Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Tepotinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.

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 Tepotinib 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** Lung cancer remains the leading cause of cancer death worldwide. The 2017 figures from the Office for National Statistics showed that lung cancer was the second most common malignancy for both men and women. Around 40,000 cases were diagnosed, accounting for about 13% of all cancers. It remained the fifth most common cause of death in England and Wales with a mortality rate of 65.8 per 100 000 in men and 46.1 per 100 000 in women. Non-small cell lung cancer (NSCLC) accounts for 85% of all diagnosed lung cancer cases. Most newly diagnosed NSCLC patients have advanced disease: the proportion of NSCLC patients with Stage IV disease at diagnosis differs from region to region and has been reported in the range of 47% to 55% and Stage III disease at diagnosis in the range of 25% to 30%. **(b) High unmet need: existing methods/licensed medicines have serious limitations** Patients with advanced NSCLC whose tumour has no actionable mutations suitable for the currently approved targeted therapies (ie. for EGFR, ALK and ROS-1 positive disease) only have the options of chemotherapy and/or immune checkpoint inhibitors (NICE guideline NG122, updated December 2020). There is currently no approved medicinal product that specifically targets NSCLC with *MET*ex14 skipping alterations in the UK. This mutation is detected with higher frequency in older patients who may not tolerate chemotherapy well. *MET*ex14 skipping is considered to be a strong primary oncogenic driver, as this alteration is almost mutually exclusive of other known oncogenic drivers such as EGFR, ALK, ROS1, BRAF, KRAS, ERBB2, and RET alterations.
2	**The medicinal product offers major advantage over existing methods in the UK**

	In the first-line setting, the efficacy results of tepotinib in patients with advanced NSCLC harbouring *MET*ex14 skipping alterations were: • ORR: 44.6% (95% CI: 32.3, 57.5) • Median DOR: 10.8 months (95% CI: 6.9, not estimable) • Median PFS: 8.5 months (95% CI: 5.5, 11.3) • Median OS: 16.3 months (95% CI: 9.7, 29.7) In the second-line setting and beyond, the results were: • ORR: 45.7% (95% CI: 34.6, 57.1) • Median DOR: 11.1 months (95% CI: 9.5, 18.5) • Median PFS: 10.9 months (95% CI: 8.2, 12.7) • Median OS: 19.7 months (95% CI: 15.0, 21.0) Although there is no head-to-head comparison of tepotinib with standard of care, indirect comparisons indicate that tepotinib is more efficacious than available therapies in the second-line setting and beyond. In the first-line setting, tepotinib has similar efficacy to available therapies, but it offers the convenience of being orally administered. Prior to initiation of treatment with tepotinib the presence of *MET*ex14 skipping alterations should be confirmed by a test method using nucleic acids isolated from either tumour or plasma specimens.
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 most frequent treatment-emergent adverse events of tepotinib irrespective of causality were: • Oedema (peripheral oedema, generalised oedema, localised oedema) • Fatigue • Digestive symptoms (nausea, vomiting, diarrhoea, constipation, abdominal pain) • Musculoskeletal pain • Respiratory symptoms (dyspnoea, cough, pleural effusion) The adverse reactions considered causally related were interstitial lung disease/pneumonitis, oedema, fatigue, hypoalbuminaemia, nausea, vomiting, diarrhoea, constipation, abdominal pain, increased liver enzymes, increased creatinine, increased amylase and increased lipase. Around 20% of patients discontinued tepotinib due to an adverse event, mainly oedema. Overall, adverse reactions were manageable with dose interruption and dose modification. Therefore, the benefit/risk is considered positive.
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.