HEMOPHILIA

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Hemophilia

Clinical Guidance- Issued May 2020

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Abbreviations

AAV	Adeno-Associated Virus
ABR	Annual Bleed Rate
ADA	Antidrug Antibodies
aPCC	Activated Prothrombin Complex Concentrate
aPTT	Activated Partial Thromboplastin Time
ASH	American Society of Hematology
BPA	Bypassing Agents
CB	Consensus-Based
CBA	Collagen Binding Assays
CCC	Comprehensive Care Centre
CFC	Clotting Factor Concentrates
CHI	Council of Health Insurance
CSA	Chromogenic Substrate Assays
DDAVP	Desmopressin Acetate
EACA	Epsilon Aminocaproic Acid
EDs	Exposure Days
EHL	Extended Half-Life
EMA	European Medicines Agency
EU	Emergency Units
FDA	Food and Drug Administration (US)
FFP	Fresh Frozen Plasma
FIX	Factor IX
FIXa	Factor IXa
FVIII	Factor VIII
FVIIIa	Factor VIIIa
FXa	Factor Xa
GT	Gene Therapy

HA	Hemophilia A
HCP	Healthcare Provider
HTC	Hemophilia Treatment Center
IDF	CHI Drug Formulary
ISTH	International Society on Thrombosis and Hemostasis
ITI	Immune Tolerance Induction
IV	Intravenous
NHF	National Hemophilia Foundation
OSA	One-Stage Assay
PCCs	Prothrombin Complex Concentrate
PK	Pharmacokinetics
PO	Per Os (Orally)
PwHA	People with Hemophilia A
PwHB	People with Hemophilia B
QDS	Four Times Daily
RBD	Rare Bleeding Disorder
RCo	Ristocetin Cofactor Activity
rFVIIa	Recombinant Activated Factor VIIa
RICE	Rest, Ice, Compression, and Elevation
SFDA	Saudi Food and Drug Authority
SHL	Standard Half-Life
TDS	Three Times Daily
TFPI	Tissue Factor Pathway Inhibitor
TMA	Thrombotic Microangiopathy
VTE	Venous Thromboembolism
VWD	Von Willebrand Disease
VWF	Von Willebrand Factor
vWF:RCo	Von Willebrand Ristocetin Cofactor
WFH	World Federation of Hemophilia

Executive Summary

Hemophilia is typically an inherited bleeding disorder characterized by impaired blood clotting. Individuals with hemophilia may experience spontaneous bleeding episodes, as well as increased bleeding following injuries or surgical procedures. The blood contains various proteins known as clotting factors, which play a crucial role in controlling and halting bleeding. In individuals with hemophilia, deficiencies or abnormalities in these clotting factors can lead to prolonged bleeding and a heightened risk of bleeding-related complications[1].

Hemophilia A and B are X-linked disorders that primarily impact males. It is vital to distinguish between hemophilia and other conditions, such as specific types of von Willebrand disease, rare coagulation factor deficiencies, or acquired factor inhibitors, as well as to differentiate between hemophilia A and B. This distinction is crucial for ensuring the correct and effective management of these bleeding disorders. Hemophilia typically refers to an inherited bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A), factor IX (hemophilia B), or factor XI (hemophilia C)[2].

Hemophilia affects more than 1.2 million individuals (mostly males) worldwide. Hemophilia A is more common than hemophilia B[2]. The prevalence of bleeding disorders in many Arab countries, including Saudi Arabia, remains unknown. However, clinical practice suggests that these disorders might be relatively more common, possibly due to a higher concentration of mutated genes and increased rates of consanguineous marriages. In a limited bleeding surveillance study involving approximately 4,000 adolescents and young adults, it was observed that around 20% of individuals exhibited one or more bleeding symptoms. Additionally, up to 10% of the participants, particularly females, were found to have iron deficiency[3].

Hemophilia is categorized into mild, moderate, or severe forms, depending on the residual or baseline factor activity level, which is often expressed as a percentage of normal or in international units (IU) per milliliter (mL). The clinical manifestations of hemophilia are associated with bleeding resulting from impaired hemostasis, the consequences of bleeding episodes, or complications arising from the administration of coagulation factor infusions[2].

In individuals with hemophilia experiencing acute bleeding, the primary objective is to elevate the factor activity to a level that ensures effective hemostasis. The specific targeted factor activity level depends on factors such as the location and severity of the bleeding, the expected duration of the administered treatment product, and the presence of any related injuries or incidents, as detailed in the following sections[4].

The main treatment options for hemophilia include emicizumab (hemophilia A), bypassing agents, recombinant porcine factor VIII (hemophilia A), desmopressin (DDAVP) (hemophilia A), and antifibrinolytics such as tranexamic acid (TXA) and epsilon aminocaproic acid (EACA)[4].

CHI issued Hemophilia clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Hemophilia clinical guidance and seeks to offer guidance for the effective management of Hemophilia. It provides an **update on Hemophilia** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely **WFH Guidelines** for the Management of Hemophilia, 3rd edition **(2020)**. Moreover, new guidelines are added to the report such as **Consensus recommendations** on appropriate coagulation tests during emicizumab administration in **Saudi Arabia (2022)**, **ASH ISTH NHF WFH 2021 guidelines** on the management of von Willebrand disease, **Adults with Hemophilia and Related Bleeding Disorders Acute Treatment Guidelines 2023**, **New Zealand National Guidelines** for the Management of Hemophilia **2022**, **International consensus** recommendations on the management of people with hemophilia B **(2022)**, Emergency management in patients with hemophilia A and inhibitors on prophylaxis with emicizumab: **AICE practical guidance in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET (2019)** and **Practical Guidance of the GTH** Hemophilia Board on the Use of Emicizumab in Patients with Hemophilia A **(2020)**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, new medications were added to the report that were already registered in the SFDA including: **Anti-inhibitor coagulant complex, (Antihemophilic factor, pegylated (MW 20000) human sequence recombinant), Catridecacog, Efmoroctocog alfa, Eftrenonacog alfa, Human coagulation factor VIII / human von Willebrand factor, Moroctocog alfa, Omfiloctocog alfa, Plasma Protein fraction, Turoctocog alfa and Eptacog alfa. Furthermore, "Emergency Use (EU)" was removed as a prescribing edit from multiple medications including** ANTIHEMOPHILIC FACTOR, PEGYLATED (MW 20000) HUMAN SEQUENCE RECOMBINANT, CATRIDECACOG, EFMOROCTOCOG ALFA, EFTRENONACOG ALFA, HUMAN COAGULATION FACTOR VIII, HUMAN VON WILLEBRAND FACTOR, MOROCTOCOG ALFA, OMFILOCTOCOG ALFA, Turoctocog alfa and EPTACOG ALFA. Moreover, MD was added as a

prescribing edit for EFTRENONACOG ALFA and HUMAN COAGULATION FACTOR VIII, HUMAN VON WILLEBRAND FACTOR.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the therapeutic management of hemophilia.

Below is a table summarizing the major changes based on the different Hemophilia guidelines used to issue this report:

Table 1. General Recommendations for the Management of Hemophilia

Management of Hemophilia		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Comprehensive education is essential for individuals with hemophilia to empower them with knowledge and self-management skills.	Consensus - based	WFH Guideline 2020[5]
Encourage consistent engagement in physical activities and fitness routines to preserve bone health and improve physical capabilities.	Consensus - based	WFH Guideline 2020[5]
Follow PRICE (protection, rest, ice, compression, elevation) protocol for muscle or joint bleeding.	Consensus - based	WFH Guideline 2020[5]
For people with hemophilia with venous access pain, discomfort**,** or anxiety, the WFH recommends the application of a local anesthetic spray or cream at the site of venous access.	Consensus - based	WFH Guideline 2020[5]
The WFH does not show a preference for recombinant clotting factor concentrates over those derived from plasma when it comes to individuals with hemophilia. The decision between these categories of products should be determined based on local considerations, including factors like	Consensus - based	WFH Guideline 2020[5]

availability, expenses, and patient inclinations.		
For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends considering desmopressin (DDAVP) as an option for treatment.	Consensus - based	WFH Guideline 2020[5]
Tranexamic Acid, an antifibrinolytic medication, is prescribed for patients with hemophilia for short-term use (ranging from two to eight days) with the aim of minimizing or averting bleeding episodes.	Not graded	Guidelines Adult Comprehensive Care Centres (CCC) Ireland (2023)[6]
Bypassing agents are used in Hemophilia A with inhibitors and prophylaxis as well as in hemophilia B.	Not graded	Guidelines Adult Comprehensive Care Centres (CCC) Ireland (2023)[6]
In most cases, patients diagnosed with type I von Willebrand disease (VWD) are typically managed using Tranexamic acid and/or DDAVP (Desmopressin) as the conventional treatment approach.	Not graded	New Zealand National Guidelines 2022[7]

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI hemophilia report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the May 2020 hemophilia report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 Diagnosis and Management Guidelines of Hemophilia in **Saudi Arabia** [**2016**]	N/A*
1.2 Nordic Hemophilia Guidelines [Updated 2020]	1.1.1 **Nordic** Hemophilia Guidelines (Updated October **2022**)
1.3 GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA (2nd edition)- Prepared by the Treatment Guidelines Working Group, on behalf of the **World Federation of Hemophilia** (WFH) [**2012**] [updated 2013] & GUIDLEINES FOR ACQUIRED HEMOPHILIA- Revised edition [2012]	1.1.2 **WFH** Guidelines for the Management of Hemophilia, 3rd edition (**2020**)
1.4 GUIDELINES FOR EMERGENCY DEPARTMENT MANAGEMENT OF INDIVIDUALS WITH HEMOPHILIA AND OTHER BLEEDING DISORDERS- **National Hemophilia Foundation** [**2019**]	N/A*
1.5 Treatment guidelines for acquired hemophilia A- Department of	N/A*

Hemostasis Disorders and Internal Medicine, **Institute of Hematology and Transfusion Medicine**, Warsaw, Poland [**2019**]	
1.6 Guidelines for the management of acute joint bleeds and chronic synovitis in hemophilia A United Kingdom Hemophilia Centre Doctors' Organisation (**UKHCDO**) guideline [**2017**]	N/A*
1.7 Updated **Australian consensus** statement on management of inherited bleeding disorders in pregnancy [**2019**]	N/A*
1.8 Guideline for the diagnosis and management of the rare coagulation disorders- A United Kingdom Hemophilia Centre Doctors' Organization (**UKHCDO**) guideline on behalf of the **British Committee for Standards in Haematology** [**2014**]	N/A*
1.9 The diagnosis and management of von Willebrand disease (VWD): a United Kingdom Hemophilia Centre Doctors Organization (**UKHCDO**) guideline approved by the **British Committee for Standards in Haematology** [**2014**]	N/A*
1.10 **Nordic Hemophilia Council's** Practical Guidelines on Diagnosis and Management of von Willebrand Disease [2011]	N/A*
1.11 The diagnosis, evaluation, and management of Von Willebrand disease- **U.S Department of Health and Human Services** [**2008**]	N/A*

*****: *No updated versions available*

1.1.1 Nordic Hemophilia Guidelines (2022)

The Nordic Hemophilia Council published in October 2022 an updated guideline on the management of **congenital hemophilia**. The main recommendations are detailed below[8]:

- Primary prophylaxis in severe hemophilia should start around the age of one or earlier before joint bleeds occur.
- Patients with moderate hemophilia with a factor level of 0.01-0.02 kIU/L should also be offered primary prophylaxis.
- Prophylaxis is recommended to continue during adulthood and in elderly patients.
- The goal is prevention of joint disease and intracranial bleeds (ICH).

Choice of prophylaxis

- In hemophilia A, early prophylaxis with emicizumab to avoid ICH can be considered, when available. The pros and cons of continuous prophylaxis with clotting factor concentrates (CFC) versus emicizumab should be discussed with the family.
- Recombinant rather than plasma derived CFC should be used when available. In families with high risk of inhibitors, the choice should be discusse.
- Prophylaxis with CFC can be initiated with standard CFC or EHL products.

Prophylaxis with CFC

- Prophylaxis with CFC is initiated with a dose of FVIII around 25 IU/kg once or twice a week, or FIX around 50 IU/kg once a week.
- In hemophilia B, the first five injections could be done in a hospital setting, due to the risk of anaphylactic reactions.
- As soon as venous access allows, the frequency is increased. A central venous access device may be considered. The aim is full scale prophylaxis. For hemophilia A, that corresponds to a dose of 20-40 IU/kg standard FVIII every second day, or at least three times weekly, or 20-50 IU/kg EHL FVIII two or three times weekly. For hemophilia B the dose is 30-40 IU/kg standard FIX every third day, or twice weekly, or 30-50 IU/kg EHL FIX once weekly. The dose is tailored according to clinical response. Dose per kg body weight can often be lowered with age. At routine checkup, the previous factor infusion should be registered in detail (time point, dose), and a blood sample taken, for pharmacokinetic calculation (PK).

- When switching to EHL CFC, PK measurement is recommended. A recommended PK sampling schedule is sampling at peak and trough and one sampling in between. Frequency of injections should be planned individually, according to patient activities and need for peak levels, and doses adjusted according to trough and bleeding pattern. Trough levels should be reassessed at steady state, after 5 doses.
- Assessment of individual clinical response should include bleeding rate, recorded by the patient/parents, and joint score by a physiotherapist. Ultrasound (US) is recommended as a supplement in joint assessment. Quality of life (QOL) should be monitored. Young children with severe or moderate hemophilia are monitored at least every 6 months. Older children and adults can be monitored every 12 months. In mild hemophilia, monitoring depends on bleeding phenotype.

Treatment of bleeds

- Acute bleeds during prophylaxis are initially treated with a single or a double prophylactic dose of CFC depending on severity of the bleeding. Potentially life-threatening bleeds, such as head trauma, are initially treated with a double dose, to reach a factor level of minimum 0.70-1.00 kIU/L.
- In patients with moderate or mild hemophilia, treatment of acute bleeds on demand is tailored to reach a factor level of 0.40-0.60 kIU/L in minor bleeds, and 0.70-0.80 kIU/L in severe or life-threatening bleeds.
- In mild hemophilia A, DDAVP should be tested as alternative to factor replacement therapy.

Adolescence

- A transition program is recommended to secure continuous adherence in adolescents during transfer from pediatric to adult service.

Bypassing agents for the treatment of bleeds

- FVIII and FIX should be used as the first option in patients with a current low inhibitor titer, to saturate the inhibitor and reach a hemostatic factor level. In the case of life-threatening bleeds and a low inhibitor titer, irrespective of the type of inhibitor response, the deficient factor may initially be infused, but FVIII/IX:C should be frequently monitored - at least daily. The risk of allergic reactions associated with FIX concentrates should be taken into consideration.
- The use of bypassing agents at the doses of aPCC 50-100 IU/kg every 6-12 h or rFVIIa 90-120 μg/kg every 2-3 h is indicated for patients with inhibitor levels >5 BU/mL for treatment of any bleed and in those with high-responding

inhibitors but a current low level (< 5 BU/mL) in case of a non-life-threatening bleed to avoid a boostering effect. Children may need higher doses up to 270 μg/kg of rFVIIa as an initial dose followed by lower doses depending on the hemostatic effect.

- rFVIIa is preferred in patients with a known anamnestic response prior to start of ITI, as well as in patients previously not being exposed to plasma products.
- Antibody removal by immunoadsorption might be considered in patients with high inhibitor titers in order to allow treatment with FVIII/IX concentrates.
- Concurrent use of tranexamic acid should always be considered with rFVIIa treatment, but basically also in association with aPCC to improve the hemostatic effect.
- Higher doses of rFVIIa (up to 270 μg/kg) and/or shorter intervals (< 2hrs) should be considered in young children and in the case of treatment failures.
- The daily dose of aPCC should not exceed 200 IU/kg.
- In hemophilia B patients with inhibitors, rFVIIa is preferred. FIX-containing agents e.g. aPCC should not be routinely used.
- In the case of bleeds resistant to monotherapy with each bypassing agent, a sequential use in the order of aPCC (50-75 IU/kg) and rFVIIa (90-100 μg/kg) with an interval of ≥ 2 hrs or a combined use of aPCC (20-30 IU/kg) and rFVIIa (30-60 μg/kg) may be considered. The risk of thromboembolic complications should however be taken into account.

Prevention of bleeds

- Emicizumab subcutaneously (3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly or 3 mg/kg every 2nd week) should be considered as a first-line prophylactic option in patients with hemophilia A and inhibitors following a severe/life-threatening bleed and/or repeated bleeds before, during or in the case of ITI failures. Second-line options in hemophilia A include rFVIIa (90 to 270 μg/kg) once daily intravenously and aPCC (85 IU/kg) every other day intravenously. In hemophilia B patients with inhibitors, the first-line option will be rFVIIa.
- For treatment of breakthrough bleeds requiring additional hemostatic drug intervention during prophylaxis with emicizumab, rFVIIa should be used as first-line option and the initial dose of rFVIIa should not exceed 90 μg/kg. Doses of 45 and 90 μg/kg at a dose interval of 2 to 4 hours may be considered. Due to the hemostatic effect of emicizumab, the number of doses of rFVIIa should be minimized.

- If aPCC and emicizumab together will be required as second line treatment and/or resistant severe bleeds, the initial dose of aPCC should not exceed 50 U/kg. Then, if a second dose of aPCC is considered, the patient should be referred to the hospital for treatment and surveillance for TMA. The total dose of aPCC should not exceed 100 U/kg/d and not provided for more than 24 hours per treatment episode. The recommendation regarding by-pass therapy together with emicizumab should be followed for 6 months after the infusion of emicizumab.
- For all three prophylactic agents, a hemostatic improvement of the bleeding phenotype should be required defined as a reduction in the number of significant bleeds with ≥ 50%.

Immune tolerance induction (ITI) therapy

- The principal goal in all patients with inhibitors should be to eradicate the immune response and tolerize the patient.
- Children and adults with confirmed low-responding inhibitor should continue on regular factor therapy to induce tolerance.
- Children with high-responding inhibitor, but no bleedings may wait with ITI until decline of the inhibitor below 10 BU/mL, but the main approach, and in all cases of bleedings, should however be to start ITI immediately.
- Adult patients with high-responding inhibitors should be offered ITI as for children.
- A high factor dose seems to reduce the time to reach a negative inhibitor titer, and since bleeds mainly occur during this period, a dose of 100-200 IU/kg/d should be first-line option whenever possible. Lower dose, such as 50 IU/kg 3 times weekly, may be used with a similar final outcome – at least in patients with peak inhibitor titers < 200 BU.
- No consistent data indicate the beneficial use of one type of product over the others, but in patients who fail the initial attempt of ITI with high purity FVIII, a VWF-containing FVIII concentrate or EHL products should be considered. The potential role of EHL products for tolerization in resistant cases is however not known.
- Switch of ITI protocol or discontinuation of ITI should be considered when no further significant decline or improvement in clinical phenotype has occurred for 4-6 months.
- In resistant cases and in poor risk patients as well as in adults, the combined use of the deficient factor and immunosuppression should be considered - even as first-line treatment in adult patients.

Surgery in hemophilia - practical guidelines

- Surgical and invasive procedures can be performed safely in PWHs.
- Any surgery in patients with hemophilia and especially inhibitor patients should be planned and executed in close conjunction with a hemophilia treatment center (HTC). PWH undergoing surgery should be daily monitored with daily factor measurements.
- Factor replacement in PWH undergoing surgery can either be given as repetitive bolus infusions or as a continuous infusion.
- Major surgery: FVIII/IX level 0.7-1.0 kIU/L immediately before a surgical procedure and replacement therapy for 7-10 days.
- Tranexamic acid (25 mg/kg p.o / 10 mg/kg i.v.) should be combined with factor replacement 3-4 times daily for 7-10 days.

Surgery in PWHs with inhibitors

- APCC and recombinant activated factor VII (rFVIIa, NovoSeven®) are the treatment of choice in patients where the inhibitor level exceeds 5 BU/mL.

Comorbidities in the ageing patients with hemophilia

- The challenges with comorbidities developing during aging are best managed in close multidisciplinary collaboration with different medical and surgical specialists and networking with patient's local hematologist and primary care physician.
- Joint disease: The goal is to try to protect and improve joint function, relieve pain, and assist the patient in resuming normal activities of daily living by secondary factor prophylaxis, physiotherapy, lifestyle changes, pain management, and orthopedic procedures.
- Osteoporosis: Assessment of bone mineral density status by imaging studies (DEXA scan) and laboratory evaluation are recommended as part of comprehensive hemophilia care. Osteopenia can be prevented or reduced by supplement of calcium, vitamin D and exercise, while osteoporosis necessitates specialist treatment with bisphosphonates, estrogens, calcitonins or monoclonal antibodies.
- Infection related issues: HAART treatment may increase the risk of metabolic syndrome, diabetes, renal insufficiency and atherosclerotic cardiovascular disease and frequency and severity of hemarthrosis, thus close laboratory monitoring and follow-up is recommended.

- Metabolic syndrome: Effective prevention strategies are necessary throughout life. Lipid profile should be measured in ageing hemophilia patients at risk of cardiovascular disease and treatment initiated according to the general guidelines. Glucose levels should be checked annually, especially if overweight. Treatment management, regular clinical and laboratory follow-up should be coordinated with the primary care physician, with consultation services from internal medicine and endocrinology.
- Cardiovascular disease: PWH with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist. DDAVP (desmopressin) should be avoided, and thrombolysis is not recommended. Bare-metal stent should be favored over drug-eluting stent or alternatively coronary artery bypass grafting. Radial artery access site is preferred to reduce bleeding risk. For valve replacement, material that does not necessitate anticoagulation should be chosen. Anticoagulation and antiplatelet therapies are possible with replacement therapy. For atrial fibrillation, no anticoagulation, low-dose aspirin, or warfarin are considered depending on basal factor levels and stroke risk.
- Renal disease: Etiology for recurrent hematuria should be evaluated especially in older patients. Peritoneal dialysis could be the preferred choice since no anticoagulation is needed. Hemodialysis is performed with tailored prophylactic factor dosing.
- Cancer: New, aggravated, or recurring bleeding episodes should be promptly investigated, and relevant hemostatic treatment must be given to prevent bleeds in the setting of diagnostic interventions and prior to surgical, chemo-, or radiotherapeutic treatment. For prostate cancer diagnostics and treatment, antifibrinolytics should be used with caution.

1.1.2 WFH Guidelines for the Management of Hemophilia, 3rd Edition (2020)

*Please refer to **Section 1.3** of CHI Hemophilia original clinical guidance.*

The methods for recommendations grading from the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, 3rd edition (2020)[5] are stated below:

"By design, no recommendations were graded as the vast majority of the evidence base in the field, given the barriers to clinical research and data collection in rare diseases, is insufficient to support meta-analyses. Grading is based on two components, the quality of the evidence and the balance of benefits to harms and/or risks. The former is an assessment of the quality of the evidence supporting the recommendations specific to each outcome. When low-level evidence is partitioned by outcomes, the remaining data are not feasible to support

quantitative analyses. Attempting to grade such recommendations can be misleading to the target audience of healthcare providers. The second component is not explicit in the absence of the quality assessments, so we did not assign a level of strength to the recommendations. Therefore, in the interest of transparency, the WFH guideline recommendations were ***not graded*** *but were clearly marked* ***"CB" for consensus based****."*

A. Self-management and physical exercise

The WFH suggests the provision of **comprehensive education** to individuals with hemophilia, their family members, and other individuals involved in caregiving. This education aims to empower them with the knowledge and skills necessary for effective self-management and a thorough grasp of the condition. This understanding is vital for preventing bleeds, managing associated complications, and making informed decisions for their overall life planning. (CB)

Individuals with hemophilia are advised to encourage consistent engagement in **physical activities** and fitness routines. This recommendation emphasizes the significance of preserving bone health, enhancing muscle strength, refining coordination, improving physical capabilities, maintaining a healthy body weight, and fostering a positive self-image. (CB)

People living with hemophilia are advised to **consult a physical therapist** or another expert specializing in musculoskeletal issues before participating in sports and physical exercises. This consultation is important to determine the suitability of these activities based on the individual's unique condition and to assess any specific physical abilities or protective equipment needed. (CB)

Individuals with hemophilia who experience muscle or joint bleeding are advised to adhere to the **PRICE guidelines** (protection, rest, ice, compression, and elevation) along with elevating their factor level. (CB)

Individuals with hemophilia who have developed hemophilic arthropathy or who are recovering from musculoskeletal bleeding should consider engaging in **physical therapy and rehabilitation exercises**. (CB)

Individuals with hemophilia are advised to consider the utilization of **antifibrinolytic medications** (such as tranexamic acid or epsilon aminocaproic acid [EACA]), either on their own or in combination with other treatments. This is particularly beneficial for managing mucosal bleeds and when facing invasive dental procedures. (CB)

Patients (or caregivers of children) with hemophilia should be taught how to manage their care at home and be able to demonstrate understanding of **how to recognize bleeds** and the ability to infuse or self-infuse, with monitoring of venous access skills over the patient ' s lifetime. (CB)

For children with hemophilia, **central venous access devices** could be considered to facilitate early access to bleed treatment and prophylaxis. (CB)

B. Pain management

The WFH suggests that individuals with hemophilia who experience acute or persistent pain should employ suitable **pain evaluation** instruments suitable for their age. This is to identify the source of pain and direct suitable management approaches. (CB)

For people with hemophilia with venous access pain, discomfort, or anxiety, the application of a **local anesthetic** spray or cream at the site of venous access is recommended. (CB)

For patients with hemophilia and postoperative pain, the WFH recommends **analgesia** similar to that used in patients without hemophilia including, as appropriate, the use of intravenous morphine or other narcotic analgesics, followed by an oral opioid (e.g., tramadol, codeine, hydrocodone, etc.) and paracetamol/acetaminophen as pain decreases. Except for selective COX-2 inhibitors, NSAIDs should not be used in patients with hemophilia. The intramuscular route for administration of analgesia is not advised. (CB)

For people with hemophilia and chronic hemophilic arthropathy in need of pain management, the WFH recommends **functional training and adaptations** alongside appropriate analgesics. (CB)

For children and adults with hemophilia with pain due to chronic hemophilic arthropathy, the WFH recommends the use of paracetamol/acetaminophen, selective COX-2 inhibitors, tramadol, or morphine, and avoidance of other NSAIDs. Codeine may be used for children over 12 years of age but is contraindicated in younger children. Prolonged use of these medications may have risks of dependence or addiction, as well as organ damage, and must be carefully monitored. People with persistent pain should be referred to a specialized pain management team. (CB)

Individuals with hemophilia who are dealing with debilitating pain caused by chronic hemophilic arthropathy are advised by the WFH to be referred to an **orthopedic specialist**. This referral is made in order to assess the possibility of undergoing orthopedic surgery as a potential solution. (CB)

C. Dental care and management

The WFH suggests that children with hemophilia should be directed to a **specialized dental care facility** when their first tooth emerges (typically around 6 months old) or by the age of 1. This is advised to minimize the risks, negative health, and psychosocial effects, as well as the costs associated with oral conditions in individuals with hemophilia. (CB)

The WFH advises individuals with hemophilia to prioritize **preventive dental and oral care**. This is crucial to maintain excellent oral health and hygiene, which in turn helps prevent conditions like periodontal disease and dental cavities. These conditions can lead to issues such as gum bleeding, dental discomfort, tooth loss, challenges in chewing, and social implications. (CB)

D. Dental surgery and invasive procedures

For individuals with hemophilia, the utilization of **systemic or topical tranexamic acid or epsilon aminocaproic acid (EACA)** as supplementary measures in the care of dental procedures both before and after the operation should be considered. This approach aims to minimize the necessity for factor replacement therapy. (CB)

Individuals with hemophilia are advised to opt for suitable **local anesthesia** during dental procedures, which is a crucial aspect of managing pain and anxiety. Most dental injections carry a minimal risk for hemophilia patients when administered by a dental care expert utilizing local anesthesia containing a **vasoconstrictor**. The process should involve slow delivery with a fine-gauge needle designed for single use. (CB)

The use of **antifibrinolytic medications** as a beneficial **supplementary** approach in the care of dental hygiene procedures should be considered. This strategy can aid in ensuring consistent access to routine dental care provided by a dental hygienist for individuals with hemophilia. (CB)

E. Hemostatic Agents

The WFH does not show a preference for recombinant clotting factor concentrates over those derived from plasma when it comes to individuals with hemophilia.

The decision between these categories of products should be determined based on local considerations, including factors like availability, expenses, and patient inclinations. (CB)

a. Clotting Factors Concentrates (CFCs)

Factor VIII (FVIII) CFCs

- For people with hemophilia receiving FVIII concentrates who would benefit from optimization of prophylaxis, the WFH recommends **individualized pharmacokinetic monitoring**. Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 32-96 hours), or with limited sampling in combination with population PK estimates. (CB)
- For individuals with hemophilia who require consistent hemostatic correction over an extended duration, such as during perioperative care or when managing a severe bleeding episode in a patient with a low-responding inhibitor, the use of **continuous infusion of FVIII concentrates** should be considered. Continuous infusion might result in decreased overall consumption of clotting factor concentrates and could potentially offer better cost-effectiveness, particularly for individuals dealing with severe hemophilia. Nevertheless, the assessment of cost-effectiveness in this context could be influenced by the specific dosages employed for continuous infusion as opposed to intermittent bolus infusions.

  Continuous infusion mandates the use of dedicated pumps and an understanding of the stability of the particular clotting factor concentrate once it's mixed within the infusion apparatus. Additionally, patients need to undergo regular monitoring to promptly identify any instances of pump malfunction. (CB)

Factor IX (FIX) CFCs

- When addressing FIX deficiency in individuals with hemophilia B, the WFH advises the use of a **product solely containing FIX** rather than prothrombin complex concentrates (PCCs), which encompass additional clotting factors like II, VII, and X. These factors, potentially activated during production, could increase the risk of thromboembolism for the patient.
- Pure FIX products have **reduced risk of thrombosis** or disseminated intravascular coagulation, compared to what was observed with large doses of older-generation PCCs.
- Current PCCs are considered safer than earlier products due to the inclusion of coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z. Nonetheless, during extensive treatment scenarios such as perioperative care, excessive amounts of prothrombotic clotting factors might accumulate in the bloodstream, potentially raising the likelihood of thromboembolic

complications. When PCCs are administered in elevated quantities to achieve normal FIX levels, it's advisable to think about implementing thromboprophylaxis measures. (CB)

- For hemophilia B patients requiring prolonged therapy at high doses, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. (CB)
- For hemophilia B patients undergoing surgery, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. (CB)
- For hemophilia B patients with liver disease, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. (CB)
- For hemophilia B patients with previous thrombosis or known thrombotic tendency, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. (CB)
- For hemophilia B patients concomitantly using drugs known to have thrombogenic potential, including antifibrinolytic agents, the use of pure FIX concentrates is recommended over prothrombin complex concentrates. (CB)
- For patients with hemophilia B receiving FIX concentrates who would benefit from optimization of prophylaxis, the WFH recommends **pharmacokinetic monitoring**.

  Peak factor level should be measured 15-30 minutes after the infusion to verify calculated dose. Plasma half-life can be determined via full PK (10-11 blood samplings taken over a period of 1-2 weeks), or with limited sampling in combination with population PK estimates. (CB)
- For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of clotting factor concentrates. (CB)

<u>Extended half-life (EHL) products</u>

- For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of clotting factor concentrates. (CB)
- Patients with hemophilia who are transitioning from standard half-life clotting factor concentrates to extended half-life clot-ting factor concentrates would typically require decreased dose frequencies, but EHL products may also be used to maintain higher trough levels to optimize prophylaxis.

b. Bypassing agents

Bypassing agents are used for the treatment and prevention of bleeding complications in patients with hemophilia A or B who develop FVIII or FIX alloantibodies (called inhibitors) that typically neutralize the function of infused CFCs. These agents are based on different mechanisms of action to achieve hemostasis, thereby bypassing the need for FVIII or FIX replacement to treat and prevent bleeds.

- For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used.
- Bypassing agents include recombinant activated factor VIIa or activated prothrombin complex concentrate. (CB)
- For patients with hemophilia B and an inhibitor with a history of anaphylaxis to FIX-containing clotting factor concentrates, recombinant activated factor VIIa must be administered as activated prothrombin complex concentrate cannot be used. (CB)
- The WFH recommends that patients with hemophilia with an inhibitor should be considered for regular prophylaxis to prevent bleeding events. (CB)
- In addition to bypassing agents, non-factor replacement therapies (e.g., emicizumab) are becoming available that offer new treatment paradigms including for the treatment of inhibitors.

c. Other plasma products

<u>Fresh frozen plasma (FFP)</u>

- For patients with hemophilia, fresh frozen plasma is **not recommended** due to concerns about safety and quality. (CB)
- However, the WFH acknowledges the existing and inevitable situation in certain regions of the globe, where the continued use of these products persists due to the absence of alternative or cost-effective treatment choices. (CB)

<u>Cryoprecipitate</u>

- Patients with hemophilia are advised **against** using cryoprecipitate because of reservations related to safety and quality.
- Employing cryoprecipitate is only warranted when clotting factor concentrates are inaccessible, as there is no demonstrated benefit in using cryoprecipitate over clotting factor concentrates (CFCs). If possible, it is highly

recommended to utilize viral-inactivation methods when using cryoprecipitate. (CB)

d. Other pharmacological options

Desmopressin (DDAVP)

- For patients with mild or moderate hemophilia A and carriers of hemophilia A, desmopressin (DDAVP) **should be considered** as an option for treatment. (CB)
- For adults, the WFH recommends DDAVP not be used for more than **3 consecutive days** and only **under close supervision**. If DDAVP is administered twice in a single day, subsequent daily dosing should be limited to once per day.
- For children, the WFH recommends using no more than 1 dose of DDAVP per day for no more than 3 consecutive days.
- The WFH suggests conducting a test with DDAVP before using it as a treatment in order to assess the specific FVIII response of the individual. The decision to use DDAVP should be made considering factors like the patient's initial FVIII activity, the increase achieved, and the duration of treatment needed.
- In general, the most common adverse events observed are tachycardia, flushing, tremor, abdominal discomfort, and headache, especially during rapid infusion, and are mostly mild and transient. However, hypotension and/or severe hyponatremia can also occur.
- For pregnant women during labor and delivery, the WFH recommends caution in the use of DDAVP, and it should be avoided in pre-eclampsia and eclampsia.
- When using DDAVP for more than three consecutive days, the desired treatment effects might diminish (a phenomenon known as tachyphylaxis), and the likelihood of complications increases. Therefore, in situations demanding sustained elevated factor levels over an extended period, clotting factor concentrates might become necessary. (CB)
- For children under 2 years of age, the WFH alerts that DDAVP is contraindicated due to increased risk of seizures as consequences of water retention and hyponatremia. (CB)
- For patients at risk of cardiovascular disease or thrombosis, the WFH recommends that DDAVP should be used with caution due to the risk of thromboembolism and myocardial infarction. (CB)

Tranexamic acid

Tranexamic acid, an antifibrinolytic agent, competitively hinders the activation of plasminogen into plasmin. This supports the stability of clots and serves as supplementary treatment for certain types of hemophilic bleeding. However, using tranexamic acid alone doesn't offer any benefit in preventing hemarthroses in hemophilia.

Tranexamic acid is effective in managing surface-level soft tissue and mucosal bleeds, such as oral bleeding, nosebleeds, and excessive menstrual bleeding. It proves particularly advantageous during dental surgeries and can be employed to control oral bleeding connected to tooth eruption or shedding.

- Tranexamic acid is usually given as oral tablets (25 mg/kg/dose) 3-4 times daily. It can also be given by intravenous infusion (10 mg/kg/dose) 2-3 times daily. It is also available as an oral rinse.
- A syrup formulation of tranexamic acid is also available for pediatric use. If this is not obtainable, a tablet can be crushed finely and dissolved in clean water for topical use on bleeding mucosal lesions.
- Tranexamic acid is commonly prescribed for 7 days following dental extractions to prevent postoperative bleeding.
- Tranexamic acid can be administered on its own or in conjunction with regular doses of clotting factor concentrates (CFCs), which may also include bypassing agents like aPCC and rFVIIa.
- However, it's important to note that for patients with hemophilia B who are undergoing PCC treatment, the use of tranexamic acid is not advised due to an increased risk of thromboembolism.
- The WFH suggests that antifibrinolytic medications serve as a beneficial option for individuals with hemophilia, either used independently or as supplementary treatment. These are especially valuable in managing mucocutaneous bleeding (such as nosebleeds, oral and gastrointestinal bleeding, and heavy menstrual bleeding) and for situations like dental procedures during tooth eruption or shedding.
- Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism. (CB)
- For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy. (CB)

- For patients with renal impairment, the WFH recommends reduced dosing of antifibrinolytics and close monitoring. (CB)

Epsilon aminocaproic acid

Epsilon aminocaproic acid is similar to tranexamic acid but is less widely used as it has a shorter plasma half-life, lower potency, and higher toxicity.

