

[Coagulation factor IX, recombinant](#)

Statut de médicament essentiel

Section:

[11. Blood products, coagulation factors, and plasma substitutes 11.3. Coagulation factors](#)

Codes ATC: [B02BD04](#)

EMLc

Indication

Haemophilia B Code ICD11: [3B11.0](#)

Type de médicament

Biological agent

Type de liste

Liste de base

Formulations

Parenteral > General injections > IV: 250 IU per mL in vial lyophilized powder for solution for injection ; 500 IU in vial lyophilized powder for solution for injection ; 1000 IU in vial lyophilized powder for solution for injection ; 1500 IU in vial lyophilized powder for solution for injection ; 2000 IU in vial lyophilized powder for solution for injection ; 3000 IU in vial lyophilized powder for solution for injection ; 4000 IU in vial lyophilized powder for solution for injection

Historique des statuts LME

Ajouté pour la première fois en 2025 ([TRS 1064](#))

Sexe

Tous

Âge

Aussi recommandé pour les enfants

Équivalence thérapeutique

La recommandation concerne ce médicament spécifique

Renseignements sur le brevet

Patents have expired in most jurisdictions

Lire la suite [sur les brevets](#).

Wikipédia

[Coagulation factor IX, recombinant](#)

DrugBank

[Coagulation factor IX \(recombinant\)](#)

Recommandation du comité d'experts

The Expert Committee recalled the request of the 2023 Expert Committee for an application be sought for recombinant coagulation factors so that the available evidence for their comparative efficacy, safety, and cost/cost-effectiveness could be fully evaluated. The Committee recognized the importance of coagulation factor concentrates, both plasma-derived and recombinant, for patients with haemophilia. The Committee considered that the evidence presented supported the effectiveness of recombinant FVIII and IX being equal to plasma-derived coagulation factors for important outcomes including reduced bleeding rates, the percentage of patients without bleeding events, improving joint health scores, and improving health-related quality of life measurement scores. In terms of safety, the Committee noted that recombinant coagulation factors have virtually no risk of bloodborne virus transmission while plasma-derived coagulation factors undergoing multiple rigorous safety processes (e.g. donor screening, nucleic acid testing, viral inactivation/removal steps) have an extraordinarily low (but not zero) risk of transmission of lipid-enveloped viruses. Overall, the Committee considered the balance of benefits to harms to be favourable. The Committee noted that the prices of recombinant products has decreased over time, and is currently almost comparable with plasma-derived products. The Committee recognized that plasma-derived coagulation factors continue to represent an important treatment option, and may offer advantages over recombinant products in the context of inhibitor development, and may be more affordable in some settings. Based on these considerations, the Expert Committee recommended the inclusion of recombinant coagulation factor VIII for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia A, and of recombinant coagulation factor IX for prophylactic treatment and on-demand treatment of acute bleeds in people with haemophilia B on the core list of the EML and EMLc.

Contexte

Plasma-derived coagulation factors VIII and IX have been included on the EML and EMLc since 1979 and 2007, respectively. In 2007, in consideration of the inclusion of plasma-derived coagulation factors on the first EMLc, the EMLc Subcommittee recognized that plasma fractions were essential medicines for both adults and children. The Subcommittee noted comments that recombinant products should be used in preference to dried and plasma-derived products and considered that recombinant products would be covered by the existing square box listings (1). 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 (2). Thus, the Secretariat invited the World Federation of Hemophilia to submit an application reviewing the therapeutic alternatives for these medicines. At its meeting in 2023, the Expert Committee considered a submission from the World Federation of Hemophilia addressing the request of the 2021 Expert Committee. The submission recommended the inclusion of recombinant factors VIII and IX as therapeutic alternatives to their respective plasma-derived counterparts based on: human-derived and recombinant coagulation factor products being classified with the same Anatomical Therapeutic Chemical (ATC) code; 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; and recommendations in Federation's guidelines for the management of haemophilia. A comprehensive review of the available evidence was not provided in the application. In making its recommendation, the 2023 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 (3).

