July 10, 2024

Dr. Lorenzo Moja
Team Lead
WHO Secretariat of the Selection and Use of Essential Medicines
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20, avenue Appia
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Dear Dr. Moja,

As you know, in 2022 ISBT and WHO/BTT jointly submitted an application for inclusion of cryoprecipitate, pathogen-reduced and cryoprecipitate, non-pathogen-reduced on the WHO EMLs for adults and children. More specifically, we proposed:

- Inclusion of Cryoprecipitate, Pathogen Reduced, Method Unspecified as an essential blood component in Section 11.1 of the EML and EMLc;
- Inclusion of cryoprecipitate (i.e., "native" non-pathogen-reduced cryoprecipitate) as a therapeutic alternative to Cryoprecipitate, Pathogen Reduced, Method Unspecified as a blood component in Section 11.1 of the EML and EMLc for use in settings where Cryo-PR is unavailable; and
- Inclusion of Cryoprecipitate, Pathogen Reduced, Method Unspecified, as a therapeutic alternative to Coagulation FVIII in section 11.2.2 of the EML and EMLc for use in settings where Coagulation FVIII is unavailable.

The application received significant international support including from the World Federation of Hemophilia (WFH). However, the inclusion in 2023 of cryoprecipitate (non-pathogen-reduced) in sections 11.1 of the EMLs and not more specifically as a therapeutic alternative to coagulation Factor VIII in sections 11.2.2 has caused great concern to WFH due to the serious infectious risks that use of a non-virus-inactivated product would present to patients with hemophilia A. Additionally, WFH believes that coagulation Factor VIII (plasma-derived and recombinant) and mimetic bifunctional antibodies should be identified in the core rather than complementary listings to emphasize their primary role as current standard of care for patients with hemophilia A.

It is our understanding that WFH seeks the immediate removal of cryoprecipitate (non-pathogen-reduced) from the EMLs and may submit a formal application for removal from the EMLs that would take effect in 2025. The purpose of this letter is to express the contrary position that cryoprecipitate (non-pathogen-reduced) should remain listed in sections 11.1 for

Blood and blood components, as an essential medicine within the larger class of fresh-frozen plasma, platelets, red blood cells and whole blood.

The arguments for retention of cryoprecipitate (non-pathogen-reduced) in sections 11.1 of the EMLs are as follows:

- The indications for use of cryoprecipitate extend well beyond hemophilia A, especially to treat deficiencies of fibrinogen associated with massive hemorrhage in the settings of trauma and peripartum bleeding and to treat major bleeding episodes in von Willebrand Disease.
- Access to cryoprecipitate, pathogen-reduced is limited globally because the technologies available to produce it are not in wide use. Authorized devices for virus-inactivation of plasma are costly and/or relatively new to the marketplace.
- Removal of cryoprecipitate (non-pathogen-reduced) from sections 11.1 of the EMLs 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 that are mostly used in higher income countries.
- Continued listing of cryoprecipitate (non-pathogen reduced), which is a widely needed product, 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.

Whereas we advocate for retention of cryoprecipitate (non-pathogen-reduced) on the EMLs for the above stated reasons, we further argue that a distinction is needed to stress the importance of preferred use of cryoprecipitate, pathogen-reduced rather than cryoprecipitate (non-pathogen-reduced) as an alternative product to coagulation Factor VIII in hemophilia A due to the added risks from repeated product administrations. For similar reasons, use of cryoprecipitate, pathogen-reduced rather than cryoprecipitate (non-pathogen-reduced) should be strongly preferred for treatment of bleeding episodes in von Willbrand Disease. The 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 products is limited or unavailable due to resource limitations.

Additionally, we appreciate the concern expressed by WFH that including coagulation factor VIII on the complementary list while cryoprecipitate, pathogen-reduced is included on the core list creates the misleading impression that cryoprecipitate, pathogen-reduced is the preferred product.

In conclusion, we agree with WFH that coagulation Factor VIII (plasma derived and recombinant) and mimetic bifunctional antibodies should be recognized on the core list of

essential medicines, but disagree that removal of cryoprecipitate (non-pathogen-reduced) is appropriate at this stage of limited global access to cryoprecipitate, pathogen reduced as an alternative product. While cryoprecipitate, pathogen-reduced should be the strongly preferred alternative product to coagulation Factor VIII, cryoprecipitate (non-pathogen-reduced) remains essential globally for fibrinogen replacement in massive hemorrhage and as a therapy of last resort for acute management of major bleeding in hemophilia A and von Willebrand Disease in circumstances were this is the only available option for patients.

