Coagulation factor IX, plasma-derived

Section: 11. Blood products, coagulation factors, and plasma substitutes > 11.3. Coagulation factors

EMLc | ATC codes: B02BD04

Indication	Haemophilia B ICD11 code: 3B11.0
Medicine type	Biological agent
List type	Core
Additional notes	All human plasma-derived medicines should comply with the WHO requirements.
Formulations	**Parenteral > General injections > IV:** 500 IU in vial powder for injection ; 1000 IU in vial powder for injection
EML status history	First added in 1979 (TRS 641) Changed in 1989 (TRS 796) Changed in 2007 (TRS 950) Changed in 2013 (TRS 985) Changed in 2021 (TRS 1035) Changed in 2023 (TRS 1049) Changed in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Tags	Biological
Wikipedia	Coagulation factor IX, plasma-derived
DrugBank	Factor IX (Factor IX Complex (Human))

Expert Committee recommendation

The Expert Committee considered the request made by the World Federation of Hemophilia for changes to the listings of non-pathogen-reduced cryoprecipitate, pathogen-reduced cryoprecipitate and plasma-derived coagulation factors on the EML and EMLc. In making its recommendations, the Committee also took into consideration the following: • the recommendation of the 2023 Expert Committee to remove non-pathogen-reduced cryoprecipitate from the Model Lists at the 2025 meeting unless an application was received in support of its retention; • the strong objection from the World Federation of Hemophilia to the listing of non-pathogen-reduced cryoprecipitate for all listed indications, and to the listing of pathogen-reduced cryoprecipitate as an alternative to coagulation factor concentrates in the treatment of haemophilia A and von Willebrand disease; • the request received from the International Society of Blood Transfusion in support of the retention of non-pathogen-reduced cryoprecipitate; and • contributions received from stakeholders during the public consultation period and the input from the Blood and Other Products of Human Origin team at WHO. After consideration of all relevant factors, the Expert Committee made the following recommendations. The Expert Committee recommended that non-pathogen-reduced (i.e. native) cryoprecipitate and pathogen-reduced cryoprecipitate be removed from the Model Lists for use in prophylactic treatment of haemophilia A and von Willebrand disease. The Committee recognized the increased risks of transfusion-transmitted infections associated with repeated transfusions in

patients with these conditions. The Committee acknowledged that there remains a role for cryoprecipitate as on-demand management of acute bleeding episodes and in patients with haemophilia A and von Willebrand disease undergoing surgery in circumstances where preferred alternatives are not available. The Committee acknowledged that cryoprecipitate may be the only available treatment option in some settings and that despite the iatrogenic risks, clinical circumstances clearly justify its use. In such cases, pathogen-reduced cryoprecipitate is preferred over non-pathogen-reduced cryoprecipitate. The Expert Committee recommended that non-pathogen-reduced cryoprecipitate be retained on the EML and EMLc as a therapeutic alternative to pathogen-reduced cryoprecipitate for use in cases of life-threatening major haemorrhage and rapid loss of blood volume (e.g. severe trauma, major surgery, obstetric haemorrhage). The Committee considered that at this time and under the aforementioned clinical circumstances, native cryoprecipitate is still a therapeutic alternative to coagulation factors or pathogen-reduced cryoprecipitate when these are not available. In such situations, the iatrogenic risks are clearly outweighed by the potential life-saving benefits of native cryoprecipitate. The Committee recognized the importance of preferential use of coagulation factor concentrates or pathogen-reduced cryoprecipitate over native cryoprecipitate due to the reduced risk of transfusion-transmitted infections. However, the Committee noted that widespread global access to pathogen-reduced cryoprecipitate is currently limited. In settings where pathogen-reduced cryoprecipitate is not available, native cryoprecipitate is a last resort alternative. The Expert Committee recommended that the current listings for plasma-derived coagulation factors VIII and IX be transferred from the complementary to the core list of the EML and EMLc. For consistency across listings for other medicines used in the treatment of haemophilia and von Willebrand disease, the Committee recommended that the listing for desmopressin also be transferred from the complementary to the core list. The Expert Committee recommended the removal of coagulation factor IX complex as a therapeutic alternative under the square box listing of plasma-derived coagulation factor IX on the EML and EMLc given the increased risk of thrombosis associated with this product.