Pertinence pour la santé publique



The public health relevance of treatments for haemophilia is well established. According to the 2022 World Federation of Hemophilia annual global survey, more than 250 000 people (mostly males) were living with haemophilia. The incidence of haemophilia A was about 1 in 4000 to 5000 live male births, about 50–60% of whom have severe disease (FVIII activity < 1% of normal), which is associated with high rates of spontaneous bleeding that may necessitate prophylactic treatment. The incidence of haemophilia B was about 1 in 15 000 to 30 000 live male births, of whom about a third to a half have severe disease (FIX activity < 1% of normal) (4). For haemophilia A, the estimated prevalence per 100 000 males is 17.1 cases for all severities and 6.0 cases for severe haemophilia A. For haemophilia B, the estimated prevalence per 100 000 males is 3.8 cases for all severities of haemophilia B and 1.1 cases for severe haemophilia B (5). Globally, almost 12 000 females with haemophilia have been identified (4). Studies have shown that lack of treatment results in lower life expectancy with life expectancy disadvantages of about 93% for people with haemophilia in low-income countries, 77% in lower middle-countries and 64% in upper middle-countries (5). Until the introduction of coagulation factor concentrates in the mid-1960s, the average life expectancy for boys with severe haemophilia was less than 20 years and quality of life was generally afflicted by joint bleeding complications and, in many cases, intracranial haemorrhage (6). Those who survived had complications of frequent bleeding involving their weight-bearing joints, resulting severe and incapacitating joint damage. The incidence of intracranial haemorrhage was about 1 in 200 per year and often resulted in severe permanent brain damage in those who survived the initial bleeding episode (6, 7).

Bénéfices



Clotting factor concentrates are used in the treatment of haemophilia as on-demand/episodic factor replacement administered after the onset of bleeding and as prophylactic therapy administered regularly to provide sufficient FVIII and FIX to prevent spontaneous bleeding and to have normal coagulation function after any trauma (6). Substantial evidence exists that prophylaxis is associated with improved joint outcomes, decreased physical pain and better health-related quality of life compared with episodic treatment (8). Without prophylactic treatment, individuals with haemophilia may have on average two to five spontaneous bleeding episodes each month including joint bleeds and deep-muscle haematomas. They may also experience prolonged bleeding or excessive pain and swelling from minor injuries, surgery and tooth extractions (9). Accordingly, primary prophylaxis with clotting factor concentrates has become the standard of care for people with severe haemophilia. A 2022 systematic review and meta-analysis of nine randomized controlled trials compared the effects of factor replacement therapies on people with haemophilia (10). Six of the trials compared episodic versus prophylactic treatment in patients with haemophilia A, with two studies using plasma-derived FVIII and four using recombinant FVIII. Meta-analyses of these studies found very-low-certainty evidence of significant differences in annualized bleeding rates and annualized joint bleeding rates favouring prophylaxis. Compared with episodic treatment, the annualized bleeding rate was lower for: low-dose prophylaxis (ratio of means (RM) 0.27, 95% confidence interval (CI) 0.17 to 0.43; two randomized controlled trials, 71 participants); intermediate-dose prophylaxis (RM 0.15, 95% CI 0.07 to 0.36; four randomized controlled trials, 237 participants); and high-dose prophylaxis (RM 0.07, 95% CI 0.04 to 0.13; one randomized controlled trial, 52 participants). Similarly, compared with episodic treatment, annualized joint bleeding rates were lower for: low-dose prophylaxis (RM 0.17, 95% CI 0.06 to 0.43; two randomized controlled trials, 71 participants); intermediate-dose prophylaxis (RM 0.14, 95% CI 0.07 to 0.27; four randomized controlled trials, 237 participants); and high-dose prophylaxis (RM 0.08, 95% CI 0.04 to 0.16; one randomized controlled trial, 52 participants). Meta-analysis also showed that patients who received intermediate-dose prophylaxis had a lower rate of radiographical findings compared with those who used episodic treatment (risk ratio (RR) 0.36, 95% CI 0.18 to 0.71; two randomized controlled trials, 95 participants). In comparison to the on-demand group, the low-dose group had a lower median score on the Haemophilia Joint Health Score. One of the studies evaluated administration of recombinant FIX at the same dose at different time intervals (50 IU/kg twice weekly versus 100 IU/kg weekly) compared with on-demand therapy (11). Both prophylaxis regimens were significantly reduced annualized bleeding rates compared with on-demand therapy: mean annualized bleeding rates 35.1 with on-demand therapy, 2.6 with twice weekly prophylaxis and 4.6 with weekly prophylaxis. No significant difference was seen in mean annualized bleeding rates between prophylaxis regimens. The mean annualized joint bleeding rate was 25.4 in the on-demand group, 1.9 in the twice-weekly group and 3.6 in the weekly group (no P-value provided). These results had a very-low-certainty of evidence. Prophylactic use of FVIII and FIX has been shown to offer better outcomes for patients with moderate or severe haemophilia compared with on-demand use, including in resource-constrained settings (12–15).

