A.12 Emicizumab – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Hemophilia A is caused by a deficit in the coagulation cascade protein Factor VIII (FVIII) and severe hemophilia is defined by baseline FVIII levels of <1%. The disease is characterized by frequent bleeding into exposed joints and muscles. Repeated bleeding causes hemophilia arthropathy and severe disability. When bleeding occurs in a vital area (brain, neck, throat, …), it can be fatal. The prevalence at birth per 100,000 males is estimated to be 24.6 cases for all severities of hemophilia A, 9.5 cases for severe hemophilia A. According to this prevalence, the expected number of people born with severe hemophilia should be about 500.000 with a worldwide distribution. Treatment for hemophilia A can be either regular *prophylaxis* to prevent bleeding, which is recommended as the standard of care, or periodic, *on-demand* treatment when bleeding occurs, which is more commonly used for non-severe disease and for people with severe hemophilia in low-income countries. In approximately 30% of cases of patients with severe hemophilia A will develop inhibitors to FVIII and infusions of FVIII are no longer possible. In these cases, the traditionally recommended treatments are a) massive doses of FVIII over months and even years to tolerize the patient, called immune tolerance induction (ITI), or b) prophylactic or on-demand infusion of bypassing agents such as recombinant FVIIa or activated prothrombin complex concentrate (PCC). Those patients experience worse outcomes and increased morbidity and death. Emicizumab is the first non-factor medicine for subcutaneous administration in patients with severe and moderate hemophilia A with or without factor VIII inhibitors. It's a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X to mimetic the function of missing procoagulant activated factor VIII. It has been developed as a bypassant agent in patients with Hemophilia A regardless of their inhibitor status. It is not used to stop active bleeding, but as a prophylactic agent. In first published pivotal phase 3 studies (HAVEN 1 and 2), Emicizumab was compared to prophylactic treatment with bypassing agents (activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII) as prophylaxis in Hemophilia A with inhibitors males 12 years and old with hemophilia A with a prior history of inhibitors (HAVEN 1) and children with <12 years of age (HAVEN 2). Emicizumab prophylaxis has been shown to dramatically reduce bleeding events compared to prophylaxis or on-demand treatment with bypassing agents in infants, children, adolescents, and adults with a reduction of consumption of bypassing agents in surgical situations. This represented an 85% to 95% reduction in annualized bleeding rate (ABR); The Haven 4, included participants aged 12 years and older with severe haemophilia A with or without FVIII inhibitors, treated with emicizumab once every 4 weeks for 24 weeks. The results were as well very effective. HAVEN 3, HAVEN 5 and HAVEN 7 enrolled adults and adolescents aged 12 years and older and children under 12 years of age, with severe Hemophilia A and without FVIII inhibitors. The ABR was reduced by 68% in patients on prophylaxis and by 96% in patients previously been on on-demand (episodic) FVIII treatment. Emicizumab was given every other week or every 4 weeks. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors, after 2 to 3 years of treatment, 82.4% of participants had 0 treated bleeds, 97.6% had ≤3 treated bleeds,

	and 94.1% reported no treated target joint bleeds demonstrating that emicizumab prophylaxis maintained low bleed rates in all ages with and without FVIII inhibitors. Emicizumab prophylaxis was associated with substantial and meaningful improvements in health-related outcomes and was accompanied by substantial and sustained improvements in Health-Related Quality of Life (HRQoL), even using specific evaluation form like the Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) Coagulation factor VIII	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors, after 2 to 3 years of treatment, 82.4% of participants had 0 treated bleeds, 97.6% had ≤3 treated bleeds, and 94.1% reported no treated target joint bleeds demonstrating that emicizumab prophylaxis maintained low bleed rates in all ages with and without FVIII inhibitors.	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) The most frequently observed adverse events were local injection site reactions (erythema, pain, and pruritus), which were reported in 26.1% of treated participants. The reactions were mild to moderate severity and resolved without treatment in over 90% of cases. Anaphylaxis was extremely rare. The most concerning of the adverse events has been the occurrence of thromboembolic events and thrombotic microangiopathy. These complications were mostly associated with concomitant replacement therapy with aPCC at a high dose. In additional cases of non-aPCC-related events they occurred in patients with pre-existing cardiovascular or thrombotic risk factors, including age over 50 or central venous access device. Emicizumab was associated with the development of anti-drug antibodies in 5.1% of patients. Most patients did not experience a change in emicizumab plasma concentrations or an increase in bleeding events. Neutralizing antibodies were detected in <1% of cases	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable

Are there any issues regarding price, cost-effectiveness and budget implications in different settings? The studies showed emicizumab to be cost-effective for the treatment of hemophilia A with inhibitors in France, Italy, Portugal and Turkey, India, Peru, Brazil, USA, south Africa, Spain, Korea, Iran, Malaysia, For hemophilia A without inhibitors, results vary by country. Studies show cost savings and cost-effectiveness with emicizumab compared to FVIII in India and the United States, but not in Europe and the United Kingdom.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes)	☒ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable