Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for
Risankizumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant or contraindicated to tumour necrosis factor-alpha (TNFα) antagonist therapies, vedolizumab and ustekinumab and for the treatment of adolescent patients aged 16 to 17 years with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant or contraindicated to TNFα antagonist therapies.

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 risankizumab 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** Crohn's disease is a serious debilitating chronic inflammatory bowel disease that is characterised by transmural mucosal inflammation and ulceration of any part of the gastrointestinal tract. It has a progressive and destructive course that leads to strictures, which causes complications such as obstruction, fistula formation and perforation that leads to surgery. Currently there is no cure for Crohn's disease and the aim of medical treatment in Crohn's disease has been focused on controlling inflammation, reducing symptoms, and minimising surgery to preserve intestinal luminal length. Whilst surgical rates have decreased over time in the era of biological therapies, surgery is still required in significant proportion of patients with Crohn's disease. Moderate to severe disease activity is associated with a substantial impact on quality of life, work productivity impairment and an increased number of surgeries and hospitalisations. Evolution of treatment goals to reduce complications of steroids and uncontrolled disease efficacy from medical therapy has been highlighted by inflammatory bowel disease patients as the most important treatment goal, including the reduction in abdominal pain and rapid cessation of symptoms. The burden of Crohn's disease is also related to the adverse effects of the currently available treatments; the over-use of, and/or reliance on corticosteroids to manage disease activity poses a significant problem particularly when used excessively. The treatment goals of Crohn's disease have evolved over time from symptom relief to clinical remission with mucosal healing. The key driver has been to achieve greater disease control and ultimately prevent cumulative bowel wall damage, which leads to disease complications and surgery as described above.

	(b) High unmet need: licensed medicines have serious limitations TNFα antagonist Therapy TNFα antagonist therapy is the most common first line biologic used in moderate to severe Crohn's disease patients in the UK, yet not all patients will respond, with primary non-response being reported to occur in 10% to 40%. In those Crohn's disease patients who initially respond to TNFα antagonist therapy, secondary loss of response has been reported as high as 50% of patients after 12 months on therapy, which will prompt either dose intensification, discontinuation of treatment or switching to another TNFα antagonist therapy. In addition, there is also a cohort of Crohn's disease patients who will be intolerant to anti-TNF with the occurrence of adverse events or either have a contra-indication to the use of TNFα antagonist therapies or be considered clinically inappropriate to be commenced on TNFα antagonist therapy. Interleukin 12/23 Therapy Interleukin 12/23 therapy is used either as a second- or third-line biologic. Ustekinumab is currently the only licensed interleukin 12/23 therapy available to UK patients suffering from moderate to severe Crohn's disease. Whilst ustekinumab will offer some moderate to severe Crohn's disease patients a treatment that will induce and maintain clinical remission, phase III clinical trial data demonstrates that only 21% of TNFα antagonist experienced patients treated with ustekinumab will achieve clinical remission at week 8. Secondary loss of response to ustekinumab has been reported to be as frequent in 20% of patients within the IM-UNITI study (registry clinical trial study) and as high as 35% in real-world observational studies. Integrin α4β7 Antibody Vedolizumab offers patients a favourable safety profile, however, the serious limitations of rapid onset and efficacy of induction and maintenance of clinical remission leaves a significant proportion of Crohn's disease patients with an unmet need of achieving clinical remission, reduction in steroid burden and limit the risk of complications of disease. For these reasons, vedolizumab is commonly used as third-line therapy in Crohn's disease patients where all other biologic therapies have been exhausted. In addition to the slow onset, there are also limitations in efficacy, where only 26.6% percentage of TNFα antagonist experienced patients achieve clinical remission at week 10. A large unmet need remains in Crohn's disease patients achieving clinical remission due to the limitations that existing available medical therapies can offer.
2	**The medicinal product offers major advantage over existing methods in the UK** Risankizumab studies Subgroup analyses of subjects who had previously received and failed therapy with ustekinumab and vedolizumab, show that there is a benefit of Risankizumab treatment vs placebo, and therefore the major advantage in these patients is agreed. This patient group represents and area with unmet clinical need and an EAMS indication of use of Risankizumab in adult patients who have failed vedolizumab and ustekinumab is granted. Adolescents (16-17 years old) Currently the only advanced therapies that are approved for use in < 18-year-olds are

	TNFα antagonist therapies. Therefore, there is a significant unmet clinical need for approved therapies following TNFα antagonist therapy failure in patients aged between 16 to 17 years. The number of adolescents included in the pivotal studies was very small and evidence of efficacy and safety of risankizumab on this age group based on clinical data only is not possible. However, Risankizumab exposure in the limited number of adolescents studied were comparable to adults, this was confirmed using simulated exposures using the population PK model. Keeping in consideration the clinical need for an approved drug for adolescents and the PK modelling data, an indication for 16-17 years old with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant or contraindicated to TNFα antagonist therapies' is considered acceptable.
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 efficacy of risankizumab against placebo has been demonstrated in patients with Crohn's disease in both the induction and the maintenance studies. There is post - marketing data for risankizumab 150mg in patients affected by plaque psoriasis and psoriatic arthritis. The most reported adverse events were upper respiratory infections (very common) followed by headache, pruritus, injection site reactions, tinea infections and fatigue (common). For the Crohn's disease indication, doses up to 1200mg were investigated. The data collected didn't show any dose-related increase in adverse events. During the induction and maintenance studies the safety profile of risankizumab was generally consistent with its known safety profile of risankizumab. No new safety risks were observed. Clinical data on adolescents (16-17 years old) are limited (only 12 patients dosed). Risankizumab exposure in the limited number of adolescents studied were comparable to adults, this was confirmed using simulated exposures using the population PK model. No differences are expected from this age group and the adult population. Furthermore, proactive pharmacovigilance and monitoring of the experience of this population in the periodic safety update reports will be provided. In conclusion, the benefit/risk of risankizumab in the proposed indication 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.