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Information for Medical Directors

Regarding EAMS scientific opinion for

Atezolizumab, in combination with bevacizumab, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma who have received no prior systemic therapy

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 condition</p> <p>Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the eighth most common cause of cancer death in the UK representing 2% of new cancer cases. HCC accounted for 5,417 deaths in 2016 with 5,736 new cases diagnosed in the UK in 2015, with a current incidence rate of 9/100,000 people. In the UK, the overall age-standardised 1-year survival rates range from 34-39% with 5-year survival estimates ranging from 10-13%. Most cases in the UK develop in the presence of advanced chronic liver disease related to non-alcoholic fatty liver disease, excessive alcohol intake and viral hepatitis C / hepatitis B infection, along with other causes of chronic liver disease such as metabolic syndrome.</p> <p>HCC is a medically complex and difficult to treat disease as the majority (70-90%) of HCC patients have underlying liver cirrhosis requiring management of both the malignancy and underlying liver disease. It is a debilitating condition and serious and often life-threatening complications include hepatic vein occlusion and portal vein invasion and thrombosis, encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis. The prognosis for advanced stage HCC patients is typically very poor as the tumour has often grown or metastasised to the extent that surgical resection is not feasible. Due to the late appearance of symptoms, this is the case at first diagnosis for up to 80% of the large majority of patients suffering from cirrhosis. In addition, up to 70% of patients who initially undergo potentially curative procedures will have recurrent disease within 5 years.</p> <p>(b) High unmet need: existing methods/licensed medicines have serious limitations</p> <p>Patients with unresectable advanced HCC have few approved systemic treatments and most have significant liver damage which can further limit therapy options. Their prognosis is dismal, with rapid progression and short overall survival OS. In the UK (and worldwide) sorafenib is currently the first-line systemic treatment standard of care for unresectable HCC; lenvatinib is another option. For sorafenib, the current median overall survival ranges from ~12 to 14 months; however, no treatment has demonstrated a statistically significant and clinically meaningful improvement in overall</p>
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	<p>survival beyond sorafenib in over a decade. Both sorafenib and lenvatinib are associated with toxicities that impact patients' quality of life, with an overall modest benefit-risk ratio. Phase III studies of single agent PD-1 inhibitors in both first- and second-line HCC setting failed to meet overall survival primary endpoints. Therefore, there is an ongoing high unmet medical need to treat patients with unresectable HCC with novel combination treatments that have a more favourable benefit-risk profile.</p>
<p>2</p>	<p>The medicinal product offers major advantage over existing methods in the UK</p> <p>Major benefit in terms of progression free survival (PFS) and overall survival (OS) has been shown with the combination of atezolizumab and bevacizumab in the head-to-head comparison of the pivotal trial (IMbrave 150; 501 patients enrolled with locally advanced or metastatic HCC who had received no prior systemic therapy) in comparison to sorafenib, which is the current standard of care in this setting:</p> <ul style="list-style-type: none"> • Median PFS: 6.8 vs 4.3 months, HR 0.59 p-value <0.0001 • Median OS: Not reached vs 13.2 months, HR 0.58 p-value 0.0006 <p>Also considered a major advantage is the fact that, compared with sorafenib, treatment with atezolizumab + bevacizumab resulted in a clinically meaningful delay in median time to deterioration of patient-reported physical functioning, role functioning and global health status/quality of life.</p> <p>In conclusion, the combination of atezolizumab + bevacizumab in the treatment of adult patients with unresectable hepatocellular carcinoma who have received no prior systemic therapy offers major advantage over the current standard of care sorafenib.</p>
<p>3</p>	<p>The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance</p> <p>The safety profile of the combination of atezolizumab and bevacizumab was generally consistent with that seen with the individual treatments and/or underlying disease. One new adverse reaction, peripheral oedema, was observed with the combination. Thyroid disorders and infusion-related reactions were more common with the combination than with atezolizumab treatment alone.</p> <p>The most frequent adverse reactions of the combination in the pivotal trial, affecting at least 20% of patients were:</p> <ul style="list-style-type: none"> • hypertension (high blood pressure), • proteinuria (protein in the urine), • fatigue (tiredness) and • decreased appetite. <p>The most frequent serious adverse reactions were:</p> <ul style="list-style-type: none"> • pyrexia which affected 3% of patients • oesophageal varices haemorrhage which affected 2% of patients • gastrointestinal haemorrhage which affected 2% of patients <p>Approximately 15% of patients discontinued atezolizumab and/or bevacizumab due to an adverse event. The most common adverse reaction leading to treatment discontinuation was oesophageal varices haemorrhage (1.2%). Haemorrhage is a recognised adverse reaction with bevacizumab. All other adverse events leading to treatment discontinuation occurred in less than one percent of patients.</p>

	In conclusion, the potential adverse effects of atezolizumab + bevacizumab in the treatment of adult patients with unresectable hepatocellular carcinoma who have received no prior systemic therapy are outweighed by the 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.