Background

The application from the World Federation of Hemophilia proposed: i. To remove cryoprecipitate, non-pathogen-reduced for all listed indications; ii. To limit the listed indications of cryoprecipitate, pathogen-reduced to those outside of haemophilia A and von Willebrand disease; iii. To transfer the current listings of plasma-derived coagulation factors VIII and IX from the complementary to the core list; and iv. To remove plasma-derived coagulation factor IX complex as a therapeutic alternative to plasma-derived coagulation factor IX for the treatment of haemophilia B. All proposals apply to listings on both the EML and EMLc. ---------- In 2023, the Expert Committee considered an application from the International Society of Blood Transfusion for the addition of pathogen-reduced cryoprecipitate (cryoprecipitate-PR) to the EML and EMLc for replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and deficiency of coagulation factor XIII, and as a therapeutic alternative to coagulation factor VIII for treatment of haemophilia A in settings where coagulation factor VIII is not available or affordable. Listing was proposed as a square box listing for cryoprecipitate-PR, with non-pathogen reduced cryoprecipitate specified as a therapeutic alternative. The Committee recognized that insufficient access to clotting factor replacement products contributes to early death in patients with bleeding disorders. Accessibility to these products is especially problematic in low- and middle-income countries where many patients have no access to treatment. The Committee considered that the evidence and extensive clinical experience suggest that cryoprecipitate is superior to plasma for replacement of certain clotting factors in a variety of indications in adults and children. However, the Expert Committee noted that concentrated clotting factors remain the preferred treatment for many bleeding disorders and should be prioritized for selection and use wherever possible. The Committee noted and agreed with the WHO Blood Regulators Network position statement and emphasized that cryoprecipitate-PR ought only to be used in settings where commercial clotting factors are unaffordable or unavailable. The Committee was not in the position to recommend specific methods of pathogen reduction but considered that cryoprecipitate-PR developed using validated, approved pathogen-reduction methods should be ensured. The Committee also noted that comparative evidence for cryoprecipitate-PR versus non-pathogen-reduced cryoprecipitate was limited but acknowledged that pathogen reduction can eliminate major risks of transmission of bloodborne infectious agents and increase the safety of administration. While there is a

risk of alloimmunization and allergic transfusion reaction, these adverse events are lower than rates reported for other blood components, including fresh frozen plasma. The Expert Committee therefore recommended the inclusion of cryoprecipitate-PR on the core list of the EML and EMLc for use in the replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and deficiency of coagulation factor XIII. It may also be used as an alternative to coagulation factor VIII concentrate for patients with haemophilia A in settings where coagulation factor VIII is unavailable of unaffordable. The Committee also recommended that non-pathogen-reduced cryoprecipitate be included in the Model Lists as a therapeutic alternative given that transition to cryoprecipitate-PR at the country level may take some time. The Committee acknowledged that solvent and detergent virus inactivation technologies and medical devices used in the plasma fractionation industry are gaining momentum and are being adopted by an increasing number of blood establishments and national blood service centres. For this reason, the Committee considered that removal of non-pathogen-reduced cryoprecipitate from the Model Lists as a therapeutic alternative to cryoprecipitate-PR should be considered at the earliest opportunity unless an application is received to support its retention. The Committee emphasized the requirement that all blood, blood components and plasma derivates used as essential medicines should comply with WHO requirements developed by the WHO Expert Committee on Biological Standardization. The Committee also emphasized that blood donor and donation screening for infections before use of blood products should always be implemented.

