Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for pemigatinib monotherapy indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

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 pemigatinib 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** Cholangiocarcinoma (CCA) is rare cancer in the UK with an approximate incidence of 3.58/100,000. CCA an aggressive disease with a poor prognosis. Approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease, and these patients have an estimated 5-year survival rate of ≤10%. **(b) High unmet need: there is no approved medicinal product** Second line, there are no approved therapies and no established standard of care for cholangiocarcinoma patients. FGFR2 rearrangements/fusions are found in approximately 10%–16% of all CCA patients, principally intrahepatic CCA. There are no authorised targeted therapies for patients with cholangiocarcinoma with FGFR2 fusion/ mutation in the UK. Options include further chemotherapy and radiotherapy. In the ABC-06 trial in advanced biliary cancer patients post cisplatin-gemcitabine chemotherapy, second line mFOLFOX chemotherapy with active supportive care (ASC) resulted in a median OS of 6.2 months, objective response rate (ORR) of 5% and median PFS of 4.0 months. Systematic literature reviews and retrospective data reviews of chemotherapy treatment in molecularly unselected patients with CCA reported objective response rates of 8 to 12%. Radioembolization is an option in patients with inoperable intrahepatic CCA. There are retrospective reports of a disease control rate (DCR) of 72-95% and median OS of 9.3-22 months with Y^{90} transarterial radioembolization. This procedure should be performed only in specialist centres with patients entered in a registry.
2	**The medicinal product offers major advantage over existing methods in the UK** No trials have prospectively assessed the efficacy of chemotherapy in FGFR2 altered CCA. Retrospective data review does not suggest that FGFR2 rearranged CCA has a superior response to first line chemotherapy compared to the molecularly unselected CCA population, although second line is more uncertain due to the small patient numbers. In the Phase 2 study in 107 patients with CCA with FGFR2 fusion or rearrangement, the objective response rate was 35.5% with 3 complete and 35 partial responders. The

	median duration of response was 9.1 months, with 24 (63%) patients responding for at least 6 months and 7 (18%) patients responding for at least 12 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** All of the patients in the Phase 2 study reported an adverse event; 64% of participants reported an adverse event that was at least Grade 3; 9% discontinued treatment due to adverse events; 14% had their dose of pemigatinib reduced and 42.5% had their treatment interrupted due to an adverse event. The most common adverse events were hyperphosphatemia, alopecia, diarrhoea, fatigue and dysgeusia. Most of these events were Grade 1 or 2 in severity. The most common Grade ≥3 adverse events were hypophosphatemia, arthralgia, hyponatremia, and stomatitis. Related to the mechanism of action of pemigatinib, retinal detachment occurred in 4.1% of patients in Phase 2 study, of which one event was Grade 3. Adverse events should be manageable with regular patient monitoring and associated risk minimisation measures. These include a low phosphate diet, phosphate binders, routine ophthalmic monitoring and advice for dose interruptions, reductions and, if needed, treatment discontinuation. Given the unmet medical need and paucity of other treatment options, the benefit of pemigatinib outweighs the potential adverse effects in the applied indication.
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.