Please inform us whether any further actions on our part would be helpful to your consideration of this matter.

Respectfully yours,

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October 31, 2024

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Dear Dr. Moja,

In a previous correspondence (copy attached) the ISBT Working Party for Global Blood Safety shared with the Secretariat our opinion, in contrast to that communicated by the World Federation of Hemophilia (WFH), that cryoprecipitate (non-pathogen-reduced) should remain listed in sections 11.1 in the EML for adults and for children as a therapeutic alternative to cryoprecipitate, pathogen-reduced. Continued listing of this product under "Blood and blood components" aligns with listing of fresh-frozen plasma, platelets, red blood cells and whole blood which are not pathogen reduced, while recognizing cryoprecipitate, pathogen-reduced as the preferred product due to its greater infectious safety in all settings of use. We maintain this position.

Recognizing the existing controversy concerning cryoprecipitate (non-pathogen-reduced), WHO recently disseminated a survey on the Availability and Clinical Use of Cryoprecipitates that may help to clarify the global role that these products should play as Essential Medicines for use in inherited bleeding disorders, maternal bleeding and other bleeding conditions. Importantly, the survey will gather information on use and supply sufficiency of industrial clotting factor concentrates and recombinant products for treatment of patients with inherited bleeding disorders who might otherwise be treated with cryoprecipitates.

An additional disagreement with WFH is presently arising in regard to the listing of cryoprecipitate, pathogen-reduced. Until recently, WFH recognized a role for cryoprecipitate, pathogen-reduced in treating acute bleeding in patients with hemophilia A and von Willebrand Disease if other safer products are not available. (See: www.thelancet.com/haematology Published online August 5, 2024 https://doi.org/10.1016/S2352-3026(24)00223-0.) This position would be consistent with listing of cryoprecipitate, pathogen-reduced as a therapeutic alternative to coagulation factor VIII in section 11.2.2 of the EMLs. Such a listing was recommended by ISBT in its 2022 application for consideration in the 2023 EMLs. However, it has come to our attention through public communications that WFH now plans to advocate that WHO should limit the use of cryoprecipitate, pathogen-reduced to evidence-based indications outside the treatment of hemophilia A and von Willebrand Disease (VWD). Such indications would include treatment of maternal hemorrhage and other acute massive bleeding such as in surgery or trauma, and otherwise for replacement of fibrinogen and factor XIII. Concurrently, WFH intends to

apply for listing of plasma-derived and recombinant clotting factors and FVIII mimetic bifunctional antibodies as core medicines on the EMLs.

We reiterate our previously expressed agreement with WFH that coagulation Factor VIII (plasma derived and recombinant) and the FVIII mimetic bifunctional antibodies should be recognized on the core list of essential medicines for adults and children. Moreover, we concur that similar technologically advanced products for VWD should be listed as core medicines as is expected to be proposed by WFH. Nevertheless, consistent with our 2022 application, we still advocate for listing of cryoprecipitate, pathogen reduced as an alternative therapy to coagulation FVIII (and, if they become listed, to other relevant industrially manufactured replacement products for Factor VIII and von Willebrand Factor) for treatment of acute bleeding in patients with hemophilia A and VWD.

The argument to list cryoprecipitate, pathogen-reduced as an alternative therapy to industrially manufactured coagulation products in hemophilia A and VWD rests on the premise that patients with acute bleeding should not be left without a known-effective treatment when preferred products are unavailable. Because cryoprecipitate, pathogen-reduced can be prepared locally in blood establishments its availability can be assured independent of access to industrially manufactured replacement products for Factor FVIII and von Willebrand Factor. We believe that insufficiency of relevant industrial products remains a reality in many parts of the world. Therefore cryoprecipitate, pathogen-reduced, which already has been listed as an essential blood component should be further listed specifically as an alternative therapy to industrially manufactured coagulation products for hemophilia A and VWD.

We agree with the published position of WFH that treatment with cryoprecipitates falls short of best practice in hemophilia A and VWD. The industrial coagulation products are superior in terms of safety and consistency. Additionally, home use of these products, including ones with long in-vivo half-lives, enables routine prophylaxis to prevent bleeding. This is the current state of the art in hemophilia care. Conversely, acute hospital-based treatment with cryoprecipitates cannot provide routine prophylaxis. For these combined reasons, treatment with cryoprecipitate, pathogen-reduced should be recommended only in situations of acute bleeding where the clearly preferred industrial products are unavailable.

Respectfully yours,

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