Torts



Viral safety and purity In the late 1970s to early 1980s, thousands of people with haemophilia globally were infected with human immunodeficiency virus (HIV) and hepatitis C virus through contaminated plasma-derived factor concentrates and blood products. This led to the development of viral inactivation technologies and measures in manufacturing, most commonly using a combination of solvent detergent exposure, nanofiltration and pasteurization or dry heat exposure. These techniques prevent transmission of lipid-enveloped viruses such as HIV and hepatitis C virus but not non-lipid-enveloped pathogens such as parvovirus B19 (16). The implementation of donor selection, plasma screening, nucleic acid testing, robust viral inactivation processes and post-marketing surveillance over the past 40 years has led to a substantial reduction in bloodborne infections in patients with haemophilia treated with plasma-derived and recombinant products (17). Both types of coagulation factor are now manufactured in adherence to good manufacturing practices and have strong safety records related to transmission of viruses such as HIV and hepatitis C virus and other transmissible agents such as prions. However, plasma-derived factor concentrates always carry a theoretical risk of contamination with transmissible viruses and most recombinant factor concentrates have trace amounts of human proteins which present an extremely small risk of viral infectivity. Immunogenicity and inhibitor formation An important complication of treatment of haemophilia with coagulation factor concentrates is the formation of inhibitors (neutralizing alloantibodies) against FVIII or FIX, potentially leading to failure of replacement therapy and increasing the risk of bleeding episodes. About 30% of patients with severe haemophilia A and between 9% and 23% of

