A.23 Recombinant coagulation factors – EML and EMLc

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): In order to overcome access and cost hurdles in low-income countries (LICs) and lower middle-income countries (LMICs), as well as to address long-standing inequities in hemophilia care across the globe, I recommend to include rFVIII and rFIX on the EML and EMLc. The availability of lyophilized CFCs made it possible to start preventative medication and treat spontaneous and traumatic bleeding episodes at home quickly. According to studies, by the late 1970s, persons with severe hemophilia experienced significant improvements in their mortality rates, life expectancy, and quality of life when factor replacement therapy was administered with strong medical support, mostly through hemophilia treatment centers (HTCs) and home treatment programs. Significant advancements in hemophilia diagnosis and treatment were made possible by the advent of rFVIII in 1994 and rFIX in 1997, which expanded the supply and availability of treatment medications.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? In 1979, coagulation factors VIII and IX (produced from plasma) were added to the WHO Model List of Essential Medicines. The WHO Expert Committee on the Selection and Use of Essential Medicines acknowledged that recombinant CFCs should be used instead of plasma-derived CFCs in 2007, when FVIII and FIX were added to the first EML for children (EMLc). These listings, known as "square boxes," indicate appropriate therapeutic alternatives with comparable clinical performance within the same pharmacological class.	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? As regards the treatment of hemophilia, plasma-derived and recombinant products have been shown to be equally effective**.** Summary of evidence: Fourteen studies with 429 individuals were included for hemostatic drugs. Peak factor level after infusion, bleed rate, factor level, half-life, infusion frequency, and adverse events were among the outcomes that were examined. Inter-patient variability prevented these studies' findings from demonstrating a substantial difference between the PK results of pdFVIII and rFVIII. rFVIII's in vivo recovery was somewhat greater than pdFVIII's. Furthermore, data indicated that pdFIX had higher maximum peak thrombin generation and mean peak recovery than rFIX; however, this difference was not statistically significant. Key health outcomes of rFVIII and rFIX include: •reduction in annual bleed rate (ABR) •reduction in annual joint bleed rate (AJBR) •reduction in annual rate of treated bleeds (ATBR) •reduction in number of target joints (definition: three bleeds in same joint in less than 6 months) •improvement in joint health scores as measured by the HJHS tool (Hemophilia Joint Health Score) •percentage of patients with 0 annual bleeding events •improved health-related outcomes and quality of life •survival	☒ Yes ☐ No ☐ Not applicable

Does adequate evidence exist for the safety/harms associated with the proposed medicine? Given its undeniable advantages, especially in terms of safety, recombinant technology has long been regarded as a potent therapeutic tool. Recombinant medications have been utilized for many years to treat a wide range of clinical diseases. Recombinant factor may have benefits such as immunogenicity and a decreased risk of bloodborne virus transmission. Large pools of plasma from thousands of blood donors (more than 2,000 donors per pool) are used to make plasma-derived CFCs, which have a significant risk of bloodborne infections and cause significant variation in the FVIII sequence across various products. Furthermore, the production and supply of pdFVIII and pdFIX are dependent on the volume of plasma obtained from donors, making them more vulnerable to fluctuations in supply and shortage risks. Anti-drug antibodies called inhibitors are currently the most serious complication in hemophilia treatment. Inhibitors occur more often in hemophilia A. Treatment alternatives for those who develop an inhibitor to FVIII include bypassing agents such as activated prothrombin complex concentrates (aPCC) and activated recombinant factor VII (rFVIIa); and novel therapeutics which include bispecific monoclonal antibody FVIII mimetics such as emicizumab and rebalancing agents such as concizumab and marstacimab. Inhibitor formation is rare in hemophilia B. Treatment alternatives for those who develop an inhibitor to FIX consist of rFVIIa, concizumab, and marstacimab. Divergent findings on the immunogenicity of FVIII products were reported by a number of research. The PedNet (Pediatric Network on Haemophilia Management), a comprehensive registry of PUPs with severe hemophilia A, served as the foundation for the RODIN study design. The RODIN study found that individuals exposed to a second-generation full-length rFVIII made in baby hamster kidney cells had a greater incidence of inhibitors, even though there was no discernible difference in the risk of inhibitor development between pdFVIII and rFVIII users. Other cohorts of PUPs with severe hemophilia A in the UK82 and France also showed a similar outcome. The only randomized-controlled study intended to assess the immunogenicity difference between pdFVIII and rFVIII concentrates is SIPPET (Study on Inhibitors in Plasma-Product Exposed Toddlers). Previously Untreated Patients (PUPs) and patients with severe hemophilia receiving limited treatment had a higher incidence of inhibitors. The cumulative inhibitor incidence for pdFVIII and rFVIII was 26.7% and 44.5%, respectively, for a patient treated with rFVIII products. Different post-translational changes, synthesis in distinct cell lines, and the lack of other proteins, such VWF, may all contribute to rFVIII's increased immunogenicity.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? Bleeding issues with hemophilia can have serious consequences, including decreased social engagement, lost productivity, and increased healthcare expenses in later life. Inadequate treatment also has a negative impact on the economy and society since it causes hemophiliacs, their parents, and caregivers to be less productive and participate in society less. Countries of all income levels face these difficulties. Prophylaxis supports the social and economic activities and contributions of individuals with hemophilia and their caregivers while reducing the overall resource load on healthcare and non-healthcare systems.	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? • Accurate diagnosis of hemophilia is essential to inform appropriate management. Genetic assessment, coagulation tests, and factor assessments are used to diagnose hemophilia, differentiate genotype, and predict the risk of inhibitor development. • IV administration.	☒ Yes ☐ No ☐ Not applicable

(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Recombinant FVIII and FIX have been used to treat hemophilia for over 30 years and shown to be safe and effective medicines, achieving substantial reduction in bleeding rates and improved, near-normal life expectancy in children and adults on prophylactic therapy. However, due to costs, there is wide variability globally in access, availability, and usage in primary, secondary, tertiary settings. Cost of treatment per patient depends on multiple factors such as dose, treatment frequency, joint status, individual pharmacokinetics, and the presence of inhibitors; consequently, costs per patient vary considerably country to country. The difficulties with LICs are numerous and go well beyond the prohibitive price of new, cutting-edge coagulation products and traditional clotting factor therapies. In general, LICs lack the infrastructure of a basic health system to meet basic public health demands, let alone offer hemophilia treatment.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? There are many variables that affect the safety and efficacy of a product —therefore, countries must establish a rigorous national or regional system for procurement and distribution to ensure that people with hemophilia have reliable access to safe and effective CFCs. There are multiple rFVIII and rFIX CFCs approved and available on the market across all regions worldwide. For example, one of the most frequently prescribed rFVIII product is approved in over 70 countries. A key advantage of recombinant therapies is the greater manufacturing capacity and supply. (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