Additional evidence

The rationale for the proposals made by the World Federation of Hemophilia is based on the following issues. • Non-pathogen-reduced cryoprecipitate has inadequate efficacy and poses a number of safety risks compared with available alternatives. • Many lower-income countries in which cryoprecipitate is still used for the treatment of haemophilia A and von Willebrand disease, especially in situations of urgent bleeding, also face significant challenges in blood safety, with higher prevalence rates of transfusion-transmitted infection markers than in high-income countries. • A significant residual risk of infection exists in countries where there is a high background prevalence of transfusion-transmitted infection and where donor blood screening regimens use relatively insensitive tests. Additionally, the risk of infection is increased for people with haemophilia A and von Willebrand disease as a result of the need to pool individual cryoprecipitate units to achieve a therapeutic dose. • Cryoprecipitate cannot be administered prophylactically to prevent bleeding episodes in people with haemophilia A and von Willebrand disease and therefore is only used to treat existing bleeding events. • Cryoprecipitate contains variable amounts of factor VIII and fibrinogen, resulting in less reliable dosing for treatment of bleeds compared with coagulation factor concentrates. • Currently available technologies for producing pathogen-reduced cryoprecipitate have a limited capacity to inactivate viruses without a lipid envelope (e.g. hepatitis A, parvovirus B19). • There is inconsistency with listing of cryoprecipitate on the core list and listing of plasma-derived coagulation factor concentrates on the complementary list. Coagulation factor concentrates are self-administered by patients and are the standard of care for prophylaxis in haemophilia and von Willebrand disease. • Coagulation factor IX complex has been associated with an increased risk of thrombosis when used in the treatment of haemophilia B.

Other considerations

In response to the 2023 Expert Committee’s recommendation that non-pathogen-reduced cryoprecipitate be removed from the Model Lists in 2025, a proposal was received from the International Society of Blood Transfusion in support of its retention. The following reasons were cited for retaining non-pathogen-reduced cryoprecipitate on the Model lists included: • Indications for the use of cryoprecipitate extend beyond haemophilia A, especially to treat deficiencies of fibrinogen associated with massive haemorrhage in the settings of trauma and peripartum bleeding and to treat major bleeding episodes in von Willebrand disease. • Access to pathogen-reduced cryoprecipitate is limited globally because the technologies available to produce it are not in wide use. Authorized devices for virus-inactivation are costly and/or relatively new to the market. • Removal of non-pathogen-reduced cryoprecipitate would be inconsistent with continued listing of fresh frozen plasma and platelets which are widely used as non-virus-inactivated blood components despite the existence of applicable pathogen reduction

technologies in higher income countries. • Continued listing of non-pathogen-reduced cryoprecipitate serves to remind governments of the duty to ensure that this and other blood and blood components should be made available with full attention to assuring their microbial safety. This requirement must be met through implementation of good manufacturing practices that include selection of low-risk donors, donation testing for evidence of transfusion transmissible infectious diseases, aseptic collection and sterile preparation processes, properly controlled storage conditions, and appropriate clinical use. The International Society of Blood Transfusion further highlighted the need to stress the importance of the preferred use of pathogen-reduced over non-pathogen-reduced cryoprecipitate as an alternative to coagulation factor VIII in haemophilia A due to the added risks from repeated administration. Similarly, pathogen-reduced cryoprecipitate is strongly preferred over non-pathogen-reduced cryoprecipitate for treatment of bleeding episodes in von Willebrand disease. Infectious risks from multiple exposures to non-pathogen-reduced products made from pooled plasma units are significant, particularly in the same settings where access to industrially manufactured coagulation factors is limited or unavailable due to resource limitations.

1. The use of essential drugs. Report of the WHO Expert Committee, 1989 (including the 6th Model List of Essential Drugs). Geneva: World Health Organization; 1990 (WHO Technical Report Series, No. 796; https://apps.who.int/iris/handle/10665/39338, accessed 6 October 2023).
2. The selection and use of essential medicines. Report of the WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for Children). Geneva: World Health Organization; 2007 (WHO Technical Report Series, No. 950, https://apps.who.int/iris/handle/10665/43887, accessed 6 October 2023).
3. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://apps.who.int/iris/handle/10665/351172, accessed 6 October 2023).
4. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of hemophilia. Third edition. Haemophilia. 2020;26 Suppl 6:1–158.
5. WHO Expert Committee on Biological Standardization. Forty-third report. Annex 2: Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (revised 1992) Geneva: World Health Organization; 1994 (WHO Technical Report Series, No. 840; https://apps.who.int/iris/handle/10665/39048, accessed 6 October 2023).
6. WHO Expert Committee on Biological Standardization. Fifty-second report. Annex 4, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. Geneva: World Health Organization; 2004 (WHO Technical Report Series, No. 942; https://apps.who.int/iris/handle/10665/42921, accessed 6 October 2023).
7. WHO Expert Committee on Biological Standardization. Sixty-seventh report. Annex 3: Guidelines on management of blood and blood components as essential medicines. Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1004; https://apps.who.int/iris/handle/10665/255657, accessed 6 October 2023).