patients with severe haemophilia B are reported to develop inhibitors. Inhibitor development is associated with increased morbidity and mortality (18). The SIPPET study was a randomized controlled trial that evaluated the incidence of FVIII inhibitors in previously untreated or minimally treated boys with severe haemophilia A treated with plasma-derived FVIII containing von Willebrand factor or recombinant FVIII (19). A total of 264 participants were randomized in a 1:1 ratio to receive plasma-derived or recombinant FVIII, 251 of whom received treatment and were analysed. For the primary endpoint of all inhibitors, development of inhibitors was reported in 29/125 (23.2%) patients who received plasma-derived FVIII, and 47/126 (37.3%) patients who received recombinant FVIII. The cumulative inhibitor incidence for plasma-derived FVIII and recombinant FVIII was 26.7% and 44.5%, respectively. In Cox regression models for the primary endpoint, recombinant FVIII was associated with a significantly higher incidence than plasma-derived FVIII (hazard ratio (HR) 1.87, 95% CI 1.17 to 2.96). For high-titre inhibitors, the HR was 1.69 (95% CI 0.96 to 2.98). When second-generation full-length recombinant FVIII was excluded from the analysis, the results were similar for all inhibitors (HR 1.98, 95% CI 0.99 to 3.97) and also for high-titre inhibitors (HR 2.59, 95% CI 1.11 to 6.00). An observational study conducted by the RODIN study group evaluated data from 574 previously untreated patients with severe haemophilia A receiving coagulation factors to determine the risk of inhibitor development (20). Inhibitor development was reported in 32.4% of participants. Plasma-derived and recombinant coagulation factors showed similar risk of inhibitor development (adjusted HR 0.96, 95% CI 0.62 to 1.49). However, there was a higher incidence of inhibitor formation associated with second-generation full-length recombinant products produced in baby hamster kidney cells compared with third-generation full-length recombinant products. Another observational study investigated the difference in inhibitor development between different brands of recombinant FVIII in 407 previously untreated children with severe haemophilia A in the United Kingdom (21). Inhibitors developed in 118 (29%) participants. Of 128 participants who received Kogenate Bayer/Helixate NexGen, 45 (35%) developed an inhibitor compared with 42/172 (24%) who received Advate. The adjusted HR for all inhibitors for the former compared to the latter brand was 1.75 (95% CI 1.11 to 2.76; P = 0.01). A French observational study compared the incidence of development of inhibitors in 395 previously untreated boys with severe haemophilia A following treatment with plasma-derived FVIII and two recombinant FVIII products, Kogenate Bayer and Advate (22). A total of 131, 137 and 127 boys were treated with plasma-derived FVIII, Advate and Kogenate Bayer, respectively). Clinically significant inhibitors were diagnosed in 121 patients. The cumulative incidences of inhibitors at 75 exposure days were 12.7% (plasma-derived FVIII), 20.4% (Advate) and 31.6% (Kogenate Bayer).

Rapport coût/efficacité



The cost-utility of haemophilia treatments varies based on the treatment approach, patient characteristics and disease severity (8). Direct medical costs include the cost of medical treatments, health services, and surgical and medical supplies (23). Clotting factor concentrates for patients with severe haemophilia usually account for more than 90% of treatment-related costs (24). The medical and pharmaceutical costs of treating and preventing bleeding episodes in people with haemophilia have previously been evaluated from various data sources (e.g. claims databases, surveys and chart reviews) and are substantial (25–30). Alternative medicines to recombinant FVIII and FIX include plasma-derived coagulation factors, extended half-life recombinant FVIII and FIX, FVIII mimetics (e.g. emicizumab), anti-tissue-factor pathway inhibitors, rebalancing agents (e.g. concizumab and marstacimab) and gene therapy. The application stated that when standard half-life recombinant factors VIII and IX were first marketed in 1994 and 1997, respectively, the prices tended to be significantly higher per IU than prices for plasma-derived FVIII and FIX concentrates. Following the introduction of extended half-life recombinant FVIII and FIX concentrates, the prices of standard half-life recombinant products decreased, becoming competitive with plasma-derived concentrates. This trend continued with the introduction and availability of emicizumab. The application included a summary of the global availability and prices of haemophilia treatments from unpublished data collected by the World Federation of Haemophilia (refer to Table 9, TRS 1064). A 2023 prospective study evaluated the cost-effectiveness of low- and intermediate-dose prophylaxis versus on-demand treatment in adults and children with moderate-to-severe haemophilia A from a societal perspective in India (31). Over a lifetime horizon, both low- and intermediate-dose prophylactic FVIII therapy were cost-effective for both adults and children compared with on-demand therapy at the patient level. The high costs of managing haemophilia A were reported in a 2023 review of studies on health-care costs and resources use in the United States (25). Total yearly health-care costs ranged between US\$ 213 874 and US\$ 869 940 per patient and were largely driven by treatment choice, cost and intensity of prophylaxis therapy. The mean annual costs were between US\$ 762 609 and US\$ 831 702 for standard half-life recombinant FVIII, US\$ 832 595 and US\$ 1.1 million for extended half-life recombinant FVIII, and were US\$ 693 709 for plasma-derived products and US\$ 358 384 for emicizumab. Data from five studies showed that average yearly outpatient costs ranged between US\$ 4772 and US\$ 109 776, and costs associated with emergency department visits ranged between US\$ 828 and US\$ 3929. Data from six studies showed average inpatient costs of between US\$ 12 336 and US\$ 237 648. Additionally, parents of children with haemophilia A encountered higher health-service costs than control parents, and affected individuals faced considerable indirect costs, including productivity loss, costs for caregivers' unpaid time and patient disability.

