-free survival per investigator assessment in patients with dMMR/MSI-H EC (RUBY study)



5.2 Pharmacokinetic properties

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

Dostarlimab monotherapy or in combination with chemotherapy was characterised using population PK analysis from 869 patients with various solid tumours, including 546 patients with EC. When dosed at the recommended therapeutic dose for monotherapy (500 mg administered intravenously every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks), or at the recommended therapeutic dose for combination with chemotherapy (500 mg administered intravenously every 3 weeks for 6 doses, followed by 1,000 mg every 6 weeks), dostarlimab shows an approximate two-fold accumulation (C_{min}), consistent with the terminal half-life ($t_{1/2}$). The exposure of dostarlimab as monotherapy and/or in combination with chemotherapy was similar.

Absorption

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

Distribution

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

Biotransformation

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

Elimination

The mean clearance is 0.007 L/h (CV% of 30.2%) at steady state. The $t_{1/2}$ at steady state is 23.2 days (CV% of 20.8%).

Dostarlimab clearance was estimated to be 7.8% lower when dostarlimab was given in combination with chemotherapy. There was no meaningful impact 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 [$AUC_{0\text{-}inf}$]) was approximately dose proportional.

Pharmacokinetic/pharmacodynamic relationship

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

Special populations

A population PK analysis of the patient data indicates that there are no clinically important effects of age (range: 24 to 86 years), gender or race, ethnicity, or tumour type on the clearance of dostarlimab.

Renal impairment

Renal impairment was evaluated based on the estimated creatinine clearance [CL_{CR} mL/min] (normal: CL_{CR} ≥90 mL/min, n = 305; mild: CL_{CR} = 60-89 mL/min, n = 397; moderate: CL_{CR} = 30-59 mL/min, n = 164; severe: CL_{CR} = 15-29 mL/min, n = 3 and ESRD: CL_{CR} <15 mL/min, n = 1). The effect of renal impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of dostarlimab were found between patients with mild or moderate renal impairment and patients with normal renal function. There are limited data in patients with severe renal impairment.

Hepatic impairment

Hepatic impairment was evaluated as defined using the US National Cancer Institute criteria of hepatic dysfunction by total bilirubin and AST (Normal: total bilirubin (TB) & AST < = upper limit of normal (ULN), n = 772; mild: TB > ULN to 1.5 ULN or AST > ULN, n = 92; and moderate: TB > 1.5-3 ULN, any AST, n = 5). The effect of hepatic impairment on the clearance of dostarlimab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment compared to patients with normal hepatic function. No clinically important differences in the clearance of dostarlimab were found between patients with mild hepatic impairment and normal hepatic function. There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on repeat-dose toxicity studies of duration up to 3 months in the cynomolgus monkey. No studies have been performed to assess the potential of dostarlimab for carcinogenicity or genotoxicity. Animal reproduction and development toxicity studies have not been conducted with dostarlimab. Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of dostarlimab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

No notable effects on the male and female reproductive organs were observed in monkeys in the 1-month and 3-month repeat-dose toxicology studies; however, these results may not be representative at all of the potential clinical risk because of the immaturity of the reproductive system of animals used in the studies. Therefore, fertility toxicity remains unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate dihydrate

Citric acid monohydrate

L-arginine hydrochloride

Sodium chloride

Polysorbate 80

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years

After dilution

If not used immediately, chemical, and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C and 6 hours at room temperature (up to 25°C) from the time of preparation/dilution until the end of administration.

6.4 Special precautions for storage

Store in a refrigerator 2°C – 8°C.

Do not freeze.

Store in the original package to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation/dilution

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

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

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

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

For the 1,000 mg dose, withdraw 10 mL of dostarlimab from each of two vials (withdraw 20 mL total) and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, or glucose 50 mg/mL (5%) solution for injection. The final concentration of the diluted solution should be between

2 mg/mL and 10 mg/mL. This may require withdrawing a volume of diluent from the IV bag prior to adding a volume of dostarlimab into the intravenous bag.

- For example, if preparing a 1,000 mg dose in a 500 mL diluent intravenous bag, to achieve a 2 mg/mL concentration would require withdrawing 20 mL of diluent from the 500 mL intravenous bag. Then, 10 mL of dostarlimab would be withdrawn from each of two vials, totalling 20 mL, and transferred into the intravenous bag.

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

Storage

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

- At room temperature up to 25°C for no more than 6 hours from the time of dilution until the end of infusion.
- Under refrigeration at 2°C to 8°C for no more than 24 hours from time of dilution until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Administration

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

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

Do not co-administer other medicinal products through the same infusion line.

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

7. SCIENTIFIC OPINION HOLDER

GlaxoSmithKline UK Limited

980 Great West Road, Brentford

Middlesex TW8 9GS

United Kingdom

8. EAMS NUMBER(S)

52719/0001

9. DATE OF SCIENTIFIC OPINION

29/06/2023

Additional information

Physicians or pharmacists (HCPs) interested in enrolling a patient in the Dostarlimab EAMS must first contact ukeams.request@gsk.com to begin the registration process.

Registered HCPs will be able to access documentation for the Dostarlimab EAMS and submit the necessary information for each individual patient in an electronic Patient Access Form (ePAF). The following documents will be made available to HCPs via the Inceptua IMAP portal (https://portal.inceptua.com/#/login):

- Dostarlimab EAMS – Real World Data Collection Protocol
- Dostarlimab EAMS – Treatment Protocol – Information for Healthcare Professionals (HCPs)
- Dostarlimab EAMS – Treatment Protocol – Information for Patients
- Dostarlimab EAMS – Treatment Protocol – Information on the Pharmacovigilance (PV) System and requirements for reporting safety data
- Dostarlimab EAMS – Adverse Event (AE) Report Form and Pregnancy Notification Form
- Dostarlimab EAMS – Patient Information and Consent Form (ICF)
- Dostarlimab EAMS – Patient Alert Card

Reporting adverse events (AEs) after administration of the medicinal product is mandatory within the EAMS. Prescribers will be provided with guidance on reporting Adverse Events.

CONTACT INFORMATION:

Email ukeams.request@gsk.com

Tel: 0800 221 441