- In adults, EACA is typically administered orally (100 mg/kg/dose up to a maximum of 2 g/dose) or intravenously (100 mg/kg/dose up to a maximum of 4 g/dose) every 4-6 hours up to a maximum of 24 g/day.
- A 250 mg/mL syrup formulation of EACA is also available.
- Gastrointestinal disturbances frequently arise as a complication when using EACA; this issue can often be relieved by lowering the dosage.
- Myopathy, an infrequent negative response, has been specifically linked to EACA treatment (unlike tranexamic acid). This condition usually emerges after the administration of high doses over a span of several weeks.

e. Non-factor replacement therapies

Substitution therapy

Distinguishing itself from factor replacement therapy, substitution therapy employs an alternative hemostatic agent to act in place of clotting factors. At the time of this publication, the factor mimetic emicizumab is the sole authorized substitution therapy.

- **Emicizumab**, a chimeric bispecific antibody, targets both the Factor IXa (FIXa) enzyme and the FX zymogen. It imitates the cofactor function of FVIII in hemophilia A patients, regardless of the presence of inhibitors. While it binds to FIX, FIXa, FX, and Factor Xa (FXa), it is its strong interaction with FIXa and FX that encourages FIXa-triggered FX activation and the creation of tenase complexes.
- The main advantages of emicizumab are its subcutaneous route of administration, long half-life, high efficacy in bleed prevention, and reduction of the frequency of bleeding episodes in patients with or without FVIII inhibitors.
- Since emicizumab has distinct biochemical properties from FVIII, numerous uncertainties persist concerning its prolonged effects on joint damage and potential immune responses in non-inhibitors patients.
- Emicizumab is not designed for addressing sudden bleeding episodes. Care should be exercised when managing instances of breakthrough bleeding

while using emicizumab, as some patients have encountered venous thromboembolism or thrombotic microangiopathy when concurrently administered with aPCC. It is advisable to seek guidance from the hemophilia treatment center and consult risk management recommendations.

- For patients with hemophilia A with an inhibitor, the WFH recommends that emicizumab should be used for regular prophylaxis.
- For patients with hemophilia A with no inhibitor, the WFH recommends that emicizumab can be used for regular prophylaxis. (CB)

Hemostatic rebalancing agents

- The hemostatic mechanism maintains equilibrium between clotting factors (procoagulants) and innate anticoagulants (such as antithrombin, tissue factor pathway inhibitor [TFPI], and activated protein C). Conditions causing bleeding disorders arise due to a lack of procoagulants, while insufficiencies in the natural anticoagulants lead to heightened susceptibility to thrombotic events.
- Fitusiran is an RNA interference therapy that specifically targets antithrombin messenger RNA to suppress the production of antithrombin in the liver. This therapy has the advantage of subcutaneous administration, prolonged duration of action and, due to its mechanism of action, it could be used in both hemophilia A and B patients with or without inhibitors.
- Anti-TFPI antibodies are being explored as another approach in ongoing clinical trials.

F. Prophylaxis in Hemophilia

For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.

Individualizing prophylaxis means that if patients continue to experience bleeds, their prophylaxis regimen should be escalated (in dose/frequency or both) to prevent bleeding.

In countries with significant healthcare constraints, the WFH still advocates for the use of prophylaxis over episodic therapy but recognizes that less intensive prophylaxis may be used. (CB)

Table 3. Conventional Factor Prophylaxis for Hemophilia A and B Defined According to When Prophylaxis Is Initiated (Adapted from the WFH 2020 Guidelines)

Type of Prophylaxis	Definition
Primary prophylaxis	Regular continuous prophylaxis started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and 3 years of age
Secondary prophylaxis	Regular continuous prophylaxis initiated after 2 or more joint bleeds but before the onset of joint disease; this is usually at 3 or more years of age
Tertiary prophylaxis	Regular continuous prophylaxis initiated after the onset of documented joint disease. Tertiary prophylaxis typically applies to prophylaxis commenced in adulthood

Table 4. Conventional Factor Prophylaxis with Standard Half-Life Clotting Factor Defined According to its Intensity (Adapted from the WFH 2020 Guidelines)

Prophylaxis intensity	Hemophilia A	Hemophilia B
High-dose prophylaxis	25- 40 IU FVIII/kg every 2 days (>4000 IU/kg per year)	40- 60 IU FIX/kg twice per week (>4000 IU/kg per year)
Intermediate-dose prophylaxis	15- 25 IU FVIII/kg 3 days per week (1500-4000 IU/kg per year)	20- 40 IU FIX/kg twice per week (2000-4000 IU/kg per year)
Low-dose prophylaxis (with escalation of dose intensity, as needed)[a]	10- 15 IU FVIII/kg 2- 3 days per week (1000-1500 IU/kg per year)	10- 15 IU FIX/kg 2 days per week (1000-1500 IU/kg per year)

Abbreviations: FIX, factor IX; FVIII, factor VIII; IU, international unit; kg, kilogram.
[a]Should only be taken as the starting point of replacement therapy to be tailored, as possible, to prevent bleeding.

People with hemophilia initiated on early prophylaxis (i.e., primary or secondary prophylaxis) have shown the best long-term outcomes. Furthermore, early initiation of prophylaxis also reduces the risk and incidence of intracranial hemorrhage (ICH), which is highest in very young children.

Regular prophylaxis begun at a young age and given in appropriate doses should therefore be considered the standard of care to treat hemophilia until an alternative long-term therapy such as gene therapy is available.

There have been various approaches regarding how to initiate conventional prophylaxis with IV factor replacement therapy. The two main ways (high-dose prophylaxis and low-dose escalating prophylaxis) are mainly differentiated in the frequency of CFC administration and less so in the doses use.

- For children diagnosed with severe hemophilia A or B, the WFH suggests starting prophylactic treatment using clotting factor concentrates (standard or extended half-life FVIII/FIX) or other hemostatic agents at an early stage, even before joint issues arise, and ideally before the age of 3. This proactive approach is aimed at preventing instances of spontaneous and breakthrough bleeding, including hemarthroses, which could ultimately lead to joint problems. (CB)
- For individuals, particularly children, dealing with severe hemophilia A or B, the WFH recommends the adoption of consistent and extended prophylactic treatment as the established approach. This aims to prevent hemarthrosis, spontaneous and unexpected bleeding, uphold the health of the musculoskeletal system, and enhance overall well-being. In cases where continuous prophylaxis isn't viable, treating acute hemorrhages with episodic therapy becomes essential, although this won't shield against lasting joint damage.
- Notably, for children, adopting an early and regular prophylactic regimen yields benefits like decreased occurrences of hemarthrosis and other hemophilic bleeding, improved overall health and joint outcomes, fewer hospital visits and admissions, and the potential avoidance of future orthopedic interventions, including surgery.
- Individuals with a severe form of hemophilia A or B are advised to pursue prophylactic treatment using clotting factor concentrates, which can be of either standard or extended half-life varieties. This treatment should be administered at a dose and frequency determined by the clotting factor concentrate's pharmacokinetic properties. The objective is to maintain a consistent level of circulating factor in order to preempt hemarthrosis, spontaneous and unexpected bleeding, and to cater to their unique requirements and lifestyles while safeguarding musculoskeletal function.
- In the past, maintaining a trough factor level of 1 IU/dL (1%) was considered sufficient. However, it's now acknowledged that even with this 1% trough level, patients remain susceptible to bleeding. Consequently, most healthcare practitioners now aim for higher trough levels (>3%-5% or beyond). Recent

research underscores that such elevated trough levels result in reduced bleeding incidents. Nonetheless, there's a balance to consider, as achieving higher trough levels might necessitate larger doses or more frequent infusions of clotting factor concentrates. This strategy should be tailored to each individual, considering their activities, lifestyle, and the pharmacokinetic characteristics of the clotting factor. (CB)

- For individuals who are adherent to their prescribed prophylactic treatment plan but continue to encounter unexpected bleeding episodes, the WFH advises intensifying the prophylactic regimen. This involves assessing trough levels and, if necessary, considering appropriate orthopedic interventions.

Any patient who fails to respond to adequate factor replacement therapy after past responsiveness should be tested for inhibitor development prior to escalation of therapy. (CB)

- For individuals dealing with severe hemophilia A or B and utilizing extended half-life (EHL) FVIII or FIX concentrates, the WFH suggests engaging in prophylactic treatment using these EHL clotting factor concentrates. The treatment should be administered at doses and intervals that are adequate to prevent hemarthroses, spontaneous and unexpected bleeding, and to maintain joint function.

For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding.

The WFH however notes that there is very little long-term data on patient outcomes with such an approach and recommends that such data be obtained. (CB)

- For individuals dealing with moderate to severe hemophilia A or B, particularly those who have encountered a critical bleeding event like intra-cranial hemorrhage (ICH), the WFH advises the adoption of prophylactic treatment. This can involve using FVIII or FIX concentrates or opting for non-factor therapies such as emicizumab for hemophilia A. The primary aim is to prevent the recurrence of life-threatening bleeds. This is especially crucial during the initial 3 to 6 months after an ICH, as the risk of a repeat incident is most elevated during this time frame.

As inhibitor development is associated with intense exposure as would occur in the setting of an ICH, such patients require good clinical monitoring of treatment response and frequent laboratory testing for inhibitors. (CB)

- For individuals with hemophilia who face challenges in administering regular clotting factor concentrate infusions due to venous access issues, the WFH suggests considering the placement of a central venous access device (CVAD)

to facilitate prophylactic treatment. Another currently available option is the use of emicizumab while in the future there may be other subcutaneous non-factor therapies that become available. (CB)

- For patients with severe phenotype hemophilia A or B in countries with healthcare constraints, the WFH still strongly recommends prophylaxis (even when the only option is using lower factor doses) over episodic factor therapy to reduce hemarthroses and other spontaneous and breakthrough bleeding and better preserve joint function.

G. Treatment of Specific Hemorrhages

Individuals with hemophilia who experience severe hemarthrosis should promptly undergo intravenous replacement infusion(s) of clotting factor concentrate until the bleeding is resolved. (CB)

Hemophilia patients with moderate or mild joint bleeding should be given 1 intravenous infusion of clotting factor concentrate, repeated if clinically indicated, depending on the resolution of the bleed. (CB).

a. Joint hemorrhage

Hemophilia patients with severe hemarthrosis should be treated immediately with intravenous clotting factor concentrate replacement infusion(s) until there is bleed resolution. (CB)

Hemophilia patients with moderate or mild joint bleeding should be given 1 intravenous infusion of clotting factor concentrate, repeated if clinically indicated, depending on the resolution of the bleed. (CB)

<u>Pain management</u>

- For individuals with hemophilia and hemarthrosis, the intensity of pain should be assessed and tracked using the pain scale established by the World Health Organization (WHO). (CB)
- Hemophilia patients with pain due to hemarthrosis should be given analgesic medication according to the severity of the pain. (CB)
- For individuals with hemophilia experiencing severe pain, the approach to pain management should involve the use of opioids guided by clinical symptoms. The goal is to administer opioids to a degree that allows the patient to feel comfortable while bearing weight or using the joint, without encountering pain. (CB)

Adjunctive care

- Hemophilia patients with hemarthrosis should be managed using the RICE approach (Rest, Ice, Compression, and Elevation) in addition to clotting factor concentrate replacement.
- The WFH recognizes that in some regions of the world, RICE may be the only initial treatment available or the best treatment available in the absence of an adequate supply of CFCs or other hemostatic agents. (CB)
- In hemophilia patients with hemarthrosis, weight-bearing should be avoided until the symptoms improve to an extent that the patient is comfortable to weight bear without significant pain. (CB)
- In hemophilia patients, use of opioid analgesia in managing pain should be limited in duration, as much as possible.

Physical therapy and rehabilitation

- In hemophilia patients with hemarthrosis, physical therapy exercises performed under clotting factor coverage should begin as soon as the pain symptoms cease. (CB)
- For individuals with hemophilia and hemarthrosis, the objective of physical therapy should revolve around restoring joint functionality to its condition prior to the bleeding episode. (CB)
- Hemophilia patients without inhibitors who are undergoing factor replacement therapy and experiencing joint bleeding and prolonged pain should consider arthrocentesis only in cases where there is a tense and painful hemarthrosis or if there is a concern about infection.
- In many healthcare settings, arthrocentesis is not common practice because of fear of introducing intra-articular infection. (CB)
- In hemophilia patients presenting with suspected central nervous system bleeds or bleed-related symptoms, clotting factor replacement therapy should be administered immediately before investigations are performed. (CB)

Arthrocentesis

- Hemophilia patients without inhibitors who are undergoing factor replacement therapy and experiencing joint bleeding and prolonged pain should consider arthrocentesis only in cases where there is a tense and painful hemarthrosis or if there is a concern about infection. Routine arthrocentesis is not recommended.

b. Central nervous system and intracranial hemorrhage

For individuals with hemophilia who exhibit potential symptoms of central nervous system bleeding or related issues, it's essential to promptly administer clotting factor replacement therapy prior to any investigative procedures. (CB)

In patients with hemophilia presenting with suspected central nervous system bleeding that could be life-threatening, clotting factor replacement therapy should be administered immediately before investigations are performed and continued until the bleed resolves.

In patients with hemophilia who have been treated for central nervous system bleeding, secondary prophylaxis is recommended to prevent bleed recurrence. (CB)

c. Throat and neck hemorrhage

In hemophilia patients with throat and neck bleeding, clotting factor replacement therapy should be administered immediately, and critical care evaluation sought. (CB)

For individuals with hemophilia experiencing bleeding in the throat and neck region, which may involve tongue injuries, the administration of clotting factor replacement therapy should be maintained until the bleeding symptoms have subsided. (CB)

In hemophilia patients with throat and neck bleeding and local infection, antifibrinolytics should be started to treat the bleed and antibiotics to treat the infection. (CB)

d. Gastrointestinal/abdominal hemorrhage

In hemophilia patients with gastrointestinal bleeding, factor levels should be raised immediately, and the underlying etiology of the bleed identified and treated. (CB)

Antifibrinolytics should be prescribed for hemophilia patients suffering from gastrointestinal bleeding. (CB)

e. Renal hemorrhage

In cases of urinary tract bleeding in hemophilia patients, it's crucial to locate the source of bleeding and promptly initiate clotting factor replacement therapy. (CB)

Hemophilia patients with renal bleeding should be given adequate hydration and prescribed bed rest until bleeding stops. (CB)

In hemophilia patients with renal bleeding, antifibrinolytics should not be administered. (CB)

In hemophilia patients with renal bleeding, clotting factor replacement therapy should continue until the bleeding is resolved. (CB)

f. Ophthalmic hemorrhage

In hemophilia patients with ophthalmic bleeding, clotting factor levels should be raised immediately, and the patient evaluated by an ophthalmologist. (CB)

g. Oral hemorrhage

In hemophilia patients with oral bleeding, the site of bleeding should be identified and direct pressure and/or sutures applied, if possible. (CB)

In hemophilia patients with oral bleeding, antifibrinolytics should be prescribed and administered at appropriate dosages. (CB)

In hemophilia patients with persistent oral bleeding, clotting factor replacement therapy should be administered along with local measures such as sutures and topical adrenaline application to stop the bleeding. (CB)

h. Epistaxis

In hemophilia patients with epistaxis, the head should be elevated, and cold compression applied to the Little ' s area of the nose. (CB)

In hemophilia patients with epistaxis, nasal packing should be avoided as it can cause bleeding when removed. However, in practice, nasal packing is used extensively. (CB)

In hemophilia patients with epistaxis, gauze soaked in an antifibrinolytic agent may be used in addition to clotting factor replacement therapy. (CB)

In hemophilia patients with recurrent epistaxis, the underlying pathology should be identified immediately and treated. Decongestants and antihistamines should help if bleeding is related to allergy, and antibiotics should be administered if bleeding is related to infection. (CB)

i. Lacerations and abrasions

For individuals with hemophilia experiencing cuts and abrasions, it's important to administer clotting factor replacement therapy and, if suitable, promptly suture the wound with the guidance of appropriate surgeons. (CB)

H. Inhibitors to clotting factors

a. Hemophilia A and FVIII inhibitors

For patients with hemophilia A and FVIII inhibitors who develop an acute bleed, the WFH recommends that treatment be based on whether the inhibitor is low-responding or high-responding. (CB)

For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends **FVIII concentrate** for those with low-responding inhibitors, and a **bypassing agent** (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors.

- In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), the WFH prefers rFVIIa over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab.

In patients receiving emicizumab who receive FVIII concentrate, the WFH recommends bovine reagent chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.

Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-ST segment elevation myocardial infarction (non-STEMI) and pulmonary embolism. (CB)

For patients with hemophilia A and low-responding inhibitors who develop an **acute bleed**, the WFH recommends a **FVIII containing product** or, if the hemostatic response is poor, the WFH recommends rFVIIa or aPCC. For those receiving emicizumab prophylaxis who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.

- Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.
- The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels. (CB)

For patients with hemophilia A and high-responding FVIII inhibitors receiving emicizumab who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.

For patients with hemophilia A and inhibitors who receive emicizumab, the WFH recommends bovine chromogenic assays (bovine FX in kit reagent) to monitor inhibitor levels. (CB)

As emicizumab is used to prevent, but not treat, acute bleeds in patients with hemophilia A and inhibitors, the WFH recommends clotting factor replacement therapy for acute bleeds.

For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH recommends clotting factor replacement therapy including FVIII for those with low-responding inhibitors; the WFH prefers rFVIIa over aPCC for

those with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy.

For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH prefers rFVIIa over aPCC, because of the risk of thrombotic microangiopathy.

The WFH suggests following black box warnings for emicizumab and maintaining vigilance as new evidence develops. Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. Thrombotic risks may last for up to 6 months during which plasma levels of emicizumab may persist. (CB)

For patients with hemophilia A and low-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH suggests higher, more frequent FVIII product dosing than usual due to the short half-life of FVIII.

The WFH also recognizes adjusted-dose FVIII continuous infusion as an option. (CB)

For patients with hemophilia A and high-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH recommends bypass agent therapy (rFVIIa or aPCC) at the discretion of the clinician. If single-agent bypass fails, sequential bypass agent treatment, i.e., rFVIIa alternating with aPCC, is another therapeutic approach. The WFH also recommends close clinical monitoring for thrombosis. (CB)

For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive procedure, the WFH recommends a FVIII-containing product for those with low-responding inhibitors. The WFH prefers rFVIIa over aPCC for those with high-responding inhibitors due to the risk of thrombotic microangiopathy. The WFH makes no recommendations on specific dose, frequency, or duration as there is insufficient data.

For patients with hemophilia A and inhibitors receiving emicizumab who undergo minor surgery or an invasive procedure, the WFH recommends either low-dose or no clotting factor replacement therapy.

<u>Immune tolerance induction (ITI)</u>

- For patients with hemophilia A who develop persistent low-responding inhibitors, the WFH suggests that immune tolerance induction (ITI) be considered. (CB)
- For patients with hemophilia A and persistent inhibitors who fail immune tolerance induction (ITI) or never underwent ITI, the WFH recommends emicizumab prophylaxis over bypass agent prophylaxis (rFVIIa or aPCC), as

emicizumab is more effective in bleed prevention and simpler to administer, as it is given weekly and subcutaneously. (CB)

FVIII prophylaxis after immune tolerance induction

- For patients with hemophilia A who switch to another type or brand of factor product, the WFH has no preference for the choice of specific type of therapy, as current evidence indicates product switching does not increase risk of inhibitor development. The WFH supports prospective data collection on inhibitor formation by product, particularly before and after switching products. (CB)
- For patients with severe hemophilia A and inhibitors, the WFH recommends emicizumab over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis. (CB).

b. Hemophilia B and FIX inhibitors

For patients with hemophilia B and inhibitors and an allergic reaction/anaphylaxis to FIX therapy, the WFH recommends rFVIIa to treat acute bleeds but is against use of aPCC as it contains FIX and may cause or worsen an allergic reaction.

For patients with hemophilia B and inhibitors and allergic reaction to FIX therapy, the WFH indicates there are insufficient data to recommend desensitization by small, repeated doses of FIX, intravenously or subcutaneously, and recognizes that in some, this approach may worsen an allergic reaction or cause anaphylaxis. If undertaken, FIX desensitization should be performed with caution and under close supervision by experts only. (CB)

Patients with hemophilia B and inhibitors who develop anaphylaxis to FIX therapy, the WFH recommends bypass therapy with rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. (CB)

Management of bleeding

- For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions. (CB)

Therapeutic options for patients with FIX inhibitors

- For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX-containing product to treat acute bleeds, if there is no allergic reaction to FIX. (CB)

- For patients with hemophilia B and high-responding FIX inhibitors, the WFH prefers rFVIIa over aPCC to treat acute bleeds, as aPCC contains FIX and may cause or worsen an allergic reaction. (CB)
- For patients with hemophilia B and low-responding FIX inhibitors who undergo surgery, the WFH has no preference for type of FIX products, but recommends more frequent dosing due to the short FIX half-life. (CB)
- For patients with hemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. (CB)
- For patients with hemophilia B and inhibitors and an allergic reaction to FIX who undergo surgery, the WFH prefers rFVIIa over aPCC as aPCC contains FIX and may cause or worsen an allergic reaction. (CB)
- For patients with hemophilia B and inhibitors who undergo surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis or consumptive coagulopathy. (CB)

I. Specific management issues

a. Pregnancy and prenatal planning

Pregnant carriers of hemophilia should have their FVIII/FIX levels assayed in the third trimester of pregnancy to assess their bleeding risk during delivery and in the postpartum period. (CB)

b. Labor and delivery

For pregnant carriers of hemophilia, delivery should be in a hospital with access to hemophilia specialists where complications during labor and delivery can be dealt with promptly to maintain the safety of mother and child. (CB)

For pregnant carriers of hemophilia, the WFH recommends against instrumental delivery. (CB)

Carriers of hemophilia should be monitored for both primary and secondary postpartum hemorrhage, which should be treated with appropriate hemostatic measures. (CB)

Male babies born to known or potential carriers of hemophilia should have cord blood testing of activated partial thromboplastin time (APTT) or factor level. (CB)

c. Vaccinations

Children and adults with hemophilia should be administered the same routine vaccines as the general population; however, they should preferably receive the vaccines subcutaneously rather than intramuscularly or intradermally, as it is as safe and effective as the latter and does not require clotting factor infusion.

Intramuscular injection must be the route of administration, a dose of clotting factor concentrate should be given, and the smallest gauge needle available (25-27 gauge) should be used.

Additionally, an ice pack should be applied to the injection site for 5 minutes before injection of the vaccine, and pressure should be applied to the site for at least 10 minutes to reduce bleeding and swelling. (CB)

In children and adults with hemophilia and human immunodeficiency virus (HIV) infection, the WFH recommends standard immunizations, including pneumococcal and influenza vaccines and hepatitis A and B immunization. (CB)

d. Surgery and invasive procedures

For patients with hemophilia requiring surgery, sufficient quantities of clotting factor concentrates must be available for the surgery itself and to maintain adequate coverage postoperatively for the duration required for recovery and/or rehabilitation. (CB)

For patients with mild hemophilia A undergoing surgery, the WFH recommends the use of DDAVP for hemostasis if the patient shows good therapeutic response to DDAVP in pre-surgery testing.

DDAVP is not recommended for surgical hemostasis in those patients with mild hemophilia A in whom the response to DDAVP (increase of plasma FVIII activity levels) is unsatisfactory or in whom DDAVP is contraindicated (e.g., in those with significant cardiovascular disease).

Due to the risk of tachyphylaxis, DDAVP should not be given for more than 3-5 days unless the patient can be monitored closely and switched to clotting factor concentrate if this occurs. Therefore, if the anticipated treatment duration will be longer than 3-5 days (e.g., after major surgery), providers may choose to avoid the use of DDAVP from the outset.

DDAVP is the first choice for patients with mild hemophilia A to avoid the cost of CFCs and exposure to FVIII concentrates and the potential risk of inhibitor development, which increases with the number of exposures.

Given the need for close monitoring, an experienced hematology team should manage these patients. (CB)

For patients with hemophilia undergoing surgery, antifibrinolytics and topical hemostatic agents should be considered if ancillary therapies are required beyond factor replacement. (CB)

In surgical patients with hemophilia B requiring intensive replacement therapy, the WFH recommends against use of prothrombin complex concentrate (PCC) due to risk of accumulation of clotting factors II, VII, and X, which can be associated with higher risk of thrombotic complications. (CB)

The WFH recommends replacement therapy for a duration of at least 3 days for minor surgical procedures, and at least 7-10 days for major surgical procedures. (CB)

For patients with hemophilia A and B undergoing major surgery, the WFH recommends against routine use of pharmacologic thromboprophylaxis. (CB).

e. Comorbidities

Cancer/malignancy

- In patients with hemophilia, if chemotherapy or radiotherapy is accompanied by severe long-lasting thrombocytopenia, the WFH recommends continuous prophylactic replacement therapy. (CB)
- For hemophilia patients without inhibitors diagnosed with cancer, the WFH advises that venous thromboembolism prophylaxis management decisions should be based on evaluation of the individual patient's bleeding and thrombotic risk. If used in patients receiving factor concentrates, it must be carefully managed to maintain factor levels below the risk range for VTE.
- If pharmacologic thromboprophylaxis for hemophilia patients without inhibitors diagnosed with cancer is used, it should mimic what is recommended for the general population, provided that appropriate factor replacement therapy is administered, taking into account that factor replacement to high factor levels above normal is a potential risk factor for VTE. (CB)

Atrial fibrillation

- For patients with hemophilia and atrial fibrillation at high risk of bleeding and thromboembolism, the WFH recommends left atrial appendage occlusion, particularly if long-term replacement therapy with deficient clotting factor is not feasible.
- Left atrial appendage occlusion for patients with hemophilia and atrial fibrillation should be preceded by assessments of the individual's risk of bleeding and thromboembolism and implemented under the advisement of a cardiologist. (CB)

- For patients with hemophilia in whom the risk of non-valvular atrial fibrillation-associated stroke is high or outweighs the risk of bleeding complications, the WFH recommends careful consideration of the use of anticoagulants.
- The choice between direct oral anticoagulants and vitamin K antagonists depends on the local protocols, availability of antidotes for reversal of anticoagulant activity, and feasibility of maintaining adequate trough levels of the deficient clotting factor.
- Despite the scarcity of evidence-based data for this indication in patients with hemophilia, most experts suggest maintaining trough levels of the deficient clotting factor in the individual patient at ≥15-30 IU/dL while on anticoagulant therapy for atrial fibrillation.
- Because treatment responses to DOACs and VKAs may vary, decisions on anticoagulant therapy should be based on the individual patient in consultation with a cardiologist. (CB)
- In hemophilia patients with inhibitors, antithrombotic therapy is generally contraindicated. (CB)

<u>Venous thromboembolism/thrombosis</u>

- For patients with hemophilia undergoing surgery associated with a high risk of venous thromboembolism and bleeding complications, the WFH recommends consideration of the use of mechanical methods for thromboprophylaxis.
- In contrast to pharmacological thromboprophylaxis, mechanical methods of thromboprophylaxis are not associated with the risk of bleeding complications. (CB)
- For patients with hemophilia in whom the balance of the risk of bleeding compared to the risk of developing venous thromboembolism favors pharmacological thromboprophylaxis, the WFH recommends the same practice as that applied in the general population, provided that adequate replacement therapy is administered.
- Decisions on anticoagulant therapy in a patient with hemophilia should always be preceded by assessments of the individual ' s bleeding and thrombotic risk. In some patients with hemophilia, the risk of uncontrolled bleeding may outweigh the benefit of anticoagulation. (CB)
- For patients with hemophilia without inhibitors, the WFH recommends the use of prophylactic doses of anticoagulants only after ensuring hemostatic control with adequate replacement therapy.

- If the risk of uncontrolled bleeding outweighs the benefit of anticoagulation, anticoagulants should not be used.
- This recommendation does not apply to patients with hemophilia and inhibitors in whom anticoagulants are generally contraindicated. (CB)
- In hemophilia patients without inhibitors who experience an acute episode of venous thromboembolism, the WFH recommends the use of high-intensity anticoagulation for the minimal duration and under clotting factor replacement protection and close clinical and laboratory monitoring.
- This recommendation does not apply to hemophilia patients with inhibitors in whom anticoagulants are generally contraindicated. (CB)

Metabolic syndrome

- Patients with hemophilia who are overweight or obese should be referred for dietary advice and/or weight management. (CB)
- Patients with hemophilia who are obese should have FVIII/FIX replacement therapy based on lean body weight after individual pharmacokinetic assessments. (CB)

Diabetes mellitus

- Patients with hemophilia and diabetes should have the same management strategies to control their diabetes as the general population; if treatment with insulin is indicated, subcutaneous injections can be administered without bleeding and without the need for factor replacement. (CB)

Degenerative joint disease

- All patients with hemophilia should be encouraged to engage in regular physical activity and to have adequate calcium and vitamin D intake.
- Hemophilia patients with musculoskeletal conditions and injuries should have physical therapy and rehabilitation supervised by a physical therapist with hemophilia experience. (CB)
- Hemophilia patients with osteoporosis, fragility fractures, or who are at increased fracture risk should be treated with individually adjusted anti-osteoporotic medications. (CB)

Medical issues with aging

- The WFH recommends that aging patients with hemophilia be granted the same access to health education and preventive strategies to reduce the risks or impacts of age-related morbidities as the general population. (CB)

- The WFH recommends the hemophilia team should be closely involved in managing aspects and complications of care related to aging and ensure close consultation and agreement on treatment plans. (CB)

Hypertension

- For patients with hemophilia, the WFH recommends the same management of arterial hypertension as that applied in the general population. Patients with hemophilia diagnosed with hypertension may be treated in a hemophilia treatment center or referred to primary care providers depending on the local healthcare system and practices. (CB)

Coronary artery disease

- Among patients with hemophilia and high-responding inhibitors, the WFH recommends limiting the use of antithrombotics to those patients in whom the risk of untreated thrombosis outweighs the risk of bleeding complications. More research is needed to better understand the safety of antithrombotic therapy in patients treated with emicizumab. (CB)
- The decision on use of antiplatelet therapy in a patient with hemophilia should always be made in consultation with a cardiologist. (CB)
- The decision on use of antithrombotic therapy for this indication should always be made in consultation with a cardiologist. (CB)
- The decision on use of fibrinolytic therapy for this indication should always be made in consultation with a cardiologist. (CB)
- When heart valve replacement is indicated in patients with hemophilia, a bioprosthetic valve should be the first choice to avoid the need for indefinite anticoagulation. (CB)

Chronic synovitis

- For patients with hemophilia who have chronic synovitis and no access to regular prophylaxis, the WFH recommends nonsurgical treatment, including short-term prophylaxis for 6-8 weeks to control bleeding; physical therapy to improve muscle strength and joint function; and selective COX-2 inhibitors to reduce pain and inflammation.
- Physical therapy with individualized goals and exercises based on the patient's functional level should start slowly with increasing progression of weight-bearing activities.
- For patients with acute pain and recurrent bleeding, bracing may stabilize the affected joint and limit motion, but caution is advised as prolonged

immobilization leads to muscle weakness, so isometric exercises even within bracing are advised.

- If unresponsive to nonsurgical interventions, treatment should be escalated to treat the synovitis directly, by the treatment intervention of the local expert. (CB)
- For patients with hemophilia who have unresolved chronic synovitis, the WFH recommends nonsurgical synovectomy as a first-line treatment option using radioisotope synovectomy with a pure beta emitter (phosphorus-32, yttrium-90, rhenium-186, or rhenium-188). One dose of CFC per dose of isotope should be used.
- For patients with hemophilia who have chronic synovitis that no longer responds to nonoperative interventions, the WFH recommends surgical synovectomy (preferably arthroscopic, not open) only by an experienced team in a hemophilia treatment center. (CB)

Hemophilic arthropathy

- For the prevention and treatment of chronic hemophilic arthropathy in people with hemophilia, the WFH recommends a combination of regular replacement therapy to reduce frequency of bleeding and physical therapy aimed at preserving muscle strength and functional ability. Physical therapy may be done with or without factor coverage, depending on availability and the patient's response to therapy. (CB)
- For the prevention and treatment of the sequelae of joint arthropathy in people with hemophilia, the WFH recommends nonsurgical measures such as bracing, orthotics, mobility aids, and serial casting and traction devices to aid in the correction of flexion contractures. This may be done with or without factor coverage. (CB)

Muscle hemorrhage

- All hemophilia patients with muscle bleeds should be given clotting factor replacement therapy immediately and, where applicable, be observed for neurovascular complications associated with the bleed. (CB)
- In hemophilia patients with muscle bleeds with evidence of compartment syndrome and neurovascular compromise, a fasciotomy is required within 12 hours from the time of onset of symptoms before irreversible damage sets in due to tissue necrosis. (CB)

Pseudotumors

- For patients with hemophilia who have developed small early pseudotumors (prior to acquiring a pseudocapsule) and have no access to regular prophylaxis, the WFH recommends a short course (6-8 weeks) of clotting factor replacement therapy with possible continuation of therapy if serial ultrasound evaluations indicate that the pseudotumor is shrinking, with repeat evaluation after 4-6 months. (CB)
- For patients with hemophilia who have developed large pseudotumors, the WFH recommends surgical excision of the pseudotumor with the pseudocapsule, performed only by a surgical team with experience in hemophilia, in a hemophilia treatment center wherever possible, followed by close monitoring and long-term prophylaxis to prevent recurrence of bleeding. (CB)

Fractures

- For people with hemophilia who incur fractures, the WFH recommends immediate treatment with clotting factor concentrates or other hemostatic agents, and continued treatment to maintain sufficiently high factor levels for bleed control for a week or longer, depending on the likelihood of bleeding due to fracture site or stability. Subsequently, lower factor levels may be maintained for 10-14 days to prevent soft tissue bleeding while the fracture becomes stabilized. Clinical monitoring is paramount due to the risk of compartment syndrome. (CB)

Orthopedic surgery

- For patients with hemophilia requiring orthopedic surgery, especially in cases where oozing is present at closure as well as dead space or cavities, the WFH suggests the use of local coagulation enhancers and wound infiltration with local anesthetic agents (lignocaine/lidocaine and/or bupivacaine) with an adrenaline and fibrin sealant or spray to control blood oozing when operating in extensive surgical fields. (CB)
- For patients with hemophilia requiring orthopedic surgery, the WFH recommends factor replacement therapy and close pain control and monitoring, with higher doses of analgesics in the immediate postoperative period. (CB)
- For patients with hemophilia, the WFH recommends joint replacement only in cases of established hemophilic arthropathy that is not responsive to nonsurgical or other surgical treatments, and that is accompanied by

associated pain, functional impairment, and loss of participation in activities of daily living.

- Perioperatively, tranexamic acid and fibrin sealants may be used to reduce blood loss.
- Physical therapy should ideally start on the day of surgery with early mobilization and appropriately progressive exercises to regain motion and muscle strength. (CB)

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Hemophilia report, along with their recommendations.

Table 5. Additional Guidelines

Additional Guidelines
Consensus Recommendations on Appropriate Coagulation Tests During Emicizumab Administration **in Saudi Arabia (2022)**
ASH/ISTH/NHF/WFH Guidelines on the Management of von Willebrand disease **(2021)**
Adults with Hemophilia and Related Bleeding Disorders Acute Treatment Guidelines **(2023)**
New Zealand National Guidelines for the Management of Hemophilia **(2022)**
International Consensus Recommendations on the Management of People with Hemophilia B **(2022)**
Emergency Management in Patients with Hemophilia A and Inhibitors on Prophylaxis with Emicizumab: **AICE practical guidance in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET (2019)**
Practical Guidance of the GTH Hemophilia Board on the Use of Emicizumab in Patients with Hemophilia A **(2020)**
Nordic Guidelines on Acquired Hemophilia **(2020)**

1.2.1 Consensus Recommendations on Appropriate Coagulation Tests During Emicizumab Administration in Saudi Arabia (2022)

Emicizumab is a bispecific monoclonal antibody with the ability to bridge FIXa and FX, mimic FVIII, and restore normal hemostasis in patients with hemophilia A. A consensus meeting was conducted in December 2019, including top experts on hemophilia from Saudi Arabia, to develop clear recommendations for emicizumab

laboratory monitoring to highlight which laboratory tests should be used, which tests should be avoided, and when these tests should be performed[9]. The main recommendations are detailed below:

- Emicizumab acts by bridging the activated factor IX and factor X, without the need for Factor VIIIa (FVIIIa), making it different from other drugs that aim to replace deficient FVIII.
- For individuals undergoing emicizumab treatment, clotting-related tests yield inaccurate results and should not be relied upon for making clinical treatment decisions.
- Activated partial thromboplastin time (aPTT) is overcorrected in the presence of emicizumab.
- One-stage, aPTT-based, single-factor assays (i.e., FVIII activity) appear to give results >150%.
- Bethesda assays (clotting-based) for FVIII inhibitor titers will yield false-negative results.

