Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Avelumab is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy.

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 avelumab 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

- Clinical Trials, Biologicals and Vaccines EAG, which advises the CHM on the quality, safety and efficacy of medicinal products of biological or biotechnological origin https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#clinical-trials-biologicals-and-vaccines-eag

- Oncology and Haematology EAG, which advises the CHM on the safety, quality and efficacy of medicines used in the treatment of malignant disease or blood disorders. https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#oncology-and-haematology-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 condition** Data from the UK indicate that the 5-year survival rate is 4.7% for Stage IV urothelial carcinoma. Stage IV urothelial carcinoma equates to the target population of adult patients with locally advanced or metastatic urothelial carcinoma (UC). **(b) High unmet need: no approved medicinal product** The goal of treatment for patients with advanced UC is to prevent disease progression, maintain health-related quality of life (HRQoL), provide relief from cancer symptoms and extend life. In the UK, platinum-based chemotherapy (usually 4-6 cycles of gemcitabine + cisplatin or gemcitabine + carboplatin) is standard of care for 1st line advanced UC. Median progression-free survival (PFS) and median overall survival (OS) in clinical studies of platinum-based chemotherapy are reported as 5.8–9.9 months and 5.2–20.2 months, respectively. There are no approved medicines for maintenance treatment of advanced UC following first-line chemotherapy. Therefore, there is a high unmet need for maintenance treatments to prevent disease progression, maintain HRQoL, provide relief from cancer symptoms and extend life.
2	**The medicinal product offers major advantage over existing methods in the UK** The EAMS Scientific Opinion is supported by clinical efficacy and safety data from a randomised, controlled, multi-centre, open-label study (JAVELIN Bladder 100) of 700 patients with locally advanced or metastatic UC. Eligible patients had received first-line platinum-based chemotherapy (last dose 4 to 10 weeks ago) with no radiological evidence of progression after chemotherapy. Eligible patients were randomised 1:1 to avelumab (10 mg/kg by IV infusion every 2 weeks) + best supportive care (BSC) or BSC alone. A dose of 10 mg/kg is pharmacokinetically comparable to the 800 mg flat dose proposed for the EAMS. The control arm approximated to existing methods in the UK to treat the target population. Median overall survival (95% CI) was 21.4 (18.9, 26.1) months in the avelumab + BSC arm and 14.3 (12.9, 17.9) months in the BSC alone arm, a gain of 7.1 months. The hazard ratio was 0.69 (95% CI: 0.556, 0.863; p=0.001). This translated into a 12-month overall survival rate (95% CI) of 71% (66, 76) and 58% (53, 64), for avelumab + BSC and BSC alone, respectively. The overall survival outcome was supported by a progression-free survival hazard ratio of 0.62 (95% CI: 0.519, 0.751; p<0.0001). Based

	on patient-reported outcomes, there was no evidence of a detrimental effect on bladder cancer symptoms, functioning, health status and HRQoL. The benefit of avelumab is considered clinically relevant and constitutes a major advantage over existing methods in the UK.
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 clinical safety data in patients with advanced UC were consistent with the known safety profile of avelumab. The commonest adverse drug reactions (ADRs) in the avelumab study arm were fatigue, pruritis, urinary tract infection, diarrhoea, arthralgia, asthenia, constipation, back pain and nausea. Infusion-related reactions were reported by 22% of the avelumab study arm, including 3 patients (0.9%) with severe reactions. Immune-related adverse events (irAEs) were reported by 29% of subjects in the avelumab study arm, including 5% with serious irAEs. The pattern of immune-related ADRs was consistent with the known safety profile of avelumab. Discontinuation due to an adverse event was reported for 12% of subjects in the avelumab study arm. The commonest reason was infusion-related reaction. No major new concerns are raised. The risks associated with avelumab are generally manageable and do not outweigh the benefits, which include a clinically relevant increase in overall survival.
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.