Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Dupilumab in the treatment of children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy and where existing therapies are not advisable

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	**(a) Seriously debilitating condition** Atopic dermatitis ("eczema") is the commonest childhood inflammatory skin disease and in its severest form has marked effects on a child's psychosocial wellbeing. Severe atopic eczema in children is characterized by intractable severe pruritus and disfiguring skin lesions, leading to sleep loss, impact on education and social consequences for the child and their family. In severe cases even young children can become depressed and exhibit suicidal ideation. **(b) High unmet need: existing methods/licensed medicines have serious limitations** Topical treatment (corticosteroids and/or calcineurin inhibitors) are the mainstay of treatment for mild to moderate atopic dermatitis in children, as in adults. However, topical treatments have limited usefulness on their own in severe disease and the risks of topical corticosteroids (e.g. growth suppression, adrenal axis suppression, skin atrophy) are higher in children. In severe disease topical treatments generally need to be stepped up to systemic therapy but there are no licensed systemic treatment options for severe atopic dermatitis in the age group 6 – 11 years. Systemic corticosteroids, with the attendant risks of long term use, or other non-selective systemic immunosuppressants including ciclosporin, azathioprine, methotrexate and mycophenolate, that have a range of potential serious toxicities, are sometimes used off-licence to treat the most severe cases. There is an understandable reluctance to use unlicensed treatments with significant toxicities and immunosuppressant risk in young children.
2	**The medicinal product offers major advantage over existing methods in the UK** Dupilumab is a highly targeted immunomodulator that selectively inhibits the immune and cytokine response involved in atopy and atopy-driven inflammation. As such it is not expected to share the risks associated with broad spectrum immunosuppressants and this is borne out the safety data. The pivotal 16 week efficacy and safety study submitted to support the extension of the indication of severe atopic dermatitis to children 6 to 11 years of age has clearly

	demonstrated statistically significant and clinically relevant efficacy benefit for dupilumab over placebo. All patients were allowed topical corticosteroids as background treatment, as necessary. There was evidence of steroid-sparing in dupilumab-treated patients. Dupilumab, in a pre-filled syringe, is given by subcutaneous injection every 2 or 4 weeks (for the majority of this age group it will be given 4 weekly). After the initial treatment phase, it can be administered by the patient or carer at home, after appropriate training, as for older patients. At present, the only systemic therapies available for patients in this age group with severe atopic dermatitis are unlicensed broad spectrum immunosuppressant treatments that have significant toxicities and also present a risk of infection and malignancy. Dupilumab demonstrates clear and meaningful improvement in efficacy and is overall well tolerated. As such, it represents a significant treatment advance for this patient population.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** Efficacy benefit has been clearly demonstrated with evidence of meaningful improvement in quality of life. Although long term safety data in this population are still limited, 115 patients in this age group have received dupilumab for periods of one year or more, albeit not all at the recommended posology. The safety data that are available suggest an overall low incidence of adverse reactions most of which are mild. There is no overall increase in the rate of viral, bacterial or fungal infections, consistent with an absence of broad spectrum immunosuppressant action. An increased risk of helminth (threadworm) infection has been detected in children, consistent with selective suppression of the Th2 arm of the immune response. A theoretical risk of other parasitic infestations such as strongyloides also exists. The Applicant conducted a full evaluation of potential risk to patients receiving dupilumab from COVID-19. On the basis of the available evidence, dupilumab is not considered to present an increased risk to patients of contracting or recovery from COVID-19. Guidance documents have been issued by NICE, the British Association of Dermatology and the European Task Force on Atopic Dermatitis. The advice is that well-controlled atopic dermatitis patients on immunosuppressant therapy should shield only if other risks exist. It is also acknowledged within published clinical practice guidance that dupilumab treatment may present a lower risk from COVID-19 than broad spectrum immunosuppressants although this is theoretical only. Measures proposed by the Applicant to ensure there is no increased risk to patient safety by the implementation of early access to dupilumab during the COVID-19 pandemic, are in line with government guidance to minimise risk to the patient and to limit burden on the healthcare systems. Dupilumab can be administered by the patient or carer at home, after appropriate training. Home delivery of EAMS product will be implemented in a way that maintains cold chain supply. Warnings have been implemented in the product information in relation to the potential for development of dry eye in patients receiving dupilumab. “Dry eye” has been included as a preferred adverse drug reaction term and the treatment protocols advise use of lubricant eye drops if symptoms develop and ophthalmological referral as necessary. These are considered sufficient to minimise risk.
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.