Patients with congenital HA with inhibitors

- During Immune Tolerance Induction (ITI) involving emicizumab and FVIII, the measurement of FVIII inhibitors can be accomplished using the Chromogenic Bethesda assay with bovine components. The frequency of this testing can adhere to the guidelines outlined in the United Kingdom (UK) for managing congenital hemophilia A with inhibitors.
- Testing while utilizing emicizumab for managing breakthrough bleeds involves the endorsement of a chromogenic FVIII assay that utilizes bovine components to assess FVIII levels. Both indigenous and infused FVIII can be used to monitor the response.
- During surgical procedures where emicizumab is utilized, specialists suggest that FVIII inhibitor titer assessment can be conducted employing the chromogenic Bethesda assay utilizing bovine components. This testing can occur before, during, and after the surgery for patients on emicizumab. To monitor FVIII levels both before and after surgery, the FVIII chromogenic assay with bovine components can also be used if necessary, especially in patients with low-titer inhibitors.

Patients with congenital hemophilia without inhibitors

- Testing while emicizumab is being used for managing breakthrough bleeds: The expert panel suggests employing a chromogenic FVIII assay using bovine components alongside FVIII replacement therapy during breakthrough

bleeds. This approach aids in the monitoring of FVIII levels and replacement therapy.

- Testing while emicizumab is being used for surgical procedures: The expert panel advises using a chromogenic FVIII assay with bovine components to monitor FVIII levels both prior to, during, and after surgical interventions.

General testing for emicizumab level

- The group of experts did not endorse routine testing of emicizumab levels. Nevertheless, hematologists might find it necessary to measure emicizumab levels in specific instances, such as confirming accurate dosing and patient compliance with the treatment. Additionally, this testing might be warranted in cases of perceived treatment inefficacy, especially if the presence of Antidrug antibodies (ADA) is suspected.
- Testing for emicizumab Anti-Drug Antibodies (ADA): Despite the low occurrence of Anti-Drug Antibodies to emicizumab, the panel suggests performing ADA testing when emicizumab concentration levels are found to be low, after excluding instances of incorrect dosing or patient non-compliance, provided the test is accessible. In cases where emicizumab exposure diminishes, it would result in prolonged aPTT and decreased FVIII activity. However, even at very low emicizumab plasma concentrations, aPTT would remain within the normal range.

1.2.2 ASH/ISTH/NHF/WFH 2021 Guidelines on the Management of von Willebrand Disease

The American Society of Hematology (ASH), the International Society on Thrombosis and Hemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) published joint guidelines intended to support patients, clinicians, and health care professionals in their decisions about management of von Willebrand disease (VWD)[10]. The grading methods and recommendations are as follow:

Table 6. Interpreting Strong and Conditional Recommendations from Different Perspectives

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of	A majority of individuals in this situation would want the suggested course of action,

	action, and only a small proportion would not	but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on if an appropriate decision-making process is duly documented.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.	This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Table 7. Certainty in Evidence Supporting the Recommendation

Certainty in evidence	
High or moderate	Indicates that we can be confident in our knowledge of the effects of interventions. The body of evidence needs to be grounded in randomized controlled trials (RCTs) without other reasons for concern or be based on well-done nonrandomized studies with very large effects.
Low or very low	Reflects important uncertainty regarding the effects of an intervention; guideline panelists must decide on the best course of action acknowledging that important evidence gaps exist.

- In patients with von Willebrand disease (VWD) with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Desmopressin challenge/trial and administration

- In patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of ,0.30 IU/mL, the panel suggests performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
- In these patients, the panel suggests against treating with desmopressin in the absence of desmopressin trial results (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯)

Table 8. Practical Considerations for Desmopressin Trial/Challenge and Administration (Adapted from ASH/ISTH/NHF/WFH 2021 Guidelines)

Domain	Description
Route	Desmopressin trials may be performed with either IV or intranasal desmopressin, but intranasal desmopressin trials may not be successful because of issues with administration and/or absorption. Subcutaneous administration has also been used.
Dose	IV desmopressin is given as 0.3 mg/kg, with a maximum dose of 20 mg. The desmopressin nasal spray (150 mg per spray) is

	given as 1 spray for individuals weighing < 50 kg and 2 sprays for individuals weighing ≥ 50 kg.
Timing of laboratory testing	VWF antigen, VWF activity, and FVIII activity levels should be determined immediately before administration of desmopressin, ~ 30-60 min after administration of desmopressin, and ~ 4 hours post administration, because in type 1C VWD, there is a rapid decrease in VWF levels.
Responsiveness	There are multiple definitions of desmopressin responsiveness. The panel considered that an increase of at least 2 times the baseline VWF level and the ability to achieve both VWF and FVIII levels of > 0.50 IU/mL were required to consider the patient responsive to desmopressin. Desmopressin responsiveness does not guarantee, however, that the level achieved is adequate to prevent bleeding in all procedures (eg, higher levels may be indicated based on type of procedure).
Precautions	Because of the risk of hyponatremia, desmopressin should not be given on > 3 concurrent days and is generally not administered to children age < 2 y. In addition, tachyphylaxis occurs after repeated infusions. Caution is advised when desmopressin is used in patients with active cardiovascular disease. Additionally, desmopressin trials should be avoided in pregnancy.

Antithrombotic therapy

- In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel suggests giving the necessary antiplatelet or anticoagulant therapy over no treatment (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Major surgery

- The panel suggests targeting both FVIII and VWF activity levels of ≥ 0.50 IU/mL for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
- The panel suggests against using only FVIII ≥ 0.50 IU/mL as a target level for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Minor surgery/invasive procedures

- In patients undergoing minor surgery or minor invasive procedures, the panel suggests increasing VWF activity levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate alone (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯).
- The panel suggests giving tranexamic acid alone over increasing VWF activity levels to ≥ 0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of > 0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯)

Gynecology: heavy menstrual bleeding

- The expert panel recommends opting for either hormonal therapy (such as combined hormonal contraception [CHC] or a levonorgestrel-releasing intrauterine system) or tranexamic acid instead of desmopressin in the treatment of women with von Willebrand disease (VWD) experiencing heavy menstrual bleeding and who do not desire pregnancy (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯).
- The panel suggests using tranexamic acid over desmopressin to treat women with VWD and heavy menstrual bleeding who wish to conceive (conditional recommendation based on very low certainty in the evidence ⨁◯◯◯)

Obstetrics: postpartum management

- The guideline panel suggests the use of tranexamic acid over not using it in women with type 1 VWD or low VWF levels (and this may also apply to types 2 and 3 VWD) during the postpartum period) (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).

1.2.3 National Hemophilia Council of Ireland: Adults with Hemophilia and Related Bleeding Disorders Acute Treatment Guidelines (2023)

The treatment guidelines published in 2023 by the National Hemophilia Council (NHC) of Ireland on the management of adults with hemophilia and related bleeding disorders detailed the below recommendations[6]:

A. Factor VIII Deficiency (Hemophilia A)

Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. Elocta for FVIII deficiency.

The prescriber must note that not all patients with mild FVIII deficiency require clotting factor concentrate, and the use of alternative treatments may be indicated e.g. DDAVP and/or tranexamic acid.

The patient's treatment of choice must be confirmed with the relevant Comprehensive Care Center (CCC).

a. DDAVP/Desmopressin

- DDAVP® solution for injection (Desmopressin Acetate) is a synthetic version of the hormone arginine vasopressin found naturally in the body. It is prescribed to help control bleeding episodes in certain individuals with Factor VIII deficiency and Von Willebrand disease/low VWF. This is achieved by raising the levels of FVIII and VWF in the bloodstream.
- DDAVP should be administered solely under the watchful guidance of a specialist who has access to suitable laboratory resources for patient monitoring. Maintaining proper fluid and electrolyte equilibrium is advised. Administering treatment without concurrently moderating fluid intake could result in fluid accumulation and/or hyponatremia, with or without accompanying indicative cues. According to local practices, it is customary to limit total fluid intake to no more than 1.5 liters within 24 hours after a DDAVP infusion in adults.
- When employing multiple doses for bleeding management in conditions like hemophilia or von Willebrand's disease, caution is essential to avoid excessive fluid intake. Fluid intake, whether through oral or parenteral means, should be based on the patient's actual thirst rather than being forced. It's advisable to refrain from routinely continuing intravenous infusions after surgery. Monitoring for fluid buildup can be effectively conducted by weighing the patient or assessing plasma sodium or osmolality levels.
- When using repeated doses to control bleeding in hemophilia or von Willebrand's disease, preventing fluid overload is crucial. Patients should only consume the amount of fluid they need to quench their thirst, and routine post-surgery intravenous infusions should be avoided. Monitoring fluid accumulation can be done by weighing the patient or assessing plasma sodium or osmolality.

- Due to reported cases of severe vascular events such as deep vein thrombosis, stroke, cerebral thrombosis, myocardial infarction, angina, and chest pain associated with DDAVP/Desmopressin injection in post-marketing data, caution is advised when considering its use in elderly patients and those with a history of thrombosis, thrombophilia, or cardiovascular disease. DDAVP is generally not recommended for patients over 55 years of age.

b. Tranexamic Acid

- Tranexamic acid is an anti-fibrinolytic agent, indicated in patients with hemophilia for short term use (two to eight days), to reduce or prevent hemorrhage. Tranexamic acid is available in tablet and Intravenous Injection form.
- Oral/tablet form (500 mg tranexamic acid): recommended dose 15-25 mg/kg three times a day or four times a day (usually 1g three times a day or four times a day).
- Intravenous injection (500mg in 5ml ampoule): recommended dose 10 mg/kg three times a day.

c. Bypassing agents for Factor VIII patients with inhibitors

- Bypassing agents (BPA) are clotting factor concentrates specifically formulated to circumvent the requirement for FVIII. They are administered when a patient's inhibitor level is such that FVIII concentrates would not be efficacious (high responding inhibitors), or when a patient's history of severe inhibitors prohibits further FVIII exposure.

Table 9. Dose Calculation of Bypassing Agents in Patients with Factor VIII Inhibitors (Adapted from NHC 2023 Guidelines)

BPA	Initial dose	Subsequent dose and frequency	Important notes
Feiba	50-80 units/kg	50 units/kg every 8-12 hours	DO NOT EXCEED a total dose of 200 units/kg in a 24-hour period
NovoSeven	90 micrograms/kg	90 micrograms/kg every 2-4 hours	

d. Prophylaxis in FVIII deficient patients with inhibitors

- Bypassing Agents can also be used for prophylaxis.
- Hemlibra is a bispecific antibody which acts to co-locate FIXa and FX on the surface of activated platelets and so mimics the role of FVIII as a co-factor in coagulation.
- Hemlibra is administered subcutaneously and may be given once a week, once a fortnight or once every 4 weeks.
- The purpose of Hemlibra is to prevent spontaneous bleeding – IT DOES NOT NORMALISE HAEMOSTASIS. Therefore, hemostatic treatment may still be needed on demand if a patient on Hemlibra suffers a trauma, needs surgery or invasive procedure, or suffers a breakthrough, spontaneous bleed.
- Hemlibra CANNOT be used to treat an acute bleed and a bypassing agent or a Factor VIII replacement product such as Elocta is needed if the patient has bleeding due to a trauma or spontaneously or if an invasive procedure with a major risk of bleeding is needed.
- The only BPA suitable for use in patients on Hemlibra is NovoSeven.
- Antifibrinolytic therapy (Tranexamic acid 1 g three times daily PO or IV) may be used in conjunction with Hemlibra and may be sufficient when used alone for minor bleeds or minor surgeries.

B. Factor IX Deficiency (Hemophilia B)

Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. i.e. Alprolix for FIX deficiency.

In doing so the Prescriber must note that not all patients with mild FIX deficiency require clotting factor concentrate and the use of alternative treatments may be indicated e.g. Tranexamic Acid.

- Alprolix is the clotting factor concentrate used as the first line treatment and prophylaxis of bleeding in patients with FIX deficiency. Alprolix comes as a powder with an accompanying solvent of sodium chloride solution given as bolus.

a. Tranexamic Acid

- Oral / Tablet form (500 mg Tranexamic Acid): Recommended dose 15-25 mg/kg three times daily (TDS) or four times daily (QDS) (usually 1g three times daily or four times daily)
- Intravenous Injection (500mg in 5ml ampoule): Recommended dose 10 mg/kg three times daily

- Reduction in dosage recommended in patients with renal insufficiency.
- Used with caution in patients with massive haematuria from the upper urinary tract.
- Patients with a high risk of thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should only use tranexamic acid tablets if there is a strong medical indication and under strict medical supervision.
- Patients with irregular menstrual bleeding should not use tranexamic acid tablets until the cause of the irregularity has been established.
- Tranexamic acid should be administered with care in patients receiving oral contraceptives because of increased risk of thrombosis.
- Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis)

b. Bypassing agents

- Bypassing agents (BPA) are options for the management of Hemophilia B.
- Arterial and venous thrombotic complications have been reported during and after treatment with BPAs.
- Be aware of other risk factors for thrombosis in patients receiving BPAs and mitigate these where possible e.g. use of mechanical thromboprophylaxis if appropriate, avoidance of smoking, maintain ideal body weight, minimise periods of immobility.
- Use BPAs at the lowest effective dose and for the shortest duration possible when treating acute bleeding or managing invasive procedures.
- Avoid concomitant antifibrinolytic drugs e.g. Tranexamic acid unless advised by CCC.
- FIX inhibitors in patients with FIX deficiency have been associated with hypersensitivity reactions to infused FIX, including anaphylaxis and the development of nephrotic syndrome in some patients. As Feiba contains FIX, it is important to confirm whether the patient has ever experienced such a reaction before and avoid Feiba in this setting.
- For all patients, it is prudent to have appropriate treatments available for management of allergic reactions if administering Feiba in patients with FIX deficiency and inhibitors.
- BPAs may also be used for prophylaxis.

Table 10. Dose Calculation of Bypassing Agents for Patients with Factor IX Inhibitors (Adapted from NHC 2023 Guidelines)

BPA	Initial dose	Subsequent dose and frequency	Important notes
Feiba	50-80 units/kg	50 units/kg every 8-12 hours	DO NOT EXCEED a total dose of 200 units/kg in a 24-hour period
NovoSeven	90 micrograms/kg	90 micrograms/kg every 2-4 hours	

C. Von Willebrand Disease (VWD)

VWD is subdivided into three types determined by the nature of the mutations in the VWF gene:

- Type 1 VWD: Persons who have true Type 1 have levels of VWF antigen and/or activity of < 0.3 IU/ml (activity level is measured by the Ristocetin Cofactor Activity (RCo) or collagen binding (CBA) assays). FVIII may also be low.
- Type 2 VWD: Is further subdivided into types 2A, 2B, 2M, 2N. Type 2 VWD is characterised by abnormal function of the VWF protein and the RCo or CBA assays are lower than the VWF antigen in types 2A, 2B and 2M. In Type 2N VWD, the functional abnormality involves the binding of VWF to FVIII and the FVIII is low but the VWF levels may not be low.
- Type 3 VWD: Persons with Type 3 have very low levels of VWF and FVIII and have the most severe bleeding phenotype which is akin to severe Hemophilia.

In addition, the following subcategories are recognized:

- Low VWF: This relates to persons who have low VWF levels between 0.3 and 0.5 IU/ml. The low levels are not only caused by mutations in the gene for VWF but VWF levels may be reduced in a number of ways including for example by faster clearance of the VWF protein from the blood as happens in people who are blood group O. Some people with low VWF levels have bleeding symptoms and may need to have preventative treatment if they are having surgery or other invasive procedures.
- Platelet-type VWD is a rare condition caused by a mutation in the glycoprotein on the surface of platelets which interacts with VWF.

Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. Wilate or Veyvondi for VWD.

- In doing so the prescriber must note that not all patients with VWD or with low VWF require clotting factor concentrate and the use of alternative treatments may be indicated e.g. DDAVP and/or Tranexamic Acid.
- Tranexamic acid alone is suitable for managing minor bleeding on mucosal surfaces like the nose, mouth, or female genital tract. For heavy menstrual bleeding, the treatment approach may involve combining Tranexamic acid with hormonal therapy such as the combined oral contraceptive pill or the progesterone-only pill. Alternatively, the use of a progesterone-releasing intrauterine system like Mirena can be considered.
- In cases of significant or major bleeding, DDAVP or VWF concentrate should be employed. The selection of the suitable treatment will hinge on factors such as the patient's age, the presence of arteriovascular disease or associated risk factors, and the patient's known reaction to DDAVP. The Clinical Care Committee (CCC) will offer guidance on the appropriate treatment choice.
- Wilate is the clotting factor concentrate recommended for use in the prevention and treatment of hemorrhage or surgical bleeding in von Willebrand disease (VWD).
- Veyvondi is the recombinant clotting factor concentrate recommended for use in the prevention and treatment of hemorrhage or surgical bleeding in von Willebrand disease (VWD) in adults aged 18 and over.
- DDAVP is administered intravenously at a dose of 0.3 micrograms/kg.

<u>Tranexamic acid</u>

- Oral / Tablet form (500 mg Tranexamic Acid): Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- Intravenous Injection (500mg in 5ml ampoule) Recommended dose 10 mg/kg TDS.

D. Rare Bleeding Disorders (RBDs)

Rare bleeding disorders (RBDs) include deficiencies of factors I (Fibrinogen), II, V, VII, X, XI and XIII. These deficiencies can be severe or mild. Severe deficiencies may present with bleeding symptoms similar to hemophilia. Not all mild deficiencies are associated with bleeding, but the bleeding tendency may be variable in some RBDs. Expert advice from a CCC is always required.

Prescribers must ensure that they prescribe the correct factor replacement treatment, if indicated.

The required dose of CFC must be determined by calculating the patient's weight and the required post treatment factor level which is determined by the severity and location of the bleed.

Tranexamic acid

- Oral / Tablet form (500 mg Tranexamic Acid): Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- Intravenous Injection (500mg in 5ml ampoule): Recommended dose 10 mg/kg TDS
- Coagadex is the plasma clotting factor concentrate recommended for use in the prevention and treatment of hemorrhage or surgical bleeding in individuals with Factor X deficiency (FX)

Table 11. Rare Bleeding Disorders – CFC treatments (Adapted from NHC 2023 Guidelines)

Deficiency	Factor Replacement Treatment (If indicated)
Fibrinogen	Riastap (Fibrinogen concentrate)
Factor II	Octaplex (Prothrombin complex concentrate)
Factor V	Octaplas (Solvent detergent treated frozen plasma)
Factor VII	NovoSeven (Recombinant factor VIIa)
Factor X	Coagadex (Factor X Concentrate)
Factor XI	Octaplas (Solvent detergent treated frozen plasma)
Factor XIII	Fibrogammin P (FXIII concentrate)

Management of Allergic Reaction to Treatment

- **Clotting Factor Concentrates**
    - In the event of a reaction or suspected reaction the Clinician should undertake the following:
        - Discontinue the Factor Concentrate
        - Assess the patient
        - Contact the relevant CCC for advice on alternative treatments
        - Report reactions as per your local hospital drug reaction policy
    - In the event of mild to moderate reaction the Clinician should undertake the following:

        - Administer Chlorpheniramine 10-20 mg IM or slow IV (at least over one minute)
        - If required, add Hydrocortisone 100 - 200mg slow IV (over three minutes)
    - In the event of severe allergic or anaphylactic reaction should be managed in accordance with the guidance from the National Immunization Advisory Committee (NIAC,2023).

- **DDAVP/Desmopressin**
    - **Mild reactions** should be treated by slowing the intravenous infusion so that it is administered over 60 minutes.
    - **Moderate reactions** to DDAVP s: Treatment should be discontinued, patient assessed, and all reactions should be reported as per local hospital reaction policy and should be managed in accordance with the guidance from the National Immunization Advisory Committee.
    - **Severe allergic reactions** to DDAVP should be managed in accordance with the guidance from the National Immunization Advisory Committee.
- **Platelet or Plasma Transfusion**
    - Adverse reactions to platelets should be managed in accordance with the guidance from the National Immunization Advisory Committee.

<u>Supportive care for joint bleeds</u>

- Initiate 'PRICE' as supportive care for all joint bleeds:
    1. **Protection:** Lessen the load or strain on the impacted joint or muscle by offering crutches or similar aids like an 'arm sling'. Refrain from putting any weight on the affected side entirely for the initial 48 hours, and potentially for an extended period if the bleeding is severe.
    2. **Rest:** Position the injured arm or leg delicately on a cushion, in a sling, or with a bandage. It's important for the person not to manipulate the joint that is bleeding.
    3. **Ice:** Wrap an ice pack in a moist cloth and put it on the bleeding area. After 5 minutes, take off the ice for a 10-minute interval. Repeat this process as long as the affected joint remains warm. This approach might assist in reducing pain and bleeding.
    4. **Compression:** Applying mild pressure using a tensor bandage (like Tubigrip, sized correctly for the patient's limb) can be beneficial in controlling bleeding and providing support to the joint. However,

exercise caution when using compression for muscle bleeds, particularly if there's a suspicion of nerve injury.

5. **Elevation:** Elevate the impacted region higher than the heart level. This action could potentially reduce blood loss by decreasing pressure in the bleeding area.

- Ensure that the patient is referred to a physiotherapist for assessment and treatment.

Surgical Management of the Patient with a Bleeding Disorder

- Ideally, individuals with bleeding disorders should undergo surgery at a hospital equipped with a Hemophilia Comprehensive Care Centre (CCC), and the management of bleeding control should be overseen by the CCC Team.
- In exceptional situations, surgery might be necessary in a hospital lacking a CCC, particularly in emergencies or when specialized surgical services are required.
- In such cases, the CCC should guide the bleeding control strategy, and it is advisable for the local Hematology service to offer in-person consultation on-site.

Management of the infant during labor and delivery

- Women who are carriers of FVIII or FIX deficiency or who have a factor deficiency or other bleeding disorder should have an individual management plan for labor and delivery determined collaboratively by the woman, her CCC and the woman's Obstetrician.
- Patients with low factor levels or a bleeding disorder which does not correct in pregnancy may require hemostatic treatment at the time of delivery.
- The use of epidural or spinal anesthesia is contra-indicated in patients with factor levels less than the laboratory lower limit of the reference range in the third trimester or in patients whose bleeding disorder does not correct in pregnancy.
- Patients with confirmed normal factor levels in the third trimester may receive epidural or spinal anesthesia if required.
- The use of Intramuscular injections e.g. Pethidine are contra-indicated in women with low factor levels or a bleeding disorder which does not correct in pregnancy.
- Alternative analgesia such as inhaled nitrous oxide and oxygen or intravenous Remifentanil is acceptable for patients with low factor levels or a bleeding disorder which does not correct in pregnancy.

- For women with low factor levels or a bleeding disorder which does not correct in pregnancy, appropriate options for analgesia MUST be discussed with the local Maternity unit Anaesthetic service in advance.

1.2.4 New Zealand National Guidelines for the Management of Hemophilia (2022)

The following recommendations are retrieved from New Zealand National Guidelines for the Management of Hemophilia, which were compiled by the National Hemophilia Treaters Group in 2022[7].

All patients with hemophilia, other significant congenital bleeding problems or acquired factor deficiencies, should be registered with a Regional Hemophilia Centre, and reviewed if required by a specialist hematologist.

Pain relief must be adequate especially for large joint and muscle bleeds. Nonsteroidal anti-inflammatories should not be used. Cox2 inhibitor use should be discussed with the regional treatment center.

Minor joint bleeds should be treated with ice application, analgesics and rested in a functional position. All joint bleeds should be assessed by, or discussed with, the hemophilia center physiotherapist.

a) Applying ice – wrap the icepack in fabric and put it on the skin for 20 minutes every hour.

b) Ensure comfortable positioning – stabilize upper limb joint bleeds using a sling. For serious lower limb bleeds, remain in bed or use crutches to avoid putting weight on the limb. In specific cases, a back slab might aid in immobilizing and safeguarding the joint from additional harm.

c) Initiate exercises (starting with stationary movements) once the pain diminishes and have a physiotherapist supervise them.

A. Vaccinations

Routine vaccinations are recommended for all patients. Patients who are receiving factor prophylaxis should receive these intramuscularly (IM) on the day of factor administration.

Moderate and severe patients who are not yet receiving factor prophylaxis should receive these subcutaneously (SC).

For mild patients the balance between the risk of bleeding and potential decrease in vaccine efficacy needs to be considered.

Many children will manage with an experienced IM administrator, an icepack applied 5 minutes prior to the injection and application of firm pressure for 5–10 minutes after the vaccination.

Prolonged local pressure for 5-10 minutes is recommended at the injection site.

Immunizations may be less effective in patients with HIV. Live vaccinations are also contraindicated in patients with HIV. Pneumococcal vaccination and yearly influenza vaccination is recommended for patients with HIV.

a. Hepatitis B Vaccination

Hepatitis B vaccination is recommended for all patients. Patients necessitating human-derived products or components should undergo regular monitoring of their immunity to hepatitis B and receive additional vaccinations when deemed necessary.

b. Hepatitis A Vaccination

Patients using plasma products and testing negative for Hepatitis A IgG antibodies should contemplate vaccination. Those who are positive for hepatitis C but lack Hepatitis A IgG antibodies should be administered the Hepatitis A vaccine.

B. Prophylaxis

This refers to the infusion factor products (usually recombinant) in anticipation of bleeding or in order to prevent bleeding. There are different types of prophylaxis:

- ✓ **Primary Prophylaxis (long term):** This is administered to infants identified as having a high risk of recurrent bleeding, which puts them in danger of developing joint issues. Primary preventive treatment is typically reserved for individuals with severe hemophilia (with factor VIII or factor IX activity below 1%), although those with factor levels between 1% and 5% could still experience debilitating joint problems. Routine preventive treatment is often initiated after one or two severe bleeding episodes within the initial 12-18 months of life and is considered the standard care for children with severe hemophilia A or B. The goal is to minimize instances of sudden bleeding. Nowadays, there is a range of products available with regular and extended half-lives.
- ✓ **Single Dose Prophylaxis:** An injection of product may be given prior to an event (e.g. sporting) to prevent bleeding occurring in relation to that activity.
- ✓ **Secondary Prophylaxis:** Refers to limited term prophylaxis where there is a high requirement for on demand therapy. Regular injections over a limited time period may reduce the frequency of bleeding or re-bleeding from a target joint. Often used in the treatment of chronic synovitis.

- ✓ **Prophylaxis in Hemophilia A:**

  The main goal is to prevent spontaneous bleeding. This is generally achieved by preventing a trough of <1%. Many international guidelines in first world countries are now recommending higher troughs where this can be achieved. The way FVIII (factor VIII) functions in terms of recovery and duration in the body can differ with age and among people, making it advisable to assess the pharmacokinetics to fine-tune the prophylactic approach (dosage and frequency).

- ✓ **Prophylaxis in Hemophilia B**

  The aim is to prevent spontaneous bleeding. This is generally achieved by preventing a trough of <1 %. Recovery and half-life of FIX can vary with age and between different individuals and therefore pharmacokinetic assessment is recommended to optimize prophylaxis (dose and frequency).

C. Management of major and minor bleeding episodes in hemophilia patients

The approach to handling bleeding incidents in individuals with hemophilia differs based on the severity of their condition, the location of the bleed, and the reason behind the episode. People with hemophilia don't necessarily bleed more profusely than those without the condition, but without intervention, their bleeding tends to persist longer, leading to increased blood loss.

Generally, administering **1 international unit (IU) per kilogram of body weight** of **factor VIII** can elevate the person's levels by **2%**, whereas for **factor IX**, the same dosage will raise the level by **1%**, but its effect will be more prolonged.

- ✓ **Major head injury or intra cerebral bleed**

Promptly address suspected intracranial bleeding or significant head injury. Avoid waiting for radiological tests to confirm bleeding.

1. Admit the patient to the hospital and initiate immediate treatment.
2. Administer the initial dose of therapy: 50-70 IU/kg rFVIII or 80-100 IU/kg rFIX before any investigations.
3. Seek urgent consultation with a hematologist: during regular hours from the local hemophilia treatment center, and outside of regular hours from the regional hematology service.
4. If there's a likelihood of continued need for factor product in a smaller medical facility, consider requesting additional doses of factor at this stage or contemplate patient transfer as appropriate. Transfer should

be seriously considered if timely monitoring of ongoing factor levels can't be conducted for informed management.

Objective: Raise factor levels to 80-100%, with trough levels at 50%, for 72 hours. Subsequently, gradually reduce the dosage over a span of 14 days or more under supervision. Monitor factor levels both before and after treatment.

D. Mild Hemophilia

Individuals with mild hemophilia frequently receive conservative management using the RICE method for mild injuries. In cases of minor bleeds and minor surgical procedures related to mild hemophilia A, non-blood product treatments such as DDAVP and Tranexamic acid are employed. DDAVP is not effective for addressing hemophilia B.

DDAVP

- The DDAVP effect on factor VIII parameters lasts for 6–8 hours. However, with repeated doses, patients may gradually become less responsive to DDAVP as their stored resources are utilized. Their responsiveness to DDAVP will be restored after a two-day discontinuation of the drug.
- It's recommended to conduct a DDAVP trial before a surgical procedure to gauge the response, as some individuals may not respond well to the treatment. However, it's advised not to conduct a DDAVP trial within four days of planned surgery.
- Rapid administration of DDAVP may result in symptoms like flushing, headache, and tachycardia. Frequent administration could potentially lead to excessive fluid retention due to its antidiuretic effects, thus necessitating electrolyte monitoring.
- DDAVP is contraindicated for patients under 2 years of age, those with hyponatremia, and individuals with closed head injuries. There is a relative contraindication for individuals with recent myocardial infarction or stroke, or those with known severe vascular disease.
- Patients should receive guidance on fluid restriction for a 24-hour period before being discharged.
- Treatment regimen: 0.3 µg/kg I.V. 30 minutes prior or subcutaneously 60 minutes prior to procedures. Used with Tranexamic Acid 20mg/kg/dose (max 1g) PO tds to qid (IV dose is 10mg/kg). The SC route is generally preferred due to lower risk of side effects.

Tranexamic acid

Tranexamic Acid is a fibrinolytic inhibitor, should be administered concurrently unless there is renal bleeding, liver disease with the threat of disseminated intravascular coagulation, or an increase of thrombotic events.

Factor viii concentrate in mild hemophilia

- Certain individuals with mild or moderate hemophilia might develop inhibitors, hence the utilization of recombinant products should be deliberated with a hemophilia center, unless the circumstance is urgent.
- In cases of significant bleeding episodes or surgeries among patients with mild hemophilia, the desired factor levels should align with the recommendations applicable to patients with severe or moderate deficiencies.

E. Management of pregnancy and delivery in hemophilia

Pre-pregnancy

- Pre-pregnancy counselling should be offered to all potential carriers.
- Some families may wish to consider assisted pregnancy options such as pre-implantation genetic diagnosis.
- Establish carrier status.
- Determine factor VIII/IX gene abnormality.
- Assay clotting factor (VIII/IX) level
- Some females have factor levels that can put them at risk of bleeding.

For females affected by hemophilia

Management is complex and should be discussed with a trained hemophilia treater or genetic counsellor regarding options.

Parents who wish to consider termination of pregnancy

- Chorionic villus sampling (CVS) and gene testing on male fetuses.
- Determination of sex of fetus at 14 - 16 weeks can be performed and if male, proceed to amniocentesis and gene testing – however this may lead to less time for consideration of options.
- In some cases, a blood test non-invasive prenatal testing (NIPT) testing for fetal DNA in the maternal blood may be available but it is not currently publicly funded.

Parents who do not want termination and are not insistent about prior knowledge of hemophilia status of fetus or mother not informative on DNA testing

- Determine sex of infant by conventional ultrasound during second trimester.
- If female fetus, manage mother as detailed below but no additional intervention needed for newborn.
- If male fetus, 50% risk of hemophilia, so proceed as if fetus affected until proven otherwise.

During pregnancy

- Assay maternal factor VIII/IX level at booking. If reduced, repeat in the third trimester or before any invasive procedures.
- If factor VIII/IX level 50% for procedures such as CVS, amniocentesis, or termination.
- For females in the third trimester, with a level < 80% rFVIII is required for most surgical procedures.
- Factor IX deficiency rFIX is required for most surgical procedures.
- Discuss delivery plan – a written management plan from the hemophilia treatment center may be required for more complex deliveries. Have appropriate treatment available at the time of delivery in line with the proposed treatment plan.

Postpartum

For females with a factor level of if < 50% before pregnancy

- Monitor factor VIII level daily after birth (acute phase protein and level falls post delivery).
- Give rFVIII or consider DDAVP (note significant hyponatraemia can occur particularly if oxytocin was administered during delivery) if levels <80%
    - **i.** 3 days if normal vaginal delivery
    - **ii.** 5 days if caesarean section
- Tranexamic acid 1g tds can be used for 5-7 days post-delivery.

For hemophilia B carrier with a factor level of if <50% before pregnancy

- Give replacement with one dose for normal delivery and a second dose at D3 for caesarean section no need to monitor daily.
- Tranexamic acid 1g tds can be used for 5–7 days post-delivery.

Newborn males

- Take blood from umbilical cord (or peripheral vein if cord blood specimen unobtainable or unsatisfactory) for urgent (result < 3 hours) factor VIII/IX level.
- If urgent factor VIII/IX assay unavailable, do coagulation screen (upper limit normal APTT in newborn approximately 40 seconds).
- Avoid heel pricks for coagulation studies or factor assays.
- Oral Vitamin K prophylaxis is effective in preventing classical hemorrhagic disease of the newborn, but ineffective in preventing late HDN. Increasing the dose or giving it weekly for a longer period increases the efficacy of the oral prophylaxis. Alternatively, IM Vitamin K can be given providing pressure is maintained for a minimum of 5-10 minutes.
- Factor IX concentration may be unreliable in the newborn (until approximately 6 months of age). A low level does not confirm hemophilia and a repeat may be necessary.

Newborn females

In females born to families with severe hemophilia cord blood factor VIII/IX level should be measured detect the occasional carrier female with low levels at risk of symptomatic bleeding.

F. Von Willebrand Disease

Minor bleeds

- The management of most patients with type I von Willebrand disease (VWD) typically involves the use of Tranexamic acid and/or DDAVP (Desmopressin). DDAVP is effective in increasing VWF (von Willebrand factor) and FVIII (Factor VIII) levels. In some cases of type IIA VWD, DDAVP can be beneficial, but not all patients with this subtype respond to it.
- However, in type IIB VWD, DDAVP is ineffective in reducing bleeding time and may even cause a severe transient thrombocytopenia (low platelet count). As a result, DDAVP is contraindicated in type IIB VWD as well as in cases of pseudo-von Willebrand disease. Furthermore, DDAVP is predictably ineffective in type III VWD.

Surgery and major bleeds

- For patients with mild Type I von Willebrand disease, DDAVP with or without Tranexamic Acid is usually satisfactory for many surgical procedures. Patients with more severe Type I or Type II disease and in particular Type III disease

usually require the infusion of normal von Willebrand factor. Currently this is available in concentrates of plasma-derived factor VII.

- Effective bleeding control is typically achieved when adequate Factor VIII (FVIII) levels, exceeding 50%, are maintained, regardless of the bleeding time. Perioperatively, it is crucial to pay close attention to local hemostasis, which may involve techniques such as sutures, cautery, and wound packing.
- In most situations, concurrent administration of tranexamic acid is recommended to further assist in managing bleeding.

Pregnancy

- During pregnancy, von Willebrand factor (vWF) and factor VIII levels rise, which can make initial von Willebrand disease (VWD) testing unreliable. While these levels may normalize in VWD type 1, bleeding may persist in VWD type 2 and 3. If factor VIII levels normalize during pregnancy, it typically happens before the 34th week. After delivery, factor VIII levels drop rapidly, posing a risk of delayed postpartum hemorrhage at 10-14 days. The risk of bleeding during delivery is approximately 40%, with primary postpartum hemorrhage at 15-20% and secondary postpartum hemorrhage at 20-28%. This risk is not limited to women who don't normalize factor levels during pregnancy. Even when levels normalize, unaffected women have supra-normal vWF levels in late pregnancy.

