Medicines & Healthcare products Regulatory Agency

MHRA

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**Information for NHS Medical Directors**

Regarding EAMS scientific opinion for lutetium ($^{177}$Lu) vipivotide tetraxetan for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes.

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 [lutetium ($^{177}$Lu) vipivotide tetraxetan] 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.

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| **1** | **(a) Life threatening or seriously debilitating condition**<br>Prostate cancer (PC) is the most common cancer among men in the United Kingdom (UK), with 48,588 cases diagnosed in 2017 (26% of all new male cancer diagnoses; age-standardised incidence of 80.7 per 100,000). Patients with early prostate cancer often have no apparent symptoms, and if present, symptoms may be inconsistent; therefore diagnosis may not occur until the disease is locally advanced or metastatic. Prostate cancer is the second most common cause of cancer death among men in the UK, with 11,890 deaths in 2018 (13% of all cancer deaths; age-standardised mortality of 45.9 per 100,000 males). While survival rates are high in patients with localised to locally advanced disease (Stages 1-3), prognosis worsens when patients progress to advanced/metastatic PC (Stage 4). One-year survival rates of 100% for those diagnosed at Stages 1–3, compared with 84-88% at Stage 4. Five-year survival rates of 96–100% for Stage 1–3 disease, compared with 39–49% for Stage 4 disease. Onset of castration-resistance increases the risk of death; patients with metastatic castration resistant PC (mCRPC) have an expected median overall survival of just 13-19 months, with a 5-year survival rate of 21–26%.<br><br>Expression of prostate-specific membrane antigen (PSMA) is an independent predictor of poor prognosis, with significantly shorter survival and a higher risk of disease recurrence reported in patients with high levels of PSMA expression.<br><br>In addition to the mortality burden, PC results in a significant negative impact on quality of life (QoL). QoL deteriorates further in more advanced cases and is particularly poor in patients with mCRPC.<br><br>**(b) High unmet need: there is no method available/approved medicinal product or existing methods/licensed medicines have serious limitations**<br>Androgen-deprivation therapy (ADT) is a standard treatment for prostate cancer (PC), used to lower androgen levels and slow growth or shrink tumours; in metastatic PC, it may be used with or without chemotherapy, to prolong survival, palliate symptoms and reduce the risk of potentially serious sequelae of advanced disease.<br><br>Following progression to metastatic, castration-resistant PC (mCRPC), patients may receive docetaxel, abiraterone, enzalutamide, cabazitaxel and/or radium-223 ($^{223}$Ra) |

