Medicines & Healthcare products Regulatory Agency

MHRA

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Information for NHS Medical Directors

Regarding EAMS scientific opinion for

Asciminib indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) without T315I mutation previously treated with two or more tyrosine kinase inhibitors.

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 Asciminib 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 or seriously debilitating condition** Chronic myeloid leukaemia (CM)L is a tri-phasic disease, with patients presenting predominantly in a chronic phase (CP). Unless properly treated, the disease progresses through an accelerated phase (AP) which leads to an aggressive acute leukaemia, known as blast phase (BP), that has a dismal prognosis. Therefore, CML is a life-threatening condition. With the introduction of tyrosine kinase inhibitors (TKIs), the outcome in patients with CML-CP improved with overall survival (OS) in newly diagnosed patients after 5 years ranging between 85% and 95%. However, some patients may fail or become intolerant to front line TKI. The risk of progressing from CML-CP to AP or BP, increases with subsequent lines of treatment. Life expectancy of CML-CP in second and further lines of treatment is dramatically shorter compared with first line (e.g. in second-line, OS and progression-free survival (PFS) for dasatinib during 7 years of follow-up were 65% and 42%, respectively). In addition, intolerance to available TKIs remains a challenge and many patients require discontinuation. TKI therapy is considered for a majority of patients a lifelong treatment and quality of life is generally dictated by TKI-associated adverse events (AEs). **(b) High unmet need: existing methods/licensed medicines have serious limitations** Hydroxyurea or Interferon-Alpha have limited effect on BCR-ABL1 proliferative cells. Despite treatment with first generation of ATP-competitive TKI imatinib, some patients may fail to achieve an adequate response, will lose response to frontline therapy or can be intolerant to frontline TKI. Second-generation ATP-competitive TKIs (nilotinib, bosutinib, dasatinib) were developed with a greater inhibitory potency than imatinib, effective control of many kinase domain mutations, and different off-target profile. The third-generation ATP-competitive TKI ponatinib, displays activity against native and all single mutant forms of BCR-ABL1 including the T315I mutation. Primary or secondary resistance to TKIs is most commonly resulting from mutations affecting the ATP-binding site in BCR-ABL1 oncoprotein, thereby preventing activity of ATP-binding TKIs. Despite the current availability of ATP-binding TKIs, with each line of treatment

	with TKIs, failure rates increase. Intolerance to current available ATP-binding TKIs remains a challenge and although AEs may be managed by dose reductions or interruptions many patients require discontinuation. In the UK, resistance and intolerance are the two major reasons for switching treatment in the real-world setting. While a majority of patients in the UK receive imatinib in first line, and either nilotinib or dasatinib in second line, there is no standard of care in third and later lines of treatment. Allogeneic stem cell transplantation may be considered only in patients with resistance or intolerance to two or more TKIs that have good performance status and normal organ functions, and for whom an appropriate donor is available. .
2	**The medicinal product offers major advantage over existing methods in the UK** Imatinib is often used as first line treatment but some patients fail to achieve an adequate response, will lose response or become intolerant. Approximately one-third of patients no longer maintain therapy with imatinib after 5 years. Asciminib is not intended as first line treatment and has demonstrated efficacy in patients who have received at least two prior TKIs. The 2G ATP-competitive TKIs (nilotinib, bosutinib, dasatinib) have a greater target inhibitory potency than imatinib, effective control of many kinase domain mutations, and different off-target profile and all have demonstrated efficacy following prior intolerance or resistance to imatinib. Once patients have failed a 2G TKI, few consensus guidelines exist for subsequent therapy and the use of an alternative 2G TKI (nilotinib or dasatinib) in third and further lines of therapy does not result in a durable response. Asciminib is intended as third line treatment and beyond. It has demonstrated superior efficacy and improved safety profile over the 2G TKI bosutinib in study A2301. Whilst no direct comparison over dasatinib or nilotrinib is available it is reported in the literature that the use of an alternative 2G TKI (nilotinib or dasatinib) in third and further lines of therapy does not result in a durable response. Overall, it appears that asciminib could provide a major advantage as third line of treatment over dasatinib and nilotinib. The 3G ATP-competitive TKI ponatinib, displays activity against native and all single mutant forms of BCR-ABL1 including the T315I mutation. After treatment failure on a 2G TKI, ponatinib is an option but it is not recommended in case of existing cardiovascular risk factors (serious arterial occlusive adverse reactions occurred in 20% of patients in the phase II trial). Asciminib provides a major advantage over ponatinib in terms of a better safety profile. Allogeneic stem cell transplantation may be considered in patients with resistance or intolerance to two or more TKIs but it is only an option for patients with good performance status and normal organ functions, and with a donor available. All available current TKIs are associated with distinct safety profiles. For patients failing two lines of TKI, treatment selection from any remaining TKIs that may be used is complex, and it is limited by patients' comorbidities, emergence of mutations, and the safety profile of each TKI. Patients either failing or being intolerant to previous TKI may have limited sensitivity to the remaining available TKIs or comorbidities that prevent the use of specific TKIs. In contrast to imatinib, nilotinib, dasatinib, ponatinib, and bosutinib that bind within the ATP-binding site of the ABL kinase domain, asciminib is an allosteric inhibitor of ABL tyrosine kinase activity by binding to a myristoyl site on the kinase domain, which has only been identified on ABL1, ABL2, and BCR-ABL1. By not interacting with the ATP-

	binding site, asciminib maintains activity against cells expressing clinically observed ATP-binding TKI resistance mutations. Asciminib could in theory provide an advantage over other TKIs in terms of activity against ATP-binding TKI resistance mutations. The activity against the T3151 mutation has been shown although at higher doses than recommended. Overall, it can be concluded that for the proposed indication in CML-CP after at least 2 prior TKIs asciminib has shown a major advantage over all available existing methods.
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 safety profile of asciminib as monotherapy is based on data from 356 patients. The most common adverse reactions (treatment related adverse effects) of any grade were musculoskeletal pain (36.2%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (25.8%), headache (23.6%), increased pancreatic enzymes (21.3%), arthralgia (21.3%) and nausea (20.2%). The most common adverse reactions of ≥ grade 3 (incidence ≥5%) were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.4%), hypertension (8.4%) and anaemia (5.3%). Serious adverse reactions occurred in 12.4% of patients receiving asciminib. The most frequent serious adverse reactions were pleural effusion (2.5%), lower respiratory tract infections (2.2%), thrombocytopenia (1.7%), pyrexia (1.4%), pancreatitis (1.1%), non cardiac chest pain (1.1%) and vomiting (1.1%). Asciminib presents a manageable safety profile in heavily pre-treated patients with two or more prior ATP competitive TKIs. In the pivotal study A2301 the safety profile of asciminib appears more favourable than that of the approved TKI bosutinib. In conclusion, the toxicity associated with asciminib is outweighed by its benefits.
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.