Management in Pregnancy

- A careful personal and family bleeding history is important.
- In patients with suspected vWD test at 30-34 weeks (or earlier if preterm delivery is likely).
- Request von Willebrand screen (record blood group).
- Avoid epidural anesthesia (see below)

Management at delivery

- Many patients will not need treatment at the time of delivery or post partum. If the Factor VIIIc parameters are normal at 30-34 weeks manage expectantly but with a high index of suspicion for postpartum hemorrhage.
- In women with type 1 whose factor levels fail to normalize (>50%) or in those with types 2 or 3, consider prophylaxis as below:
    a) DDAVP (0.3 µg/kg) given following clamping of umbilical cord

b) Plasma derived factor VIII (CSL Biostate 500 units/reconstituted bottle). This should be used if there is a history of significant bleeding with a previous delivery. 20–30 FVIII units/kg (40–60 VWF units/kg). This may need to be continued 12 hourly for 3–5 days

- The use of DDAVP (Desmopressin) can lead to significant hyponatremia, especially if oxytocin was administered during delivery.

Post partum hemorrhage

In the event of postpartum bleeding, where prophylaxis has not been given, treatment will be:

a) DDAVP (0.3 µg/kg) given following clamping of umbilical cord (note this is not appropriate for repeated use as stores become used and it becomes ineffective.

b) Plasma derived factor VIII (CSL Biostate 500 units/reconstituted bottle). 20–30 FVIII units/kg (40–60 VWF units/kg). This may need to be continued 12 hourly for 3-5 days

The infant

Von Willebrand disease is an autosomal dominant inherited condition with variable penetrance (approximately one third of at-risk infants will inherit the condition).

- Avoid invasive fetal monitoring (e.g. scalp vein sampling) when possible. Care with instrumental deliveries.
- Give vitamin K at birth.
- Infants are not routinely tested unless they have unexplained bleeding problems.

Miscarriage

- Bleeding during pregnancy requires urgent obstetric consultation.
- Patients with an early miscarriage may require no additional treatment. If there is a need for intervention to remove retained products or prolonged bleeding, treatment with Tranexamic acid and /or DDAVP should be considered.
- Patients with a personal history of miscarriage or bleeding during pregnancy may require more frequent monitoring of von Willebrand factor parameters during pregnancy.

G. Platelet Disorders

Congenital platelet function defects

Platelet disorders can be treated with DDAVP, platelet transfusion or recombinant factor VIIa. In all cases antiplatelet drugs such as aspirin and anti-inflammatories should be avoided.

Management:

- Tranexamic acid and compression for minor bleeding
- Platelet transfusions for more major bleeding
- DDAVP and/or rFVIIa may be useful in some disorders

H. Specific conditions

Bernard Soulier syndrome

- Tranexamic acid
- Treat with platelets

Glanzmanns thrombasthenia

- Tranexamic acid
- DDAVP anecdotally beneficial (0.3mcg/kg)
- Recombinant Factor VIIa 80-140mcg/kg. (may require NPPA)
- Platelets for bleeding

Platelet storage pool disorders

- Tranexamic acid
- Platelets for bleeding
- DDAVP can be trialed

1.2.5 International Consensus Recommendations on the Management of People with Hemophilia B (2020)

The International consensus on the management of people with hemophilia B[11] issued the following explanation to the recommendations:

"A Delphi approach was used to reach consensus on the proposed recommendations. Individual authors assigned each recommendation a score between 1 (lowest) and 9 (highest), and scores were collated into one of three ranges: 1–3, 4–6 and 7–9. The percentage of individuals scoring within the 7–9 range

indicated the level of agreement. Consensus was reached when ⩾75% of individuals had assigned a score of 7–9 for a given recommendation."

Factor product choice, switching and clinical indications

- Prophylaxis with FIX (Factor IX) should be considered for all individuals with severe hemophilia B, including those classified as non-severe based on their baseline FIX levels but who exhibit a severe bleeding phenotype. For these individuals, prophylaxis should ideally be initiated as early as possible, even before the onset of joint bleeding, and the treatment should be continuous without interruption.
- Both standard half-life FIX (SHL-FIX) and extended half-life recombinant FIX (EHL-rFIX) are effective treatment options for prophylaxis in people with hemophilia B (PwHB).
- Either SHL-FIX or EHL-FIX products can provide sufficient hemostatic coverage for managing bleeds, surgeries, and invasive procedures. When using EHL products, it's important to consider laboratory requirements for product-specific monitoring.
- When selecting a treatment product or contemplating a switch to alternative products, factors such as venous access, patient adherence, bleeding patterns, lifestyle, patient preferences, and pharmacokinetics (PK) should be considered, while considering local licensing and approval status.
- The dosage and frequency of prophylactic FIX treatment should be tailored to the individual's clinical phenotype, such as their bleeding rates, and lifestyle considerations. It should not be solely determined based on plasma trough levels.

Specific therapeutic agent laboratory monitoring considerations

- Laboratories should be mindful of potential discrepancies between chromogenic substrate assays (CSA) and one-stage assays (OSA) when conducting diagnostic testing for non-severe hemophilia B.
- When monitoring FIX therapy, laboratories should participate in proficiency testing for the specific product, for example, using External Quality Assessment (EQA) programs. Additionally, they should employ assays that have been validated through field studies or local validation processes.
- CSA assays offer higher levels of precision and accuracy in assessing FIX activity, whereas variability may exist with different OSA assays. However, CSA may not be suitable for routine monitoring of recombinant FIX-albumin fusion protein (albutrepenonacog alfa).

- Clinicians should be aware that there is insufficient evidence to support the routine use of thrombin generation assays or other global assays for guiding the clinical management of people with hemophilia B (PwHB).
- Laboratories and clinicians should be cognizant that current FIX genetic testing (FIX-GT) consistently yields lower FIX activity measurements when assessed by CSA compared to OSA. The choice of which assay to use to aid clinical decision-making remains unclear.

Pharmacokinetic (PK) considerations – modelling, predictions, and dose optimization

- Clinicians are advised to assess both product-specific attributes and the patient's phenotype and joint condition to evaluate whether pharmacokinetic (PK) analysis can assist in tailoring individualized prophylaxis dosing.
- Population PK analysis should be considered, taking note of the distinct extravascular distribution patterns and optimal sampling times associated with each specific FIX (Factor IX) product.

Inhibitor management and preparing for novel agents

- In individuals diagnosed with severe hemophilia B, prompt determination of the underlying F9 genetic defect is essential to identify those at higher risk of developing inhibitors or experiencing severe allergic reactions.
- Routine inhibitor screening should be conducted for all individuals with severe hemophilia B. Close attention should be paid if they exhibit allergic reactions to FIX (Factor IX) or if their response to FIX replacement therapy is inadequate.
- For individuals with severe hemophilia B, FIX infusion and careful clinical monitoring for allergic reactions should take place in a hospital setting during the initial 20 exposure days (EDs).
- In cases of severe hemophilia B with high-responding inhibitors or those who have experienced allergic reactions, recombinant activated factor VII should be the preferred choice for managing bleeding and providing surgical coverage. While activated prothrombin complex concentrate (aPCC) is an option, consideration should be given to its FIX content and the associated risks of immune memory and potential exacerbation of allergic reactions.
- Immune tolerance induction (ITI) should be considered for individuals with severe hemophilia B who have persistent inhibitors. However, the decision should carefully weigh the relative benefits and risks, and ITI should be initiated only at a specialized hemophilia treatment center.

- Patients undergoing ITI should undergo close monitoring for the development of nephrotic syndrome and/or severe allergic reactions.
- In the case of patients experiencing allergic reactions, desensitization should be contemplated. It's important to anticipate the possibility of further severe allergic reactions in these patients, and subsequent infusions should occur in a hospital setting with appropriate resuscitation resources and expertise.
- To address FIX inhibitor eradication, ITI protocols that combine FIX and immunosuppressive agents may be considered as a primary treatment option.

Preparing for Gene therapy (GT)

- Based on current clinical trial data for adeno-associated virus (AAV) gene therapy, this treatment should be considered as a potential future option for adults with severe hemophilia B.
- During the informed consent process, patients should be informed about the unpredictability of the achieved FIX (Factor IX) levels and the duration of FIX expression following gene therapy.
- Patients considering liver-directed AAV gene therapy for hemophilia B should be aware that pre-existing liver pathology may be an exclusion criterion. Those proceeding with gene therapy should receive counseling regarding potential sources of hepatotoxicity that could impact FIX expression, such as medication use or alcohol consumption.
- Clinicians should be vigilant about monitoring transaminase levels, as a rise in these liver enzymes during the acute phase of gene therapy may signal an immune response that could threaten FIX expression. Close monitoring allows for timely implementation of immunosuppression if necessary.
- Clinicians should consider the specific geographic pattern of AAV seropositivity when selecting the appropriate gene therapy, as it may help guide the choice.
- When establishing a program for hemophilia B gene therapy, it is crucial to create a network of care led by experienced hemophilia specialists. This network should include comprehensive education programs for patients, hemophilia center staff, the extended multidisciplinary team, and allied services.
- Patients and healthcare providers (HCPs) should be well-informed about the potential need for prophylactic or interventional immune suppression following gene therapy administration. This includes understanding the

duration and potential side effect profiles associated with immune suppression.

- Patients and HCPs should recognize the importance of long-term safety and efficacy follow-up, which includes assessing liver health and monitoring FIX expression levels. This follow-up should be coordinated by the hemophilia center.
- Hemophilia treatment centers, along with various stakeholders such as regulators, payers, and patients, should acknowledge the significance of participating in a post-authorization registry. This registry is essential for gathering real-world data on the safety and efficacy of hemophilia B gene therapy.

1.2.6 Emergency Management in Patients with Hemophilia A and Inhibitors on Prophylaxis with Emicizumab: AICE Practical Guidance in Collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET (2019)

The following recommendations are retrieved from the AICE practical guidance on emergency management in patients with hemophilia A and inhibitors on prophylaxis with emicizumab, published in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET in 2019[12]:

Emicizumab offers a valuable treatment option for the long-term prevention of bleeding in individuals with congenital hemophilia A and inhibitors against factor VIII (FVIII). Nevertheless, this innovative therapeutic approach poses challenges for Hemophilia Treatment Centers (HTCs). HTCs need to establish specialized protocols to effectively manage and monitor these patients to ensure the treatment's optimal efficacy and safety. This involves conducting appropriate laboratory tests and carefully evaluating potential adverse drug interactions.

Emicizumab is a bi-specific, humanized monoclonal antibody which bridges factor (F) IX/activated (FIX) and FX/activated (FX) and leads to activation of FX, thus mimicking the physiological function of activated FVIII.

Emicizumab is injected subcutaneously once weekly, at 3 mg/kg during the first 4 weeks (loading dose) and subsequently at 1.5 mg/kg (maintenance dose). By using this schedule, the steady state of plasma concentration of emicizumab is usually achieved after the first 4 doses, remaining stable thereafter with an average plasma level of 40-50 µg/mL.

Emicizumab significantly reduces the frequency of bleeding, particularly spontaneous bleeds. However, it does not completely normalize the coagulation process. As a result, patients may still experience bleeding following trauma or,

although rarely, spontaneous bleeding episodes. In such cases, treatment with bypassing agents may become necessary.

Furthermore, bypassing agents may be necessary to manage surgical procedures or invasive interventions. The timing of their administration and the appropriate doses are determined based on the specific clinical circumstances.

Guidance for the use of bypassing agents during prophylaxis with emicizumab

- Bypassing agents should be discontinued at least 24 hours before starting prophylaxis with emicizumab.
- Before initiating emicizumab treatment, it is advisable to check the levels of anti-FVIII antibodies to determine the potential utility of FVIII concentrate, especially until an anamnestic response is observed.
- In cases where treatment with bypassing agents is necessary, recombinant activated factor VII (rFVIIa) is the preferred initial option. If the clinical response to rFVIIa is inadequate or if alternative treatment options are limited, activated prothrombin complex concentrate (aPCC) can be considered, typically at doses not exceeding 50 U/kg.
- Patients on prophylaxis with emicizumab should be trained as to the dose of rFVIIa to be used as home-treatment when required.
- The initial dose should be 90-120 µg/kg , to be repeated 2-4 hours apart according to the severity of bleeding and the clinical response, as recommended by the HTC. The suggested dose and schedule are based on the safety analysis conducted on the data from the HAVEN clinical programme on the concomitant use of rFVIIa for the treatment of breakthrough bleeds in patients receiving emicizumab prophylaxis.
- A megadose of rFVIIa (270 µg/kg) should be avoided, even as a single infusion.
- Patients receiving emicizumab prophylaxis, as commonly advised for individuals with inhibitors, should maintain a supply of at least 2-3 treatment doses of recombinant activated factor VII (rFVIIa) at home. These doses should typically be in the range of 90-120 µg/kg. This supply is essential to ensure prompt and accurate treatment when needed, such as during travel, vacations, or visits to Emergency Units (EU) at hospitals.

Management of inhibitor patients on emicizumab in the emergency unit

- If there is suspicion of a bleeding episode or if the patient reports recent trauma, it is crucial to conduct a diagnostic evaluation to confirm or rule out ongoing bleeding. Even though patients with inhibitors who are on prophylaxis with emicizumab are generally protected against most

spontaneous bleeding episodes, this protection is not absolute. There is always a remaining risk of hemorrhage following trauma or in the context of surgical or invasive procedures.

- In cases of highly suspected or active bleeding, major trauma, or the need for an urgent invasive procedure, it is recommended to infuse rFVIIa at a dose of 90-120 µg/kg before contacting the Hemophilia Treatment Centre (HTC). This information should be available on the patient's ID card issued by the HTC.
- The use of aPCC (activated prothrombin complex concentrate) during emicizumab prophylaxis should only be considered for patients who do not respond adequately to the first-line treatment with rFVIIa. Additionally, the administration of aPCC should be specifically prescribed by the HTC responsible for the patient.
- It is important that physicians in the Emergency Unit (EU) do not modify the established therapeutic schedule with emicizumab (such as administering an additional dose or skipping a subsequent dose) unless prescribed by the HTC.
- If a patient visits the EU for reasons other than bleeding symptoms, it is essential to consider the possibility of thromboembolic complications, although they are rare. This is particularly important for patients on emicizumab prophylaxis who have self-infused bypassing agents. Therefore, conducting a diagnostic evaluation to differentiate or exclude such complications is advisable.

- In cases of highly suspected or active bleeding, major trauma, or the need for an urgent invasive procedure, it is recommended to infuse rFVIIa at a dose of 90-120 µg/kg before contacting the Hemophilia Treatment Centre (HTC). This information should be available on the patient's ID card issued by the HTC.
- The use of aPCC (activated prothrombin complex concentrate) during emicizumab prophylaxis should only be considered for patients who do not respond adequately to the first-line treatment with rFVIIa. Additionally, the administration of aPCC should be specifically prescribed by the HTC responsible for the patient.
- It is important that physicians in the Emergency Unit (EU) do not modify the established therapeutic schedule with emicizumab (such as administering an additional dose or skipping a subsequent dose) unless prescribed by the HTC.
- If a patient visits the EU for reasons other than bleeding symptoms, it is essential to consider the possibility of thromboembolic complications, although they are rare. This is particularly important for patients on emicizumab prophylaxis who have self-infused bypassing agents. Therefore, conducting a diagnostic evaluation to differentiate or exclude such complications is advisable.

Management of bleeding or suspicion of bleeding in inhibitor patients on emicizumab prophylaxis

- In cases of life-threatening or debilitating hemorrhage (e.g., intra-cranial bleeding) or severe bleeding events due to anatomical site or related symptoms (e.g., muscle hematoma with risk of compartment syndrome), strict monitoring and re-evaluation by the Hemophilia Treatment (HT) specialist should occur after the first 2-3 doses of rFVIIa. The HT will determine how to proceed with subsequent doses and monitor laboratory parameters.
- For moderate hemorrhage, it's possible to extend the interval between doses of rFVIIa (every 6 hours) if bleeding is controlled and clinical improvement is observed.
- If bleeding does not respond or only partially responds to the first 3 doses of rFVIIa, the patient should be re-evaluated by the HT. If the patient is not hospitalized, reassessment at the HTC within 24-48 hours is necessary to monitor the clinical outcome and update therapeutic prescriptions.
- For cases of moderate trauma or minor bleeding, topical measures (e.g., applying ice, local hemostasis, antifibrinolytics for topical use) may suffice to prevent or stop bleeding. Tranexamic acid can be used systemically (10 mg/kg intravenously) or topically (15-25 mg/kg orally every 8 hours) to control bleeding episodes, such as epistaxis or gum bleeding (using a mouthwash with a 10 mL 5% solution for 2 minutes, four times a day). Additionally, tranexamic acid can be combined with rFVIIa treatment for the management of moderate to severe bleeding episodes.
- If there is suspicion of a loss of efficacy of emicizumab due to poor patient compliance (missed doses for an extended period) or the development of anti-drug antibodies (ADAs), although this is rare, it is advisable to conduct an activated partial thromboplastin time (aPTT) test. The aPTT will be prolonged in cases of very low plasma concentrations of emicizumab (<5 µg/mL). This testing can help assess the drug's effectiveness and guide further treatment decisions.
- In situations of severe bleeding or inadequate response to rFVIIa, it is essential to determine the inhibitor titre using a Bethesda assay with a bovine reagent-based FVIII chromogenic assay. It's crucial to note that the Bethesda clotting assay with human reagents may yield false-negative inhibitor results in patients receiving emicizumab, so this should be considered. Evaluating the inhibitor titre is necessary to assess the potential use of FVIII concentrate when the inhibitor titre is <5 BU/mL.

- In cases of severe bleeding that does not respond adequately to rFVIIa and when a high-titre inhibitor (>5 BU/mL) is present, the second-line treatment is aPCC at an initial dose of ≤50 U/kg. If this dose of aPCC is insufficient to control bleeding, repeated low doses of aPCC every 8-12 hours could be considered. These infusions should be administered under medical supervision in the hospital, with the total 24-hour dosage kept below <100 U/kg to reduce the risk of VTE and/or TMA.
- If aPCC administration is required for ≥24 hours, daily monitoring is recommended, including tests for disseminated intravascular coagulation (DIC) such as D-dimer, fibrinogen, platelet count, tests for haemolysis (lactate dehydrogenase [LDH], bilirubin, haptoglobin, reticulocytes), renal function, complete blood count, and a peripheral blood smear to check for schistocytes.
- In cases where there is no response to bypassing agents or when FVIII concentrate cannot be used due to high-titre anti-human FVIII inhibitors, recombinant porcine FVIII (susoctocog alfa, Obizur ®) may be considered as a rescue option. Susoctocog alfa can also be an option when contraindications to second-line treatment with aPCC are present, such as patients with previous VTE on aPCC therapy or those with VTE or TMA when aPCC was used as second-line therapy while on emicizumab prophylaxis.
- Susoctocog alfa is not approved for treating congenital hemophilia with inhibitors. Its off-label use in such cases is at the discretion of the healthcare team and must be authorized by the hospital. There is no established treatment regimen for using susoctocog alfa in patients on emicizumab prophylaxis. Decisions regarding its use should be made carefully.
- Testing for anti-porcine FVIII inhibitors should be conducted before considering treatment with rpFVIII. This assessment should be done before starting emicizumab because emicizumab can affect the measurement of anti-porcine FVIII inhibitors, which are based on aPTT.
- Plasma FVIII levels when using rpFVIII are typically measured with an APTT-based assay, making this test unreliable in individuals receiving emicizumab prophylaxis.

Management of surgery in inhibitor patients

- For minor procedures like central venous catheter removal/insertions, dental extractions, and endoscopies with biopsies, prophylaxis with bypassing agents may not be necessary. However, EU physicians should administer a dose of rFVIIa at 90-120 µg/kg as specified on the patient's ID card if an HT is not available.

- The administration of rFVIIa can be repeated at the same dose every 2-4 hours during and after surgery, considering factors like bleeding risk, the type of surgery, and HT advice. Tranexamic acid at standard doses can be used alongside rFVIIa.
- For minor procedures, especially at mucosal sites, tranexamic acid alone at standard doses may suffice, but rFVIIa should be readily available in case of bleeding complications, as prescribed by the HT and agreed upon by other specialists involved.
- In major invasive procedures with a high risk of bleeding, spinal or epidural anesthesia should be avoided if possible. A pre-operative dose of rFVIIa at 90-120 µg/kg is recommended, to be repeated every 2-4 hours while assessing the clinical outcome and following HT instructions.
- For major surgery and if the inhibitor titre is <5 BU/mL, a high dose of FVIII concentrate is advisable, with consideration of continuous infusion and at least daily monitoring of FVIII plasma levels using a bovine reagent-based FVIII chromogenic assay. Once there is an anamnestic response, rFVIIa will be administered at the specified doses and frequencies.
- If severe hemorrhagic complications occur during or after surgery, rFVIIa fails to yield a response, and there's a high-titre inhibitor (>5 BU/mL) present, the use of aPCC should be considered at a daily dose of <100 U/kg, starting with a dose of <50 U/kg. During emicizumab prophylaxis, it is not recommended to use tranexamic acid alongside aPCC.
- Consideration of rpFVIII as a rescue therapy may be warranted, but this should be done while keeping in mind the limitations and considerations associated with the off-label use of this product, as mentioned previously.
- If aPCC administration is required for ≥24 hours, it is advisable to monitor the patient daily, including tests for DIC, signs of hemolysis (LDH, bilirubin, haptoglobin, reticulocytes), renal function, complete blood count, and peripheral blood smear for schistocytes.
- For major surgery, it is recommended that the evaluation and management of second-line treatments be overseen by the HT responsible for the patient.

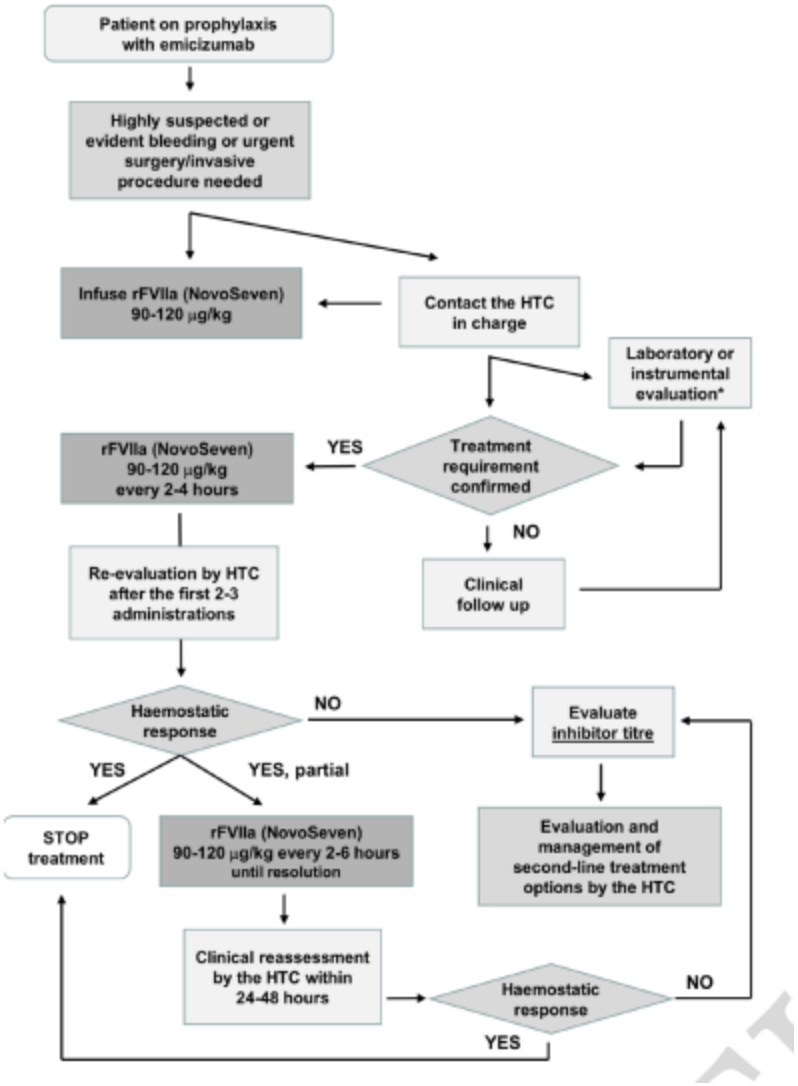

Figure 1. *Algorithm for the Management of Emergency Situations in Patients with Hemophilia A and Inhibitors on Emicizumab Prophylaxis (Retrieved from the AICE 2019 Guidelines)*

1.2.7 Practical Guidance of the GTH Hemophilia Board on the Use of Emicizumab in Patients with Hemophilia A (2020)

The practical guidance issued by the German, Austrian, Swiss Society for Thrombosis and Haemostasis Research (GTH) Hemophilia Board on the Use of Emicizumab in Patients with Hemophilia A (2020)[13] issued a set of recommendations as explained below:

"A revised draft of recommendations was discussed among the authors in a telephone conference as well as few statements, in which complete consensus was not reached, decided by using an electronic survey. A final set of recommendations was circulated to all 13 authors for approval via an online survey analogous to the

Delphi method with a 5-point Likert scale with rating as follows: strong agreement, agreement, limited agreement, concern, and no agreement. Consensus was determined if a statement reached >80% responses indicating 'strong agreement' or 'agreement' according to one suggested threshold for the Delphi method."

General aspects

- Emicizumab therapy should be administered under the supervision of specialized hemophilia centers with experienced healthcare professionals. (100% agreement)

Patient education

- Patients must receive comprehensive education before initiating Emicizumab therapy. This education should cover various aspects, including its mechanism of action, effects on standard coagulation tests, how it is administered and dosed, proper storage, and strategies for managing breakthrough bleeds or surgical procedures. (100% agreement)
- An informative emergency card has to be issued to every patient on Emicizumab. (100% agreement)
- Each Emicizumab administration needs to be recorded meticulously in a patient diary on every occasion. (100% agreement)

Management of breakthrough bleeds and surgery

- Every patient should maintain an emergency supply of FVIII or bypassing agents (BPAs) at their residence for addressing breakthrough bleeding episodes. (92.3% agreement, 7.7% limited agreement)
- Hemorrhage management in individuals with hemophilia A, both with and without inhibitors, should be provided when there are applicable bleeding events or substantial injuries. (92.3% agreement, 7.7% limited agreement)
- Patients under Emicizumab prophylaxis may not require treatment for every non-severe bleeding episode. (92.3% agreement, 7.7% limited agreement)
    a) Minor bleeds or injuries such as subcutaneous hematomas, nosebleeds, mucosal bleeds, and small wounds should be assessed on a case-by-case basis.
    b) Tranexamic acid can be applied either locally or systemically as needed.
- In individuals with hemophilia A (PWHAs) who do not have inhibitors, clinically significant breakthrough bleeds should be managed with factor VIII (FVIII) treatment. (100% agreement)
    a) Standard FVIII treatment regimens based on the type of bleeding have been employed without any complications.

b) When deciding the duration of additional FVIII treatment, it's important to take into account the baseline hemostatic activity provided by Emicizumab.

c) If needed, the monitoring of FVIII replacement can be conducted using a bovine chromogenic FVIII assay.

d) Following an intensive FVIII treatment, inhibitor testing should be carried out using a chromogenic bovine Bethesda assay.

- In individuals with hemophilia A (PWHAs) who have inhibitors, recombinant factor VIIa (rFVIIa) should be the initial treatment choice for significant breakthrough bleeds. It's important to note that the prolonged use of activated prothrombin complex concentrate (aPCC) at doses exceeding 100 units per kilogram for more than 24 hours has been linked to an increased risk of thrombotic or thrombotic microangiopathy (TMA) events. (92.3% agreement, 7.7% limited agreement)

    a) Treating bleeding with rFVIIa following the recommended prescription information was both safe and clinically effective.

    b) If there is an inadequate clinical response to rFVIIa, FVIII can be considered as an option for patients with low FVIII inhibitor activity.

    c) Recombinant porcine FVIII might be a potential choice, although it is not approved for use in patients with congenital hemophilia and inhibitors.

    d) Activated prothrombin complex concentrate (aPCC) should be reserved for situations where no other treatment options are available or effective.

    e) The initial aPCC dose should not exceed a maximum of 50 units per kilogram. Lower doses, ranging from 15 to 25 units per kilogram, have been reported as effective and safe in individual cases.

    f) If a second dose of aPCC is required, it is advisable for the patient to be admitted to a hospital for close monitoring, including assessment for thrombotic microangiopathy (TMA), thrombotic events, and bleed control.

- The necessity, dose, and duration of FVIII replacement for surgery in PWHAs without inhibitors should be customized based on the surgical procedure and post-operative progress. (100% agreement)

    a) In minor surgery cases, additional FVIII treatment may not always be required, but patients should undergo clinical monitoring to detect any signs of abnormal bleeding.

b) Surgical procedures categorized by bleeding risk have been managed successfully using standard FVIII regimens without complications.

c) When deciding the duration of additional FVIII treatment, it's important to take into account the baseline hemostatic activity provided by Emicizumab.

d) Monitoring of FVIII replacement should be conducted using a bovine chromogenic FVIII assay.

e) Following intensive FVIII treatment, inhibitor testing should be conducted using a chromogenic bovine Bethesda assay to assess the presence of inhibitors in the patient's blood.

f) Currently, there is limited experience with major surgery in individuals with hemophilia A (PWHAs) who do not have inhibitors and are under Emicizumab prophylaxis.

- Surgery in PWHAs with inhibitors typically involves using recombinant factor VIIa (rFVIIa) as the primary additional hemostatic treatment. The necessity, rFVIIa dose, and duration of replacement should be customized for each surgical situation and post-operative recovery. (100% agreement)

    a) Minor surgeries may not always require additional bypassing agent (BPA) treatment, but patients should be clinically monitored for any signs of abnormal bleeding.

    b) For major surgeries, preventive treatment with rFVIIa should be administered based on the bleeding risk associated with the surgery and the patient's clinical course.

    c) Inhibitor testing should be conducted before surgery to assess the possibility of using FVIII treatment in case of low or negative inhibitory activity.

    d) If rFVIIa proves to be insufficiently effective, the recommendations for second-line treatment align with those for bleeding management.

    e) If the intention is to employ activated prothrombin complex concentrate (aPCC) at standard doses to manage major surgery, it's necessary to discontinue Emicizumab (4-5 weeks) approximately six months prior to the surgery. This precaution is due to the extended half-life of Emicizumab, which can lead to potential interactions that persist for up to six months.

Immune Tolerance Induction

- In case of newly developed FVIII-inhibitors, ITI should be considered. (100% agreement)
    a) Successful Immune Tolerance Induction (ITI) offers the opportunity to manage bleeds, cover surgeries, and use FVIII therapy, as well as potentially access gene therapy.
    b) Established ITI protocols, such as the Bonn protocol, have demonstrated effectiveness (60-80%) and safety.
    c) To prevent breakthrough bleeds, ITI should commence immediately following confirmation of inhibitor presence.
    d) If the start of ITI needs to be delayed, considering prophylactic Emicizumab treatment is an option.
    e) For patients on ITI experiencing frequent breakthrough bleeds, a prophylactic approach involving bypassing agents (BPAs) or Emicizumab can be considered.
    f) In patients who have received Emicizumab for less than six months, the use of activated prothrombin complex concentrate (aPCC) as a prophylactic agent during ITI should be avoided.
- There are only limited case series where immune tolerance induction (ITI) protocols incorporating both FVIII and Emicizumab for prophylaxis have been employed. Consequently, there is insufficient evidence to provide recommendations regarding the specific indications, dosages, and durations for this combined approach of ITI with Emicizumab prophylaxis. (92.3% agreement, 7.7% limited agreement)
    a) When determining the FVIII dose, it's important to consider the peak inhibitor titre.
    b) For individuals undergoing immune tolerance induction (ITI) combined with Emicizumab prophylaxis, monitoring of FVIII and FVIII inhibitors should be conducted using chromogenic bovine FVIII assays.

Previously Untreated Patients

- Emicizumab is approved for use in all age groups; however, its licensure for children relies on limited available data. Therefore, the decision to employ Emicizumab in very young children, especially those who are previously untreated (PUPs), should be made on a case-by-case basis, considering the individual patient's needs and circumstances. (92.3% agreement, 7.7% limited agreement)

Elderly Patients

- Emicizumab can be used in elderly patients with hemophilia A, but treatment decisions should be based on individual risk factors and any coexisting medical conditions. (100% agreement)

Laboratory Tests

- Emicizumab can influence laboratory clotting assays associated with the intrinsic pathway, starting after the initial dose and lasting for up to six months following the last dose. (100% agreement)
- It is important to have access to tests that can monitor FVIII replacement and FVIII inhibitors, as well as measure Emicizumab concentration. (100% agreement)
    a) To monitor FVIII replacement in the presence of Emicizumab, a chromogenic test containing bovine components should be employed.
    b) Inhibitor testing should be conducted using a bovine chromogenic test as well, with inhibitory activity expressed in CBU/mL.
    c) Monitoring Emicizumab concentration is valuable for detecting therapy adherence or neutralizing anti-drug antibodies (ADAs). Fully neutralizing ADAs can be identified by observing a prolonged aPTT, while more sensitive tests may be needed for partially neutralizing ADAs.
    d) When considering the use of standard-dose aPCC, sensitive tests to monitor Emicizumab concentration can be helpful in ruling out significant concentrations. Due to Emicizumab's extended half-life, relevant concentrations can persist for up to six months after the last dose.
    e) Emicizumab concentration can be measured using a chromogenic test with human components or a diluted one-stage clotting assay calibrated against Emicizumab.
    f) We recommend monitoring Emicizumab concentration one week after the final loading dose and subsequently every three months for a year. Afterward, monitoring can be extended to every six to twelve months, or as needed, especially in cases of treatment inefficacy. Expected trough levels in the steady state with the 1.5 mg/week dosing regimen typically range from 25 to 75 µg/L.
    g) For monitoring FVIII replacement or conducting FVIII inhibitor testing when Emicizumab is present, a chromogenic test containing bovine components can be employed.

1.2.8 Nordic Guidelines on Acquired Hemophilia (2020)

In addition to the 2022 guidelines on congenital hemophilia detailed in section 1.1.1, the Nordic guidelines published in 2020 recommendations on the management of **acquired hemophilia**, detailed below[14]:

- Acquired hemophilia should be suspected in patients with prolonged APTT, but normal INR and signs of bleeding.
- If coagulations factor analyses are not readily available, a mixing test could be performed to strengthen the suspicion. The presence of an inhibitory antibody against a coagulation factor does not give a correction of APTT after mixing with normal plasma.
- The diagnosis should be confirmed at a specialized coagulation laboratory.
- The recommended procedure for diagnosing inhibitory antibodies to coagulation factors is the Bethesda-Nijmegen method.
- Type II kinetics of the antibodies result in poor correlation between antibody titer and FVIII levels and caution is warranted when interpreting the results.

I. Treatment of bleeding

a. First-line treatment

- Bypassing agents are recommended for significant bleeds. Choice of agent depends primarily on availability and clinical experience. Upon treatment failure with one agent, it is recommended to use the other. When switching treatments, an interval of at least 3 hours (when switching from NovoSeven® to FEIBA®) and 6 hours (when switching from FEIBA® to NovoSeven®) is recommended. Combination treatment can be considered if monotherapy is inefficient.
- Factor VIII concentrates in high dosages can be used as first line treatment in patients with AHA, if bypassing agents are not available and especially in patients with low antibody titres and if daily measurement of FVIII is possible.
- Tranexamic acid can be used as concomitant treatment both in patients receiving bypassing agents and factor concentrates. In mild bleeds, tranexamic acid can be used as monotherapy or in combination with desmopressin.

b. Second line treatment

- Either factor concentrates or bypassing agents can be used as second line treatment, depending on the medication used as first line treatment.
- Porcine FVIII is recommended if adequate bleeding control is not achieved on treatment with bypassing agents.

II. Eradication therapy

Although spontaneous remission occurs, immunosuppressive therapy is recommended to eradicate the inhibitors as soon as possible to reduce the length of time the patient is at risk for severe bleeding.

a. First line treatment

- Start Immunosuppressive therapy as soon as possible after diagnosis.
- Corticosteroids in combination with rituximab or cyclophosphamide is recommended as first line therapy.
- Corticosteroids as monotherapy can also be considered.
- Rituximab monotherapy as first line treatment is not recommended due to longer time to remission.

b. Second line treatment

- If the patient is not in responding within 3 weeks (ongoing bleeding, no increase in FVIII) consider adding second line treatment with rituximab or cyclophosphamide, whatever option not used as first line. Alternatively, azathioprine, cyclosporine or immunoadsorption can be used for second line treatment.
- In refractory bleeding consider immunoadsorption/Modified Bonn/Malmö protocol.

