Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM)

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 nivolumab in combination with ipilimumab 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 the EAMS medicines, including a risk management plan. As the safety profile of the EAMS medicines are 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 medicines has in place to enable systematic collection of information on adverse events.

For more detailed information on the EAMS medicines, 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** Mesothelioma is an aggressive cancer of the cell linings of various organs that is associated with occupational exposure to asbestos. Malignant pleural mesothelioma (MPM) is the most common of all mesotheliomas: 80% to 90% of cases are MPM. Diagnosis and screening for MPM is challenging as symptoms can often be non-specific, coupled with the approximately 40-year delayed onset of disease. MPM is often diagnosed at an advanced stage: approximately 40% of cases in the 2016-2018 UK audit were diagnosed at stage III/IV, and a high proportion were unstaged (35%). In the United Kingdom (UK) in 2017, MPM accounted for <1% of all new cancer cases of lung cancer. UK registry data from 2015-2017 show there were 2,727 new cases and 2,490 deaths per year. The UK national mesothelioma audit from 2016-2018 showed low rates of survival: only 10% of patients with MPM were alive after ≥ 3 years and 40% after ≥1 year. There is a lack of reliable UK-wide survival statistics for MPM by stage due to lack of staging information; however, 1-year survival is highest for stage I (59%) and lowest for stage IV (30%). Registry data from 1990-2017 in the United States (US) show median overall survival (OS) for patients with MPM was 12 months at stage III/IV and 20 months at stage I. **(b) High unmet need: existing methods/licensed medicines have serious limitations** The only chemotherapy approved for the first-line treatment of MPM is a PDC regimen of pemetrexed in combination with cisplatin, administered intravenously every 3 weeks and is often not tolerated. As patients with MPM are often older at diagnosis, they can be too frail to receive systemic anticancer therapy or travel for treatment, and as a result, UK audit data show only 40% of patients received chemotherapy from 2016 to 2018. Clinical practice guidelines highlight the limited treatment options available in the UK for patients with MPM eligible for first-line systemic therapy. The British Thoracic Society 2018 MPM Guideline and the European Society for Medical Oncology 2015 guidelines for MPM both recommend PDC for first-line therapy as the only approved standard of care, using pemetrexed in combination with cisplatin (raltitrexed or carboplatin can be used as alternatives). Second-line treatment options are not

	defined, and therapies undergoing clinical trials are recommended above any other option. Treatment durations for second-line therapies are brief and survival is poor.
2	**The medicinal product offers major advantage over existing methods in the UK** The goals of treatment for MPM are to prolong survival and to maintain quality of life for as long as possible, while minimising the side effects of treatment. In the pivotal EMPHACIS trial, the pemetrexed and cisplatin combination demonstrated a median overall survival of 12.1 (95%CI: 10-14.4) compared to cisplatin alone (median OS of 9.3 months; 95%CI: 7.8-10.7). During the study, low-dose folic acid and vitamin B12 supplementation was introduced to patients' therapy to reduce toxicity. A subgroup analysis was performed on patients who received folic acid and vitamin B12 supplementation during the entire course of study therapy (fully supplemented). These patients had a median OS of 13.3 months (95%CI: 11.4-14.9). The use of nivolumab in combination with ipilimumab for MPM has been compared against standard chemotherapy, with pemetrexed in combination with cisplatin or carboplatin, in study CA209-743. The study showed a major benefit in terms of improvement in overall survival (OS) with the use of nivolumab in combination with ipilimumab. • Median OS: 18.1 (95% CI: 16.8, 21.5) months compared to 14.1 (95% CI: 12.5, 16.2) months with chemotherapy. • 24 month OS rate: 41% compared to 27% with chemotherapy. The improvement in overall survival was seen in both the epithelioid and non-epithelioid histology of malignant pleural mesothelioma. <u>Non-epithelioid Histology:</u> • Overall survival: 16.89 (95% CI: 11.83, 25.20) months compared to 8.80 (95% CI: 7.62, 11.76) months with chemotherapy. <u>Epithelioid Histology:</u> • Overall survival: 18.73 (95% CI: 17.05, 21.72) months compared to 16.23 (95% CI: 14.09, 19.15) months with 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 above mentioned MPM study (CA209-743), the most frequent adverse reactions (incidence ≥ 10%) for nivolumab in combination with ipilimumab were rash, fatigue, diarrhoea, pruritus, hypothyroidism and nausea. The majority of adverse reactions were mild to moderate (Grade 1 or 2). The safety profile of nivolumab in combination with ipilimumab is characterised by immune-related adverse reactions (irARs), i.e. adverse reactions observed during treatment with ipilimumab and/or nivolumab that are believed to have an immune-related aetiology consistent with the mechanism of action of these drugs. In study CA209-743, irARs reported included pneumonitis, diarrhoea/colitis, liver function test abnormalities, renal dysfunction, endocrinopathies (including thyroid disorders, hypophysitis, hypopituitarism and adrenal insufficiency) and rash. With appropriate medical therapy, irARs resolved in most cases. A proportion of irARs resulted in permanent discontinuation of treatment. For further information on adverse reactions (including irARs) reported in the MPM study CA209-743, please refer to the EAMS Treatment Protocol – Information for healthcare professionals which is available on the MHRA website.

	The potential adverse effects of nivolumab in combination with ipilimumab could be outweighed by the benefits seen in the overall study population with an improved 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 medicines are manufactured/packaged according to GMP.