Directives de l'OMS



WHO guidelines for the treatment of haemophilia are not currently available. The application presented a summary of consensus-based guidelines for the management of haemophilia from the World Federation of Hemophilia (23). Among the recommendations is one that states that the Federation does not express a preference for recombinant over plasma-derived clotting factor concentrates and that the choice between these classes of product must be made according to local criteria including availability, cost and patient preference. Additionally, for patients with severe haemophilia A or B in countries with health-care constraints, the guidelines include a strong recommendation for prophylaxis over episodic factor replacement therapy to reduce haemarthroses and other spontaneous and breakthrough bleedings and better preserve joint function

Disponibilité



Recombinant FVIII and FIX products are approved by regulatory agencies in high- and upper middle-income countries. Recombinant FVIII and FIX products that were approved between 1992 and 2004 are now off patent. Multiple recombinant FVIII and FIX products are reported to be available globally. There are multiple recombinant FVIII and recombinant FIX clotting factor concentrates approved and available on the market across all regions of the world. The

application stated that 49/103 countries that reported FVIII use indicated having purchased recombinant products, and 36/92 countries that reported FIX use indicated having purchased recombinant products. In addition, more than 70 countries receive donations of treatment products, mostly recombinant clotting factor concentrates, from the World Federation of Haemophilia Humanitarian Aid Program each year.

Autres considérations



Accurate diagnosis of haemophilia is essential to inform appropriate management. Genetic assessment, coagulation tests and factor assessments are used to diagnose haemophilia, differentiate genotypes and predict the risk of inhibitor development. Haemophilia should be suspected in a male or female presenting with any of the clinical manifestations of haemophilia (such as spontaneous or injury-related bleeding, particularly in the joints and muscles; easy bruising and haematoma; excessive bleeding associated with medical procedures, surgery or trauma; mucosal bleeding (oral, nasal and genitourinary membranes); intracranial haemorrhage; gastrointestinal and abdominal bleeding; and central nervous system bleeds), and blood tests show normal platelet count, prolonged activated partial thromboplastin time, and normal prothrombin time (9). The diagnosis of haemophilia is established by identification of decreased FVIII and FIX clotting activity and a normal, functional level of von Willebrand factor, and/or identification of an F8 or F9 gene variant by molecular genetic testing. A definitive haemophilia diagnosis is based on a factor assay to demonstrate deficiency of FVIII or FIX clotting activity. Occasionally, discrepancies in test results may occur. A standard one-stage factor assay shows near-normal or low-normal FVIII and FIX activity (40%-80%), whereas a two-stage chromogenic assay shows low FVIII and FIX activity therefore, low-normal in vitro clotting activity does not always exclude the presence of mild haemophilia (9). Genetic assessment of haemophilia is important in defining disease biology, establishing diagnosis in difficult cases, predicting risk of inhibitor development, identifying female carriers, and providing prenatal diagnosis, if desired. Genotype analysis should be offered to all people with haemophilia and their at-risk female family members (23). The Blood and Other Products of Human Origin team within the Department of Health Products, Policy and Standards reviewed the application and supported the inclusion of recombinant coagulation factors on the EML and EMLc.