III. Follow-up

- Monitor clinical bleeding, FVIII and inhibitor level initially every 1-2 weeks after discharge from hospital. Follow-up should continue for at least a year after Immunosuppressive therapy is stopped.

IV. Relapse

- Repeat first line treatment with corticosteroids and consider adding other Immunosuppressive therapy.

Section 2.0 Drug Therapy in Hemophilia

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

Many new medications were registered in the SFDA for the treatment of Hemophilia and Von Willebrand disease. Hence, relevant information pertaining to these drugs can be found below.

2.1.1 Factor VII Drugs

2.1.1.1 Eptacog Alfa

This section includes pertinent information regarding the use of Eptacog alfa (NOVOSEVEN®)[15] in hemophilia:

Table 12. Eptacog Alfa Drug Information

SCIENTIFIC NAME **Eptacog alfa**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D66, D67, D68.1
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD08
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Acquired hemophilia: IV:**

	Bleeding episodes: 70 to 90 mcg/kg/dose every 2 to 3 hours until hemostasis is achieved. *Perioperative management:* 70 to 90 mcg/kg/dose immediately before surgery; repeat every 2 to 3 hours for the duration of surgery and until hemostasis achieved. **Congenital factor VII deficiency: IV:** *Bleeding episodes:* 15 to 30 mcg/kg/dose every 4 to 6 hours until hemostasis is achieved. Doses as low as 10 mcg/kg have been effective. *Perioperative management:* 15 to 30 mcg/kg/dose immediately before surgery; repeat every 4 to 6 hours for the duration of surgery and until hemostasis achieved. Doses as low as 10 mcg/kg have been effective. **Congenital hemophilia A or B with inhibitors: IV:** *Bleeding episodes:* 90 mcg/kg/dose every 2 hours until hemostasis is achieved or until the treatment is judged ineffective. The dose, interval, and duration of therapy may be adjusted based upon the severity of bleeding and the degree of hemostasis achieved. For patients experiencing

	severe bleeds, dosing should be continued at 3- to 6-hour intervals post-hemostasis. The duration of any post-hemostatic dosing should be minimized. *Perioperative management:* 90 mcg/kg/dose immediately before surgery (additional bolus doses may be administered for major surgery if required); repeat at 2-hour intervals for the duration of surgery. For minor surgery, continue 90 mcg/kg/dose postoperatively every 2 hours for 48 hours, then every 2 to 6 hours until healed. For major surgery, continue 90 mcg/kg/dose postoperatively every 2 hours for 5 days, then every 4 hours or by continuous infusion at 50 mcg/kg/hour until healed. *Secondary prophylaxis of bleeding events (off-label use):* 90 mcg/kg once daily. In a clinical trial, male patients with frequent bleeds (mean ≥4 bleeding events per month requiring hemostatic therapy) received prophylaxis for a duration of 3 months.
Maximum Daily Dose Adults*	N/A

Dose (pediatrics)	**<u>Hemophilia A or B (congenital) with inhibitors:</u>** Note: Dose, frequency and duration of therapy should be individualized based on severity of the bleeding, need for urgent hemostasis, and prior patient response to factor VIIa bypassing agents in previous bleeding events. *Bleeding episodes:* Infants, Children, and Adolescents: IV: 90 mcg/kg/dose every 2 hours until hemostasis is achieved or until the treatment is judged ineffective. Doses between 35 to 90 mcg/kg have been used successfully in clinical trials. The dose, frequency, and duration of therapy should be adjusted based on severity of bleeding and the degree of hemostasis achieved. For patients experiencing severe bleeds to maintain the hemostatic plug, dosing should be continued at 3- to 6-hour intervals; the duration of post-hemostatic dosing has not been studied. Monitor and minimize the duration of post-hemostatic dosing. *Perioperative management:* Infants, Children, and Adolescents: IV: 90 mcg/kg immediately before surgery (additional bolus doses may be administered for major surgery if required); repeat

	at 2-hour intervals for the duration of surgery. For minor surgery, continue 90 mcg/kg/dose every 2 hours for 48 hours, then every 2 to 6 hours until healing achieved. For major surgery, continue 90 mcg/kg/dose every 2 hours for 5 days, then every 4 hours or by continuous infusion at 50 mcg/kg/hour until healing achieved. *Secondary prophylaxis of bleeding events:* Very limited data available: Children ≥5 years and Adolescents: IV: 90 mcg/kg/dose **OR** 270 mcg/kg/dose once daily **Congenital factor VII deficiency:** Infants, Children, and Adolescents: IV: *Bleeding episodes:* 15 to 30 mcg/kg/dose every 4 to 6 hours until hemostasis is achieved. Doses as low as 10 mcg/kg/dose have been effective. Adjust dose and frequency to each individual patient. *Perioperative management:* 15 to 30 mcg/kg immediately before surgery; repeat every 4 to 6 hours for the duration of surgery and until hemostasis achieved. Doses as low as 10 mcg/kg/dose have been effective. Adjust dose and

	frequency to each individual patient.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Prescribing edits*	PA, MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is a step-therapy, is expensive, needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Eptacog alfa is used when other lines of therapy fail in the treatment of Hemophilia A and B as well as Congenital Factor VII deficiency.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Hypertension, thrombosis, decreased serum fibrinogen, antibody development, discomfort at injection site, hematoma at injection site, infusion site reaction, dizziness, headache, intracranial hypertension, hemarthrosis, fever **Most serious:** Acute myocardial infarction, angina pectoris, cerebral ischemia, cerebrovascular accident, deep vein thrombosis, localized phlebitis, occlusion of cerebral arteries, pulmonary embolism, shock, disseminated intravascular coagulation, anaphylactic shock

Drug Interactions	There are no drug interactions classified as Risk X. Anti-inhibitor Coagulant Complex (Human): Risk D Concizumab: Risk D Factor XIII A-Subunit (Recombinant): Risk C
Special Population	N/A
Pregnancy	Pregnant patients with inherited bleeding disorders, including factor VII deficiency and Glanzmann's thrombasthenia, may have an increased risk of bleeding following abortion, antenatal procedures, delivery, and miscarriage; close surveillance is recommended. Patients with factor VII deficiency and severe or abnormal bleeding should be treated with recombinant factor VIIa. Patients with Glanzmann's thrombasthenia and a history of bleeding can be treated prophylactically with recombinant factor VIIa at delivery.
Lactation	It is not known if factor VIIa (recombinant) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	There are no contraindications listed in the manufacturer's labeling. Canadian labeling: Additional contraindications (not in the US labeling): Known hypersensitivity to eptacog alfa (activated), any component of the formulation, or to mouse, hamster, or bovine protein.

Monitoring Requirements	Hemoglobin and hematocrit; evidence of hemostasis; blood loss; signs/symptoms of thrombosis. Note: There are no reliable laboratory tests to measure recombinant factor VIIa efficacy. Tests used to monitor hemostatic efficacy, such as PT/INR, aPTT, factor activity assays, and thromboelastography, are not useful. In factor VII deficient patients, monitor for factor VII antibodies if the expected clinical response is not achieved with recommended doses.
Precautions	- Antibody formation: If factor VIIa activity does not reach the expected level, prothrombin time is not corrected, or bleeding is uncontrolled (with recommended doses), suspect antibody formation and perform antibody analysis. Prothrombin time and factor VII coagulant activity should be measured before and after administration in patients with factor VII deficiency. - Hypersensitivity reactions: Hypersensitivity reactions, including anaphylaxis, have been reported with use. Patients with known hypersensitivity to rabbit, mouse, hamster, or bovine proteins, or IgE-based hypersensitivity to casein may be at higher risk. If hypersensitivity reaction occurs, discontinue use and administer appropriate treatment. - Thromboembolic events: **[US Boxed Warning]: Serious arterial and venous thrombotic events following administration of Factor VIIa (recombinant) have been**

	reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive factor VIIa (recombinant). Monitor patients for signs and symptoms of activation of the coagulation system and for thrombosis. All patients receiving factor VIIa should be monitored for signs and symptoms of activation of the coagulation system or thrombosis; thrombotic events may be increased in patients with history of congenital or acquired hemophilia receiving concomitant treatment with activated or nonactivated prothrombin complex or other hemostatic agents, older patients with acquired hemophilia receiving other hemostatic agents, or patients with a history of atherosclerotic or coronary artery disease, cerebrovascular disease, crush injury, septicemia, or thromboembolism. Decreased dosage or discontinuation is warranted with confirmed intravascular coagulation or presence of clinical thrombosis.
Black Box Warning	**Thrombosis:** Serious arterial and venous thrombotic events following administration of Factor VIIa (recombinant) have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive Factor VIIa (recombinant). Monitor patients for signs and symptoms of activation of the coagulation system and for thrombosis.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Eptacog alfa for the treatment of Hemophilia A and B and Congenital Factor VII defficiency**. Despite this, **Eptacog alfa** has been available on the market for many years.

Conclusion Statement – Eptacog Alfa

Eptacog alfa is s indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- In patients with congenital hemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
- In patients with congenital hemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
- In patients with acquired hemophilia
- In patients with congenital FVII deficiency
- In patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available.

It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use Eptacog alfa in the treatment of Hemophilia A and B as well as Congenital factor VII.

2.1.2 Factor VIII Drugs

2.1.2.1 Anti-Inhibitor Coagulant Complex

This section includes pertinent information regarding the use of an anti-inhibitor coagulant complex (FEIBA®)[16]. *Please refer to **section 2.1** of CHI Hemophilia original clinical guidance.*

Table 13. Anti-Inhibitor Coagulant Complex Drug Information

SCIENTIFIC NAME **Anti-inhibitor coagulant complex**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes

EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D66, D67
Drug Class	Antihemophilic Agent; Blood Product Derivative
Drug Sub-class	Activated Prothrombin Complex Concentrate (aPCC)
ATC Code	B02BD03
Pharmacological Class (ASHP)	20:28.16 Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	1. **Control and prevention of bleeding episodes in patients with hemophilia:** IV: **Note**: Considered a first-line treatment when factor VIII inhibitor titer is >5 Bethesda units (BU) (antihemophilic factor VIII concentrate may be preferred when titer <5 BU). Avoid use in patients with hemophilia A with inhibitors receiving concomitant emicizumab prophylaxis due to increased risk of thrombotic microangiopathy and for patients with hemophilia B with inhibitors due to risk for allergic reactions **General dosing guidelines:** 50 to 100 units/kg/dose. Dosage, dosing frequency, and duration of treatment depend on the location and extent of bleeding and clinical condition of the patient. • *Joint hemorrhage:* 50 to 100 units/kg every 12 hours until pain

	and acute disabilities are improved • *Mucous membrane bleeding:* 50 to 100 units/kg every 6 hours for at least 1 day or until bleeding is resolved • *Soft tissue hemorrhage (eg, retroperitoneal bleed):* 100 units/kg every 12 hours until resolution of bleed • *Other severe hemorrhage (eg, intracranial hemorrhage):* 100 units/kg every 6 to 12 hours; continue until resolution of bleed . • *Perioperative management:* Preoperative: 50 to 100 units/kg (single dose) administered immediately prior to surgery. Postoperative: 50 to 100 units/kg every 6 to 12 hours until resolution of bleed and healing is achieved • *Routine prophylaxis:* 85 units/kg every other day. **2. Hemorrhage (moderate to severe) due to acquired hemophilia (off-label use):** IV: **Optimal dosing has not been established:** 50 to 100 units/kg every 8 to 12 hours until bleeding controlled has been suggested; may continue for 24 to 72 hours based on site, type, and severity of bleeding
Maximum Daily Dose Adults*	• **For joint hemorrhage:** maximum: 100 units/kg/dose; 200 units/kg/day

	• **For mucous membrane bleeding:** maximum: 100 units/kg/dose; 200 units/kg/day • **For soft tissue hemorrhage (eg, retroperitoneal bleed):** maximum: 100 units/kg/dose; 200 units/kg/day • **For other severe hemorrhage (eg, intracranial hemorrhage):** maximum: 100 units/kg/dose; 200 units/kg/day • **For preoperative management:** 50 to 100 units/kg (single dose) • **For postoperative management:** maximum: 100 units/kg/dose; 200 units/kg/day • **For Hemorrhage (moderate to severe) due to acquired hemophilia:** maximum: 200 units/kg/day
Dose (pediatrics)	1. **Control and prevention of bleeding episodes:** Infants, Children, and Adolescents: **Note:** Dosage will vary with the bleeding site and severity. • *Joint hemorrhage:* IV: 50 to 100 units/kg/dose every 12 hours until pain and acute disabilities are improved; • *Mucous membrane bleeding:* IV: 50 to 100 units/kg/dose every 6 hours for at least one day or until bleeding is resolved • *Soft tissue hemorrhage (eg, retroperitoneal bleeding):* IV: 100 units/kg/dose every 12 hours until resolution of bleed • *Other severe hemorrhages (eg, CNS bleeds):* IV: 100 units/kg/dose every 6 to 12 hours until resolution of bleed;

	2. **Perioperative management:** Infants, Children, and Adolescents: *Preoperative:* IV: 50 to 100 units/kg (single dose) administered immediately prior to surgery. *Postoperative:* IV: 50 to 100 units/kg/dose every 6 to 12 hours until resolution of bleed and healing is achieved; 3. **Routine prophylaxis:** Infants, Children, and Adolescents: IV: 85 units/kg/dose every other day.
Maximum Daily Dose Pediatrics*	• **For joint hemorrhage:** maximum daily dose: 200 units/kg/**day** • **For mucous membrane bleeding:** maximum daily dose: 200 units/kg/**day**. • **For soft tissue hemorrhage:** maximum daily dose: 200 units/kg/**day** • **For other severe hemorrhages:** maximum daily dose: 200 units/kg/**day** • **For preoperative management:** 50 to 100 units/kg (single dose) • **For postoperative management:** maximum daily dose: 200 units/kg/**day**
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, ST, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	

MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive, needs to be prescribed by a specialized physician and is used as alternative therapy.	
QL (Quantity Limit): N/A	
ST (Step Therapy): FEIBA (Bypassing agent) is typically used as a second-line therapy for the treatment of bleeding episodes in individuals with hemophilia who have developed inhibitors to factor VIII (FVIII) or factor IX (FIX).	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Diarrhea, nausea, vomiting, anemia, infusion-related reaction, headache and hemarthrosis **Most serious:** Thromboembolic complications (including cerebrovascular accident, deep vein thrombosis, pulmonary embolism), bronchospasm, disseminated intravascular coagulation, tachycardia
Drug Interactions	**Category X**: • Antifibrinolytic Agents
Special Population	N/A
Pregnancy	Limited outcome information is available from a pregnancy registry following use of anti-inhibitor coagulant complex (human) in pregnant patients with acquired hemophilia A Other products are preferred for the routine prophylaxis of bleeding events in pregnant patients with known hemophilia. However, the use of anti-inhibitor coagulant complex (human) may be considered in select patients with bleeding associated with postpartum acquired hemophilia A (a recombinant product may be preferred)

Lactation	It is not known if an anti-inhibitor coagulant complex is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Known anaphylactic or severe hypersensitivity to anti-inhibitor coagulant complex or any component of the formulation, including factors of the kinin generating system; disseminated intravascular coagulation (DIC); acute thrombosis or embolism (including myocardial infarction)
Monitoring Requirements	There are no reliable laboratory tests to measure activated prothrombin complex concentrate efficacy. Monitor for clinical response and evidence of hemostasis; signs/symptoms of disseminated intravascular coagulation (DIC) and thrombosis; hemoglobin and hematocrit; blood loss; hypotension; signs/symptoms of hypersensitivity reactions. Note: Tests used to monitor hemostatic efficacy, such as PT/INR, aPTT, factor activity assays, and TEG, are not useful for monitoring responses with anti-inhibitor coagulant complex (Hoffman 2012). Dosing to normalize these values may result in DIC
Precautions	• **Hypersensitivity reactions:** Hypersensitivity and allergic reactions (including severe and systemic reactions [eg, anaphylaxis with urticaria and angioedema, bronchospasm, circulatory shock]) have been observed following administration. Discontinue

	immediately with signs/symptoms of severe hypersensitivity reactions and provide appropriate supportive care. • **Infusion reactions:** Infusion reactions (eg, chills, pyrexia, hypertension) have been reported. • **Thromboembolic events: [US Boxed Warning]: Thromboembolic events (including venous thrombosis, pulmonary embolism, MI, and stroke) have been reported following administration of anti-inhibitor coagulant complex, particularly with administration of high doses and/or in patients with thrombotic risk factors. Monitor patients receiving anti-inhibitor coagulant complex for signs and symptoms of thromboembolic events,** especially if more than 200 units/kg/day is administered. Use with caution in patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with factor VIIa. Weigh the potential benefit of treatment against the potential risk of these thromboembolic events. Monitor patients receiving >100 units/kg for the development of DIC, acute coronary ischemia, and signs/symptoms of other thromboembolic events. If clinical signs/symptoms occur, discontinue use. In an emicizumab clinical trial where patients were also administered anti-inhibitor coagulant complex for breakthrough bleeding, there were reported cases

	of thrombotic microangiopathy (TMA). TMA has not been reported in clinical studies of anti-inhibitor coagulant complex. Use with caution and monitor closely if anti-inhibitor coagulant complex is used in patients receiving emicizumab.
Black Box Warning	**Thromboembolic events** have been reported during postmarketing surveillance following infusion of anti-inhibitor coagulant complex, particularly following the administration of high doses and/or in patients with thrombotic risk factors. Monitor patients receiving anti-inhibitor coagulant complex for signs and symptoms of thromboembolic events.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Feiba for the treatment of hemophilia**. Despite this, Feiba has been available on the market for many years. It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Feiba in hemophilia management, however, Feiba is recommended to be added to CHI formulary.

Conclusion Statement – Anti-Inhibitor Coagulant Complex

FEIBA is used to control and manage bleeding episodes in individuals with hemophilia who have developed inhibitors (antibodies) against factor VIII or IX. It may also be used as prophylactic (preventive) treatment in patients with hemophilia and inhibitors to reduce the frequency of bleeding episodes and before surgical procedures in individuals with hemophilia A or B with inhibitors to prevent excessive bleeding during surgery.

2.1.2.2 Antihemophilic Factor, Pegylated (MW 20000) Human Sequence Recombinant (Factor VIII)

This section includes pertinent information regarding the use of Antihemophilic factor, pegylated (MW 20000) human sequence recombinant (ADYNOVATE®)[15].

Table 14. Antihemophilic Factor, Pegylated (MW 20000) Human Sequence Recombinant Drug Information

SCIENTIFIC NAME **Anti-inhibitor coagulant complex**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D66
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD02
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Hemophilia A without inhibitors:** - **Treatment and control of bleeding episodes or perioperative management:** *i.* Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg) *ii.* Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)[17] - **Routine prophylaxis to reduce the frequency of bleeding episodes:** IV: 40 to 50 units/kg/dose twice weekly; adjust dose based on clinical response.
Maximum Daily Dose Adults*	N/A

Dose (pediatrics)	**Hemophilia A without inhibitors:** - **Treatment and control of bleeding episodes or perioperative management:** *i.* Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg) *ii.* Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL)[17] - **Routine prophylaxis to reduce the frequency of bleeding episodes:** Children <12 years: IV: 55 units/kg/dose twice weekly; adjust dose and dosing interval based on clinical response; maximum dose: 70 units/kg/dose. Children ≥12 years and Adolescents: IV: 40 to 50 units/kg/dose twice weekly; adjust dose based on clinical response.
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**<u>Renal Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling. **<u>Hepatic Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	

PA (Prior Authorization): This medication should be prior authorized since it is expensive and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache, erythema of skin, pruritis, skin rash, urticaria, abdominal pain, diarrhea, dysgeusia, nausea, vomiting, hypersensitivity reaction, injection-site reaction, dizziness, cough, fever. **Most serious:** Eosinophilia, anaphylaxis, antibody development, fixed drug eruption, ocular hyperemia.
Drug Interactions	No interactions were classified as Risk X. **Category C:** Pegloticase, pegvaliase
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia A may have an increased bleeding risk following invasive procedures, spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor VIII levels should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Although factor VIII concentrations increase in pregnant patients, factor VIII replacement is recommended if concentrations are <50 units/dL and any of the following occur: need for invasive procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic factor VIII concentrations should be maintained for at least 3 to 5 days following invasive

	procedures or postpartum. If a replacement product is indicated, a recombinant product is preferred. Initial reports using the recombinant pegylated product have been limited to use in males
Lactation	It is not known if antihemophilic factor is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Hypersensitivity (eg, anaphylactic reaction) to antihemophilic factor (recombinant [pegylated]), antihemophilic factor (recombinant), mouse or hamster protein, or any component of the formulation.
Monitoring Requirements	The WFH advises that more laboratory assay studies are required to inform recommendations about laboratory monitoring. During treatment of an acute bleeding event or in the perioperative setting using intermittent bolus administration, factor VIII levels should be measured at baseline, and as peaks 15 to 30 minutes after infusion to assess target level achievement. Measurement of FVIII trough levels may aid in calculation of subsequent doses. Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery of the individual patients. The frequency of peak factor VIII activity monitoring during active treatment depends on the indication, clinical response, and treatment day.

	When administered as a continuous infusion, monitor factor VIII activity at baseline, peak factor VIII activity 15 to 30 minutes after initial bolus administration, and at least daily while on continuous infusion therapy. Frequently assess proper functioning of vascular access devices and infusion pumps for pump failure. For long-term bleeding prophylaxis, trough factor VIII measurements should be obtained to tailor prophylaxis regimens, with the goal of achieving factor VIII troughs >3 to 5 units/dL; prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Patients with low-titer inhibitors receiving factor VIII concentrate products should undergo frequent assessment of factor VIII levels and inhibitor titers to ensure response is maintained. **Additional monitoring considerations**: Heart rate and BP before and during IV administration, signs of hypersensitivity reactions, hemoglobin/hematocrit, and signs and symptoms of intravascular hemolysis. For both intermittent bolus and continuous infusion administration, lower than expected factor VIII recovery or reduced half-life are early signs of inhibitor formation.
Precautions	- **Antibody formation:** Formation of antibodies (inhibitors) to factor VIII may occur; monitor patients for the development of antibodies by clinical observation and laboratory tests. Suspect factor VIII antibodies if the plasma factor VIII level does not

	increase as expected or if bleeding is not controlled after administration. - **Hypersensitivity reactions:** Hypersensitivity reactions, including anaphylaxis, have occurred. Angioedema, chest tightness, dyspnea, nausea, pruritus, urticaria, vomiting, and wheezing may progress to anaphylaxis. Discontinue immediately and institute appropriate treatment if hypersensitivity reactions occur.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Adynovate for the treatment of hemophilia**. Despite this, Adynovate has been available on the market for many years.

Conclusion Statement – Antihemophilic factor, pegylated (MW 20000) human sequence recombinant

Antihemophilic factor, pegylated (MW 20000) human sequence recombinant is indicated for the treatment, control of bleeding episodes and perioperative management in Hemophilia A. Furthermore, it can be also used as prophylaxis to reduce the frequency of bleeding episodes. It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Adynovate in hemophilia management.

2.1.2.3 Efmoroctocog Alfa

This section includes pertinent information regarding the use of Efmoroctocog alfa (ELOCTA®)[15] in Hemophilia.

Table 15. Efmoroctocog Alfa Drug Information

SCIENTIFIC NAME **Efmoroctocog alfa**	
SFDA Classification	Prescription

SFDA Approval	Yes
US FDA	Yes (Brand name: Eloctate)
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	D66
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD02
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**On-demand treatment:** The calculation of the required dose of recombinant factor VIII Fc is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dose is determined using the following formula: Required units = body weight (kg) × desired factor VIII rise (%) (IU/dL) × 0.5 (IU/kg per IU/dL) **Routine prophylaxis to prevent or reduce the frequency of bleeding episodes:** IV: 50 units/kg every 4 days; at 3- to 5-day intervals, may adjust dose within the range of 25 to 65 units/kg based on patient response. Preferably, dosing should be tailored to ensure trough factor VIII levels of at least 1% and ideally ≥3% to 5% are achieved, but prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Dose escalation should be considered for patients adherent to prescribed prophylaxis but

	still experiencing breakthrough bleeding events
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Hemophilia A:** Children and Adolescents: IV: Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment. In general, administration of factor VIII 1 unit/kg will increase circulating factor VIII levels by ~2 units/dL. Children <6 years may require higher doses and/or more frequent administration. **Control and prevention of bleeding episodes or perioperative management:** Refer to adult dosing. **Routine prophylaxis to prevent bleeding episodes:** Children <6 years: 50 units/kg twice weekly; at 3- to 5-day intervals, may adjust dose within the range of 25 to 65 units/kg based on patient response. More frequent or higher doses (up to 80 units/kg) may be required. Children ≥6 years and Adolescents: Refer to adult dosing.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; however, renal impairment has no bearing. **Hepatic Impairment:**

	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Increased factor VIII inhibitors, catheter site thrombosis, papular rash **Most serious:** Bradycardia, chest pain, deep vein thrombosis, flushing, hypertension, procedural hypotension, hypersensitivity reaction, catheter site thrombosis
Drug Interactions	There are no known significant interactions.
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia A may have an increased bleeding risk following invasive procedures, spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor VIII levels should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Although factor VIII concentrations increase in pregnant patients, factor VIII replacement is recommended if concentrations are <50 units/dL and any

	of the following occur: need for invasive procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic factor VIII concentrations should be maintained for at least 3 to 5 days following invasive procedures or postpartum. If a replacement product is indicated, a recombinant product is preferred.
Lactation	It is not known if antihemophilic factor (recombinant [Fc Fusion Protein]) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Life-threatening hypersensitivity to antihemophilic factor or any component of the formulation.
Monitoring Requirements	For recombinant Fc fusion protein products, the World Federation of Hemophilia (WFH) recommends use of a one-stage or chromogenic factor VIII activity assay calibrated with a plasma standard traceable to a WHO international standard. Note: For patients receiving concomitant emicizumab therapy, emicizumab interferes with chromogenic factor VIII assays which use human factor IXa and factor X; use of chromogenic assays with bovine factor IXa and X is required to obtain reliable factor VIII activity when emicizumab is present. During treatment of an acute bleeding event or in the perioperative setting using intermittent bolus administration, factor VIII levels should be measured at

	baseline, and as peaks 15 to 30 minutes after infusion to assess target level achievement. Measurement of FVIII trough levels may aid in calculation of subsequent doses. Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery of the individual patients. The frequency of peak factor VIII activity monitoring during active treatment depends on the indication, clinical response, and treatment day. For long-term bleeding prophylaxis, trough factor VIII measurements should be obtained to tailor prophylaxis regimens, with the goal of achieving factor VIII troughs >3 to 5 units/dL; prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Patients with low-titer inhibitors receiving factor VIII concentrate products should undergo frequent assessment of factor VIII levels and inhibitor titers to ensure response is maintained. **Additional monitoring considerations**: Heart rate and BP before and during IV administration; signs of hypersensitivity reactions, hemoglobin/hematocrit; and signs and symptoms of intravascular hemolysis. Lower than expected factor VIII recovery or reduced half-life are early signs of inhibitor formation.
Precautions	Antibody formation: The development of factor VIII antibodies has been reported with antihemophilic factors; monitor for signs of formation of antibodies to factor VIII; may occur at any time but more common in young

	children with severe hemophilia. Suspect factor VIII antibodies if the plasma factor VIII level does not increase as expected or if bleeding is not controlled after administration. Hypersensitivity reactions: Allergic hypersensitivity reactions (including anaphylaxis) may occur; discontinue if hypersensitivity symptoms occur and administer appropriate treatment.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hemophilia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Efmoroctocog alfa.**

Table 16. Efmoroctocog Alfa HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Efmoroctocog alfa	NICE	N/A
	CADTH	N/A
	HAS[18]	03/2016: No clinical benefit demonstrated by comparison with other coagulation factor VIII products in the treatment and prophylaxis of bleeding in patients with hemophilia A.
	IQWIG[19]	03/2016: The company presented no relevant data for the assessment of the added benefit of efmoroctocog alfa versus the alternative comparator therapy.
	PBAC	N/A

Conclusion Statement – Efmoroctocog Alfa

Efmoroctocog alfa is indicated in the treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency). HAS and IQWIG believe that there is no clinical benefit for this medication by comparison to alternative comparator therapy.

2.1.2.4 Moroctocog Alfa

This section includes pertinent information regarding the use of moroctocog alfa (XYNTHA®)[15] in hemophilia:

Table 17. Moroctocog Alfa Drug Therapy

SCIENTIFIC NAME **Moroctocog alfa**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes (Brand name: ReFacto AF)
MHRA	Yes (Brand name: ReFacto AF)
PMDA	No
Indication (ICD-10)	D66
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD06
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Hemophilia A, without inhibitors:** - **Treatment and control of bleeding episodes or perioperative management:** The required dose is determined using the following formula: Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg

	per IU/dL), where IU = International Unit - **Routine prophylaxis to prevent or reduce the frequency of bleeding episodes:** **Note:** Preferably, dosing should be tailored to ensure trough factor VIII levels of at least 1% and ideally ≥3 to 5% are achieved, but prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Dose escalation should be considered for patients adherent to prescribed prophylaxis but still experiencing breakthrough bleeding events IV: 30 units/kg 3 times weekly.[20]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Hemophilia A** - **Control and prevention of bleeding episodes or perioperative management:** The required dose is determined using the following formula: Required units = body weight (kg) x desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL), where IU = International Unit. - **Routine prophylaxis:** Children <12 years: IV: 25 units/kg/dose every other day; more frequent or higher doses may be required due to higher drug clearance.

	Children ≥12 years and Adolescents: IV: 30 units/kg/dose 3 times weekly.[15]
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive, considered as step therapy and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Pruritus, skin rash, urticaria, increased factor VIII inhibitors, headache, arthralgia, cough, nasopharyngitis, upper respiratory tract infection, fever. **Most serious:** Anaphylaxis, angioedema, facial edema, loss of consciousness, restlessness, cyanosis, laryngeal edema.
Drug Interactions	There are no known significant interactions.
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia A may have an increased bleeding risk following invasive procedures,

	spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor VIII levels should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Although factor VIII concentrations increase in pregnant patients, factor VIII replacement is recommended if concentrations are <50 units/dL and any of the following occur: need for invasive procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic factor VIII concentrations should be maintained for at least 3 to 5 days following invasive procedures or postpartum. If a replacement product is indicated, a recombinant product is preferred.
Lactation	It is not known if antihemophilic factor (recombinant) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity (eg, anaphylaxis) to antihemophilic factor, mouse or hamster protein (Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Recombinate, Xyntha, Zonovate [Canadian product]), bovine protein (Recombinate only), or any component of the formulation.
Monitoring Requirements	For patients receiving concomitant emicizumab therapy, emicizumab interferes with chromogenic factor VIII assays which use human factor IXa and

	factor X; use of chromogenic assays with bovine factor IXa and X is required to obtain reliable factor VIII activity when emicizumab is present. During treatment of an acute bleeding event or in the perioperative setting using intermittent bolus administration, factor VIII levels should be measured at baseline, and as peaks 15 to 30 minutes after infusion to assess target level achievement. Measurement of FVIII trough levels may aid in calculation of subsequent doses. Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery of the individual patients. The frequency of peak factor VIII activity monitoring during active treatment depends on the indication, clinical response, and treatment day. When administered as a continuous infusion, monitor factor VIII activity at baseline, peak factor VIII activity 15 to 30 minutes after initial bolus administration, and at least daily while on continuous infusion therapy. Frequently assess proper functioning of vascular access devices and infusion pumps for pump failure. For long-term bleeding prophylaxis, trough factor VIII measurements should be obtained to tailor prophylaxis regimens, with the goal of achieving factor VIII troughs >3 to 5 units/dL; prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Patients with low-titer inhibitors receiving factor VIII concentrate products should undergo frequent assessment of factor VIII levels and

	inhibitor titers to ensure response is maintained. **Additional monitoring considerations:** Heart rate and BP before and during IV administration, signs of hypersensitivity reactions, hemoglobin/hematocrit, and signs and symptoms of intravascular hemolysis. For both intermittent bolus and continuous infusion administration, lower than expected factor VIII recovery or reduced half-life are early signs of inhibitor formation.
Precautions	- Antibody formation: The development of factor VIII antibodies has been reported with antihemophilic factors; monitor for signs of formation of antibodies to factor VIII; may occur at any time but more common in young children with severe hemophilia and previously untreated patients. Suspect factor VIII antibodies if the plasma factor VIII level does not increase as expected or if bleeding is not controlled after administration. - Hypersensitivity reactions: Allergic hypersensitivity reactions (including anaphylaxis) may occur; discontinue if hypersensitivity symptoms occur and administer appropriate treatment.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Moroctocog alfa for the**

treatment of hemophilia. Despite this, **Moroctocog alfa** has been available on the market for many years.

Conclusion Statement – Moroctocog Alfa

Moroctocog alfa is recommended in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, for perioperative management, and for routine prophylaxis to reduce the frequency of bleeding episodes). It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Moroctocog alfa in hemophilia.

2.1.2.5 Omfiloctocog Alfa

This section includes pertinent information regarding the use of omfiloctocog alfa (KOATE DVI®) (HEMOFIL® M), (Immunate S-D ®)[15] in hemophilia:

Table 18. Omfiloctocog Alfa Drug Therapy

SCIENTIFIC NAME **Omfiloctocog alfa**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D66
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD06
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Hemophilia A, without inhibitors:** - **Treatment and control of bleeding episodes or perioperative management:**

	Each vial of KOĀTE contains the labeled amount of Factor VIII in international units (IU). Required Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 Frequency of KOĀTE administration is determined by the type of bleeding episode and the recommendation of the treating physician[21] - **Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with moderate/severe hemophilia A, without inhibitors:** IV: 25 to 40 units/kg of factor VIII concentrate every 2 to 3 days. Preferably, dosing should be tailored to ensure trough factor VIII levels of at least 1% and ideally ≥3% to 5% are achieved, but prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Dose escalation should be considered for patients adherent to prescribed prophylaxis but still experiencing breakthrough bleeding events
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Hemophilia A** - Individualize dosage based on clinical response and factor VIII activity evaluated at baseline and at regular intervals during treatment. In general, administration of factor VIII 1 unit/kg will increase circulating factor VIII levels by ~2% of normal.

	Patients with inhibitory antibodies to factor VIII may require higher doses, more frequent administration, and/or selection of alternative therapy. - **General dosing for control and prevention of bleeding episodes or perioperative management:** **Note:** Dosage is expressed in units of factor VIII activity and must be individualized based on formulation, severity of factor VIII deficiency, extent and location of bleed, individualized incremental recovery using factor VIII activity assays, and clinical situation of patient. Infants, Children, and Adolescents (ages vary by product; see product-specific labeling for approved ages): IV: *Formula for units required to raise blood level:* Number of Factor VIII Units required = body weight (in kg) x 0.5 units/kg per units/dL x desired factor VIII level increase (units/dL or %)
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD

AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Abdominal pain, nausea, increased factor VIII inhibitors, inflammation at injection site, headache, nervousness, paresthesia, blurred vision. **Most serious:** Bradycardia, chest pain, edema, flushing, hypotension, tachycardia, bronchospasm, cough, cyanosis, dyspnea, hyperventilation, tonic-clonic seizure.
Drug Interactions	There are no known significant interactions.
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia A may have an increased bleeding risk following invasive procedures, spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor VIII levels should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Although factor VIII concentrations increase in pregnant patients, factor VIII replacement is recommended if concentrations are <50 units/dL and any of the following occur: need for invasive

	procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic factor VIII concentrations should be maintained for at least 3 to 5 days following invasive procedures or postpartum. If a replacement product is indicated, a recombinant product is preferred.
Lactation	It is not known if antihemophilic factor (human) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Hypersensitivity (eg, anaphylaxis) to antihemophilic factor (human) or any component of the formulation; hypersensitivity to mouse proteins (Hemofil M only).
Monitoring Requirements	For plasma-derived factor VIII products, the World Federation of Hemophilia (WFH) recommends use of a one-stage or chromogenic factor VIII activity assay calibrated with a plasma standard traceable to a World health Organization (WHO) international standard. Note: For patients receiving concomitant emicizumab therapy, emicizumab interferes with chromogenic factor VIII assays that use human factor IXa and factor X; use of chromogenic assays with bovine factor IXa and X is required to obtain reliable factor VIII activity when emicizumab is present. During treatment of an acute bleeding event or in the perioperative setting using intermittent bolus administration,

	factor VIII levels should be measured at baseline, and as peaks 15 to 30 minutes after infusion to assess target level achievement. Measurement of FVIII trough levels may aid in calculation of subsequent doses. Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery of the individual patients. The frequency of peak factor VIII activity monitoring during active treatment depends on the indication, clinical response, and treatment day. When administered as a continuous infusion, monitor factor VIII activity at baseline, peak factor VIII activity 15 to 30 minutes after initial bolus administration, and at least daily while on continuous infusion therapy. Frequently assess proper functioning of vascular access devices and infusion pumps for pump failure. For long-term bleeding prophylaxis, trough factor VIII measurements should be obtained to tailor prophylaxis regimens, with the goal of achieving factor VIII troughs >3 to 5 units/dL; prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. Patients with low-titer inhibitors receiving factor VIII concentrate products should undergo frequent assessment of factor VIII levels and inhibitor titers to ensure response is maintained. **Additional monitoring considerations:** Heart rate and BP before and during IV administration, signs of hypersensitivity reactions, hemoglobin/hematocrit, and signs and symptoms of intravascular hemolysis.

