Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Abrocitinib is indicated for the treatment of adult and adolescent patients with severe atopic dermatitis requiring treatment with systemic therapy and have had inadequate response or have lost response to approved systemic therapies, or those who are ineligible or intolerant of approved systemic 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 [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) Life threatening condition or seriously debilitating condition** Atopic Dermatitis (AD) is a chronic or chronically relapsing inflammatory skin condition characterised by severe itch, dry skin, and acute and chronic skin lesions that can involve extensive body surface areas. The prevalence of AD in the UK is estimated to be 2.5% in adults and 10.6% in adolescents. Atopic dermatitis can cause severe disfigurement and discomfort with profound social and psychological sequelae. Severe pruritus in AD is the most difficult symptom to control despite the use of AD treatments, is associated with sleep disturbances and other mental health problems like depression and anxiety, and in worst cases can be unrelenting. Pain has also been recognised as an important symptom in AD, and together with severe itch has been reported to be associated with poor Quality of Life. Severe comorbidities are commonly reported in patients with AD such as anxiety, depression, suicidal ideation, obesity, food allergies, asthma, and allergic rhinitis/rhinoconjunctivitis; these can also be seriously debilitating and negatively impact different areas of patient's daily life. Increased risk of neuropsychiatric disorders including suicidal ideation and behaviour has been well-documented in several studies in patients with severe AD. Severe atopic dermatitis is not a life-threatening condition but is a seriously debilitating condition. **(b) High unmet need: existing methods/licensed medicines have serious limitations** Topical treatments like corticosteroids and calcineurin inhibitors are widely used in the treatment of AD, however they are less effective in the severe form of the disease, and are associated with application site reactions and long-term safety issues. Patients who are not controlled on topical therapies are candidates for systemic therapies. Treatment with systemic corticosteroids are limited to short courses for the treatment of 'flares' primarily due to their side effect profile and risk of rebound or disease worsening after treatment discontinuation. Traditional immunosuppressants (e.g., methotrexate, azathioprine, and mycophenolate mofetil) are also used to treat severe AD, mostly outside of their licensed indications, except for cyclosporin which is approved for AD in adult patients. Limitations of immunosuppressants are well-known, mainly due to their long-term systemic toxicities, including risk of organ damage like nephrotoxicity and hepatotoxicity.

	Dupilumab, an IgG monoclonal antibody which blocks IL-4/IL-13 pathway, has been approved for the treatment of moderate and severe AD in adults and adolescents. Dupilumab was shown to have a positive benefit-risk with or without concomitant use of topical corticosteroids. It has been reported that a significant proportion of patients with 'severe' AD treated with dupilumab in the pivotal studies, did not achieve an adequate response (defined as an IGA score of 0 or 1 or as at least 75% improvement in lesions extent and severity – EASI 75) after 16 weeks of treatment. Baricitinib, a JAK-1/2 inhibitor, has also been very recently approved for the treatment of moderate and severe AD, and results in the wider moderate to severe population indicate that a significant proportion of patients do not achieve an adequate response. Therefore, there is a high unmet need in patients with severe AD, as a significant proportion of patients do not respond adequately to currently available treatments or in whom these treatments cannot be administered due to intolerability.
2	**The medicinal product offers major advantage over existing methods in the UK** Abrocitinib is an orally administered JAK inhibitor, with selectivity for JAK1 enzyme, that inhibits a broad array of cytokine signalling pathways known to have an important role in the pathophysiology of AD, including interleukin IL-4, IL-13 as well as IL-22, IL-31 and thymic stromal lymphopoietin. It offers a different mechanism of action compared to other systemic therapies approved for severe AD. In the broader moderate to severe AD population, which is the subject of an ongoing regulatory procedure, abrocitinib showed efficacy in patients with moderate to severe AD when used as a monotherapy (MONO-1 and -2 studies) and in combination with topical therapies in achieving treatment response in comparison to placebo (COMPARE study), as measured using two commonly used and clinically relevant outcomes (IGA and EASI-75 response). Improvement was also seen in other signs and symptoms of the disease. *IGA* The proportion of patients with IGA response at Week 12 was significantly higher with abrocitinib 100 mg (~24-28%) and abrocitinib 200 mg (~38-44%) compared to placebo (~8-9%) in the MONO studies. In the COMPARE study, the proportion of patients with IGA response was significantly higher with abrocitinib 100 mg (~37%) and abrocitinib 200 mg (~48%) compared to placebo (~14%). *EASI-75* The proportion of patients with EASI-75 response at Week 12 was significantly higher with abrocitinib 100 mg (~40-45%) and abrocitinib 200 mg (~61-63%) compared to placebo (~10-12%) in the MONO studies. In the COMPARE study the proportion of patients with EASI-75 response was significantly higher with abrocitinib 100 mg (~59%) and abrocitinib 200 mg (~70%) compared to placebo (27%). Results from additional post hoc efficacy analyses from Phase 3 data, primarily to evaluate if abrocitinib can offer treatment benefit in the EAMS relevant populations have been made available. These include results in subsets of patients i) who had severe AD at baseline ii) who had a documented history of insufficient response to cyclosporin or dupilumab at baseline iii) who were defined as dupilumab non-responders at the end of week 16 in COMPARE study (dupilumab was included as a comparator) and subsequently switched to abrocitinib in the long-term EXTEND study.

