



MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for Doxecitine and Doxribtimine indicated for treatment of paediatric and adult patients with thymidine kinase 2 deficiency (TK2d) with an age of symptom onset on or before 12 years.

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. 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	<p>(a) Life threatening and seriously debilitating condition TK2 deficiency (TK2d) is a life-threatening and seriously debilitating inherited mitochondrial disease. It causes progressive muscle weakness, loss of motor function, respiratory insufficiency, feeding difficulties and premature death. Untreated patients experience substantial morbidity and mortality, with more than half of patients with symptom onset at or before 12 years of age dying within 10 years of symptom onset. The disease is relentlessly progressive and is not typically associated with spontaneous improvement.</p> <p>(b) High unmet need: there is no method available/approved medicinal product TK2 deficiency (TK2d) is associated with a high unmet medical need because there are currently no approved medicines that treat the underlying cause of the disease. Existing management is limited to supportive care, including ventilatory support, feeding support, mobility aids, physiotherapy and multidisciplinary specialist care. These interventions may help manage symptoms and complications but do not prevent disease progression or address the underlying mitochondrial DNA defect responsible for the condition.</p>
2	<p>The medicinal product offers major advantage over existing methods in the UK Doxecitine and Doxribtimine has been given a positive Early Access to Medicines Scientific Opinion because clinical studies suggest that it may provide a meaningful benefit for patients with TK2d whose symptoms started at or before 12 years of age. In the main analysis, none of the 39 treated patients died during follow-up, compared with 53 of 93 untreated patients in a matched comparison group. Treatment was also associated with stabilisation or improvement in important aspects of the disease, including movement, breathing and feeding abilities. Unlike current supportive care, Doxecitine and Doxribtimine is designed to address the underlying disease process by helping restore mitochondrial DNA levels. Clinical data suggest that treatment may reduce the risk of death, help patients maintain or regain physical abilities and slow the progression of the disease.</p>
3	<p>The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance The benefits observed in studies were considered to outweigh the known and potential risks, which mainly include diarrhoea, vomiting, abdominal pain and changes in liver blood tests that can be monitored during treatment.</p>

4	<p>The company is able to supply the product and to manufacture it to a consistent quality standard, including the presence of appropriate GMP certification.</p> <p>The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP.</p>
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