	For both intermittent bolus and continuous infusion administration, lower than expected factor VIII recovery or reduced half-life are early signs of inhibitor formation.
Precautions	- Antibody formation: The development of factor VIII antibodies has been reported with antihemophilic factors; monitor for signs of formation of antibodies to factor VIII. Suspect factor VIII antibodies if the plasma factor VIII level does not increase as expected or if bleeding is not controlled after administration. - Hypersensitivity reactions: Hypersensitivity reactions (including anaphylaxis) may occur; discontinue immediately if hypersensitivity symptoms occur and administer appropriate treatment.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Omfiloctocog alfa for the treatment of hemophilia**. Despite this, **Omfiloctocog alfa** has been available on the market for many years.

Conclusion Statement – Omfiloctocog Alfa

Omfiloctocog alfa is recommended for the control and prevention of bleeding episodes or to perform emergency and elective surgery in patients with hemophilia A (hereditary Factor VIII deficiency). It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Omfiloctocog alfa in hemophilia.

2.1.2.6 Turoctocog Alfa

This section includes pertinent information regarding the use of Turoctocog alfa (Esperoct®) (NOVOEIGH®)[15] in hemophilia:

Table 19. Turoctocog Alfa Drug Information

SCIENTIFIC NAME **Turoctocog alfa**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D66
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD02
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Hemophilia A, without inhibitors:** - **Treatment and control of bleeding episodes or perioperative management:** ✓ The required dosage is determined using the following formula: Dosage Required (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL) ✓ Frequency of Novoeight administration is determined by the type of bleeding episode and the

	recommendation of the treating physician.[22] - **Routine prophylaxis to prevent or reduce the frequency of bleeding episodes:** IV: 20 to 50 units/kg 3 times weekly or 20 to 40 units/kg every other day.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Hemophilia A, without inhibitors:** - **Treatment and control of bleeding episodes or perioperative management:** ✓ The required dosage is determined using the following formula: Dosage Required (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL) ✓ Frequency of Novoeight administration is determined by the type of bleeding episode and the recommendation of the treating physician.[22] **Routine prophylaxis:** ✓ Infants and Children <12 years: IV: 25 to 60 units/kg/dose 3 times weekly **or** 25 to 50 units/kg/dose every other day. ✓ Children ≥12 years and Adolescents: IV: 20 to 50 units/kg/dose 3 times weekly **or** 20 to 40 units/kg/dose every other day.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**<u>Renal Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling.

	<u>Hepatic Impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**<u>Most common:</u>** Pruritis, skin rash, urticaria, increased factor VIII inhibitors, headache, arthralgia, cough, nasopharyngitis, upper respiratory tract infection, fever **<u>Most serious:</u>** Anaphylaxis, angioedema, facial edema, loss of consciousness, cyanosis, laryngeal edema.
Drug Interactions	There are no known significant interactions.
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia A may have an increased bleeding risk following invasive procedures, spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor VIII levels should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Although factor VIII concentrations increase in pregnant patients, factor VIII

	replacement is recommended if concentrations are <50 units/dL and any of the following occur: need for invasive procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic factor VIII concentrations should be maintained for at least 3 to 5 days following invasive procedures or postpartum. If a replacement product is indicated, a recombinant product is preferred.
Lactation	It is not known if antihemophilic factor (recombinant) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity (eg, anaphylaxis) to antihemophilic factor, mouse or hamster protein (Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Recombinate, Xyntha, Zonovate [Canadian product]), bovine protein (Recombinate only), or any component of the formulation.
Monitoring Requirements	Monitor plasma factor VIII activity levels by the one-stage clotting assay or the chromogenic substrate assay to confirm that adequate factor VIII levels have been achieved and maintained, when clinically indicated. Perform assay to determine if factor VIII inhibitor is present if expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with the expected dose of Novoeight. Determine inhibitor levels in Bethesda Units.[22]

	For patients receiving concomitant emicizumab therapy, emicizumab interferes with chromogenic factor VIII assays which use human factor IXa and factor X; use of chromogenic assays with bovine factor IXa and X is required to obtain reliable factor VIII activity when emicizumab is present. During treatment of an acute bleeding event or in the perioperative setting using intermittent bolus administration, factor VIII levels should be measured at baseline, and as peaks 15 to 30 minutes after infusion to assess target level achievement. Measurement of FVIII trough levels may aid in calculation of subsequent doses. Subsequent doses should ideally be based on the FVIII half-life and on the factor recovery of the individual patients. The frequency of peak factor VIII activity monitoring during active treatment depends on the indication, clinical response, and treatment day. When administered as a continuous infusion, monitor factor VIII activity at baseline, peak factor VIII activity 15 to 30 minutes after initial bolus administration, and at least daily while on continuous infusion therapy. Frequently assess proper functioning of vascular access devices and infusion pumps for pump failure. For long-term bleeding prophylaxis, trough factor VIII measurements should be obtained to tailor prophylaxis regimens, with the goal of achieving factor VIII troughs >3 to 5 units/dL; prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics.

	Patients with low-titer inhibitors receiving factor VIII concentrate products should undergo frequent assessment of factor VIII levels and inhibitor titers to ensure response is maintained. **Additional monitoring considerations:** Heart rate and BP before and during IV administration, signs of hypersensitivity reactions, hemoglobin/hematocrit, and signs and symptoms of intravascular hemolysis. For both intermittent bolus and continuous infusion administration, lower than expected factor VIII recovery or reduced half-life are early signs of inhibitor formation.
Precautions	- Antibody formation: The development of factor VIII antibodies has been reported with antihemophilic factors; monitor for signs of formation of antibodies to factor VIII; may occur at any time but more common in young children with severe hemophilia and previously untreated patients. Suspect factor VIII antibodies if the plasma factor VIII level does not increase as expected or if bleeding is not controlled after administration. - Hypersensitivity reactions: Allergic hypersensitivity reactions (including anaphylaxis) may occur; discontinue if hypersensitivity symptoms occur and administer appropriate treatment.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hemophilia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Turoctocog alfa.**

Table 20. Turoctocog Alfa HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Turoctocog alfa	NICE	N/A
	CADTH	N/A
	HAS	- Novoeight: 04/2014: NOVOEIGHT does not provide any improvement in actual benefit (level V, non-existent) in the treatment and prophylaxis of hemophilia A compared with other available treatments[23] - Esperoct (turoctocog alfa pegol): Unfavorable opinion for reimbursement in the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital factor VIII deficiency)[24]
	IQWIG	04/2014: No added benefit of turoctocog alfa was proven in comparison to the alternative comparator therapy[25]
	PBAC	N/A

Conclusion Statement – Turoctocog Alfa

Turoctocog alfa is indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

Furthermore, HAS and IQWIG concluded that there is no added benefit for the use of Turoctocog alfa in the treatment of Hemophilia A.

2.1.3 Human Coagulation Factor VIII / Human von Willebrand Factor

This section includes pertinent information regarding the use of Human coagulation factor VIII / human von Willebrand factor[15] (wilate®) or (Haemate® P) in Hemophilia and Von Willebrand Disease:

Table 21. Human Coagulation Factor VIII/Human von Willebrand Factor Drug Information

SCIENTIFIC NAME **Human coagulation factor VIII / human von Willebrand factor**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes (Brand name: Voncento)
MHRA	Yes (Brand name: Alphanate)
PMDA	No
Indication (ICD-10)	D66, D68.0
Drug Class	Antihemophilic Agent, Blood Product Derivative
Drug Sub-class	N/A
ATC Code	B02BD06
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**<u>Hemophilia A</u>** **i. Treatment and control of bleeding episodes or perioperative management:** One International Unit (IU) of factor VIII (FVIII) activity per kg body weight increases the circulating FVIII level by approximately 2 IU/dL (1.7 IU/dL for adolescents and 2.3 IU/dL for adults) Use the following formula to determine required dosage (2.1): Required IU =

	body weight (BW) in kg x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL) **ii. Routine prophylaxis:** 20 to 40 units/kg of factor VIII concentrate every 2 to 3 days. Individualize dosage based on the patient's weight, type and severity of hemorrhage, FVIII level, presence of inhibitors and the patient's clinical condition. **Von Willebrand Disease** Use the following formula to determine required dosage (2.1): Required IU = body weight (BW) in kg x desired VWF:RCo rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL) Adjust dosage and duration of the substitution therapy depending on the severity of the VWD, on the location and extent of the bleeding, and on the patient's clinical condition Dosing recommendations: **a) Minor Hemorrhages:** ✓ **Loading dose:** 20-40 IU/kg ✓ **Maintenance dose:** 20-30 IU/kg every 12-24 hours ✓ **Therapeutic goal:** VWF:RCo and FVIII activity trough levels of >30% **b) Major Hemorrhages:** ✓ **Loading dose:** 40-60 IU/Kg ✓ **Maintenance dose:** 20-40 IU/kg every 12-24 hours ✓ **Therapeutic goal:** VWF:RCo and FVIII activity trough levels of >50% **c) Minor Surgeries (including tooth extractions):** ✓ **Loading dose:** 30-60 IU/kg ✓ **Maintenance dose:** 15-30 IU/kg or half the loading dose every 12- 24 hours for up to 3 days

	✓ **Therapeutic goal:** VWF:RCo peak level of 50% after loading dose and trough levels of > 30% during maintenance doses **Routine prophylaxis in patients with frequent bleeding episodes:** IV: 40 to 60 VWF:RCo units/kg once per week, 2 times per week, 3 times per week, or every other day, depending on bleeding severity and clinical response[26]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Hemophilia A (Factor VIII deficiency)** Individualize dosage based on clinical response and factor VIII activity evaluated at baseline and at regular intervals during treatment. In general, administration of factor VIII 1 unit/kg will increase circulating factor VIII levels by ~2% of normal. Patients with inhibitory antibodies to factor VIII may require higher doses, more frequent administration, and/or selection of alternative therapy. **General dosing for control and prevention of bleeding episodes or perioperative management:** **Note:** Dosage is expressed in units of factor VIII activity and must be individualized based on formulation, severity of factor VIII deficiency, extent and location of bleed, individualized incremental recovery using factor VIII activity assays, and clinical situation of patient o Infants, Children, and Adolescents: IV: *Formula for units required to raise blood level:* Number of Factor VIII Units required = body weight (in kg) x 0.5 units/kg per

	units/dL x desired factor VIII level increase (units/dL or %) **Routine prophylaxis: Note:** Maintain factor VIII trough levels >3% to 5% or higher as clinically indicated. *Product-specific dosing:* o Wilate: Children ≥12 years and Adolescents: IV: 20 to 40 units/kg/dose every 2 to 3 days. o Infants, Children, and Adolescents: IV: High dose: 25 to 40 units/kg/dose every 2 days. Intermediate dose: 15 to 25 units/kg/dose 3 times weekly. Low dose: 10 to 15 units/kg/dose 2 to 3 times weekly. **Note:** Low dose prophylaxis may be used in young patients as initial therapy to allow patients and families to gradually adjust to prophylaxis and improve adherence; close monitoring is required since patients are at a higher risk for bleeding until escalation occurs. **von Willebrand disease** **von Willebrand disease (VWD), treatment:** Dosage is expressed in international units of von Willebrand factor: Ristocetin cofactor (VWF:RCo): Dose must be individualized based on type of VWD, extent and location of bleeding, clinical status of patient, and coagulation studies performed prior to and at regular intervals during treatment. For major bleeds where repeated dosing is required, monitor and maintain the FVIII plasma concentration as described for the treatment of hemophilia A.

	Products are not identical and should not be used interchangeably **Hemorrhage, treatment: Product-specific dosing:** ***Humate P:*** Infants, Children, and Adolescents: **Note:** In general, administration of 1 unit/kg of factor VIII would be expected to raise circulating VWF:RCo ~5 units/dL. General dosing: IV: VWF:RCo 40 to 80 units/kg/dose every 8 to 12 hours; adjust based on extent and location of hemorrhage. Dosing based on Von Willebrand type and hemorrhage severity: ***Type 1, mild VWD (baseline VWF:RCo activity typically >30%):*** *Minor hemorrhage (if desmopressin is known or suspected to be inadequate) or major hemorrhage (eg, severe or refractory epistaxis, GI bleeding, CNS trauma, traumatic hemorrhage):* IV: Loading dose: VWF:RCo 40 to 60 units/kg. Maintenance dose: VWF:RCo 40 to 50 units/kg/dose every 8 to 12 hours for 3 days to maintain VWF:RCo nadir >50%; follow with VWF:RCo 40 to 50 units/kg/dose once daily for up to 7 days. ***Type 1, moderate or severe VWD (baseline VWF:RCo activity typically <30%):*** IV: Minor hemorrhage (eg, epistaxis, oral bleeding, menorrhagia): VWF:RCo 40 to 50 units/kg/dose for 1 to 2 doses. Major hemorrhage (eg, severe or refractory epistaxis, GI bleeding,

	CNS trauma, hemarthrosis, traumatic hemorrhage): Loading dose: VWF:RCo 50 to 75 units/kg. Maintenance dose: VWF:RCo 40 to 60 units/kg/dose every 8 to 12 hours for 3 days to maintain VWF:RCo nadir >50%; follow with VWF:RCo 40 to 60 units/kg/dose once daily for up to 7 days. ***Types 2 (all variants) and 3 VWD:*** IV: Minor hemorrhage (eg, epistaxis, oral bleeding, menorrhagia): VWF:RCo 40 to 50 units/kg/dose for 1 to 2 doses. Major hemorrhage (eg, severe or refractory epistaxis, GI bleeding, CNS trauma, hemarthrosis, traumatic hemorrhage): Loading dose: VWF:RCo 60 to 80 units/kg. Maintenance dose: VWF:RCo 40 to 60 units/kg/dose every 8 to 12 hours for 3 days to maintain VWF:RCo nadir >50%; follow with 40 to 60 units/kg/dose once daily for up to 7 days. ***Wilate:*** Children ≥5 years and Adolescents: IV: **Note:** Patients with Type 3 VWD and those with GI bleeding may require higher doses. In general, administration of VWF:RCo 1 unit/kg will increase the plasma VWF activity by ~2 units/dL (or 2% of normal), as demonstrated by the following formulas: Dosage (units) based on desired factor VWF:RCo increase (units/dL or % normal) Dosage (units) = Body weight (kg) x 0.5 (units/kg per units/dL) x desired

	VWF:RCo increase (units/dL or % normal) **Minor hemorrhage:** IV: Loading dose: VWF:RCo 20 to 40 units/kg. Maintenance dose: VWF:RCo 20 to 30 units/kg/dose every 12 to 24 hours for ≤3 days, keeping the nadir of VWF:RCo and FVIII activity >30%. **Major hemorrhage:** IV: Loading dose: VWF:RCo 40 to 60 units/kg. Maintenance dose: VWF:RCo 20 to 40 units/kg/dose every 12 to 24 hours for 5 to 7 days, keeping the nadir of VWF:RCo and FVIII activity >50%. **Prophylaxis, surgical/procedural:** ***Humate-P:*** Infants, Children, and Adolescents: *General dosing recommendations:* Whenever possible, the in vivo recovery (IVR) should be calculated and baseline plasma VWF:RCo and FVIII activity should be assessed in all patients prior to surgery. The loading dose may then be calculated using the IVR. **Note:** If the calculated IVR is not available, assume IVR to be 2 unit/dL per units/kg of VWF:RCo administered. *Procedure-specific target VWF:RCo and FVIII:C plasma concentrations and minimum durations:* ***Oral surgery (extraction of ≤2 nonmolar teeth with no bony involvement):*** IV: Loading dose: Calculate the loading dose to achieve a target peak

	plasma VWF:RCo concentration of 50 to 60 units/dL and target peak plasma FVIII:C concentration of 40 to 50 units/dL; administer 1 to 2 hours prior to surgery. Repeat doses may be required to attain target concentrations. Maintenance: One-half loading dose every 8 hours as needed to maintain trough VWF:RCo concentration ≥30 units/dL up to 3 days postsurgery and trough FVIII:C concentration >30 units/dL after day 3. Patients with shorter half-lives may require dosing every 6 hours; may lengthen the dosing interval to every 12 hours as appropriate based on pharmacokinetic data. Administer at least one maintenance dose. Do not exceed VWF:RCo or FVIII:C trough concentration of 100 units/dL. ***Minor surgery:*** IV: Loading dose: Calculate the loading dose to achieve a target peak plasma VWF:RCo concentration of 50 to 60 units/dL and target peak plasma FVIII:C concentration of 40 to 50 units/dL; administer 1 to 2 hours prior to surgery. Repeat doses may be required to attain target concentrations. Maintenance: One-half loading dose every 8 hours for at least 48 hours to maintain trough VWF:RCo concentration ≥30 units/dL up to 3 days postsurgery and trough FVIII:C concentration >30 units/dL after day 3. Patients with shorter half-lives may require dosing every

	6 hours; may lengthen the dosing interval to every 12 hours as appropriate based on pharmacokinetic data. Do not exceed VWF:RCo or FVIII:C trough concentration of 100 units/dL. ***Major surgery/Oral surgery (extraction of >2 teeth or >1 impacted wisdom tooth):*** IV: Loading dose: Calculate the loading dose to achieve a target peak plasma VWF:RCo concentration of 100 units/dL and target peak plasma FVIII:C concentration of 80 to 100 units/dL; administer 1 to 2 hours prior to surgery. Repeat doses may be required to attain target concentrations. Maintenance: One-half loading dose every 8 hours for at least 72 hours to maintain both trough VWF:RCo and FVIII:C concentrations >50 units/dL for up to 3 days postsurgery and >30 units/dL after day 3. Patients with shorter half-lives may require dosing every 6 hours; may lengthen the dosing interval to every 12 hours as appropriate based on pharmacokinetic data. Do not exceed VWF:RCo or FVIII:C trough concentration of 100 units/dL. ***Emergency surgery:*** IV: VWF:RCo 50 to 60 units/kg prior to surgery to achieve a target VWF:RCo peak plasma concentration of 100 units/dL; monitor trough coagulation factor levels and administer subsequent doses as needed to maintain FVIII:C activity level of 80 to 100 units/dL.

	Wilate: Infants, Children, and Adolescents: *General dosing recommendations:* The in vivo recovery (IVR) should be calculated and baseline plasma VWF:RCo activity should be assessed in all patients prior to surgery. The loading dose may then be calculated using the IVR. The formula to calculate the loading dose is as follows: Loading dose (units) = [(Target peak VWF:RCo [units/dL] – Baseline VWF:RCo [units/dL]) x weight (kg)] divided by IVR (units/dL per units/kg) **Note:** If the calculated IVR is not available, assume IVR to be 2 units/dL per unit/kg of VWF:RCo administered. If the calculated IVR is >2.5, assume IVR to be 2.5 units/dL per units/kg of VWF:RCo administered. *Procedure-specific dosing and target VWF:RCo concentrations:* ***Minor surgery (including tooth extraction):*** IV: Loading dose: VWF:RCo 30 to 60 units/kg administered within 3 hours prior to surgery to achieve VWF:RCo peak concentration 50% of normal. Maintenance: VWF:RCo 15 to 30 units/kg/dose (or one-half the loading dose) every 12 to 24 hours to maintain VWF:RCo trough concentrations >30% of normal until wound healing is achieved, for up to 3 days. Do not exceed FVIII:C activity concentrations of 250%. ***Major surgery:*** IV:

	Loading dose: VWF:RCo 40 to 60 units/kg administered within 3 hours prior to surgery to achieve VWF:RCo peak concentration 100% of normal. Maintenance: VWF:RCo 20 to 40 units/kg/dose (or one-half the loading dose) every 12 hours for the first 24 hours after the start of surgery to maintain VWF:RCo trough concentrations >50% of normal; then may adjust to every 12 to 24 hours to maintain VWF:RCo trough concentrations > 50% of normal and continue until wound healing is achieved, up to 6 days or more. Do not exceed FVIII:C activity concentration of 250%.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Nausea, hemorrhage, postoperative pain.

	<u>Most serious:</u> Thrombocythemia, hypersensitivity reaction, respiratory distress, cerebral hemorrhage, phlebitis, pulmonary embolism, subdural hematoma, thrombophlebitis, anaphylaxis, angioedema, sepsis.
Drug Interactions	There are no known significant interactions.
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia A and those with von Willebrand disease may have an increased bleeding risk following invasive procedures, spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor VIII concentrations may increase in pregnant patients; changes in von Willebrand factor levels may vary during pregnancy depending on type. Patients should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Replacement is recommended if concentrations are <50 units/dL and any of the following occur: need for invasive procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic concentrations should be maintained for at least 3 to 5 days following invasive procedures or postpartum. When VWF replacement therapy is needed, a recombinant product or a product made from a safe plasma source with viral testing that contains both factor VIII and von Willebrand factor is recommended. A recombinant product is one of the preferred agents if prophylaxis or

	treatment is needed for hemophilia A during pregnancy.
Lactation	It is not known if antihemophilic factor/von Willebrand factor (human) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity reaction, including anaphylactic or severe systemic reaction to antihemophilic factor or von Willebrand factor or any component of the formulation; hypersensitivity to human plasma derived products (Wilate only).
Monitoring Requirements	Heart rate and blood pressure (before and during administration); AHF concentrations prior to and during treatment; in patients with circulating inhibitors, the inhibitor concentration should be monitored; hematocrit; monitor for signs and symptoms of intravascular hemolysis; bleeding; VWF activity (circulating levels of functional VWF are measured as ristocetin cofactor activity [VWF:RCo]). In surgical patients, monitor VWF:RCo at baseline and after surgery, trough VWF:RCo and FVIII:C at least daily; hypersensitivity reactions during infusion.
Precautions	- Antibody formation: Neutralizing antibodies (inhibitors) may develop to factor VIII or von Willebrand factor, particularly in patients with type 3 (severe) von Willebrand disease. Patients who develop antibodies against von Willebrand factor will not have an effective clinical

	response to therapy and infusions may result in anaphylactic reactions; these patients should be managed by an experienced physician and alternatives to therapy should be considered. Patients with hemophilia should have an appropriate laboratory assessment if expected factor VIII plasma levels are not attained or if bleeding is not controlled following an adequate dose. Any patient who has an inadequate response to therapy or a severe adverse reaction should be evaluated for the presence of inhibitors. - Hypersensitivity reactions: Hypersensitivity or allergic reactions have been observed, including anaphylaxis and shock (with or without fever). Monitor patients closely during infusion; if allergic symptoms occur, discontinue administration and initiate treatment immediately. Patients experiencing anaphylactic reactions should be evaluated for the presence of inhibitors. - Thrombotic events: Thromboembolic events have been reported; especially in patients with known risk factors for thrombosis. Risk of thromboembolic events may be increased in female patients, patients with endogenous high concentrations of factor VIII, and in patients who receive continued treatment resulting in an excessive rise in factor VIII activity; monitor concentrations of von Willebrand factor and factor VIII closely. Use with

	caution and consider antithrombotic measures when treating patients with von Willebrand disease that are at an increased risk for thrombosis. - Vasomotor reactions: Rapid administration may result in vasomotor reactions; do not exceed administration rate recommendations.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of** Human coagulation factor VIII / human von Willebrand factor **for the treatment of hemophilia an von Willebrand Disease**. Despite this, Human coagulation factor VIII / human von Willebrand factor has been available on the market for many years.

Conclusion Statement – Human Coagulation Factor VIII/Human von Willebrand Factor

Human coagulation factor VIII / human von Willebrand factor is indicated in children and adults with von Willebrand disease (for on-demand treatment and control of bleeding episodes and perioperative management of bleeding) and in adolescents and adults with hemophilia A (for routine prophylaxis to reduce the frequency of bleeding episodes and on-demand treatment and control of bleeding episodes). It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Human coagulation factor VIII / human von Willebrand factor in Hemophilia A and von Willebrand disease.

2.1.4 Factor IX Drugs

2.1.4.1 Eftrenonacog Alfa

This section includes pertinent information regarding the use of Eftrenonacog Alfa (ALPROLIX®)[15] in hemophilia:

Table 22. Eftrenonacog Alfa Drug Information

SCIENTIFIC NAME **Eftrenonacog Alfa**

SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	D67
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD04
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**On-demand treatment and control of bleeding episodes:** On average, one unit per kilogram body weight of ALPROLIX increased the circulating Factor IX level by approximately 1% (IU/dL) in adults. **Minor and Moderate bleeding:** 30-60 IU/dL. Repeat every 48 hours as needed if there is further evidence of bleeding. **Major bleeding:** 80-100 IU/dL. Consider repeat dose after 6-10 hours, then every 24 hours for 3 days, then every 48 hours until healing achieved. **Perioperative management:** ➢ **Minor surgery:** a single infusion to reach FIX level of 50-80 IU/dL may be sufficient. Repeat as needed after 24-48 hours until bleeding stops, and healing is achieved. ➢ **Major surgery:** initial infusion to reach FIX level of 60-100 IU/dL. Consider a repeat dose after 6-10 hours and then every 24 hours for the first 3 days, then every 48 hours

	until bleeding stops, and healing is achieved. **<u>Routine prophylaxis:</u>** For adults and adolescents ≥12 years of age, start at 50 IU/kg once weekly or 100 IU/kg once every 10 days[27]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Control or prevention of bleeding in patients with factor IX deficiency (hemophilia B or Christmas disease):** IV: Dosage is expressed in units of factor IX activity; dosing must be individualized based on severity of factor IX deficiency, extent and location of bleeding, clinical status of patient, pharmacokinetic profile, and recovery of factor IX. ***Formula for units required to raise blood level %:*** **Note:** If patient has severe hemophilia (ie, baseline factor IX level is or presumed to be <1%), then may just use "desired factor IX level" instead of "desired factor IX level *increase*". Infants, Children, and Adolescents: IV: Number of factor IX units required = patient weight (in kg) x desired factor IX level increase (as % or units/dL) x reciprocal of observed recovery (as units/kg per units/dL) **Alternative recommendations (off label):** Infants, Children, and Adolescents: o Prophylaxis: Refer to adult dosing. o Treatment: Refer to adult dosing. **Routine prophylaxis to prevent bleeding episodes in patients with factor IX deficiency (hemophilia B or Christmas disease):** IV: o Infants and Children <12 years of age: Initial: 60 units/kg once weekly;

	adjust dose based on individual response. More frequent or higher doses may be needed, especially in children <6 years of age. o Children ≥12 years of age and Adolescents: Refer to adult dosing.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; monitor factor IX levels. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; monitor factor IX levels. Use with caution due to the risk of thromboembolic complications.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is expensive and needs to be prescribed by a specialized physician.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Oral paresthesia, obstructive uropathy, factor IX inhibitor in hemophilia B, hypersensitivity reaction, erythema at injection site, headache. **Most serious:** Thromboembolic complications, anaphylaxis, antibody development, hypotension, palpitations.
Drug Interactions	There are no interactions classified as Risk X.

	Category C: Efgartigimod Alfa, rozanolixizumab.
Special Population	N/A
Pregnancy	Pregnant carriers of hemophilia B may have an increased bleeding risk following invasive procedures, spontaneous miscarriage, termination of pregnancy, and delivery; close surveillance is recommended. Factor IX levels should be monitored at the first antenatal visit, once or twice during the third trimester, prior to surgical or invasive procedures, and at delivery. Although factor IX levels remain stable during pregnancy, factor IX replacement is recommended if concentrations are <50 units/dL and any of the following occur: need for invasive procedures (including delivery), spontaneous miscarriage, insertion and removal of epidural catheters, or active bleeding. Hemostatic factor IX concentrations should be maintained for at least 3 to 5 days following invasive procedures or postpartum. If replacement with a factor IX concentrate is indicated to increase factor IX during pregnancy, a recombinant product is preferred.
Lactation	It is not known if factor IX (recombinant [Fc fusion protein]) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity (eg, anaphylaxis) to factor IX (recombinant [Fc fusion protein]) or any component of the

	formulation (ie, sucrose, mannitol, sodium chloride, L-histidine, and polysorbate 20).
Monitoring Requirements	For Alprolix, the World Federation of Hemophilia recommends use of a chromogenic FIX assay or aPTT-based, one-stage FIX activity assay with validated reagents, calibrated with a plasma standard traceable to a WHO international standard. One-stage FIX assays with STA-PTT automate or kaolin activator (CK Prest) reagents significantly underestimate true Alprolix factor IX activity and should not be used. During treatment of an acute bleeding event or in the perioperative setting using intermittent bolus administration, factor IX levels should be measured at baseline, and as peaks 15 to 30 minutes after infusion to assess target level achievement. The frequency of peak factor IX activity monitoring during active treatment depends on the indication, clinical response, and treatment day. Measurement of FIX trough levels may aid in calculation of subsequent doses. For long-term bleeding prophylaxis, trough factor IX measurements should be obtained to tailor prophylaxis regimens, with the goal of achieving factor IX troughs >3 to 5 units/dL; prophylaxis targets should be tailored to individual level of activity, lifestyle, and pharmacokinetics. **Additional monitoring considerations:** Heart rate and BP before and during IV administration, signs of hypersensitivity reactions (which may be an early sign of inhibitor

	development), hemoglobin/hematocrit, and signs and symptoms of intravascular hemolysis. Lower than expected factor IX recovery or reduced half-life are early signs of inhibitor formation.
Precautions	- Hypersensitivity reactions: Hypersensitivity and anaphylactic reactions have been reported with use. Risk is highest during the early phases of initial exposure in previously untreated patients, especially those with high-risk gene mutations. Delayed reactions (up to 20 days after infusion) in previously untreated patients may also occur. Due to potential for allergic reactions, the initial ~10 to 20 administrations should be performed under appropriate medical supervision. Hypersensitivity reactions has been associated with the presence of factor IX inhibitors; patients experiencing allergic reactions should be evaluated for factor IX inhibitors. If hypersensitivity reactions occur, discontinue immediately and consider the use of alternative hemostatic measures. Patients with factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge. - Nephrotic syndrome: Nephrotic syndrome has been reported following immune tolerance induction with factor IX products in hemophilia B patients with factor IX inhibitors and a history of allergic reactions to factor IX. - Neutralizing antibody formation: The development of factor IX antibodies

	(or inhibitors) has been reported with factor IX therapy (usually occurs within the first 10 to 20 exposure days); the risk of severe hypersensitivity reactions occurring may be greater in these patients. When clinical response is suboptimal, the patient has reached a specified number of exposure days, or patient is to undergo surgical procedure, screen for inhibitors. Patients with severe hemophilia compared to those with mild or moderate hemophilia are more likely to develop inhibitors. - Thrombotic events: Observe closely for signs or symptoms of intravascular coagulation or thrombosis; risk is generally associated with the use of factor IX complex concentrates (containing therapeutic amounts of additional factors); however, potential risk exists with use of factor IX products (containing only factor IX) especially when administered as a continuous infusion through a central venous catheter, including life-threatening superior vena cava (SVC) syndrome. Use with caution when administering to patients with liver disease, postoperatively, neonates, patients at risk of thromboembolic phenomena or disseminated intravascular coagulation, or patients with signs of fibrinolysis due to the potential risk of thromboembolic complications.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hemophilia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Eftrenonacog alfa.**

Table 23. Efmoroctocog Alfa HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Eftrenonacog alfa	NICE	N/A
	CADTH	N/A
	HAS[28]	10/2016: Minor improvement relative to other factor IX products in the treatment of hemophilia B.
	IQWIG	N/A
	PBAC	N/A

Conclusion Statement – Eftrenonacog Alfa

Eftrenonacog alfa is indicated in the treatment and prophylaxis of bleeding in patients with hemophilia B (congenital factor IX deficiency). HAS implicates that that there is Minor improvement with the use of Eftrenonacog alfa relative to other factor IX products in the treatment of hemophilia B.

2.1.5 Factor XIII Drugs

2.1.5.1 Catridecacog

This section includes pertinent information regarding the use of Antihemophilic factor, pegylated (MW 20000) human sequence recombinant (NovoThirteen®)[15] in Factor XIII A deficiency:

Table 24. Catridecacog Drug Information

SCIENTIFIC NAME Catridecacog	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes

EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D68.26
Drug Class	Antihemophilic Agent
Drug Sub-class	N/A
ATC Code	B02BD11
Pharmacological Class (ASHP)	20:28.16 - Hemostatics
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Factor XIII A-subunit deficiency:** IV: 35 units/kg once monthly to achieve a target trough level of factor XIII activity ≥10%; consider dose adjustment if adequate coverage is not achieved (higher doses may not increase the levels of tetrameric factor XIII).
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Factor XIII A-subunit deficiency:** Infants, Children, and Adolescents: IV: 35 units/kg/dose once monthly to achieve a target trough level of factor XIII activity ≥10%; consider dose adjustment if adequate coverage is not achieved (higher doses may not increase the levels of tetrameric factor XIII).
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, MD
AGE (Age Edit): N/A	

CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized physician.	
PA (Prior Authorization): This medication should be prior authorized since it is used specifically for factor XIII A-subunit deficiency.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache, increased fibrinolysis, antibody development, pain at injection site, limb pain **Most serious:** Thrombotic events, antibody development, hypersensitivity reactions
Drug Interactions	No interactions were classified as Risk X. **Category C:** Factor VIIa (Recombinant)
Special Population	N/A
Pregnancy	Pregnant patients with factor XIII deficiency may have an increased risk of bleeding following abortion, antenatal procedures, and delivery. There is also a high rate of pregnancy loss without treatment; close surveillance is recommended. Maternal factor XIII concentrations decrease during pregnancy and dosing frequency should be increased. Additional treatment may be needed prior to delivery or procedures. Factor XIII A-Subunit (Recombinant) may be used in patients with a factor XIII A-subunit deficiency.
Lactation	It is not known if Factor XIII A-Subunit (Recombinant) is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant

	exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to coagulation factor XIII A-subunit (recombinant) or any component of the formulation.
Monitoring Requirements	Monitor Factor XIII trough levels; for development of factor XIII inhibitory antibodies; for hypersensitivity reactions; for thrombotic events.
Precautions	- Antibody formation: Inhibitory antibodies may occur. Patients with inhibitory antibodies may manifest as an inadequate response to treatment. Factor XIII inhibitory antibodies should be measured when breakthrough bleeding or factor XIII activity levels are suboptimal after apparent adequate dosing. - Hypersensitivity reactions: May cause allergic reactions; discontinue immediately if signs or symptoms of anaphylaxis or hypersensitivity reactions (including urticaria, rash, tightness of the chest, wheezing, hypotension) occur and institute appropriate management. - Thrombotic events: Thromboembolic complications may occur; monitor patients with known risk factors for thrombosis.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of hemophilia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for catridecacog.**

Table 25. Catridecacog HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Catridecacog	NICE	N/A
	CADTH	N/A
	HAS[29]	12/2020: Favorable opinion for reimbursement in long-term prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency.
	IQWIG	N/A
	PBAC	N/A

Conclusion Statement – Catridecacog

Catridecacog is indicated for the long-term prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency and management of breakthrough bleeding episodes during regular prophylaxis. HAS provides a favorable opinion for the reimbursement of this medication.

