CPAG Summary Report for Clinical Panel – Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors NHS England Unique Reference Number 1717

The Benefits of the Proposition – emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	A total of 198 adverse events (side effects) were reported in 103 participants who received emicizumab in the included study. Around three-quarters of participants reported at least one adverse event. The most common adverse events were injection-site reactions, upper respiratory tract infection, headache, fatigue and arthralgia (joint pain). In the main study there were 3 cases of thrombotic microangiopathy (blood

			clots in the small blood vessels), 1 case of cavernous sinus thrombosis ((blood clots in the hollow spaces under the brain) and 1 case of superficial thrombophlebitis (blood clots in a vein just below the surface of the skin) in people receiving emicizumab. In all cases participants had received multiple infusions of activated prothrombin complex concentration while receiving emicizumab. Two of the cases of thrombotic microangiopathy resolved after the activated prothrombin complex concentrate was stopped, and neither thrombotic events required anticoagulation. The third case of thrombotic microangiopathy (that occurred after data cut-off for the primary analysis) happened 5 days after the person's last emicizumab dose and 4 days treatment with activated prothrombin complex concentration for a rectal bleed. The rectal bleed was recurrent and ultimately fatal. Investigators assessed that the thrombotic microangiopathy had resolved at the time of death. The safety profile of emicizumab is acceptable, but its use in combination with high doses aPCC is not recommended based on the evidence presented. This is reflected in the draft policy proposition which recommends that anyone who has a bleed while taking emicizumab as prophylaxis should be treated at a comprehensive care centre.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review			
No	Outcome measure	Grade of evidence	Summary from evidence review

1.	Bleeding rate Reported using annualised rate of treated bleeding events	Grade B	A 'treated' bleed is any bleeding event that required treatment with a haemophilia medication used to treat bleeds. In the study this was a bypassing agent (either recombinant activated factor VII or active prothrombin complex concentrate). The investigators calculated the bleeding rate per day, and converted this to an annual bleeding rate. The main study included 53 randomised participants who had previously received episodic treatment with bypassing agents. People treated with emicizumab (n=35) had an annual treated bleeding rate of 2.9 events (95% CI 1.7 to 5.0), compared with 23.3 events (95% CI 12.3 to 43.9) in the no prophylaxis group (n=18), risk ratio 0.13 (95% CI not reported, p<0.001). This is an 87% reduction in treated bleeds (statistically significant difference p<0.001) These results suggest that a person who has previously received on-demand bypassing agents for treating bleeds who switches to regular emicizumab can expect to see a reduction in the number of bleeds. These results should be interpreted with a degree of caution as the study was open-label, which may have introduced bias.
2.	Quality of life Reported used the Haemophilia Quality of Life Questionnaire (Haem-A-QoL) physical health subscale and total score	Grade B	The Haem-A-QoL is a tool for assessing quality of life in people with haemophilia. The questionnaire has 2 main parts which look at 'physical health' and 'sports and leisure'. Scores range from 0 to 100, with lower scores indicating better quality of life. In the main study, compared with those receiving no prophylaxis

			(n=18), people treated with emicizumab (n=35) had a significantly greater reduction in Haem-A-QoL physical health subscale score (adjusted mean difference 21.6 points (95% CI 7.9 to 35.2, p=0.003) and Haem-A-QoL total score (adjusted mean difference 14.0 points, 95% CI 5.6 to 22.4, p=0.002). The mean reductions in both scores were greater than the minimal clinically meaningful difference (MCID) reported in the literature (10 and 7 points respectively), however it should be noted that the lower 95% CI limit falls below the MCID. These results suggest that a person who has previously received on-demand bypassing agents for treating bleeds who switches to regular emicizumab treatment will have a significant improvement in quality of life. These results should be interpreted with caution as the people in the study knew which treatment they were receiving, which may have affected their perception of quality of life.
3.	Health status Reported using the EQ-5D-5L visual analogue scale and index utility score	Grade B	The EQ-5D-5L is a standardised questionnaire used to measure health status. There are 2 parts, the EQ-5D-5L visual analogue scale (scored from 0 to 100) and the EQ-5D-5L index utility score (scored from −0.4 to 1.0); higher scores in both parts indicate better health status. In the main study people treated with emicizumab prophylaxis (n=35) had a significantly greater reduction in EQ-5D-5L visual analogue scale score (adjusted mean difference −9.7 points (95% CI −17.6 to −1.8, p=0.02) and EQ-

			5D-5L index utility score (adjusted mean difference −0.16 points, 95% CI −0.25 to −0.07, p=0.001) compared with those receiving no prophylaxis (n=18). All participants in this comparison had previously received episodic bypassing agents. The mean reductions in both scores were greater than the published MCID reported in the literature (7 and 0.07 points respectively), however it should be noted that the lower 95% CI limit falls below the MCID. These results suggest that a person who has previously received on-demand bypassing agents for treating bleeds who switches to regular emicizumab will have a significant improvement in health status, which may be clinically meaningful. These results should be interpreted with caution as the people in the study knew which treatment they were receiving, which may have affected how they responded to the questionnaire.
4.	Development of anti-drug antibodies	Grade B	No participants tested positive for antibodies to emicizumab. A reduction in emicizumab levels in 2 participant's over-time (which may suggest anti-drug antibodies) were observed - these participants are being followed up.