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| | as first- or second line therapies. However, as mCRPC remains incurable, the treatment goals are to prolong life and improve quality of life (QoL).<br><br>Despite available treatments, outcomes for patients with advanced/metastatic PC remain poor, with five-year age-standardised survival rates of 39%–49% for Stage 4 disease, and just 5–26% for mCRPC.<br><br>Current treatments are particularly limited in their ability to treat visceral disease (present in 10–30% of patients with mCRPC), which is associated with significantly worse prognosis than non-visceral mCRPC. In addition to poor outcomes on a treatment-by-treatment basis, patients with mCRPC are limited to very few treatment options due to a lack of approved therapies, strict eligibility criteria and multiple reimbursement restrictions.<br><br>Taxane-based chemotherapy, anti-androgen hormone therapies and $^{223}$Ra are also associated with poor tolerability, with Grade 3–4 adverse events (AEs) reported in up to 66% of patients in Phase 3 studies. In particular, taxane-based chemotherapy is associated with high rates of Grade 3–4 haematological AEs, such as leukopenia and neutropenia. Due to the limitations in efficacy and safety of current treatments, there is an unmet need for additional mCRPC treatment options, with improved survival outcomes and tolerability. |
| **2** | **The medicinal product offers major advantage over existing methods in the UK**<br><br>The efficacy of $^{177}$Lu-PSMA-617 for the treatment of mCRPC is has been evaluated in the ongoing, Phase 3 PSMA-617-01 (VISION) study, a randomized, Phase III, international, prospective, open label, multicentre study to evaluate the efficacy and safety of $^{177}$Lu-PSMA-617 plus BSC/BSoC in patients with progressive PSMA-positive mCRPC. Subjects were adult male patients with confirmed prostate cancer with progressive, metastatic, castrate resistant disease; who had received at least one novel androgen axis drug (NAAD, i.e. abiraterone acetate or enzalutamide) and at least one but no more than 2 previous taxane-based chemotherapy regimens.<br>.<br>• Compared with standard of care (SoC) alone, $^{177}$Lu-PSMA-617 + SoC improved median overall survival (OS) by 4 months, with a statistically significant 38% risk reduction for death (hazard ratio [HR]: 0.62; one-sided p<0.001).<br>• Addition of $^{177}$Lu-PSMA-617 to SoC also extended median radiographic progression-free survival (rPFS) by 5.3 months, with a statistically significant 60% risk reduction in progression or death (HR: 0.40; one-sided p <0.001).<br>• All key secondary endpoints showed a statistically significant benefit:<br>o overall response rate (ORR) of 29.8% with a durable response,<br>o median duration of response (DoR) of 9.8 months,<br>o disease control rate (DCR) of 89.0%, and<br>o time to symptomatic skeletal event (SSE)- an estimated 50% reduction in the risk of an SSE or death when compared with BSC/BSoC only.<br>• PFS analyses showed an estimated 70% risk reduction of radiographic disease progression, clinical progression, PSA progression, or death in the $^{177}$Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR = 0.30; 95% CI: 0.24, 0.38). The median PFS was 5.9 months (95% CI: 5.2, 6.6) in the $^{177}$Lu-PSMA-617+BSC/BSoC arm vs. 2.4 months (95% CI: 2.2, 3.0) in the BSC/BSoC only arm.<br>• Compared to current available treatments in the , an improvement in overall survival was observed. In the historical comparisons an OS of around 10 months was observed in patients who had exhausted therapies available at the |

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| | time. A median overall survival of 15.3 months was measured with the use of $^{177}$Lu-PSMA-617 + SoC in the VISION study. |
| **3** | **The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance**<br><br>The safety profile of $^{177}$Lu-PSMA-617 treatment, based on the results from the 2 prospective clinical studies (PSMA-617-01 and PSMA-617-02), was as anticipated given its mechanism of action, and is generally consistent with previous literature reports of $^{177}$Lu-PSMA-617 in similar populations of patients with mCRPC.<br><br>Generally, the reported adverse events appeared to be predominantly grade 1 or 2 and most frequently reported as salivary gland, haematological, and gastrointestinal toxicities. While the grade $\geq$ 3 AEs were mainly restricted to haematological events, more adverse events were reported in patients receiving $^{177}$Lu-PSMA-617+BSC/BSoC (52.7%) vs. those receiving BSC/BSoC only (38.0%). The most frequent myelosuppression related adverse events were anaemia, thrombocytopenia, lymphopenia, leukopenia, and neutropenia, which may be attributed to the effects of ionizing radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic bone lesions, but which may also be impacted by bone marrow impairment at baseline from prior therapy. The most frequent non-hematologic adverse events with $^{177}$Lu-PSMA-617 treatment were fatigue, dry mouth, nausea, back pain, arthralgia, decreased appetite, constipation, vomiting, and diarrhoea. Most of these (except dry mouth) were nonspecific and attributable to the administration of therapeutic levels of a radioactive compound.<br><br>Overall, the data showed that adverse events were manageable and often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. The safety of $^{177}$Lu-PSMA-617+BSC/BSoC was also evaluated across relevant patient subgroups, and no unexpected differences were observed in any of the subgroups or between the two treatment arms.<br><br>Overall, a well-tolerated and manageable safety profile was demonstrated for $^{177}$Lu-PSMA-617 in proposed population of heavily pre-treated patients with progressive PSMA-positive mCRPC. |
| **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.**<br><br>The company has provided all documentation necessary to prove that the EAMS medicine is manufactured/packaged according to GMP. |