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): Hemophilia is caused by a congenital deficiency of factor VIII or IX, proteins in the coagulation cascade. Severe hemophilia is defined by basic factor levels <1%. The disease is characterized by frequent bleeding into exposed joints and muscles. Repeated bleeding causes hemophilic arthropathy and severe disability. When bleeding occurs in a vital area (brain, neck, throat, etc.), it can be fatal. The birth prevalence per 100,000 males is estimated at 24.6 cases for all severities of hemophilia A, and 9.5 cases for severe hemophilia A. Based on this prevalence, the expected number of people born with severe hemophilia should be around 500,000, with a worldwide distribution. Despite considerable progress in the treatment of hemophilia over the past 50 years, 70-75% of the world's hemophiliac population remains undiagnosed and/or without access to treatment, resulting in poor health outcomes and reduced life expectancy. Clotting factors, also known as antihemophilic factors, have been the standard treatment for hemophilia since the early 1970s. Previously, hemophilia treatment consisted of transfusing large volumes of blood and fresh frozen plasma to stop bleeding episodes, which usually required hospitalization, delayed treatment, led to poor compliance and development of joint disease. One of the most significant advances in hemophilia therapy occurred in the 1970s, due to the industrial manufacturing and large-scale commercial availability of **freeze-dried plasma concentrates containing FVIII and FIX**. Plasma-derived FVIII (pdFVIII and FIX (pdFIX) are produced using fractionation technology to extract FVIII and FIX clotting proteins from large pools of donated human plasma. This innovation revolutionized hemophilia care because factor concentrates could be stored easily, which made it possible to infuse these products at home and a reduction in the requirement of hospital visits, resulting in drastic improvements of quality of life and life expectancy, **and most importantly, it allows a primary prophylaxis**. Unfortunately, exposure to large-pool, plasma-derived products had been responsible for the transmission of blood-borne viruses (HIV and hepatitis B and C viruses) during 1980s. This imposed progress in viral removal techniques and increased the safety of plasma derived coagulation products, but also **to the development of productions of recombinant coagulation FVIII and IX.** The capacity to produce FVIII independently from the blood and plasma donation system has also led to the potential of unlimited supply and the attainment of treatment for all the global population of people with haemophilia. **It is also clear that around half of the FVIII required is not covered by plasma concentrates.** Since 1990s the use of recombinant products has progressively increased, so that in some European countries, they have almost completely replaced the plasma-derived products. Recombinant anti-hemophilic products can be divided into three different generations. First generation products used animal derived proteins in cell culture, with the presence of human serum albumin in the final formulation. Since 2000, in an effort to improve safety concerns, second generation products removed human albumin and used sucrose as a stabilizing agent in contrast to first generation products that contained both human and animal proteins as well as albumin as a stabilizer. In 2003, third generation products eliminated any animal or human proteins during the production and final formulation process. Given the generally short half-life of conventional rFVIII and rFIX products (˜12 h and ˜16-18 h, respectively), frequent infusions are required in order to maintain a trough level that is>1% for effective bleed prophylaxis. The need for frequent infusions becomes problematic in the setting of challenging venous access, which is often the case in infants and young children, as well as posing an issue with adherence in adolescents and young adults. Today, a number of extended half-life (EHL) r-FVIII and r-FIX coagulation factors have been licensed and marketed over the last 8 years. The two techniques mainly adopted were coagulation factor fusion to proteins such as the fragment crystallizable (Fc) component of IgG1 or albumin; and conjugation with chemicals such as polyethylene glycol (PEG). EHL products are as effective and safe in managing surgical interventions as well as in stopping or preventing bleeding in the context of episodic and prophylactic treatment regimens.

	Thanks to their better pharmacokinetic profile, EHL FVIII products can be administered effectively twice a week and EHL FIX products can be administered every 10 or 15 days, but still with a need for intravenous access. Despite these developments, FVIII concentrates derived from human plasma continue to represent an important sector of the market, with a relatively strong presence in the emerging economies. Recent studies indicate that some plasma-derived FVIII (pd-FVIII), at least those containing von Willebrand factor, may offer some therapeutic advantages relative to recombinant products, particularly in the area of FVIII inhibitors. Hence, a role for pd-FVIII still exists, not only in the emerging markets where the vagaries of cost allocation in plasma fractionation allows some manufacturers to sell it for lower prices than rFVIII.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**) Complementary list coagulation factor IX 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;)	☒ 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;) Prophylactic replacement therapy has led to the development of alloantibodies or neutralizing inhibitors to FVIII and FIX, a significant complication of factor replacement therapy. These inhibitors result in an increased risk for bleeding and require less efficacious and more expensive treatment regimens with the use of bypassing agents (BPA) and the use of high doses of factor products as part of immune tolerance induction (ITI) regimens. With the increasing use of recombinant products, an increased number of patients with anti-FVIII inhibitors has been observed, so that inhibitors have become the most pressing, unresolved problem in patients with severe haemophilia A. Indeed, meta-regression found that the pooled incidence rate of inhibitor development was about 15% for plasma-derived FVIII and 30% for recombinant FVIII. But, using the multivariable analysis, including study period, testing frequency and median follow-up the difference was not any more significant. Studies have revealed the importance of genetic risk factors (e.g., ethnicity, *F8* gene mutations, major histocompatibility complex genotype, polymorphisms of immune-response genes [interleukin-10, tumour necrosis factor-a, cytotoxic T-lymphocyte antigen-4]) and environmental risk factors (e.g., number of days of exposure to FVIII, age at first exposure to FVIII concentrate, type of FVIII concentrate administered and modality of treatment) in the development of those inhibitors. This research confirms that inhibitor formation in haemophilia is a complex multifactorial process. Thus, it is still unclear whether the plasma-derived concentrate is better than the recombinant concentrate.	☒ Yes ☐ No ☐ Not applicable

25th WHO Expert Committee on Selection and Use of Essential Medicines
Expert review

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?	☐ 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