Medicines & Healthcare products Regulatory Agency

MHRA

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Information for Medical Directors

Regarding EAMS scientific opinion for
nivolumab as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based 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 [product INN or code number] 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. Physicians 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** Oesophageal cancer is relatively rare in the UK (8,919 new diagnoses in 2014) and 70-80% of patients are diagnosed at an advanced stage III or IV with around 40% diagnosed at metastatic stage. Survival rates are very poor with only around 12% of patients surviving for 10 years or more. Survival is even worse in the metastatic setting with less than 5% surviving 5 years after diagnosis. Oesophageal cancer typically presents in two forms: squamous cell carcinoma (SCC), which accounts for around a quarter of diagnoses, and adenocarcinoma, which accounts for more than half of cases in the UK. Risk factors for oesophageal cancer include advanced age, male gender and genetics; however, the majority of oesophageal cancer cases are linked to lifestyle factors such as smoking, alcohol consumption and diet. Advanced oesophageal cancer has a major impact on the patient's quality of life, as well as that of carers and other family members. Factors affecting the quality of life include the stage and location (where quality of life is lowest for metastatic oesophageal cancer), extent of weight loss and whether the patient experiences dysphagia. **(b) High unmet need: existing methods/licensed medicines have serious limitations** Patients with unresectable locally advanced, locally recurrent or metastatic disease should receive palliative treatment with systemic chemotherapy, local tumour treatment including stenting or palliative radiotherapy and/or best supportive care (BSC).

	In first-line (1L) therapy, two-drug cytotoxic regimens are preferred because of lower toxicity: fluoropyrimidine or fluorouracil modifications and cisplatin, fluoropyrimidine and oxaliplatin or docetaxel. Second-line (2L) treatment is dependent on prior therapy and performance status (PS) with taxane or irinotecan monotherapy being the preferred regimens. Further treatment depends on PS and availability of clinical trials; there is currently no evidence to support any specific regimen after platinum doublet and single agent chemotherapy. European Society for Medical Oncology guidelines highlight that for the SCC subset, the value of palliative chemotherapy is less proved, in 1L cisplatin-based combination showed increased response rate but no survival advantage. In second line, BSC or palliative taxane monotherapy should be considered. When choosing palliative chemotherapy for patients with incurable OC, the primary aim is about maximising quality of life. Beyond 1L treatment, the quality of life is likely to deteriorate; cancer-induced complications are likely to increase and follow-up should focus on symptoms (dysphagia, bleeding and nausea/vomiting), nutrition and psychological support. BSC include local radiotherapy for pain, bleeding or dysphagia and stent placement for dysphagia and other medication for nausea/vomiting. In conclusion, there is no medicine licensed for the treatment of unresectable locally advanced, locally recurrent or metastatic disease and patients receive BSC or palliative chemotherapy with a taxane (about half of the patients), which allows for median survival < 1 year. These modest benefits are associated with significant haematological, gastrointestinal, and neurological toxicities leading to frequent treatment interruptions, delays, and dose reductions, further limiting the benefit of chemotherapy whilst still negatively impacting quality of life. Therefore, there is a high unmet need in this clinical setting.
2	**The medicinal product offers major advantage over existing methods in the UK** In a comparative confirmatory trial which mainly enrolled Asian patients, a total of 419 subjects was randomised to receive either nivolumab 240 mg administered intravenously over 30 minutes every 2 weeks (n=210) or investigator's choice of taxane chemotherapy: either docetaxel (n=65) 75 mg/m^2 intravenously every 3 weeks, or paclitaxel (n=144) 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off. Compared to taxanes, nivolumab prolonged median overall survival (OS) by 2.5 months, which is clinically and statistically meaningful ($p < 0.02$ by stratified log-rank test). After 12 months, the difference in OS rate was 12.5% (46.9% vs 34.4%) and 10% after 18 months (30.5% vs 20.7%). Despite no difference between treatments in the other main outcomes (best overall response and progression-free survival [PFS]), the duration of response and long-term PFS rates were numerically higher with nivolumab. In conclusion, nivolumab offers advantage over existing methods since there is no medicine licensed in this clinical setting and nivolumab showed significant survival benefit over the most commonly used chemotherapy.

3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** In the clinical trial previously mentioned, the most frequent (incidence ≥10%) adverse drug reactions (ADRs) were rash and diarrhoea. Other common ADRs were hypothyroidism, pruritus, decreased appetite, fatigue and pyrexia. Immune-related adverse reactions, e.g., skin reactions, abnormal thyroid function tests, diarrhoea, pneumonitis/interstitial lung disease, were consistent with the known safety profile of nivolumab and accounted for most of the treatment discontinuations (9%). Furthermore, the overall safety profile of nivolumab compared favourably with the safety profile of taxanes. In conclusion, the safety profile of nivolumab is well known with immune-related adverse reactions that are usually manageable. The prolongation of overall survival outweighs these safety risks.
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 Good Manufacturing Practice.