Afficher les références Masquer les références

1. 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>).
2. 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>).
3. The selection and use of essential medicines. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2023 (including the 23rd WHO Model List of Essential Medicines and the 9th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2024 (WHO Technical Report Series, No. 1049; <https://iris.who.int/handle/10665/376570>).
4. World Federation of Hemophilia. Report on the Annual Global Survey 2022. World Federation of Hemophilia, 2023 (<https://www1.wfh.org/publications/files/pdf-2399.pdf>).
5. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C et al. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. *Ann Intern Med.* 2019;171(8):540-6 (<https://doi.org/10.7326/M19-1208>).
6. Powell JS. Recombinant factor VIII in the management of hemophilia A: current use and future promise. *her Clin Risk Manag.* 2009;5(2):391-402 (<https://doi.org/10.2147/tcrm.s4412>).
7. Ljung RC. Intracranial haemorrhage in haemophilia A and B. *Br J Haematol.* 2008;140(4):378-84 (<https://doi.org/10.1111/j.1365-2141.2007.06949.x>).
8. Thorat T, Neumann PJ, Chambers JD. Hemophilia Burden of Disease: A Systematic Review of the Cost-Utility Literature for Hemophilia. *J Manag Care Spec Pharm.* 2018;24(7):632-42 (<https://doi.org/10.18553/jmcp.2018.24.7.632>).
9. Konkle BA, Nakaya Fletcher S. Hemophilia A. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. *GeneReviews®* ([Internet]. Seattle (WA)1993: (Available from: <https://www.ncbi.nlm.nih.gov/pubmed/20301578>).
10. Delgado-Flores CJ, García-Gomero D, Salvador-Salvador S, Montes-Alvis J, Herrera-Cunti C, Taype-Rondan A. Effects of replacement therapies with clotting factors in patients with hemophilia: A systematic review and meta-analysis. *PLoS One.* 2022;17(1):e0262273 (<https://doi.org/10.1371/journal.pone.0262273>).
11. Valentino LA, Rusen L, Elezovic I, Smith LM, Korth-Bradley JM, Rendo P. Multicentre, randomized, open-label study of on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in haemophilia B subjects. *Haemophilia.* 2014;20(3):398-406 (<https://doi.org/10.1111/hae.12344>).
12. Chozie NA, Primacakti F, Gatot D, Setiabudhy RD, Tulaar ABM, Prasetyo M. Comparison of the efficacy and safety of 12-month low-dose factor VIII tertiary prophylaxis vs on-demand treatment in severe haemophilia A children. *Haemophilia.* 2019;25(4):633-9 (<https://doi.org/10.1111/hae.13770>).
13. Gouider E, Jouini L, Achour M, Elmahmoudi H, Zahra K, Saied W et al. Low dose prophylaxis in Tunisian children with haemophilia. *Haemophilia.* 2017;23(1):77-81 (<https://doi.org/10.1111/hae.13048>).
14. Tang L, Wu R, Sun J, Zhang X, Feng X, Zhang X et al. Short-term low-dose secondary prophylaxis for severe/moderate haemophilia A children is beneficial to reduce bleed and improve daily activity, but there are obstacle in its execution: a multi-centre pilot study in China. *Haemophilia.* 2013;19(1):27-34 (<https://doi.org/10.1111/j.1365-2516.2012.02926.x>).
15. Verma SP, Dutta TK, Mahadevan S, Nalini P, Basu D, Biswal N et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - A success story from a resource limited country. *Haemophilia.* 2016;22(3):342-8 (<https://doi.org/10.1111/hae.12838>).
16. Key NS, Negrier C. Coagulation factor concentrates: past, present, and future. *Lancet.* 2007;370(9585):439-48 ([https://doi.org/10.1016/S0140-6736\(07\)61199-4](https://doi.org/10.1016/S0140-6736(07)61199-4)).
17. Mannucci PM. Clinical evaluation of viral safety of coagulation factor VIII and IX concentrates. *Vox Sang.* 1993;64(4):197-203 (<https://doi.org/10.1111/j.1423-0410.1993.tb03055.x>).
18. Abdi A, Bordbar MR, Hassan S, Rosendaal FR, van der Bom JG, Voorberg J et al. Prevalence and Incidence of Non-neutralizing Antibodies in Congenital Hemophilia A- A Systematic Review and Meta-Analysis. *Front Immunol.* 2020;11:563 (<https://doi.org/10.3389/fimmu.2020.00563>).
19. Peyvandi F, Mannucci PM, Garagiola I, El-Beshlawy A, Elalfy M, Ramanan V et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *N Engl J Med.* 2016;374(21):2054-64 (<https://doi.org/10.1056/NEJMoa1516437>).
20. Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeysens-Donadel S et al. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med.* 2013;368(3):231-9 (<https://doi.org/10.1056/NEJMoa1208024>).
21. Collins PW, Palmer BP, Chalmers EA, Hart DP, Liesner R, Rangarajan S et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. *Blood.* 2014;124(23):3389-97 (<https://doi.org/10.1182/blood-2014-07-580498>).
22. Calvez T,

