Medicines & Healthcare products Regulatory Agency

Information for NHS Medical Directors

Regarding EAMS scientific opinion for:

Glofitamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

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mhra.gov.uk

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** Diffuse Large B-Cell Lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) accounting for more than 30% of NHL cases and 80% of aggressive lymphomas. There are around 14,100 new NHL cases in the UK every year (Cancer Research UK statistics 2016-18) with approximately 5,500 diagnosed as DLBCL. Without treatment, median survival is less than 6 months. **(b) High unmet need: existing methods/licensed medicines have serious limitations** Relapses of DLBCL are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Following failure of first line treatment, options for next-line therapy are mainly guided by eligibility for autologous stem cell transplantation (ASCT), which is potentially curative. However, less than half of patients who are eligible for transplant will be cured. For those patients who are not fit enough for ASCT, options available in the UK include: • Chimeric antigen receptor T cell (CAR-T) therapies (axicabtagene ciloleucel [Yescarta], tisagenlecleucel [Kymriah]) for the treatment of R/R DLBCL after two or more lines of therapy. The data are promising but CAR-T cell therapies have limitations, including the need for bridging therapy, the intensive process for which patients with rapidly progressive disease may not have time to wait for.

	• The CD79b-targeted antibody-drug conjugate, polatuzumab vedotin (Polivy), in combination with rituximab and bendamustine. ORR (overall response rate), CR (complete response) rate and mDOR (median duration of response) were 47.5%, 40% and 10.3 months, respectively, after at least one line of systemic treatment. • The anti-CD19 monoclonal antibody, tafasitamab (Minjuvi) in combination with lenalidomide. ORR (overall response rate), CR (complete response) rate and mDOR (median duration of response) were 56.8%, 39.5% and 43.9 months respectively, after at least one line of systemic treatment. • further lines of chemotherapy combinations with or without rituximab (e.g. R-GemOx [rituximab + gemcitabine + oxaliplatin], R-DHAP [rituximab + dexamethasone + cytarabine + cisplatin]). However, outcomes are poorer with a complete response rate of less than 10% and median overall survival of around 6 months.
2	**The medicinal product offers major advantage over existing methods in the UK** Indirect comparisons of glofitamab with currently available therapies (B-cell targeted therapies (polatuzumab vedotin [Polivy] in combination with bendamustine and rituximab and tafasitamab [Minjuvi] in combination with lenalidomide & CAR-T cell therapies (axicabtagene ciloleucel [Yescarta] and tisagenlecleucel [Kymriah]) for relapsed / recurrent DLBCL in the UK appear to indicate that CAR-T cell therapy is the most effective, B-cell targeted therapies and glofitamab have similar efficacy and glofitamab is the most tolerable (lowest incidence of ≥Grade 3 adverse reactions). Given that CAR-T cell treatment requires special preparation and is only delivered in selected centres, glofitamab is considered to fulfil an unmet need by offering an additional treatment option.
3	**The potential adverse effects of the medicinal product are outweighed by the benefits, allowing for a conclusion of a positive benefit/risk balance** Adverse effects were manageable with dose interruption and dose modification.
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.