2.1.6 Plasma Protein Factor

2.1.6.1 Plasma Protein Fraction

This section includes pertinent information regarding the use of Plasma protein fraction (Pentaglobin ®) (Plasmanate®) (Octaplas®)[15] in the treatment of shock due to due to loss of plasma fluids or emergency treatment of shock due to hemorrhage:

Table 26. Plasma Protein Fraction Drug Information

SCIENTIFIC NAME **Plasma protein fraction**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D68.1
Drug Class	Blood Product Derivative

Drug Sub-class	N/A
ATC Code	J06BA02
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	- **Shock:** IV: Usual minimum dose: 250 to 500 mL (12.5 to 25 g of protein); adjust dose based on clinical response.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, EU, ST, CU in factor XI Deficiency
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): if factor XI concentrate is unavailable for patients with factor XI deficiency, a combination of pathogen-treated plasma (SD-FFP) and tranexamic acid is recommended in cases of severe bleeds, major surgeries, or delivery in women with low levels of factor XI.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): human plasma albumin (Octaplas) is an essential substitution therapy in coagulation factor deficiencies, when a specific coagulation factor concentrate (e.g., factor V or factor XI) is not available for use or in emergency situations when a precise laboratory diagnosis is not possible. for patients with prothrombin (FII) deficiency, factor X deficiency, and vitamin K-dependent coagulation factor deficiency; pathogen-reduced plasma is an alternative if prothrombin complex is unavailable. the specialist should review the case and approve the drug before use.	
QL (Quantity Limit): N/A	

ST (Step Therapy): For patients with prothrombin (fii) deficiency, factor x deficiency and vitamin k-dependent coagulation factor deficiency, pathogen reduced plasma is an alternative if prothrombin complex is unavailable.	
EU (Emergency Use Only): In cases of life-threatening bleeding, the immediate use of the indicated drug is lifesaving.	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Postmarketing:** Cardiovascular: Flushing Dermatologic: Urticaria Gastrointestinal: Nausea Hypersensitivity: Anaphylaxis Nervous system: Headache Neuromuscular & skeletal: Back pain
Drug Interactions	There are no known significant interactions.
Special Population	N/A
Pregnancy	Animal reproduction studies have not been conducted.
Lactation	N/A
Contraindications	Hypersensitivity to plasma protein fraction or any component of the formulation; patients on cardiopulmonary bypass; severe anemia; heart failure; increased blood volume.
Monitoring Requirements	Monitor blood pressure, pulse, pulmonary exam.
Precautions	- Hypotension: Rapid infusions may cause hypotension. Decrease or stop infusion if sudden hypotension occurs.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Plasma Protein Fraction for the**

the treatment of shock due to due to loss of plasma fluids or emergency treatment of shock due to hemorrhage. Despite this, **Plasma Protein Fraction** has been available on the market for many years.

Conclusion Statement - Plasma Protein Fraction

Plasma Protein Fraction is recommended for the **treatment of shock due to due to loss of plasma fluids or emergency treatment of shock due to hemorrhage**. It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use Plasma Protein Fraction in **the treatment of shock due to due to loss of plasma fluids or emergency treatment of shock due to hemorrhage.**

2.1.7 Immunosuppressive Therapy

2.1.7.1 Azathioprine

This section includes pertinent information regarding the use of Azathioprine (IMURAN®) in acquired hemophilia.

Table 27. Azathioprine Drug Information

SCIENTIFIC NAME **Azathioprine**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D68.311
Drug Class	Immunosuppressant Agent
Drug Sub-class	Anti-CD20
ATC Code	L04AX01
Pharmacological Class (ASHP)	92:44 - Immunosuppressive Agents
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Acquired hemophilia: 2 mg/kg BW once daily for 6 weeks. Thereafter the dose is tapered

	slowly depending on the antibody titre and the factor level[14]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	<u>Renal Impairment:</u> **Altered kidney function:** - CrCl ≥30 mL/minute: Initial: No dosage adjustment necessary. - CrCl 10 to <30 mL/minute: Initial: Administer 75% to 100% of the usual indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended). - CrCl <10 mL/minute: Initial: Administer 50% to 100% of the usual indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended). **Hemodialysis, intermittent (thrice weekly): Dialyzable (45% removed during 8 hours of hemodialysis):** Initial: Administer 50% to 100% of the indication-specific dose; if the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended). When scheduled dose falls on a dialysis day, administer after hemodialysis. If not administered after

	hemodialysis, provide a 50% supplemental dose. **Peritoneal dialysis:** Initial: Administer 50% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended). **CRRT:** Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important. Initial: Administer 75% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended). **PIRRT (eg, sustained, low-efficiency diafiltration)**: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important. Initial: Administer 75% to 100% of the indication-specific dose. Administer the dose after PIRRT therapy ends on PIRRT days . If the initial dose is a dose range then it is recommended to begin with the lowest end

	of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended) Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	ST, PA, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized experienced physician.	
PA (Prior Authorization): Should be prior authorized since it is used specifically for acquired hemophilia.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Considered as second line therapy for the eradication therapy of acquired hemophilia.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Leukopenia, thrombocytopenia, less often anemia, nausea, vomiting, alopecia, exanthema, liver dysfunction, susceptibility to infections. Most serious: Leukopenia, thrombocytopenia, hepatotoxicity, malignant lymphoma, hepatosplenic T-cell lymphoma (HSTCL), hemophagocytic lymphohistiocytosis (HLH), acute myelocytic leukemia, myelodysplastic syndrome, and malignant neoplasm of skin, pancreatitis.
Drug Interactions*	Risk X interactions: - Abrocitinib - Baricitinib - BCG (Intravesical) - BCG Products - Brivudine - Cladribine

	- Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Febuxostat - Fexinidazole - Filgotinib - Mercaptopurine - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery: Patients with severe SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE without severe disease, hold azathioprine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk)
Pregnancy	Azathioprine crosses the placenta.

	Adverse events, including congenital anomalies, immunosuppression, hematologic toxicities (lymphopenia, pancytopenia), and intrauterine growth retardation have been observed in case reports following maternal use in kidney allograft recipients. Some of these adverse outcomes may be dose-related or a result of maternal disease. Adverse pregnancy outcomes may also be associated with a kidney transplant, including preterm delivery and low birth weight in the infant and hypertension and preeclampsia in the mother. Appropriate maternal use of lower risk immunosuppressants may help decrease these risks. Azathioprine can be continued and should be substituted for mycophenolate in patients who become pregnant following a kidney transplant. Azathioprine may also be used in some pregnant patients who have had a liver, heart or uterine transplant. Although use for rheumatoid arthritis in pregnant patients is contraindicated by the manufacturer, available guidelines suggest that use of azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy. Patients with inflammatory bowel disease who are on maintenance therapy with azathioprine monotherapy may continue treatment during pregnancy; initiating treatment during pregnancy is not recommended. Combination therapy with azathioprine should be avoided due to increased risk of newborn infection. Treatment with azathioprine for autoimmune hepatitis should be continued during pregnancy. Because pregnancy may increase the risk of a flare, monitor closely for 6 months' postpartum. Azathioprine may also be useful for the treatment of immune

	thrombocytopenia in a pregnant patient refractory to preferred agents. Azathioprine is considered acceptable for the treatment of myasthenia gravis in pregnant patients who are not controlled with or unable to tolerate corticosteroids.
Lactation	The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk. Azathioprine is a prodrug which is rapidly metabolized to 6-MP. 6-MP is present in breast milk; however, it is inactive until further metabolized to 6-TGN metabolites which are present only within red blood cells. Peak breast milk concentrations of 6-MP occurred within 4 hours in a study of eight lactating women. Another study measured the active metabolite concentrations in RBCs of four breastfeeding women ≥3 months' postpartum on chronic azathioprine therapy; sampling was conducted at variable times after the dose. Women in the study had normal thiopurine methyltransferase (TPMT) activity. All women had therapeutic concentrations of 6-TGN; however, none of the infants had detectable concentrations. Newborn serum concentrations of 6-MP and 6-TGN were also undetectable in a study which evaluated seven breastfed infants between 1 and 28 days' postpartum. Mothers in this study were taking azathioprine 100 mg/day. Information is available from a report of 29 women taking azathioprine 50 to 175 mg/day throughout pregnancy and postpartum and their 30 breastfed newborns. Among 20 infants with blood cell counts evaluated after delivery, one infant was diagnosed with asymptomatic neutropenia on day 15 of life. Neutropenia fluctuated over 1.5 months of breastfeeding, continued for 15 days after

	breastfeeding was discontinued, and resolved 3.5 months later. No adverse outcomes were observed in the remaining infants who were followed for 1 to 17 months .A second study of 11 women taking azathioprine maintenance doses for inflammatory bowel disease (median: 150 mg/day) did not find an increased risk of infection in their 15 breastfed infants. The infants were followed for 6 months to 6 years. Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. The World Health Organization also recommends breastfeeding be avoided during maternal treatment. Recommendations for breastfeeding in females taking azathioprine following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses. Azathioprine is considered compatible for use in women with inflammatory bowel disease who wish to breastfeed. Azathioprine may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding. Patients who are concerned with the theoretical risks of immunosuppression may consider pumping and discarding breast milk for the first 4 hours after an azathioprine dose to decrease potential exposure to the breastfed infant.
Contraindications	Hypersensitivity to azathioprine or any component of the formulation; pregnancy (in patients with rheumatoid arthritis [see Pregnancy Considerations]); patients with rheumatoid arthritis and a history of treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan)

	may have a prohibitive risk of malignancy with azathioprine treatment.
Monitoring Requirements	- CBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dosage modifications or as clinically indicated), total bilirubin, LFTs (every 3 months), CrCl, monitor for signs/symptoms of infection and malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Azathioprine has been associated with skin cancer with long-term use after kidney transplantation. Patients taking azathioprine for a prolonged time period should avoid sun exposure and be monitored for skin cancer regularly. - Thiopurine S-methyltransferase (TPMT) genotyping or phenotyping: Consider testing for TPMT deficiency, particularly in patients with abnormally low CBC unresponsive to dose reduction. TPMT genotyping or phenotyping may assist in identifying patients at risk for developing toxicity (CPIC [Relling 2019]). - Nudix hydrolase 15 (NUDT15) genotyping: Consider genotyping for NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated myelosuppressive episodes. NUDT15 genotyping may assist in identifying patients at risk for developing toxicity (CPIC [Relling 2019]). - TPMT and NUDT15 testing cannot substitute for monitoring CBC in patients receiving azathioprine.
Precautions	- Hepatic impairment: Use with caution in patients with hepatic impairment. - Renal impairment: Use with caution in patients with renal impairment.

	- Mercaptopurine: Azathioprine is metabolized to mercaptopurine; concomitant use may result in profound myelosuppression and should be avoided. - Vaccines: Immune response to vaccines may be diminished. Toxicity or adverse reactions to live vaccines may be enhanced (depending on the azathioprine dose).
Black Box Warning	Malignancy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *azathioprine* for the treatment of acquired hemophilia**. Despite this, ***azathioprine*** has been available on the market for many years.

Conclusion Statement – Azathioprine

Azathioprine is recommended for the eradication of inhibitors in acquired hemophilia. However, its use was only mentioned in one guideline, and the data is based only on retrospective and case studies. Therefore, more studies are needed in order to be able to recommend the addition of this medication to the CHI formulary for acquired hemophilia.

2.1.7.2 Rituximab

This section includes pertinent information regarding the use of Rituximab[15] (MABTHERA®), (TRUXIMA®), (Rixathon®), (Ruxience®) in acquired hemophilia.

Table 28. Rituximab Drug Information

SCIENTIFIC NAME **Rituximab**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No

PMDA	No
Indication (ICD-10)	D68.311
Drug Class	Monoclonal Antibody; Antirheumatic, Miscellaneous; Immunosuppressant Agent
Drug Sub-class	Anti-CD20
ATC Code	L01XC02
Pharmacological Class (ASHP)	10:00 - Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Acquired hemophilia:** 375 mg/m2 intravenously once weekly for four weeks. HIV and hepatitis B virus screening should be performed prior to start[14]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: **Altered kidney function: IV:** No dosage adjustment necessary for any degree of kidney dysfunction **Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2):** Augmented renal clearance (ARC) is a condition that occurs in certain critically ill patients without organ dysfunction and with normal serum creatinine concentrations. Younger patients (<55 years of age) admitted post trauma or major surgery are at highest risk for ARC, as well as those with sepsis, burns, or hematologic malignancies. An 8- to 24-hour measured urinary CrCl is necessary to identify these patients IV: No dosage adjustment necessary

	Hemodialysis, intermittent (thrice weekly): Not significantly dialyzed IV: No dosage adjustment or supplemental dose necessary. **Peritoneal dialysis:** In general, unlikely to be significantly dialyzed (expert opinion); however, significant amounts reported to be dialyzed in a patient with nephrotic syndrome. IV: No dosage adjustment necessary **CRRT:** IV: No dosage adjustment necessary. **PIRRT** (eg, sustained, low-efficiency diafiltration): IV: No dosage adjustment necessary <u>Hepatic Impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	PA, CU, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Should be used in combination with corticosteroids for eradication of inhibitors in acquired hemophilia.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized experienced physician.	
PA (Prior Authorization): Indicated specifically for the eradication of inhibitors in acquired hemophilia.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	<u>Most common:</u> Cardiac disorder, flushing, hypertension, peripheral edema, night sweats, pruritus, skin rash, hypophosphatemia, weight gain, abdominal pain, diarrhea, nausea, anemia, febrile neutropenia, hypogammaglobulinemia, leukopenia,

	lymphocytopenia, neutropenia, thrombocytopenia, hepatobiliary disease, increased serum alanine aminotransferase, angioedema, antibody development, bacterial infection, herpes simplex infection, parvovirus B19 seroconversion, varicella zoster infection, hepatitis C, and lower respiratory tract infection), serious infection, chills, fatigue, headache, insomnia, pain, peripheral sensory neuropathy, arthralgia, asthenia, muscle spasm, bronchitis, cough, epistaxis, nasopharyngitis, pulmonary disease, pulmonary toxicity, rhinitis, upper respiratory tract infection, fever, infusion related reaction Most serious: Hepatitis B virus reactivation, hypogammaglobulinemia and infection, infusion-related reactions, progressive multifocal leukoencephalopathy (PML)
Drug Interactions*	Risk X interactions: - Abrocitinib - Anifrolumab - Baricitinib - BCG (Intravesical) - BCG Products - Belimumab - Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Fexinidazole - Filgotinib - Mumps- Rubella- or Varicella-Containing Live Vaccines

	- Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	• Granulomatosis with polyangiitis/microscopic polyangiitis: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with granulomatosis with polyangiitis or microscopic polyangiitis after rituximab-induced B-cell depletion. • Older adult: There is a higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis), and the incidence of grade 3 or 4 adverse reactions are higher in patients ≥65 years of age. • Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs (DMARDs) prior to surgery and plan surgery after the next dose is due. Surgery can occur after holding medication for 1 full dosing cycle (eg, for medications

	administered every 4 weeks, schedule surgery 5 weeks from last administered dose); therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). Decisions to withhold therapy should be based on shared decision making; ensure the patient and their provider weigh risks of interrupting therapy and disease control versus risks of continuing therapy and surgical complications. • Pemphigus vulgaris: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with pemphigus vulgaris after rituximab-induced B-cell depletion. • Rheumatoid arthritis: There are limited data on the safety of other biologics or DMARDs other than methotrexate in patients with rheumatoid arthritis (RA) with B-cell depletion following rituximab treatment. Monitor patients closely for infection if biologic agents or DMARDs are used concomitantly. The use of rituximab is not recommended in RA patients who have not had prior inadequate response to one or more tumor necrosis factor antagonists.
Pregnancy	Rituximab crosses the placenta and can be detected in the newborn. Rituximab is a humanized monoclonal antibody (IgG1). Human IgG crosses the placenta. Fetal exposure is dependent

	upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and GA, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester. In one infant born at 41 weeks' gestation, in utero exposure occurred from week 16 to 37; rituximab concentrations were higher in the neonate at birth (32,095 ng/mL) than the mother (9,750 ng/mL) and still measurable at 18 weeks of age (700 ng/mL infant; 500 ng/mL mother). Outcome data following maternal use of rituximab during pregnancy are available. Although reassuring, available safety data are limited. B-cell lymphocytopenia generally lasting <6 months may occur following in utero exposure. Infants and newborns exposed to rituximab during pregnancy should be monitored for infection. The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy. The guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team) approach. Based on limited data, if pregnancy occurs during rituximab treatment, rituximab should ideally be withheld. However, if postponing rituximab would significantly compromise maternal outcomes in patients diagnosed with B-cell lymphoma during pregnancy, rituximab

	use is not discouraged. An international consensus panel has published guidelines for hematologic malignancies during pregnancy. In patients with aggressive lymphomas, rituximab (as a component of the R-CHOP chemotherapy regimen) may be administered in the second and third trimesters, however, it should be avoided within 3 weeks of anticipated delivery. Although approved for the treatment of rheumatoid arthritis, based on available data, rituximab should be discontinued once pregnancy is detected in patients treated for rheumatic and musculoskeletal diseases; treatment during pregnancy should only be considered for pregnant patients with life- or organ-threatening disease. Rituximab is used off-label for the treatment of primary immune thrombocytopenia (ITP). Although data specific to pregnancy are limited, use can be considered in pregnant patients with very severe ITP. Monitor for perinatal and neonatal immunosuppression and subsequent infection. Rituximab has been evaluated off-label for neurological indications such as multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD). Maternal NMOSD may be associated with adverse pregnancy outcomes, including miscarriage and preeclampsia. Data related to the treatment of NMOSD during pregnancy are limited; however, use of rituximab prior to pregnancy may prevent pregnancy-related attacks

Lactation	Rituximab is present in breast milk. Data related to the presence of rituximab in breast milk are available from case reports and small studies: - The presence of rituximab in breast milk was evaluated following administration of rituximab 1,000 mg for the treatment of granulomatosis with polyangiitis to a woman within 6 months' postpartum. Following infusion, breast milk and maternal serum concentrations were evaluated for 4 days, beginning 7 days after administration. Breast milk concentrations of rituximab (0.4 to 0.6 mcg/mL) were significantly less than those in the maternal serum (110 to 130 mcg/mL). Corresponding serum concentrations were not available from the fully breastfed infant; however, serious infections were not observed and normal growth and development were noted. - Breast milk was sampled for 4 consecutive days in a patient treated with a dose of rituximab 500 mg at 4 months' postpartum. The maximum rituximab concentration in breast milk was 0.004 mcg/mL, 2 days after the maternal dose. Rituximab was not detected in the infant serum when tested 4 and 24 hours after the dose. The authors of this study calculated the relative infant dose (RID) of rituximab to be 0.006% to 0.007% of the weight-adjusted maternal dose. - Data are available from a prospective study of 9 lactating women with multiple sclerosis treated with

	rituximab. Breast milk samples were obtained prior to the infusion and at intervals up to 30 days following a 500 mg or 1,000 mg dose (30 samples obtained). The median maximum milk concentration of rituximab was 0.074 mcg/mL (range: 0.061 to 0.12 mcg/mL). Using the maximum milk concentrations from 4 women who provided serial samples, the authors of this study calculated the RID of rituximab to be 0.1% of the weight-adjusted maternal dose, providing an estimated daily infant dose via breast milk of 0.011 mg/kg/day. There were no serious infections reported in the 5 infants who were breastfed. In addition, they were reported to have normal growth and development up to 12 months of age. - Rituximab concentrations were evaluated in 6 mother-infant pairs following maternal treatment for relapsing-remitting multiple sclerosis. Rituximab infusions (500 mg n = 5; 1,000 mg n = 1) were initiated between 13 and 31 days' postpartum. Breast milk was sampled prior to dosing, then 2, 7, ~22, ~66, and ~110 days after the infusion (the later samples were obtained after 1, 3, and 5 half-lives). Maximum concentrations of rituximab in breast milk occurred ~4.5 days after the infusion. The highest breast milk concentrations were 0.09 to 0.25 mcg/mL. Using the maximum breast milk concentration (0.25 mcg/mL), which occurred following a dose of rituximab 1,000

	mg, authors of the study calculated the RID to be 0.26% of the weight-adjusted maternal dose, providing an estimated daily infant dose via breast milk of 0.038 mg/kg/day. Serum concentrations of rituximab in all breastfed infants were <0.01 mcg/mL, and all but 2 cases were below the lower limit of quantification (0.005 mcg/mL). Infant B-cell counts were in the normal range. - In general, breastfeeding is considered acceptable when the RID of a medication is <10%. - According to the manufacturer, breastfeeding is not recommended during treatment and for 6 months after the last dose of rituximab. However, based on available data, rituximab is considered compatible with breastfeeding in patients treated for rheumatic and musculoskeletal diseases. In addition, rituximab is unlikely to be absorbed by the infant gastrointestinal tract following exposure via breast milk
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy (PML); patients with severe, active infections.
Monitoring Requirements	- CBC with differential and platelets (obtain prior to treatment and prior to each treatment course, and at weekly to monthly intervals and

	more frequently in patients with lymphoid malignancies, or at 2- to 4-month intervals in rheumatoid arthritis patients, granulomatosis with polyangiitis and microscopic polyangiitis); continue to monitor for cytopenias after the final rituximab dose and until resolution. Monitor electrolytes (in patients at risk for tumor lysis syndrome [TLS]), renal function (in patients at risk for TLS or nephrotoxicity), fluid/hydration status balance. Monitor BP and vital signs. Evaluate pregnancy status (prior to treatment initiation in patients who may become pregnant). - Hepatitis B virus reactivation screening: Screen all patients for hepatitis B virus (HBV) infection prior to therapy initiation (eg, hepatitis B surface antigen [HBsAG] and hepatitis B core antibody measurements). Screen patients for latent infections (eg, hepatitis C, HIV, tuberculosis) in high-risk populations or in countries with high tuberculosis burden (baseline). In addition, carriers and patients with evidence of current infection or recovery from prior hepatitis B infection should be monitored closely for clinical and laboratory signs of HBV reactivation and/or infection during therapy and for up to 2 years following completion of treatment. The American Society of Clinical Oncology HBV screening and management provisional clinical opinion recommends HBV screening with HBsAg, hepatitis B

	core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up. Monitor for signs of active hepatitis B infection. - Monitor closely for infusion-related reactions, especially in patients with a history of prior cardiopulmonary reactions or with preexisting cardiac or pulmonary conditions or patients with high numbers of circulating malignant cells (≥25,000/mm3). Perform cardiac monitoring during and after rituximab infusion (in rheumatoid arthritis patients and in patients with preexisting cardiac disease, a history of arrhythmia or angina, or if clinically significant arrhythmias develop during or after subsequent infusions). Monitor for signs/symptoms of bowel obstruction/perforation (abdominal pain, vomiting), tumor lysis syndrome, and/or mucocutaneous skin reactions. Monitor for signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, which may present as hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits); if progressive multifocal leukoencephalopathy is suspected,

	obtain brain MRI scan and lumbar puncture.
Precautions	- Herpes zoster reactivation: Herpes zoster reactivation has been reported. - Hyperlipidemia: Therapy is associated with increases in total cholesterol, triglycerides, low-density lipoprotein, and/or high-density lipoprotein. - Malignancy: Use of tocilizumab may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined; however, malignancies were observed in clinical trials. - Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy) have occurred. - Hepatic impairment: Use with caution in hepatic impairment; see "Dosage: Hepatic Function Impairment" for additional information. - Tuberculosis: Consider anti-tuberculosis (TB) treatment in patients with a history of latent or active TB infection or disease (latent or active TB) if adequate treatment course cannot be confirmed, and for patients with risk factors for TB despite a negative test.
Black Box Warning	Infusion-related reactions, mucocutaneous reactions, hepatitis B

	virus reactivation, progressive multifocal leukoencephalopathy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *rituximab* for the treatment of acquired hemophilia**. Despite this, ***rituximab*** has been available on the market for many years.

Conclusion Statement – Rituximab

Rituximab is recommended for the eradication of inhibitors in acquired hemophilia. However, its use was only mentioned in one guideline, and the data is based only on retrospective and case studies. Therefore, more studies are needed in order to be able to recommend the addition of this medication to the CHI formulary for acquired hemophilia.

2.1.7.3 Cyclosporine

This section includes pertinent information regarding the use of Cyclosporin[15] in acquired hemophilia.

Table 29. Cyclosporine Drug Information

SCIENTIFIC NAME **Cyclosporine**	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D68.311
Drug Class	Immunosuppressant Agent
Drug Sub-class	Calcineurin Inhibitor
ATC Code	L04AD01
Pharmacological Class (ASHP)	92:44 Immunosuppressive Agents
DRUG INFORMATION	

Dosage Form	Capsule, hard
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Acquired hemophilia:** 5 mg/kg BW a day divided in two doses; if renal insufficiency is present the dose has to be reduced[14]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: - **kidney impairment prior to treatment initiation:** **Altered kidney function:** ➢ CrCl ≥60 mL/minute: No dosage adjustment necessary. ➢ CrCl <60 mL/minute: No dosage adjustment necessary (0.1% excreted in the urine unchanged). For nontransplant indications (eg, autoimmune disease), the manufacturer's labeling states use is contraindicated in patients with abnormal renal function (not defined); however, when potential benefits outweigh the risks, may consider cautious use with frequent monitoring of kidney function, or consider use of an alternative agent due to increased risk of worsening kidney function, especially for patients with more severe impairment. **Hemodialysis, intermittent (thrice weekly)**: Not dialyzable: No supplemental dose or dosage adjustment necessary. For nontransplant indications (eg, autoimmune disease) the

	manufacturer's labeling states use is contraindicated in patients with abnormal renal function (not defined); however, may use with extreme caution if benefits outweigh risks, or consider use of an alternative agent, especially if the patient has residual kidney function. **Peritoneal dialysis:** Unlikely to be significantly dialyzable (large Vd): No dosage adjustment necessary. For nontransplant indications (eg, autoimmune disease) the manufacturer's labeling states use is contraindicated in patients with abnormal renal function (not defined); however, may use with extreme caution if benefits outweigh risks, or consider use of an alternative agent, especially if patient has residual kidney function. **CRRT:** No dosage adjustment necessary. However, cyclosporine can potentially worsen acute kidney injury; therefore, avoid use unless benefits outweigh the risks. Monitor kidney function closely. **PIRRT** (eg, sustained, low-efficiency diafiltration): No dosage adjustment necessary. However, cyclosporine can potentially worsen acute kidney injury; therefore, avoid use unless benefits outweigh the risks. Monitor kidney function closely. - **Nephrotoxicity or acute kidney injury during treatment:** **Altered kidney function:** ➢ Nontransplant indications (eg, autoimmune disease): The following general recommendations may be considered; individualize therapy according to risks/benefits and

	institutional protocols, when available: If serum creatinine increases 25% to 30% above baseline (measured on 2 separate occasions at least 2 weeks apart), or by ≥50% at any time during therapy, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, further reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, discontinue cyclosporine. - **Patients receiving renal replacement therapies (eg, hemodialysis, peritoneal dialysis, CRRT):** **Nontransplant indications (eg, autoimmune disease):** Consider temporary interruption of therapy or switching to an alternative agent to help promote renal recovery and preserve residual kidney function if other factors (eg, concurrent nephrotoxins, dehydration) contributing to decreased kidney function cannot be mitigated. Continued use should only be considered if benefits outweigh risks of further kidney injury. <u>Hepatic Impairment:</u> - **Mild-to-moderate impairment:** There are no dosage adjustments provided in the manufacturer's labeling; monitor blood concentrations.

	- **Severe impairment:** There are no dosage adjustments provided in the manufacturer's labeling; however, metabolism is extensively hepatic (exposure is increased). Monitor blood concentrations; may require dose reduction.
Prescribing edits*	PA, ST, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized experienced physician.	
PA (Prior Authorization): Indicated specifically for the treatment of acquired hemophilia.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Should be used as second-line therapy for eradication of inhibitors in acquired hemophilia.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Renal dysfunction, liver dysfunction, tiredness, headache, abdominal pain, hypertension, nausea, vomiting, hyperlipidemia, electrolyte changes, muscle cramp. Most serious: Diabetes mellitus, hepatotoxicity, hyperkalemia, hypertension., infections, malignancy, nephrotoxicity, neurotoxicity.
Drug Interactions*	Risk X interactions: - Abrocitinib - Aliskiren - Asunaprevir - Atorvastatin - Baricitinib - BCG Products - Bilastine

	- Bosentan - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Disulfiram - DOXOrubicin - Dronedarone - Elagolix - Elagolix, Estradiol, and Norethindrone - Elbasvir and Grazoprevir - Erdafitinib - Fexinidazole - Filgotinib - Foscarnet - Fusidic Acid - Grapefruit Juice - Lasmiditan - Lercanidipine - Lovastatin - Methotrimeprazine - Mifamurtide - MiFEPRIStone - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Ornidazole - Pacritinib - PAZOPanib - Pimecrolimus - Pimozide - Pitavastatin - Poliovirus Vaccine (Live/Trivalent/Oral) - Potassium-Sparing Diuretics - Red Yeast Rice - Revefenacin

	- Ritlecitinib - Ruxolitinib (Topical) - Secnidazole - Simeprevir - Simvastatin - Sirolimus (Protein Bound) - Sparsentan - Tacrolimus (Systemic) - Tacrolimus (Topical) - Talimogene Laherparepvec - Taurursodiol - Tertomotide - Tofacitinib - Topotecan - Treosulfan - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - VinCRIStine (Liposomal) - Voxilaprevir - Yellow Fever Vaccine - Zavegepant
Special Population	- **Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery**: Patients with severe SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE without severe disease, hold cyclosporine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing

	nonsurgical site infections (typically ~14 days to reduce infection risk). - **Transplant recipients:** Make dose adjustments based on blood concentrations; dependent on organ transplanted, time after transplant, organ function, and CsA toxicity.
Pregnancy	Cyclosporine crosses the placenta. In a study of 15 pregnant patients, maternal concentrations did not correlate with those found in the umbilical cord (n=14). Cyclosporine was detected in the serum of one newborn for several days after birth. Cyclosporine is not associated with specific teratogenic effects, but maternal use may be associated with an increased risk of intrauterine growth restriction, small for gestational age babies, maternal hypertension, and preeclampsia. Premature births and low birth weight were consistently observed in pregnant transplant recipients (additional pregnancy complications also present). In utero exposure to cyclosporine has not been found to influence renal function or blood pressure in children followed up to 7 years of age (limited data). Some formulations may contain alcohol; the alcohol content should be taken into consideration prior to prescribing to patients who are pregnant. Cyclosporine levels decline during pregnancy and increased monitoring is recommended.
Lactation	Cyclosporine is present in breast milk. Concentrations of cyclosporine in milk vary widely. Due to the potential for serious adverse in the breastfeeding infant, the

	manufacturer recommends a decision be made to discontinue cyclosporine or to discontinue breastfeeding, considering the importance of treatment to the mother.
Contraindications	Hypersensitivity to cyclosporine or any component of the formulation. IV cyclosporine is contraindicated in hypersensitivity to polyoxyethylated castor oil (Cremophor EL). Rheumatoid arthritis and psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies. Concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, coal tar, or radiation therapy are also contraindications for use in patients with psoriasis. *Canadian labeling:* Additional contraindications (not in the US labeling): Concurrent use with bosentan; rheumatoid arthritis and psoriasis patients with primary or secondary immunodeficiency excluding autoimmune disease, uncontrolled infection, or malignancy (excluding non-melanoma skin cancer).
Monitoring Requirements	- Measure creatinine, liver enzymes, electrolytes, blood level of ciclosporin.
Precautions	- Hepatic impairment: Cyclosporine has extensive hepatic metabolism and exposure is increased in patients with severe hepatic impairment. May require dose reduction. - Psoriasis: Appropriate use: If receiving other immunosuppressive agents,

	radiation or UV therapy, concurrent use of cyclosporine is not recommended.
Black Box Warning	Experienced physician, Immunosuppression, Bioavailability, Hypertension/nephrotoxicity
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *cyclosporine* for the treatment of acquired hemophilia**. Despite this, ***cyclosporine*** has been available on the market for many years.

Conclusion Statement – Cyclosporine

Cyclosporine is recommended for the eradication of inhibitors in acquired hemophilia. However, its use was only mentioned in one guideline, and the data is based only on retrospective and case studies. Therefore, more studies are needed in order to be able to recommend the addition of this medication to the CHI formulary for acquired hemophilia.

2.1.7.4 Cyclophosphamide

This section includes pertinent information regarding the use of Cyclophosphamide[15] (Endoxan®) in acquired hemophilia.

Table 30. Cyclophosphamide Drug Information

SCIENTIFIC NAME Cyclophosphamide	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D68. 311
Drug Class	Immunosuppressant Agent
Drug Sub-class	N/A

ATC Code	L01AA01
Pharmacological Class (ASHP)	92:44 Immunosuppressive Agents
DRUG INFORMATION	
Dosage Form	Film-coated tablet, powder for solution for injection
Route of Administration	Oral use, intravenous use
Dose (Adult) [DDD]*	**Acquired hemophilia:** 1.5-2 mg/kg BW p.o. once daily at maximum 3-4 months, alternatively 10 mg/kg BW i.v. on 2 consecutive days, followed by 1.5-2 mg/kg BW p.o. for 8 days[14]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: **Altered kidney function:** - CrCl ≥30 mL/minute: No dosage adjustment necessary. - CrCl 10 to 29 mL/minute: Administer 75% or 100% of normal dose. - CrCl <10 mL/minute: Administer 50%, 75%, or 100% of normal dose. **Hemodialysis, intermittent (thrice weekly):** Moderately dialyzable (20% to 50% removal based on limited data with low-flux dialyzers. Administer 50% or 75% of the normal dose. On dialysis days, administer after hemodialysis, allowing at least 12 hours before the next hemodialysis session. **Peritoneal dialysis:** Administer 75% of the normal dose. If possible, allow at least 12 hours before next peritoneal dialysis exchange. **CRRT:** Administer 100% of the normal dose. Hepatic Impairment:

	The conversion between cyclophosphamide to the active metabolite may be reduced in patients with severe hepatic impairment, potentially reducing efficacy. Some dosage forms may contain ethanol; consider alcohol content of the product when administering to patients with hepatic impairment. There are no dosage adjustments provided in the manufacturer's labeling. The following adjustments have been recommended: **Floyd 2006:** ➢ Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose. ➢ Serum bilirubin >5 mg/dL: Avoid use. **Krens 2019:** ➢ Mild or moderate impairment: Dosage adjustment is not likely needed. ➢ Severe impairment: Use is not recommended due to risk of reduced efficacy.
Prescribing edits*	PA, CU, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Should be used in combination with corticosteroids as first-line therapy for the eradication therapy of inhibitors in acquired hemophilia.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a specialized experienced physician.	
PA (Prior Authorization): Indicated specifically for the treatment of acquired hemophilia.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, alopecia, exanthema. Most serious: Bone marrow suppression and infection, cardiotoxicity, hemorrhagic cystitis, hepatotoxicity, pulmonary toxicity, second primary malignancy.
Drug Interactions*	Risk X interactions: - Abrocitinib - Baricitinib - BCG (Intravesical) - BCG Products - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Etanercept - Fexinidazole - Filgotinib - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Voclosporin

	- Yellow Fever Vaccine
Special Population	N/A
Pregnancy	Cyclophosphamide crosses the placenta and can be detected in amniotic fluid. Birth defects (including malformations of the skeleton, palate, limbs, and eyes), miscarriage, fetal growth retardation, and fetotoxic effects in the newborn (including anemia, gastroenteritis leukopenia, pancytopenia, and severe bone marrow hypoplasia) have been reported.
Lactation	Cyclophosphamide and its metabolites are present in breast milk. Cyclophosphamide breast milk concentrations were evaluated following maternal treatment for stage IV diffuse large B-cell lymphoma at 4 months postpartum. Peak breast milk concentrations occurred within 7 days; however, cyclophosphamide was detectable in breast milk for 21 days after the first dose. Leukopenia and thrombocytopenia were noted in an infant exposed to cyclophosphamide while breastfeeding. The mother was treated with one course of cyclophosphamide 6 weeks prior to delivery then cyclophosphamide IV 6 mg/kg (300 mg) once daily for 3 days beginning 20 days postpartum. CBCs were obtained in the breastfed infant on each day of therapy; WBC and platelets decreased by day 3. Cyclophosphamide is not recommended for use in breastfeeding mothers with autoimmune and systemic inflammatory diseases. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by

	the manufacturer during therapy and for 1 week after the last cyclophosphamide dose. Others recommend breastfeeding be avoided for at least 6 weeks after the last dose of cyclophosphamide.
Contraindications	History of severe hypersensitivity to cyclophosphamide, its metabolites, or any component of the formulation; urinary outflow obstruction. Canadian labeling: Additional contraindications (not in the US labeling): Severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression.
Monitoring Requirements	Blood count is checked 3 times the first week if i.v. doses are given, otherwise once a week the first month, thereafter once a month.
Precautions	Hypersensitivity: Possible cross-sensitivity with other alkylating agents may occur. Hepatic impairment: Use with caution in hepatic impairment. Renal impairment: Use with caution in patients with renal impairment. Cyclophosphamide injection: Some cyclophosphamide injection dosage forms may contain alcohol. The alcohol content (in some dosage forms) may affect the CNS and impair the ability to drive or operate machinery; review available dosage forms for ethanol content in order to select the appropriate product, particularly for patients who should avoid or minimize alcohol intake, including patients with hepatic impairment.
Black Box Warning	N/A

REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *cyclophosphamide* for the treatment of acquired hemophilia**. Despite this, ***cyclophosphamide*** has been available on the market for many years.