	In patients who had a severe disease at baseline, significantly greater response rates were observed with abrocitinib compared to placebo at Week 12 when used as a monotherapy (MONO-1 and -2 studies) or in combination with topical therapies. In the COMPARE study (which had dupilumab as a comparator arm) higher responder rates were observed with abrocitinib 200 mg compared to dupilumab in the severe subgroup of patients (p-values not calculated) after 16 weeks of treatment. The efficacy of abrocitinib 100 mg and dupilumab was similar in this subgroup. The results indicate that abrocitinib 200 mg may provide a higher probability of treatment response compared to dupilumab in patients with severe AD. In the subset of patients who had documented history of insufficient response to either cyclosporin or dupilumab prior to enrolment in the study, a significant proportion of patients showed treatment response after treatment with either doses of abrocitinib, especially in the presence of background topical therapy, although it is acknowledged that the number of patients who had documented history of insufficient response to dupilumab was very small. The most relevant evidence in the context of this EAMS application is from the post hoc analysis performed in patients who were defined as dupilumab non-responders at end of 16-week treatment period in the COMPARE study and subsequently were switched to receive abrocitinib in the long-term EXTEND study. A significant proportion of patients demonstrated a treatment response after receiving either dose of abrocitinib during the long-term extension study (EXTEND) for IGA (~34% with 100 mg and ~47% with 200 mg in patients who were IGA non-responders) and EASI-75 (~68% with 100 mg and 80% with 200 mg in patients who were EASI-75 non responders). The 16 weeks duration is consistent with dupilumab pivotal trials and it is recommended that discontinuation of dupilumab treatment should be considered in patients who have shown no response after 16 weeks. Although there was no difference in the responder rates in the severe subgroup of patients in COMPARE study between dupilumab and abrocitinib 100 mg, a significant proportion of dupilumab non-responders showed treatment response even after treatment with the lower abrocitinib dose. These results indicate that abrocitinib can benefit patients who may not benefit from dupilumab, and there is a possibility that these treatments may be more efficacious in different subsets of AD patients. In an indirect comparison of abrocitinib to baricitinib (Olumiant), that was recently approved for the treatment of moderate to severe AD, using data from the respective trials which employed similar key inclusion criteria, the response rates (IGA and EASI-75) appear to be greater with abrocitinib 100 mg and 200 mg compared to baricitinib 2 mg and 4 mg in both monotherapy as well as combination settings. Although some modest differences are noted in the baseline characteristics across the two sets of trials, the use of placebo-corrected response rates (all the trials included a placebo arm), especially in the studies which assessed the efficacy in combination with topical therapies, may to some extent minimise any potential impact of observed baseline differences. The placebo corrected rates also show favourable responder rates with abrocitinib 100 mg and 200 mg compared to baricitinib 2 mg and 4 mg on both the endpoints. These results collectively demonstrate that abrocitinib (100 mg and 200 mg once daily) offers major advantage over existing methods in the UK in the EAMS subgroup.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance**

	Abrocitinib has shown a safety profile broadly consistent with other JAK inhibitors. Some differences exist, presumably due to differences in the selectivity of target JAK enzymes, but overall, the pattern was consistent with that expected after JAK inhibition. Overall, both doses of abrocitinib were well tolerated in short- and long-term trials in patients 12 years and older. Most common ADRs reported in a dose related fashion were nausea, headache, acne, vomiting, upper abdominal pain, herpes simplex, blood creatine phosphokinase increase, and dizziness. Venous thromboembolism and serious/ opportunistic infections, including herpes zoster and erythema herpeticum, have been reported in abrocitinib treated patients. Dose dependent increases in LDL-cholesterol have also been observed. Confirmed absolute lymphocyte count < $0.5 \times 10^3/mm^3$ and platelet count < $50 \times 10^3/mm^3$ were seen in less than 0.5% of patients. These identified and potential risks could be adequately addressed in product information (HCP Treatment Protocol) and Risk Management Plan. The safety data in adolescents did not indicate any unique safety signals. Overall, the potential adverse effects of abrocitinib are outweighed by the benefits in the subgroup of AD patients, targeted in this EAMS indication, who have a high unmet need.
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.