MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
02 07 2019

Agenda Item No	02.1
National Programme	Blood & Infection
Clinical Reference Group	Specialised Blood Disorders
URN	1819 / CSP ID014

Title
Emicizumab for prophylaxis of bleeding episodes in patients with severe congenital haemophilia A without factor VIII inhibitors (all ages)

Actions Requested	1. Agree the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Recommended to be routinely commissioned. The aim of treatment for haemophilia A is to prevent bleeding episodes from occurring. Bleeds can be prevented or reduced by injections of factor VIII into the vein (either directly or via a central venous access device for patients who require it), given every 2 to 3 days. If a bleed occurs, it is treated with injections of factor VIII. Emicizumab is a drug used to prevent bleeding or reduce the number of bleeds in people with haemophilia A. Emicizumab works by mimicking the action of factor VIII. Emicizumab binds to factor X (ten) and activated factor IX (nine) which brings those clotting factors near each other and activates the blood clotting system even if no factor VIII is present. Emicizumab is a subcutaneous biologic drug which can be given once-weekly, fortnightly, or once every four weeks to achieve effective bleeding control in patients with Haemophilia A. **Associated clinical commissioning documents** Clinical commissioning policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages) NHS England Reference: 170067/P

Clinical panel recommendation
The Clinical panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Metric*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	Emicizumab has a much longer half-life than Factor VIII (26.7 days vs 19 hours for enhanced half-life factor VIII), meaning patients have more steady level of drug in their blood (fewer peaks and troughs in plasma concentration).

10.	Safety	In Mahlangu et al. (2018), a total of 543 adverse events were reported in 127/150 participants (85%) receiving emicizumab prophylaxis. The most common adverse events were injection-site reaction, arthralgia (joint pain) and nasopharyngitis (inflammation of the pharynx and nasal cavities). Fourteen serious adverse events were reported, including bleeding events, a cardiac disorder and infections. One person discontinued treatment with emicizumab due to a number of adverse events that were considered to be related to emicizumab. There were no deaths, no cases of thrombotic microangiopathy (blood clots in the small blood vessels) and no thrombotic (blood clots) events. People with thromboembolic disease in the previous 12 months were excluded from the study. There were no serious adverse events related to co-exposure to emicizumab and factor VIII. No new factor VIII inhibitors developed in participants receiving emicizumab. One person who had previously undergone immune tolerance induction (to remove factor VIII inhibitors) had a re-emergence of a detectable inhibitors at week 13 (1.6 Bethesda units), which was still detectable at week 25 (0.7 Bethesda units). These results suggest that many people who receive emicizumab may have side effects, although most side effects will probably be non-serious, and only a small number of people will need to stop taking emicizumab because of side effects. Although not observed in this study, the development of antibodies to emicizumab is an important safety concern that should be appropriately monitored.
11.	Delivery of intervention	Emicizumab is administered by subcutaneous injection and factor VIII is administered by intravenous injection or by central venous access device for people who require it. Emicizumab can be administered up to once every 4 weeks, which is considerably less frequent compared with factor VIII, which needs to be administered every 2 to 3 days. In addition to this, people have more flexibility to spend extended periods of time away from home without being required to carry large volumes of factor VIII. This view is supported by Mahlangu et al. (2018), which reported patient preference as an exploratory outcome, assessed using the EmiPref patient survey. It would appear that this survey had been developed for this study and has not been validated. In total, 95/134 participants (71%) completed the survey, with 94% (95% CI 87 to 98) preferring emicizumab to their previous treatment. In total, 45/46 participants previously treated with factor VIII prophylaxis in an

		observational study (98%, 95% CI 88 to 100) favouring emicizumab over factor VIII prophylaxis. These results suggest that most people treated with emicizumab preferred it to their previous treatment (including factor VIII prophylaxis). Although it is not clear from the study which properties of emicizumab they prefer.

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
12	Bleeding rate Reported using annualised rate of bleeding events treated with factor VIII Primary efficacy outcome	A 'treated' bleed is any bleeding event that required treatment with factor VIII. The investigators calculated the bleeding rate per day and converted this to an annual bleeding rate. The study by Mahlangu et al. 2018 included 89 randomised participants who had previously received on-demand treatment with factor VIII. People treated with emicizumab 1.5 mg/kg every week (n=36) or 3.0 mg/kg every 2 weeks (n=35) had an annual bleeding rate of 1.5 and 1.3 treated bleeds respectively, compared with 38.2 treated bleeds in the no prophylaxis group. These results suggest that people who take emicizumab can expect to have substantially fewer bleeds each year that require treatment with factor VIII, compared with people who take no prophylaxis. This can be interpreted to mean that the annualised bleeding rate with emicizumab is likely to be comparable to factor VIII prophylaxis. Emicizumab has a considerably longer half-life compared with factor VII, meaning patients have more steady level of drug in their blood, which may mean that they are at less risk of bleeding.
13	Health-related quality of life Reported used the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale	The Haem-A-QoL is a tool for assessing quality of life in people with haemophilia. The questionnaire consists of 10 subscales, 1 of which is 'physical health'. Scores range from 0 to 100, with lower scores indicating better quality of life. A change in the physical health subscale score of 10 points or more is considered to be clinically meaningful. The adjusted mean difference in Haem-A-QoL physical health subscale score between group A and group C was 12.5 points (95% CI −2.0 to 27.0, p=0.09, not statistically significant). The adjusted mean difference between group B and group C was 16.0 points (95% CI 1.2 to 30.8, considered non-significant due to the order of the outcomes in the hierarchical testing framework).

		In Mahlangu et al. (2018) there was no statistically significant difference in Haem-A-QoL physical health subscale score between either emicizumab group (1.5 mg/kg every week or 3.0 mg/kg every 2 weeks) and the no prophylaxis group. All participants in these groups had previously been treated with on-demand factor VIII. The study did not report on health-related quality of life in people previously treated with factor VIII prophylaxis. These results suggest that people treated with emicizumab do not have better health-related quality of life compared with people who received no prophylaxis. The difference in quality of life score was greater than the minimal clinically important difference in favour of emicizumab, although the results were not statistically significant. Changes in quality of life score from baseline to study end were not reported.
14	Development of anti-drug antibodies	No participants developed antibodies to emicizumab during the study by Mahlangu et al. (2018). However, the SPC for emicizumab states that 4 participants (2.1%) in the phase I/II clinical trials tested positive for anti-emicizumab antibodies, all of which were non-neutralising. These results suggest that the development of antibodies to emicizumab will be uncommon, although it should be noted that the development of emicizumab antibodies would have a large impact on a person's treatment.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The policy recommends emicizumab within its licensed indication. It is excluded from tariff. Treatment funding will be on condition of a submission of a Prior Approval Request at the start at treatment.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood & Infection PoC Board on the 10th June 2019