Chambost H, d'Oiron R, Dalibard V, Demiguel V, Doncarli A et al. Analyses of the FranceCoag cohort support differences in immunogenicity among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A. *Haematologica*. 2018;103(1):179-89 (<https://doi.org/10.3324/haematol.2017.174706>). 23. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158 (<https://doi.org/10.1111/hae.14046>). 24. Globe DR, Curtis RG, Koerper MA, Committee HS. Utilization of care in haemophilia: a resource-based method for cost analysis from the Haemophilia Utilization Group Study (HUGS). *Haemophilia*. 2004;10 Suppl 1:63-70 (<https://doi.org/10.1111/j.1355-0691.2004.00881.x>). 25. Chen Y, Cheng SJ, Thornhill T, Solari P, Sullivan SD. Health care costs and resource use of managing hemophilia A: A targeted literature review. *J Manag Care Spec Pharm*. 2023;29(6):647-58 (<https://doi.org/10.18553/jmcp.2023.29.6.647>). 26. Croteau SE, Cheng D, Cohen AJ, Holmes CE, Malec LM, Silvey M et al. Regional variation and cost implications of prescribed extended half-life factor concentrates among U.S. Haemophilia Treatment Centres for patients with moderate and severe haemophilia. *Haemophilia*. 2019;25(4):668-75 (<https://doi.org/10.1111/hae.13758>). 27. Thornburg CD, Adamski K, Cook K, Vembusubramanian M, Sendhil SR, Hinds D et al. Health care costs and resource utilization among commercially insured adult patients with hemophilia A managed with FVIII prophylaxis in the United States. *J Manag Care Spec Pharm*. 2022;28(4):449-60 (<https://doi.org/10.18553/jmcp.2021.21368>). 28. Samelson-Jones BJ, Guelcher C, Kuhn J, Butler R, Massey G, Guerrero MF et al. Real-world cost estimates of initiating emicizumab in US patients with haemophilia A. *Haemophilia*. 2021;27(4):591-8 (<https://doi.org/10.1111/hae.14347>). 29. Farej R, Batt K, Afonja O, Martin C, Aubert R, Carlyle M et al. Characterizing female patients with haemophilia A: Administrative claims analysis and medical chart review. *Haemophilia*. 2020;26(3):520-8 (<https://doi.org/10.1111/hae.13981>). 30. Zhou ZY, Koerper MA, Johnson KA, Riske B, Baker JR, Ullman M et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. *J Med Econ*. 2015;18(6):457-65 (<https://doi.org/10.3111/13696998.2015.1016228>). 31. Seth T, Garg K, Mandal PK, Datta A, Verma S, Hanagavadi S et al. Cost-effectiveness analysis of low-dose prophylaxis versus on-demand treatment for moderate-to-severe hemophilia A in India. *Hematology*. 2023;28(1):2277497 (<https://doi.org/10.1080/16078454.2023.2277497>).