Early Access to Medicines Scientific Opinion - Public Assessment Report
Emicizumab
Emicizumab is indicated for routine prophylaxis of bleeding episodes in patients, aged 1 year and over, with haemophilia A with factor VIII inhibitors
Roche Products Limited
EAMS Number 00031/0004

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to doctors who may wish to prescribe the unlicensed medicine under their own responsibility. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine. The General Medical Council's guidance on prescribing unlicensed medicines can be found here: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

Emicizumab

What is Emicizumab?

Emicizumab is a humanised monoclonal antibody.

What is Emicizumab used for to prevent?

Emicizumab is used for routine prophylaxis of bleeding episodes in patients, aged 1 year and over, with haemophilia A with factor VIII (FVIII) inhibitors.

How is Emicizumab used?

Emicizumab should be started and used under the supervision of a doctor experienced in the treatment of haemophilia and/or bleeding disorders. Emicizumab is given as a subcutaneous injection once every week at the recommended dose of 3 mg/kg bodyweight once weekly for the first 4 weeks, followed by 1.5 mg/kg bodyweight once weekly. Emicizumab is intended for long-term prophylactic treatment. No dosage adjustments are recommended. Management of adverse events may require temporary interruption or discontinuation of emicizumab treatment. Treatment is contraindicated in patients who are at high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy).

How does Emicizumab work?

Emicizumab binds to activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis in patients with haemophilia A. Emicizumab has no structural similarity to FVIII, allowing it to work unaffectedly by the presence of FVIII inhibitors.

How has Emicizumab been studied?

Emicizumab has been studied in two Phase III trials. Study BH29884, a randomised, open label study involving 109 patients from the age of 12 years and older, of which 35 were enrolled into the emicizumab arm and 18 into the control arm of on-demand use of bypassing agents, triggering the primary analysis of the randomized comparison. The paediatric trial BH29992, a single arm trial for

patients younger than 12 years of age, enrolled 60 patients at the time of the interim analyses, with the youngest having been 14 months of age.
Both studies could enroll patients from a non-interventional study (NIS) BH29768, providing an opportunity for intra-patient comparisons of bleeding while on the different prophylactic therapies (ie bypassing agents followed by emicizumab).

What are the benefits and risks of Emicizumab?
Benefits
Prophylactic use of emicizumab in inhibitor patients with and without previous immune tolerance induction (ITI) experience indicates a reduction of treated bleeds of 87% after 24 weeks (annual bleeding rate 2.9 [CI 1.7 - 5.0]) compared to standard of care of 'on-demand' use of bypassing agents (ABR 23.3 [12.3 – 43.9]). This is similar for all bleed related endpoints, including the intra-patient comparison for those patients on previous prophylactic use of bypassing agents. This is consistent with the calculated ABR for treated bleeds of 23 patients < 12 years of age following 12 weeks of treatment (ABR 0.2). It coherently translates into improvements in quality of life for all age groups.

Risks
The overall safety profile of emicizumab appears to be tolerable. A total of 4/189 patients (2.1%) had an adverse event (AE) leading to discontinuation from study treatment. Injection site reaction (ISR) was the most commonly reported adverse drug reaction across all patients, occurring in 19 % of patients (35/189).
The main safety concern is around the development of thromboembolic events (TEs) or thromboembolic microangiopathy (TMA), with 4 patients in study BH29884 who develop such AE (2 patients each). It was considered to be related to concomitant use of bypassing agents, particularly cumulative doses of activated prothrombin complex concentrate (aPCC).

Why has Emicizumab been given a positive Early Access to Medicine Scientific opinion?
PIM designation
The Applicant received a PIM designation for emicizumab on 29 August 2017 for the proposed indication.

Life-threatening or seriously debilitating condition
Haemophilia A is a rare genetic disorder, characterised by spontaneous or traumatic bleeding caused by inborn underproduction of or dysfunction of coagulation factor VIII (FVIII). The main bleeding sites in patients with haemophilia A are joints, muscles, skin, or even bleeds into the brain. In particular, repeated bleeds into joints are a major contributor to reduced health-related quality of life.
Nearly one in three people with severe haemophilia A develop inhibitors to standard FVIII replacement therapy which can impair its efficacy or render it ineffective. The development of inhibitors is the most severe treatment-related complication of haemophilia A, with patients suffering frequent bleeds that are difficult to control even with large doses of so called bypassing agents. Some bleeds can therefore also be life threatening. The majority of patients report bleeds into target joints. Increased bleeding resulting from suboptimal disease management leads to pain and disability through progression of joint disease. Overall, patients with inhibitors have worse outcomes of and from joint bleeding as well as reduced life-expectancy compared to people without inhibitors.

High unmet need
Current treatment options for patients with inhibitors is immune tolerance induction (ITI), with the idea to increase the dose of the missing FVIII gradually so that the individual's immune system learns to tolerate it and ceases to produce inhibitors. ITI however fails to destroy inhibitors in approximately 20-

40% of treated patients. It is also time intensive and burdensome, particularly for children, who frequently require surgical implantation of central venous access devices.
When FVIII can no longer be used to control bleeding, patients with inhibitors may be treated with agents which bypass FVIII, known as bypassing agents (BPA). However, these products are described as not being as effective as FVIII in preventing bleeding. BPAs are short-acting and may need to be administered frequently, particularly for prophylactic treatment, with long IV infusion times.
The haemostatic effect in patients with inhibitors is also described to be suboptimal compared with that of FVIII replacement therapy in patients without inhibitors. Given the above described challenges, there is a high unmet need for therapeutics that have improved efficacy, a longer half-life, and reduced treatment burden to prevent bleeding for haemophilia A patients with inhibitors.

Major advantage over methods currently used in the UK
Evidence to support the designation was provided from non-clinical and clinical data (study BH29884 and study BH29992).
Emicizumab has no structural similarity to FVIII, allowing it to be unaffected by the presence of FVIII inhibitors. With its weekly sub-cutaneous dosing schedule and what appears to be an improved efficacy profile over the existing treatment option of bypassing agents administered on demand as per current standard of care, but also in comparison to prophylactic use (intra-patient comparison), emicizumab has the potential to offer major therapeutic advantage to patients with Haemophilia A and inhibitors over methods currently used in the UK.

Positive benefit risk balance
From the clinical studies to date, it can be concluded that prophylactic use of emicizumab offers the potential for a clinically meaningful reduction of bleeding episodes in patients with haemophilia A who have developed inhibitors, compared to on-demand use of bypassing agents, as well as in comparison to prophylactic use. The safety profile can be described as tolerable, with the potential for drug-drug interaction with bypassing agents being the main safety concern identified, mitigated through clear guidance in the treatment protocol, as well as the risk management plan.

What are the uncertainties?
Paediatric data presented are only interim results with shorter follow-up compared to results from study BH29884. The safety and efficacy of emicizumab have not been formally evaluated in the surgical setting. No data are available in patients receiving ongoing immune tolerance induction.

Are there on-going clinical studies?
The paediatric trial BH29992 is still ongoing.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that emicizumab is used as safely as possible. Based on this plan, the company that makes emicizumab must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the side effects and recommendations for reducing the risk of these side effects.

Healthcare professionals will be asked by the company to report adverse effects experienced by patients receiving emicizumab through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Patients in the Early Access to Medicines Scheme will also receive an alert card from their doctor summarising the important risks with the medicine and the details of their treating doctor. Patients

should carry the card with them at all times in case they need treatment or advice from a healthcare professional who is not familiar with emicizumab treatment.

Other information about Emicizumab – see EAMS Treatment Protocol