C.1 Cryoprecipitate, pathogen-reduced cryoprecipitate, plasma-derived clotting factor concentrates – EML and EMLc

Reviewer summary

☒ Supportive of the proposal

☐ Not supportive of the proposal

Justification (based on considerations of the dimensions described below):

Removal of cryoprecipitate (Cryo) (non-pathogen-reduced) for all indications

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Limitation of the use of pathogen-reduced cryoprecipitate (PR Cryo) to evidence-based indications outside the treatment of hemophilia A and von Willebrand Disease (VWD)

Cryoprecipitate is prepared from Fresh Frozen plasma thawed at a temperature between 1°C and 6°C, the precipitation of cold-insoluble proteins and the collection of factor concentrates after centrifugation allows the separation of these proteins: fibrinogen, factor VIII, factor XIII, and von Willebrand factor. Thus produced, units are refrozen and stored at -18°C in volumes of 10 to 20 ml of plasma for up to 12 months. The current practice guidelines mandate that cryoprecipitate be transfused after 45 minutes of thawing and be infused within 4 hours. **Multiple single donor units of cryoprecipitate are combined into a single pooled unit, thus the risk of viral transmission per dose is not acceptable.** Pathogen reduction of blood products renders any source containing nucleic acids incompetent for replication through various pathogen reduction technologies. Pathogen reduction has recently been adapted to the use of cryoprecipitate; it can eliminate major risks associated with blood borne infectious agents.

Given the short half-life of FVIII, required medical setting administration, and the limited availability, cryo-PR is no more a viable solution to address the unmet needs in persons with hemophilia A or VWD. Moreover, acceptance of therapeutically inferior treatments is no longer justified when costs of purchasing efficacious products are similar or less than cryo-PR. Although, many clinical guidelines have recommended against the use of cryoprecipitate for replacement therapies in hemophilia A, FXIII deficiency, hypofibrinogenemia, and von Willebrand disease unless specific factor replacement products are not available.

Because its use can be punctual in certain indications, cryoprecipitate can be utilized as a concentrated source of fibrinogen in the setting of acquired fibrinogen deficiencies: massive blood loss from trauma, haemorrhagic obstetric complications, liver transplant, cardiac surgery, and recent studies only addressed those settings. An increase in, or maintenance of, plasma fibrinogen levels following cryoprecipitate administration has been observed in both prospective and retrospective studies in cardiac surgery and trauma. In a randomized study there was no significant difference for haemostatic effects between fibrinogen concentrate and cryoprecipitate groups of fibrinogens concentrate in the primary outcome of postoperative blood loss during 48 hours after cardiac surgery. The posttreatment incidence of allogeneic blood transfusion was also similar. Among women with major obstetric haemorrhage, retrospective observational studies showed an independent beneficial effect on mortality associated with cryoprecipitate administration additional to that of tranexamic acid. Similarly, early cryoprecipitate administration in trauma patients was associated with improved survival in prospective cohort studies.

Transfer of the listings of plasma-derived Factor VIII (FVIII) concentrates for the treatment of hemophilia A and von Willebrand Disease (VWD) and Factor IX (FIX) concentrates for the treatment of hemophilia B from the Complimentary list to the Core list

The EML core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The WHO considers that hemophilia A and B are priority diseases. The complementary list presents essential medicines for priority diseases. In other cases, drugs can also be classified as complementary based on a systematically higher cost or a less attractive cost-effectiveness ratio in various contexts.

Plasma-derived FVIII concentrates for the treatment of hemophilia A and VWD and FIX concentrates for the treatment of hemophilia B are efficacious, safe, and cost–effective medicines and should be

	reasonably transferred from complementary to core list of EML. **Removal of FIX complex (FIXc) as a therapeutic alternative to FIX concentrates for the treatment of hemophilia B** Various FIX concentrates are available to treat hemophilia B. Fresh frozen plasma is no longer used in hemophilia because of the lack of safe viral elimination and concerns regarding volume overload. Cryoprecipitate contains no FIX and is not appropriate for hemophilia B therapy. FIXc is found in the supernatant of plasma following cryoprecipitate removal. Owing to the limitations of separation technologies in the late 1980s, only FIX complex concentrates with relatively low FIXc purity and other coagulation factors (FII, FVII, and FX) could be prepared. The FIX complex comprises vitamin K-dependent factors II, IX and X, with some products including FVII. These products were the first therapeutics used for FIX supplementation in hemophilia B and **were associated with a risk of thrombosis** due to physiologically abnormal levels of the other vitamin K-dependent factors. However, after the 1990s, ion exchange, gel filtration, and affinity chromatography enabled the preparation of high purity FIXc, reducing the risk of thromboembolic complications in patients receiving long-term infusions of FIX complex concentrates. But, even after various purification techniques used in plasma-based FIX concentrates to reduce or eliminate the risk of viral transmission, including heat treatment and chemical precipitation, these techniques inactivate viruses such as hepatitis B virus, hepatitis C virus, and HIV. However, the transmission of non-enveloped viruses (eg, parvovirus and hepatitis A virus) and poorly characterized agents (eg, prions) is still a potential problem. Therefore, FXc is unsafe with unacceptable risk especially knowing that the price of FIXc may be higher than recombinant FIX products that are largely commercially available. All of the products are approved by the FDA for control and prevention of bleeding episodes and for perioperative management in adults and children.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ 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;)	☒ 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?	☐ 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