Medicines & Healthcare products Regulatory Agency

Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Dostarlimab 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.

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The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising unlicensed medicines to UK patients that have a high unmet clinical need. A positive scientific opinion is only issued by the MHRA if the criteria for the EAMS are fulfilled, which includes demonstrating a positive benefit risk balance (quality, safety and efficacy assessment) and the ability of the pharmaceutical company to supply a medicine according to a consistent quality standard.

EAMS medicines are unlicensed medicines. The term 'unlicensed medicine' is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. GMC guidance on prescribing unlicensed medicines can be found below:

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines

The opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a licensed indication or a future commitment by the MHRA to licence such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. 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.

EAMS procedural assessment at the MHRA

A full assessment of the quality, safety and efficacy of dostarlimab has been conducted by the MHRA's assessment teams, including pharmacists, toxicologists, statisticians, pharmacokinetic and medical assessors. This assessment process also includes consideration of the quality, safety and efficacy aspects by the UK independent expert committees including Expert Advisory Groups (EAGs) and the Commission on Human Medicines (CHM):

- The Commission on Human Medicines (CHM) advises ministers on the quality, safety and efficacy of medicinal products. The Chair and Commissioners are appointed in accordance with the Code of Practice for Ministerial Appointments to Public Bodies. The Chair and Commissioners follow a code of practice, in which they are precluded from holding personal interests. The Commission is supported in its work by Expert Advisory Groups (EAGs), covering various areas of medicine.

https://www.gov.uk/government/organisations/commission-on-human-medicines/about

- Chemistry, Pharmacy and Standards EAG, which advises the CHM on the quality in relation to safety and efficacy of medicinal products

  https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#chemistry-pharmacy-and-standards-eag

Pharmacovigilance system

A pharmacovigilance system for the fulfilment of pharmacovigilance tasks has been put in place for this EAMS medicine, including a risk management plan. As the safety profile of the EAMS medicine is not fully established it is particularly important that any harmful or unintended responses to EAMS medicines are reported. Healthcare professionals should be aware of their obligations to report adverse event information upon enrolment of any patients receiving EAMS medicines in the scheme. They will be required to follow the process which the pharmaceutical company which manufactures the EAMS medicine has in place to enable systematic collection of information on adverse events.

For more detailed information on this EAMS medicine, please refer to the Public Assessment Report, EAMS treatment protocol for healthcare professionals, EAMS treatment protocol for patients and EAMS treatment protocol for pharmacovigilance.

https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

Justification for the fulfilment of the EAMS criteria

There are four EAMS criteria that need to be fulfilled before a medicine can enter the scheme and a positive scientific opinion is issued by the MHRA. The fulfilment of the criteria for this particular medicine is described below.

1	**(a) Life threatening and seriously debilitating condition** In the UK, there are approximately 9,700 cases of endometrial cancer (EC) diagnosed annually (Cancer Research UK, 2022b) and of these, almost 2,900 patients are diagnosed with recurrent/advanced EC each year. Approximately 15-20% of patients will be diagnosed at advanced stages (FIGO Stage III or IV), at which point surgical cure is not possible. Only 47% of Stage IV patients survive one year compared to 99% of EC patients diagnosed at Stage I. Among the patients diagnosed and treated for earlier stages of EC, approximately 10-15% will experience disease recurrence, most recurrences occurring within 3 years of treatment. Recurrent EC is regarded as incurable disease with only 20% of patients surviving for five years or more, versus 89% of patients without disease recurrence. Primary advanced/recurrent EC is associated with a range of debilitating symptoms including periodic or continuous vaginal bleeding, pain in the lower back or pelvic region, blood in the urine, abdominal distension, early satiety, change in bowel or bladder function and pain during intercourse. Quality of life may be impacted by menopausal-like symptoms, impaired sexual function, anxiety/depression, and lasting adverse effects associated with chemotherapy. **(b) High unmet need: there is no method available/approved medicinal product or existing methods/licensed medicines have serious limitations** Currently, no systemic anticancer therapy is specifically licensed for use in the front-line treatment of primary advanced or recurrent EC. Platinum-based chemotherapy is recommended in guidelines (BGCS, 2021; Oaknin et al., 2022a) and considered a standard of care in the UK, with the most common

	regimen being carboplatin plus paclitaxel. However, survival outcomes associated with carboplatin-paclitaxel can be considered suboptimal. This is illustrated by a recent study of health outcomes experienced by patients with primary advanced or recurrent EC in England, where the majority of patients (77.8% [n=1,824]) in a cohort of patients eligible for immune checkpoint inhibitor (ICI) trials (n=2,345) received carboplatin-paclitaxel. Median OS from initiation of first-line carboplatin paclitaxel in absence of radiation therapy or other treatments in this ICI cohort (n=902) was 17.2 months (95% confidence interval [CI], 15.5 to 19.0) (Russo Garces, 2023). A study of patients with primary advanced or recurrent EC found that of those patients progressing on first line systemic chemotherapy, only 30% went on to receive second-line or further chemotherapy (Knott et al., 2021). Outcomes for patients receiving second line treatment have been historically dire with response rates of only 10-15% (Concin et al., 2021) and short survival (median OS of 10.3 months from initiation of second-line treatment, and only 1 in 5 [21%] of patients surviving ≥2 years) (Heffernan et al., 2022).
2	**The medicinal product offers major advantage over existing methods in the UK** Significant clinical benefit of the combination of dostarlimab with carboplatin/paclitaxel followed by dostarlimab monotherapy has been shown in the phase 3 pivotal trial (RUBY) in comparison to a combination of placebo with carboplatin/paclitaxel followed by placebo. The trial enrolled adult patients with primary advanced (FIGO stage III or IV) and first recurrent EC with a low potential for cure by radiation therapy or surgery alone or in combination, including patients 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. A total of 118 patients were identified as being mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H). Results based on the first interim analysis of the RUBY study showed a major advantage in dMMR/MSI-H EC patients randomised to dostarlimab plus carboplatin-paclitaxel versus carboplatin-paclitaxel: - Median PFS: not reached versus 7.7 months, HR 0.28 (95% CI 0.16, 0.50) - Probability of OS at 24 months: 83.3% versus 58.7% - Objective response rate: 77.6% versus 69.0% - Median duration of response: not reached versus 5.4 months
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** 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. The safety profile of the combination of dostarlimab with the platinum regimen of carboplatin/paclitaxel is consistent with the known safety profile of each component

	and appears manageable allowing the conclusion that the risks are outweighed by the benefits. The most common adverse reactions 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 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. The most frequent immune related adverse reaction was hypothyroidism. Other immune related adverse reactions include arthralgia, infusion related reaction, hypersensitivity, rash, pruritus, increased liver enzymes (ALT and AST) and hyperthyroidism.
4	**The company is able to supply the product and to manufacture it to a consistent quality standard, including the presence of appropriate GMP certification.** The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP.