Coagulation factor VIII, plasma-derived

Essential medicine status

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

EMLc | ATC codes: B02BD02

Indication	Haemophilia A ICD11 code: 3B10.0
Medicine type	Biological agent
List type	Complementary (EML) (EMLc)
Additional notes	All human plasma-derived medicines should comply with the WHO requirements.
Formulations	Parenteral > General injections > IV: 250 IU in vial powder for injection ; 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 1984 (TRS 722) 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)
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 VIII, plasma-derived
DrugBank	Coagulation factor viii (Antihemophilic factor human)

Expert Committee recommendation

The Expert Committee recalled the recommendation of the 2021 Committee that the square box listings for blood-derived coagulation factors VIII and IX be reviewed in 2023, such that the listings should explicitly indicate the recommended therapeutic alternatives. The application from the World Federation of Hemophilia proposed therapeutic alternatives to coagulation factor VIII (recombinant factor VIII, bypassing agents, bispecific monoclonal antibody factor VIII mimetic and desmopressin) and coagulation factor IX (recombinant factor IX, coagulation factor IX complex and bypassing agents), but did not provide a comprehensive review of the evidence supporting these suggestions. In consideration of the application, the Committee made the following comments and recommendations. Recombinant coagulation factors. The Committee noted that when plasma-derived coagulation factors were considered for inclusion on the first EMLc in 2007, the Committee at that time considered that recombinant products would be covered by the existing square box listings. However, a comprehensive review of the evidence for the comparative efficacy, safety and cost/cost–effectiveness of recombinant products had not been conducted nor evaluated at that time. The 2023 Committee therefore recommended that a full application, compliant with EML application requirements, be requested so that the available evidence could be evaluated. Until such time, recombinant coagulation factors should not be included as therapeutic alternatives to plasma-derived coagulation factors on the Model Lists. Bypassing agents The Committee considered that bypassing agents were not, as such, therapeutic alternatives to coagulation factors, but rather were currently used in a subset of patients who develop factor VIII or factor IX alloantibodies (inhibitors). With regard to the bispecific monoclonal antibody, emicizumab, the Committee also considered that this was not as such, a therapeutic alternative to factor VIII, but rather could be used as a separate treatment

strategy for patients with haemophilia A. Therefore, the Committee recommended that these therapies not be included as alternatives under the current square box listings. The Committee acknowledged the potential future role of these therapies in changing the treatment paradigm of patients with haemophilia but also noted that currently they may not be considered as cost-effective, nor are they widely available. The Committee considered that high-quality applications, compliant with EML application requirements for these therapies could be considered for independent inclusion in the Model Lists in the future. Desmopressin The Committee acknowledged that desmopressin was a therapeutic alternative to plasma-derived factor VIII. Desmopressin is already included on the EML and EMLc for use in the treatment of patients with haemophilia A and von Willebrand disease, in Section 10 (Medicines affecting the blood), instead of as a square box alternative to factor VIII in Section 11 (Blood products of human origin and plasma substitutes) since it is not a blood product of human origin. Coagulation factor IX complex The Committee noted that this complex had been previously listed on the Model Lists until 2013, when it was replaced by coagulation factor IX when Section 11 of the lists for blood products of human origin and plasma substitutes was revised and restructured. The Committee considered that coagulation factor IX complex could be considered a suitable therapeutic alternative to coagulation factor IX in situations where purified factor IX was not available. Therefore, the Committee recommended that the square box listing for coagulation factor IX specify coagulation factor IX complex as a therapeutic alternative under such circumstances. Dextran In response to the suggestion in the application to remove the plasma substitute dextran from the Model Lists because it is not used in the treatment of haemophilia, the Committee advised that dextran was still an essential plasma substitute for other patients in need of blood volume replacement and therefore should remain listed. Strengths of factor VIII and factor IX The application proposed the removal of the specification of strengths of factor VIII and factor IX from the listings, because factor VIII and IX concentrates are manufactured and supplied in strengths ranging from 250 IU to 4000 IU per vial. The Committee agreed that specifying a single strength vial could be unnecessarily limiting. The Committee recommended that for factor VIII, additional strengths of 250 IU and 1000 IU be included as these are the most commonly used and available. The Committee considered that the existing listed strengths of factor IX were appropriate and therefore did not recommend inclusion of the other strengths proposed.

Background

Plasma-derived coagulation factors VIII and IX are each listed on the EML and EMLc with a square box, which is intended to indicate similar clinical performance of different medicines within the pharmacological class and that suitable therapeutic alternative may be considered for selection at the country level for national essential medicines lists. The square box was originally added to the listings in 1989 to accommodate cryoprecipitate as a therapeutic alternative to factor VIII, and plasma and cryoprecipitate-poor plasma as therapeutic alternatives to factor IX (1). In 2007, when plasma-derived coagulation factors VIII and IX were included on the first EMLc, the Expert Committee recognized that recombinant products should be used in preference to dried and plasma-derived products and that recombinant products would be captured by the square box listings (2). At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for plasma-derived coagulation factors VIII and IX be reviewed and updated in 2023 (3). Thus, the Secretariat invited the World Federation of Hemophilia to submit an application reviewing the therapeutic alternatives for these medicines.

Public health relevance

The public health relevance of coagulation factors for use in the treatment of haemophilia is well established.

Benefits

The application proposed a series of changes to listings as summarized below. Coagulation factor VIII The World Federation of Hemophilia recommended not specifying the 500 IU strength with the listing for coagulation factor VIII as this could be unnecessarily limiting. This is because factor VIII concentrates are manufactured in a variety of vial sizes, labelled with strengths ranging from 250 to 3000 IU per vial. The administered dose is determined by the respective treatment protocol and patient weight. The Federation recommended the inclusion of recombinant factor VIII as a therapeutic alternative based on: human-derived and recombinant factor VII products being classified with the same Anatomical Therapeutic Chemical (ATC) code (B02BD02); the recognition by the Expert Committee in 2007 that recombinant products should be used in preference to plasma-derived products and would be captured under the existing square box listing (2); and recommendations in Federation's guidelines

for the management of haemophilia (4). A comprehensive review of the available evidence was not provided in the application. The World Federation of Hemophilia recommended the inclusion of bypassing agents (recombinant activated factor VIIa or activated prothrombin complex concentrate) as therapeutic alternatives for treatment and prevention of bleeding complications in patients with haemophilia A and B who develop Factor VIII or factor IX alloantibodies that typically neutralize the function of infused clotting factor concentrates. The Federation's guidelines recommend that a bypassing agent be used for people with haemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, and for people with haemophilia B with an inhibitor and with a history of an anaphylactic reaction to factor IV-containing clotting factor concentrates (recombinant activated factor VIIa only) (4). A comprehensive review of the available evidence was not provided in the application. The World Federation of Hemophilia recommended the inclusion of emicizumab, a bispecific monoclonal antibody factor VIII mimetic as a therapeutic alternative to plasma-derived factor VIII. Emicizumab is a non-factor replacement therapy that is administered subcutaneously, in some cases as infrequently as once or twice a month. The application stated that non-factor replacement agents such as emicizumab were not associated with the peak and trough curves of protection that are now seen with factor prophylaxis regimens. The Federation's guidelines include recommendations for use of emicizumab in patients with haemophilia A with an inhibitor for regular prophylaxis to prevent bleeding events. Emicizumab may also be used for regular prophylaxis in patients with haemophilia without an inhibitor (4). Emicizumab cannot be used to treat acute bleeding episodes. A comprehensive review of the available evidence was not provided in the application. The World Federation of Hemophilia recommended the inclusion of desmopressin acetate as a therapeutic alternative to factor VIII for patients with mild or moderate haemophilia and carriers of haemophilia A, in accordance with recommendations in the Federation's guidelines (4). Coagulation factor IX The World Federation of Hemophilia recommended not specifying the 500 IU and 1000 IU strengths with the listing for coagulation factor IX as this could be unnecessarily limiting. This is because factor IX concentrates are manufactured in a variety of vial sizes, labelled with strengths ranging from 250 IU to 4000 IU per vial. The administered dose is determined by the respective treatment protocol and patient weight. The World Federation of Hemophilia recommended the inclusion of recombinant factor IX as a therapeutic alternative based on: human-derived and recombinant factor IX products being classified with the same ATC code (B02BD04); the recognition by the Expert Committee in 2007 that recombinant products should be used in preference to plasma-derived products and would be captured under the existing square box listing (2); and recommendations in the Federation's guidelines for the management of haemophilia (4). A comprehensive review of the available evidence was not provided in the application. The World Federation of Hemophilia recommended the inclusion of coagulation factor IX complex (prothrombin complex concentrate) as a therapeutic alternative. However, for patients with haemophilia B, the the Federation's guidelines recommend use of products containing only factor IX in preference to prothrombin complex concentrates which also contain other clotting factors (e.g. factors II, VII and X), which may become activated during manufacture and predispose the patient to thromboembolism. Pure factor IX products have a reduced risk of thrombosis or disseminated intravascular coagulation compared with large doses of older-generation prothrombin complex concentrates. Newer prothrombin complex concentrates are considered safer than earlier products due to the inclusion of coagulation inhibitors (4). The World Federation of Hemophilia also recommended the inclusion of bypassing agents as therapeutic alternatives (see previous paragraph Coagulation factor VIII). Dextran 70 The World Federation of Hemophilia recommended the removal of the plasma substitute dextran 70 from the Model Lists since this product is not used for the treatment of haemophilia.

Harms

A comprehensive review of the available evidence for safety was not provided in the application.

Cost / cost effectiveness

No information was provided in the application.

WHO guidelines

WHO guidelines for the treatment of haemophilia are not currently available. The WHO Expert Committee on Biological Standardization has developed requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (5), guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood products (6), and guidelines on management of blood and blood components as essential medicines (7).

Availability

No information was provided in the application.

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).