Conclusion Statement – Cyclophosphamide

Cyclophosphamide is recommended for the eradication of inhibitors in acquired hemophilia. However, its use was only mentioned in one guideline, and the data is based only on retrospective and case studies. Therefore, more studies are needed in order to be able to recommend the addition of this medication to the CHI formulary for acquired hemophilia.

2.2 Modifications

- ANTIHEMOPHILIC FACTOR, PEGYLATED (MW 20000) HUMAN SEQUENCE RECOMBINANT: EU was removed since this medication is not for emergency use only.
- CATRIDECACOG: EU was removed since this medication is not for emergency use only.
- EFMOROCTOCOG ALFA: EU was removed since this medication is not for emergency use only.
- EFTRENONACOG ALFA: EU was removed since this medication is not for emergency use only. MD was added since this medication should be prescribed by a specialized physician.
- HUMAN COAGULATION FACTOR VIII,HUMAN VON WILLEBRAND FACTOR: EU was removed since this medication is not for emergency use only. MD was added since this medication should be prescribed by a specialized physician.
- MOROCTOCOG ALFA: EU was removed since this medication is not for emergency use only.
- OMFILOCTOCOG ALFA: EU was removed since this medication is not for emergency use only.
- Turoctocog alfa: EU was removed since this medication is not for emergency use only.

- EPTACOG ALFA: EU was removed since this medication is not for emergency use only.

2.3 Delisting

There are no medications that were delisted from the SFDA drug list.

2.4 Other Drugs

The three drugs below have been approved by the FDA and/or EMA for the treatment of hemophilia, however, they are not currently registered by the SFDA.

Albutrepenonacog alfa (rIX-RFP)

A recombinant fusion protein that links a recombinant coagulation factor IX (rFIX) with a recombinant human albumin (rAlbumin). It was developed by CSL Behring Canada, Inc and approved by Health Canada on April 26, 2017. It was also approved by FDA and EMA in 2016[30].

Efanesoctocog alfa (BIVV001)

FDA granted Breakthrough Therapy designation in June 2022 for the treatment of people with hemophilia A, a rare and life-threatening bleeding disorder, based on data from the pivotal XTEND-1P[31].

Simoctocog alfa

FDA-approved to treat adults and children with hemophilia A in September 2015[32].

Section 3.0 Key Recommendation Synthesis

- Comprehensive education is essential for individuals with hemophilia to empower them with knowledge and self-management skills. (CB)[5]
- Encourage consistent engagement in physical activities and fitness routines to preserve bone health and improve physical capabilities. (CB)[5]
- Adhere to PRICE guidelines (protection, rest, ice, compression, elevation) for muscle or joint bleeding. (CB)[5]
- Consider physical therapy and rehabilitation exercises for hemophilic arthropathy. (CB)[5]
- Antifibrinolytic medications may be used for mucosal bleeds and invasive dental procedures. (CB)[5]
- Apply local anesthetic spray or cream for venous access pain. (CB)[5]
- Use standard pain management approaches for postoperative pain, avoiding NSAIDs. (CB)[5]
- Consider tranexamic acid or epsilon aminocaproic acid for dental procedures. (CB)[5]
- There is no preference for recombinant clotting factor concentrates over plasma-derived products in. (CB)[5]
- Pure FIX concentrates should be used over prothrombin complex concentrates for hemophilia B. (CB)[5]
- Recombinant activated factor VIIa or activated prothrombin complex concentrate can be considered for hemophilia A. (CB)[5]
- Consider regular prophylaxis for patients with inhibitors. (CB)[5]
- Consider DDAVP for mild or moderate hemophilia A and carriers. (CB)[5]
- Fresh frozen plasma is not recommended for patients with hemophilia due to safety concerns. (CB)[5]
- Tranexamic acid for managing mucosal bleeds and during dental surgeries. It can be used alone or with clotting factor concentrates. (CB)[5]
- Epsilon Aminocaproic Acid is less widely used than tranexamic acid. It is usually administered orally or intravenously with caution for side effects. (CB)[5]
- Emicizumab is an alternative hemostatic agent for hemophilia A with or without inhibitors. (CB)[5]

- Fitusiran targets antithrombin messenger RNA and may be used in both hemophilia A and B. (CB)[5]
- Prophylaxis is strongly recommended for severe hemophilia A or B. (CB)[5]
- During Immune Tolerance Induction (ITI) involving emicizumab and FVIII, the measurement of FVIII inhibitors can be accomplished using the Chromogenic Bethesda assay with bovine components.[9]
- For individuals diagnosed with von Willebrand disease (VWD) and a history of cardiovascular disease, the expert panel recommends administering essential antiplatelet or anticoagulant treatment rather than withholding treatment altogether. (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).[10]
- For patients with a baseline VWF level below 0.30 IU/mL, primarily those with type 1 von Willebrand disease (VWD), in whom desmopressin is a viable treatment option, the panel recommends conducting a desmopressin trial and tailoring treatment based on the trial results instead of refraining from the trial and resorting to treatment with tranexamic acid or factor concentrate. (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯).[10]
- Tranexamic Acid, an antifibrinolytic medication, is prescribed for patients with hemophilia for short-term use (ranging from two to eight days) with the aim of minimizing or averting bleeding episodes.[6]
- Bypassing agents are used in Hemophilia A with inhibitors and prophylaxis as well as in hemophilia B.[6]
- Regular vaccinations are advised for all patients. Patients undergoing factor prophylaxis should receive these vaccinations via intramuscular (IM) injection on the same day as their factor treatment.[7]
- Hepatitis B immunization is advised for all patients. Those requiring human-derived products or components should undergo regular assessments of their hepatitis B immunity and receive extra vaccinations as needed.[7]
- Patients utilizing plasma-derived products and testing negative for Hepatitis A IgG antibodies should consider receiving the Hepatitis A vaccine. If patients are positive for hepatitis C but do not have Hepatitis A IgG antibodies, they should be given the Hepatitis A vaccine.[7]
- For the majority of patients with type I von Willebrand disease (VWD), the standard approach to management typically includes the use of Tranexamic acid and/or DDAVP (Desmopressin).[7]

Section 4.0 Conclusion

This report serves as **an annex to the previous Hemophilia report** and aims to provide recommendations to aid in the management of Hemophilia. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Hemophilia. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Hemophilia Scope

2020	Changes	2023	Rationale
Section 1.0 Hemophilia Clinical Guidelines			
Diagnosis and Management Guidelines of Hemophilia in Saudi Arabia [2016]	N/A		
Nordic Hemophilia Guidelines [Updated 2020]		Nordic Hemophilia Guidelines (Updated October 2022)	- Prophylaxis and on-demand treatment - Adolescence - Bypassing agents for the treatment of bleeds - Prevention of bleeds - Immune tolerance induction (ITI) therapy - Surgery in hemophilia - Surgery in PWHs with inhibitors - Comorbidities in the ageing patients with hemophilia
GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA (2nd edition)- Prepared by the Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH) [2012] [updated 2013] & GUIDLEINES FOR ACQUIRED HEMOPHILIA- Revised edition [2012]	Updated	WFH Guidelines for the Management of Hemophilia, 3rd edition (2020) [5]	**Self-management and physical exercise** **Pain management** • For people with hemophilia with venous access pain, discomfort or anxiety, the WFH recommends the application of a local anesthetic spray or cream at the site of venous access. (CB) • For patients with hemophilia and postoperative pain, the WFH recommends analgesia similar to that used in patients without hemophilia including, as appropriate, the use of intravenous morphine or other narcotic analgesics, followed by an oral opioid (e.g., tramadol, codeine, hydrocodone, etc.) and paracetamol/acetaminophen

			as pain decreases. Except for selective COX-2 inhibitors, NSAIDs should not be used in patients with hemophilia. The intramuscular route for administration of analgesia is not advised. (CB) **Dental care and management** **Dental surgery and invasive procedures** **Hemostatic Agents** • The WFH does not show a preference for recombinant clotting factor concentrates over those derived from plasma when it comes to individuals with hemophilia. The decision between these categories of products should be determined based on local considerations, including factors like availability, expenses, and patient inclinations. (CB) • Factor VIII (FVIII) CFCs **Factor IX (FIX) CFCs** • When addressing FIX deficiency in individuals with hemophilia B, the WFH advises the use of a product solely containing FIX rather than prothrombin complex concentrates (PCCs), which encompass additional clotting factors like II, VII, and X. These factors, potentially activated during production, could increase the risk of thromboembolism for the patient. • For hemophilia B patients requiring prolonged therapy at high doses, the use of pure FIX concentrates is recommended over

			prothrombin complex concentrates. (CB) • **Extended half- life products** • For patients with hemophilia A or B, there is no evidence for any clinical safety issues in persons with hemophilia to recommend a preference among the various mechanisms of action (e.g., PEGylation, Fc-fusion, albumin-fusion) used to extend the half-life of clotting factor concentrates. (CB) • **Bypassing agents** • For people with hemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, the WFH recommends that a bypassing agent be used. • **Fresh frozen plasma (FFP)** • For patients with hemophilia, fresh frozen plasma is not recommended due to concerns about the safety and quality. (CB) • **Cryoprecipitate** • **Desmopressin (DDAVP)** • For patients with mild or moderate hemophilia A and carriers of hemophilia A, the WFH recommends considering desmopressin (DDAVP) as an option for treatment. (CB) • **Tranexamic acid** • Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism. (CB)

			• For patients with hematuria, the WFH recommends against the use of antifibrinolytics, as it is contraindicated in these patients due to increased risk of obstructive uropathy. (CB) • **Epsilon aminocaproic acid** • Epsilon aminocaproic acid is similar to tranexamic acid but is less widely used as it has a shorter plasma half-life, lower potency, and higher toxicity. • **Substitution therapy** • For patients with hemophilia A with an inhibitor, the WFH recommends that emicizumab should be used for regular prophylaxis. • **Hemostatic rebalancing agents** • Fitusiran is an RNA interference therapy that specifically targets antithrombin messenger RNA to suppress the production of antithrombin in the liver. This therapy has the advantage of subcutaneous administration, prolonged duration of action and, due to its mechanism of action, it could be used in both hemophilia A and B patients with or without inhibitors. • Anti-TFPI antibodies are being explored as another approach in ongoing clinical trials. • **Prophylaxis in Hemophilia** • For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on

			prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference. • . ✓ **Treatment of Specific Hemorrhages** - Individuals with hemophilia who experience severe hemarthrosis should promptly undergo intravenous replacement infusion(s) of clotting factor concentrate until the bleeding is resolved. (CB) - Hemophilia patients with moderate or mild joint bleeding should be given 1 intravenous infusion of clotting factor concentrate, repeated if clinically indicated, depending on the resolution of the bleed. (CB) **a. Pain Management** • Hemophilia patients with pain due to hemarthrosis should be given analgesic medication according to the severity of the pain. (CB) **b. Adjunctive care** • Hemophilia patients with hemarthrosis should be managed using the RICE approach (Rest, Ice, Compression, and Elevation) in addition to clotting factor concentrate replacement. **c. Physical therapy and rehabilitation** • In hemophilia patients with hemarthrosis, physical therapy exercises performed under

			clotting factor coverage should begin as soon as the pain symptoms cease. (CB) **d. Arthrocentesis** • Hemophilia patients without inhibitors who are undergoing factor replacement therapy and experiencing joint bleeding and prolonged pain should consider arthrocentesis only in cases where there is a tense and painful hemarthrosis or if there is a concern about infection. Routine arthrocentesis is not recommended. **e. Central nervous system and intracranial hemorrhage** - For individuals with hemophilia who exhibit potential symptoms of central nervous system bleeding or related issues, it's essential to promptly administer clotting factor replacement therapy prior to any investigative procedures. (CB) **f. Throat and neck hemorrhage** • In hemophilia patients with throat and neck bleeding, clotting factor replacement therapy should be administered immediately and critical care evaluation sought. (CB) - In hemophilia patients with throat and neck bleeding and local infection, antifibrinolytics should be started to treat the bleed and antibiotics to treat the infection. (CB) **g. Gastrointestinal/ abdominal hemorrhage**

			- Antifibrinolytics should prescribed for hemophilia patients suffering from gastrointestinal bleeding. (CB) **h. Renal hemorrhage** - Hemophilia patients with renal bleeding should be given adequate hydration and prescribed bed rest until bleeding stops. (CB) - In hemophilia patients with renal bleeding, antifibrinolytics should not be administered. (CB) **i. Ophthalmic hemorrhage** - In hemophilia patients with ophthalmic bleeding, clotting factor levels should be raised immediately and the patient evaluated by an ophthalmologist. (CB) **j. Oral hemorrhage** - In hemophilia patients with oral bleeding, antifibrinolytics should be prescribed and administered at appropriate dosages. (CB) **k. Epistaxis** - In hemophilia patients with epistaxis, gauze soaked in an antifibrinolytic agent may be used in addition to clotting factor replacement therapy. (CB) - In hemophilia patients with recurrent epistaxis, the underlying pathology should be identified immediately and treated. Decongestants and antihistamines should help if bleeding is related to allergy, and antibiotics should be administered if bleeding is related to infection. (CB) **l. Lacerations and abrasions**

			- For individuals with hemophilia experiencing cuts and abrasions, it's important to administer clotting factor replacement therapy and, if suitable, promptly suture the wound with the guidance of appropriate surgeons. (CB) ✓ **Hemophilia A and FVIII inhibitors** - For patients with hemophilia A and FVIII inhibitors who develop an acute bleed, the WFH recommends that treatment be based on whether the inhibitor is low-responding or high-responding. (CB) - For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends FVIII concentrate for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors. - REMARK: In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), the WFH prefers rFVIIa over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab. - In patients receiving emicizumab who receive FVIII concentrate, the WFH

			recommends bovine reagent chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels. - For patients with hemophilia A and low-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH suggests higher, more frequent FVIII product dosing than usual due to the short half-life of FVIII. ✓ **Immune tolerance induction (ITI)** - For patients with hemophilia A who develop persistent low-responding inhibitors, the WFH suggests that immune tolerance induction (ITI) be considered. (CB) ✓ **FVIII prophylaxis after immune tolerance induction** - For patients with hemophilia A who switch to another type or brand of factor product, the WFH has no preference for the choice of specific type of therapy, as current evidence indicates

			product switching does not increase risk of inhibitor development. The WFH supports prospective data collection on inhibitor formation by product, particularly before and after switching products. (CB) - For patients with severe hemophilia A and inhibitors, the WFH recommends emicizumab over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis. (CB) ✓ **Hemophilia B and FIX inhibitors** - For patients with hemophilia B and inhibitors and an allergic reaction/anaphylaxis to FIX therapy, the WFH recommends rFVIIa to treat acute bleeds but is against use of aPCC as it contains FIX and may cause or worsen an allergic reaction. **Management of bleeding** • For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions. (CB) ✓ **Therapeutic options for patients with FIX inhibitors**

			• For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX-containing product to treat acute bleeds, if there is no allergic reaction to FIX. (CB) ✓ **Pregnancy and prenatal planning** - Pregnant carriers of hemophilia should have their FVIII/FIX levels assayed in the third trimester of pregnancy to assess their bleeding risk during delivery and in the postpartum period. (CB) ✓ **Labor and delivery** - Male babies born to known or potential carriers of hemophilia should have cord blood testing of activated partial thromboplastin time (APTT) or factor level. (CB) ✓ **Vaccinations** - Additionally, an ice pack should be applied to the injection site for 5 minutes before injection of the vaccine, and pressure should be applied to the site for at least 10 minutes to reduce bleeding and swelling. (CB) - In children and adults with hemophilia and human immunodeficiency virus (HIV) infection, the WFH recommends standard immunizations, including pneumococcal and influenza vaccines and hepatitis A and B immunization. (CB) ✓ **Surgery and invasive procedures** - For patients with hemophilia requiring surgery, sufficient quantities of clotting factor

			concentrates must be available for the surgery itself and to maintain adequate coverage postoperatively for the duration required for recovery and/or rehabilitation. (CB) - For patients with mild hemophilia A undergoing surgery, the WFH recommends the use of DDAVP for hemostasis if the patient shows good therapeutic response to DDAVP in pre-surgery testing. • **Comorbidities**
GUIDELINES FOR EMERGENCY DEPARTMENT MANAGEMENT OF INDIVIDUALS WITH HEMOPHILIA AND OTHER BLEEDING DISORDERS- National Hemophilia Foundation [2019]	N/A		
Treatment guidelines for acquired hemophilia A- Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland [2019]	N/A		
Guidelines for the management of acute joint bleeds and chronic synovitis			

in hemophilia A United Kingdom Hemophilia Centre Doctors' Organisation (UKHCDO) guideline [2017]	N/A		
Updated Australian consensus statement on management of inherited bleeding disorders in pregnancy [2019]	N/A		
Guideline for the diagnosis and management of the rare coagulation disorders- A United Kingdom Hemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology [2014]	N/A		
The diagnosis and management of von Willebrand disease (VWD): a United Kingdom Hemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology [2014]	N/A		

Nordic Hemophilia Council's Practical Guidelines on Diagnosis and Management of Von Willebrand Disease [2011]	N/A		
The diagnosis, evaluation and management of Von Willebrand disease-U.S department of Health and Human services [2008]			
	Missing	Consensus recommendations on appropriate coagulation tests during emicizumab administration in Saudi Arabia (2022)[33]	- For individuals undergoing emicizumab treatment, clotting-related tests yield inaccurate results and should not be relied upon for making clinical treatment decisions. - Activated partial thromboplastin time (aPTT) is overcorrected in the presence of emicizumab. - One-stage, aPTT-based, single-factor assays (i.e., FVIII activity) appear to give results >150%. - Bethesda assays (clotting-based) for FVIII inhibitor titers will yield false-negative results. **Patients with congenital HA with inhibitors** • During Immune Tolerance Induction (ITI) involving emicizumab and FVIII, the measurement of FVIII inhibitors can be accomplished using the Chromogenic Bethesda assay with bovine components. The frequency of this testing can adhere to the guidelines

			outlined in the United Kingdom (UK) for managing congenital hemophilia A with inhibitors. • Testing while utilizing emicizumab for managing breakthrough bleeds involves the endorsement of a chromogenic FVIII assay that utilizes bovine components to assess FVIII levels. Both indigenous and infused FVIII can be used to monitor the response. • During surgical procedures where emicizumab is utilized, specialists suggest that FVIII inhibitor titer assessment can be conducted employing the chromogenic Bethesda assay utilizing bovine components. This testing can occur before, during, and after the surgery for patients on emicizumab. To monitor FVIII levels both before and after surgery, the FVIII chromogenic assay with bovine components can also be used if necessary, especially in patients with low-titer inhibitors. **Patients with congenital hemophilia without inhibitors** • Testing while emicizumab is being used for managing breakthrough bleeds: The expert panel suggests employing a chromogenic FVIII assay using bovine components alongside FVIII replacement therapy during breakthrough bleeds. This approach aids in the monitoring of FVIII levels and replacement therapy. • Testing while emicizumab is being used for surgical procedures: The expert panel

			advises using a chromogenic FVIII assay with bovine components to monitor FVIII levels both prior to, during, and after surgical interventions. **General testing for emicizumab level** • The group of experts did not endorse routine testing of emicizumab levels. Nevertheless, hematologists might find it necessary to measure emicizumab levels in specific instances, such as confirming accurate dosing and patient compliance with the treatment. Additionally, this testing might be warranted in cases of perceived treatment inefficacy, especially if the presence of Antidrug antibodies (ADA) is suspected. • Testing for emicizumab Anti-Drug Antibodies (ADA): Despite the low occurrence of Anti-Drug Antibodies to emicizumab, the panel suggests performing ADA testing when emicizumab concentration levels are found to be low, after excluding instances of incorrect dosing or patient non-compliance, provided the test is accessible. In cases where emicizumab exposure diminishes, it would result in prolonged aPTT and decreased FVIII activity. However, even at very low emicizumab plasma concentrations, aPTT would remain within the normal range.
	Missing	ASH ISTH NHF WFH 2021 guidelines on	• In patients with von Willebrand disease

		the management of von Willebrand disease[10]	(VWD) with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis (conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯). **Desmopressin challenge/trial and administration** • In patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of ,0.30 IU/mL, the panel suggests performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯). • In these patients, the panel suggests against treating with desmopressin in the absence of desmopressin trial results (conditional

			recommendation based on very low certainty in the evidence of effects ⊕◯◯◯) **Antithrombotic therapy** • In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel suggests giving the necessary antiplatelet or anticoagulant therapy over no treatment (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). **Major surgery** • The panel suggests targeting both FVIII and VWF activity levels of ≥ 0.50 IU/mL for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). • The panel suggests against using only FVIII ≥ 0.50 IU/mL as a target level for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Minor surgery/invasive procedures** • In patients undergoing minor surgery or minor invasive procedures, the panel

			suggests increasing VWF activity levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate alone (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯). • The panel suggests giving tranexamic acid alone over increasing VWF activity levels to ≥ 0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of > 0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures (conditional recommendation based on very low certainty in the evidence of effects ⨁◯◯◯) **Gynecology: heavy menstrual bleeding** • The expert panel recommends opting for either hormonal therapy (such as combined hormonal contraception [CHC] or a levonorgestrel-releasing intrauterine system) or tranexamic acid instead of desmopressin in the treatment of women with von Willebrand disease (VWD) experiencing heavy menstrual bleeding and who do not desire pregnancy (conditional

			recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). • The panel suggests using tranexamic acid over desmopressin to treat women with VWD and heavy menstrual bleeding who wish to conceive (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯) **Obstetrics: postpartum management** • The guideline panel suggests the use of tranexamic acid over not using it in women with type 1 VWD or low VWF levels (and this may also apply to types 2 and 3 VWD) during the postpartum period) (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).
	Missing	Adults with Hemophilia and Related Bleeding Disorders Acute Treatment Guidelines 2023[6]	**Factor VIII Deficiency (Hemophilia A)** **DDAVP/ Desmopressin** **Tranexamic Acid** **Bypassing agents for Factor VIII patients with inhibitors** **Prophylaxis in FVIII deficient patients with inhibitors** • Bypassing Agents can also be used for prophylaxis. • Hemlibra is a bispecific antibody which acts to co-locate FIXa and FX on the surface of activated platelets and so mimics the role of FVIII as a co-factor in coagulation.

			• The purpose of Hemlibra is to prevent spontaneous bleeding – IT DOES NOT NORMALISE HAEMOSTASIS. Therefore, hemostatic treatment may still be needed on demand if a patient on Hemlibra suffers a trauma, needs a surgery or invasive procedure or suffers a breakthrough, spontaneous bleed. • Hemlibra CANNOT be used to treat an acute bleed and a bypassing agent or a Factor VIII replacement product such as Elocta is needed if the patient has bleeding due to a trauma or spontaneously or if an invasive procedure with a major risk of bleeding is needed. • The only BPA suitable for use in patients on Hemlibra is NovoSeven. **Factor IX Deficiency (Hemophilia B)** • Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. i.e. Alprolix for FIX deficiency. • Alprolix is the clotting factor concentrate used as the first line treatment and prophylaxis of bleeding in patients with FIX deficiency. Alprolix comes as a powder with an accompanying solvent of sodium chloride solution given as bolus. **Tranexamic Acid** • Caution should be used when administering Tranexamic acid to patients receiving FEIBA or recombinant factor VIIa (risk of thrombosis) • Bypassing agents (BPA) are options for the management of Hemophilia B.

			• Use BPAs at the lowest effective dose and for the shortest duration possible when treating acute bleeding or managing invasive procedures. • Avoid concomitant antifibrinolytic drugs e.g. Tranexamic acid unless advised by CCC. • FIX inhibitors in patients with FIX deficiency have been associated with hypersensitivity reactions to infused FIX, including anaphylaxis and the development of nephrotic syndrome in some patients. As Feiba contains FIX, it is important to confirm whether the patient has ever experienced such a reaction before and avoid Feiba in this setting. • For all patients, it is prudent to have appropriate treatments available for management of allergic reactions if administering Feiba in patients with FIX deficiency and inhibitors. **Von Willebrand Disease (VWD)** • In doing so the Prescriber must note that not all patients VWD or with low VWF require clotting factor concentrate and the use of alternative treatments may be indicated e.g. DDAVP and/or Tranexamic Acid. • Tranexamic acid alone is suitable for managing minor bleeding on mucosal surfaces like the nose, mouth, or female genital tract. For heavy menstrual bleeding, the treatment approach may involve combining Tranexamic

			acid with hormonal therapy such as the combined oral contraceptive pill or the progesterone-only pill. Alternatively, the use of a progesterone-releasing intrauterine system like Mirena can be considered. • In cases of significant or major bleeding, DDAVP or VWF concentrate should be employed. The selection of the suitable treatment will hinge on factors such as the patient's age, the presence of arteriovascular disease or associated risk factors, and the patient's known reaction to DDAVP. The Clinical Care Committee (CCC) will offer guidance on the appropriate treatment choice. • Wilate is the clotting factor concentrate recommended for use in the prevention and treatment of hemorrhage or surgical bleeding in von Willebrand disease (VWD). • Veyvondi is the recombinant clotting factor concentrate recommended for use in the prevention and treatment of hemorrhage or surgical bleeding in von Willebrand disease (VWD) in adults aged 18 and over. **Tranexamic acid:** **Rare Bleeding Disorders (RBDs)** • Rare bleeding disorders (RBDs) include deficiencies of factors I (Fibrinogen), II, V, VII, X, XI and XIII. These deficiencies can be severe or mild. Severe deficiencies may present with bleeding symptoms similar to hemophilia. Not all mild deficiencies are associated

			with bleeding but the bleeding tendency may be variable in some RBDs. Expert advice from a CCC is always required. • Prescribers must ensure that they prescribe the correct factor replacement treatment, if indicated. • The required dose of CFC must be determined by calculating the patient's weight and the required post treatment factor level which is determined by the severity and location of the bleed **Tranexamic acid:** **Management of Allergic Reaction to Treatment** • **Clotting Factor Concentrates** • **DDAVP/Desmopressin** i. **Mild reactions** should be treated by slowing the intravenous infusion so that it is administered over 60 minutes. ii. **Moderate reactions** to DDAVP s: Treatment should be discontinued, patient assessed and all reactions should be reported as per local hospital reaction policy and should be managed in accordance with the guidance from the National Immunization Advisory Committee. iii. **Severe allergic reactions** to DDAVP should be managed in accordance with the guidance from the National Immunization Advisory Committee.

			• **Platelet or Plasma Transfusion** Adverse reactions to platelet should be managed in accordance with the guidance from the National Immunization Advisory Committee. **Supportive care for joint bleeds** • Initiate 'PRICE' as supportive care for all joint bleeds: **Surgical Management of the Patient with a Bleeding Disorder** **Management of the infant during labor and delivery**
	Missing	New Zealand National Guidelines for the Management of Hemophilia 2022[7]	- Pain relief must be adequate especially for large joint and muscle bleeds. Nonsteroidal anti-inflammatories should not be used. Cox2 inhibitor use should be discussed with the regional treatment center. - Minor joint bleeds should be treated with ice application, analgesics and rested in a functional position. All joint bleeds should be assessed by, or discussed with, the hemophilia center physiotherapist. **Dosing** • Factor VIII dosing approximation: 1 unit/kg body weight = 2% rise in factor VIII activity. • Factor IX dosing approximation: 1 unit/kg body

			weight. = 1% rise in factor IX activity. **Vaccinations** • Routine vaccinations are recommended for all patients. Patients who are receiving factor prophylaxis should receive these intramuscularly (IM) on the day of factor administration. • **Hepatitis B Vaccination** Hepatitis B vaccination is recommended for all patients. Patients necessitating human-derived products or components should undergo regular monitoring of their immunity to hepatitis B and receive additional vaccinations when deemed necessary. • **Hepatitis A Vaccination** Patients using plasma products and testing negative for Hepatitis A IgG antibodies should contemplate vaccination. Those who are positive for hepatitis C but lack Hepatitis A IgG antibodies should be administered the Hepatitis A vaccine. **Prophylaxis** This refers to the infusion factor products (usually recombinant) in anticipation of bleeding or in order to prevent bleeding. There are different types of prophylaxis: **Primary Prophylaxis (long term):** **Single Dose Prophylaxis:** **Secondary Prophylaxis:**

			✓ **Prophylaxis in Hemophilia A:** ✓ **Prophylaxis in Hemophilia B** **Management of major and minor bleeding episodes in hemophilia patients** ✓ **Major head injury or intra cerebral bleed** **Mild Hemophilia** Individuals with mild hemophilia frequently receive conservative management using the RICE method for mild injuries. In cases of minor bleeds and minor surgical procedures related to mild hemophilia A, non-blood product treatments such as DDAVP and Tranexamic acid are employed. DDAVP is not effective for addressing hemophilia B. **DDAVP** **Tranexamic acid** **Factor viii concentrate in mild hemophilia** - Certain individuals with mild or moderate hemophilia might develop inhibitors, hence the utilization of recombinant products should be deliberated with a hemophilia center, unless the circumstance is urgent. - In cases of significant bleeding episodes or surgeries among patients with mild hemophilia, the desired factor levels should align with the recommendations applicable to patients with severe or moderate deficiencies. **Management of pregnancy and delivery in hemophilia** **Pre-pregnancy:**

			- Pre-pregnancy counselling should be offered to all potential carriers. • Some females have factor levels that can put them at risk of bleeding. **For females affected by hemophilia** Management is complex and should be discussed with a trained hemophilia treater or genetic counsellor regarding options. **Parents who wish to consider termination of pregnancy:** ✓ Chorionic villus sampling (CVS) and gene testing on male fetuses. ✓ Determination of sex of fetus at 14 - 16 weeks can be performed and if male, proceed to amniocentesis and gene testing – however this may lead to less time for consideration of options. ✓ In some cases, a blood test non-invasive prenatal testing (NIPT) testing for fetal DNA in the maternal blood may be available but it is not currently publicly funded. **Parents who do not want termination and are not insistent about prior knowledge of hemophilia status of fetus or mother not informative on DNA testing:** ✓ Determine sex of infant by conventional ultrasound during second trimester. ✓ If female fetus, manage mother as detailed below but no additional intervention needed for newborn. ✓ If male fetus, 50% risk of hemophilia, so proceed as if fetus affected until proven otherwise. **During pregnancy**

			• Assay maternal factor VIII/IX level at booking. If reduced, repeat in the third trimester or before any invasive procedures. • If factor VIII/IX level 50% for procedures such as CVS, amniocentesis, or termination. • For females in the third trimester, with a level < 80% rFVIII is required for most surgical procedures. • Factor IX deficiency rFIX is required for most surgical procedures. • Discuss delivery plan – a written management plan from the hemophilia treatment center may be required for more complex deliveries. Have appropriate treatment available at the time of delivery in line with the proposed treatment plan. **Postpartum** **For females with a factor level of if < 50% before pregnancy:** • Monitor factor VIII level daily after birth (acute phase protein and level falls post delivery). • Give rFVIII or consider DDAVP (note significant hyponatraemia can occur particularly if oxytocin was administered during delivery) if levels <80% **iii.** 3 days if normal vaginal delivery **iv.** 5 days if caesarean section • Tranexamic acid 1g tds can be used for 5-7 days post delivery **For hemophilia B carrier with a factor level of if <50% before pregnancy:** • Give replacement with one dose for normal delivery and a second dose at D3 for

			caesarean section no need to monitor daily. • Tranexamic acid 1g tds can be used for 5–7 days post delivery. **Newborn males** • Take blood from umbilical cord (or peripheral vein if cord blood specimen unobtainable or unsatisfactory) for urgent (result < 3 hours) factor VIII/IX level. • If urgent factor VIII/IX assay unavailable, do coagulation screen (upper limit normal APTT in newborn approximately 40 seconds). • Avoid heel pricks for coagulation studies or factor assays. • Oral Vitamin K prophylaxis is effective in preventing classical hemorrhagic disease of the newborn, but ineffective in preventing late HDN. Increasing the dose or giving it weekly for a longer period increases the efficacy of the oral prophylaxis. Alternatively, IM Vitamin K can be given providing pressure is maintained for a minimum of 5-10 minutes. • Factor IX concentration may be unreliable in the newborn (until approximately 6 months of age). A low level does not confirm hemophilia and a repeat may be necessary. **Newborn females** In females born to families with severe hemophilia cord blood factor VIII/IX level should be measured detect the occasional carrier female with low levels at risk of symptomatic bleeding. **VON WILLEBRAND DISEASE** **Minor bleeds**

			• The management of most patients with type I von Willebrand disease (VWD) typically involves the use of Tranexamic acid and/or DDAVP (Desmopressin). DDAVP is effective in increasing VWF (von Willebrand factor) and FVIII (Factor VIII) levels. In some cases of type IIA VWD, DDAVP can be beneficial, but not all patients with this subtype respond to it. • However, in type IIB VWD, DDAVP is ineffective in reducing bleeding time and may even cause a severe transient thrombocytopenia (low platelet count). As a result, DDAVP is contraindicated in type IIB VWD as well as in cases of pseudo-von Willebrand disease. Furthermore, DDAVP is predictably ineffective in type III VWD. **Surgery and major bleeds** • For patients with mild Type I von Willebrand disease, DDAVP with or without Tranexamic Acid is usually satisfactory for many surgical procedures. Patients with more severe Type I or Type II disease and in particular Type III disease usually require the infusion of normal von Willebrand factor. Currently this is available in concentrates of plasma-derived factor VII. • Effective bleeding control is typically achieved when adequate Factor VIII (FVIII) levels, exceeding 50%, are maintained, regardless of the bleeding time. Perioperatively,

			it is crucial to pay close attention to local hemostasis, which may involve techniques such as sutures, cautery, and wound packing. • In most situations, concurrent administration of tranexamic acid is recommended to further assist in managing bleeding. **Pregnancy** • During pregnancy, von Willebrand factor (vWF) and factor VIII levels rise, which can make initial von Willebrand disease (VWD) testing unreliable. While these levels may normalize in VWD type 1, bleeding may persist in VWD type 2 and 3. If factor VIII levels normalize during pregnancy, it typically happens before the 34th week. After delivery, factor VIII levels drop rapidly, posing a risk of delayed postpartum hemorrhage at 10-14 days. The risk of bleeding during delivery is approximately 40%, with primary postpartum hemorrhage at 15-20% and secondary postpartum hemorrhage at 20-28%. This risk is not limited to women who don't normalize factor levels during pregnancy. Even when levels normalize, unaffected women have supra-normal vWF levels in late pregnancy. **Management in Pregnancy** • A careful personal and family bleeding history is important. • In patients with suspected vWD test at 30-34 weeks (or earlier if preterm delivery is likely).

			• Request von Willebrand screen (record blood group). • Avoid epidural anesthesia (see below) **Management at delivery** • Many patients will not need treatment at the time of delivery or post partum. If the Factor VIIIc parameters are normal at 30-34 weeks manage expectantly but with a high index of suspicion for postpartum hemorrhage. • In women with type 1 whose factor levels fail to normalize (>50%) or in those with types 2 or 3, consider prophylaxis as below: **c)** DDAVP (0.3 µg/kg) given following clamping of umbilical cord **d)** Plasma derived factor VIII (CSL Biostate 500 units/reconstituted bottle). This should be used if there is a history of significant bleeding with a previous delivery. 20–30 FVIII units/kg (40–60 VWF units/kg). This may need to be continued 12 hourly for 3–5 days • The use of DDAVP (Desmopressin) can lead to significant hyponatremia, especially if oxytocin was administered during delivery. **Post partum hemorrhage** In the event of postpartum bleeding, where prophylaxis has not been given, treatment will be: c) DDAVP (0.3 µg/kg) given following clamping of umbilical cord (note this is not appropriate for repeated use

			as stores become used and it becomes ineffective. d) Plasma derived factor VIII (CSL Biostate 500 units/reconstituted bottle). 20–30 FVIII units/kg (40–60 VWF units/kg). This may need to be continued 12 hourly for 3-5 days **The infant** Von Willebrand disease is an autosomal dominant inherited condition with variable penetrance (approximately one third of at risk infants will inherit the condition). • Avoid invasive fetal monitoring (e.g. scalp vein sampling) when possible. Care with instrumental deliveries. • Give vitamin K at birth. • Infants are not routinely tested unless they have unexplained bleeding problems. **Miscarriage** • Bleeding during pregnancy requires urgent obstetric consultation. • Patient with an early miscarriage may require no additional treatment. If there is a need for intervention to remove retained products or prolonged bleeding, treatment with Tranexamic acid and /or DDAVP should be considered. • Patients with a personal history of miscarriage or bleeding during pregnancy may require more frequent monitoring of von Willebrand factor parameters during pregnancy **Platelet Disorders** **Congenital platelet function defects**

			Platelet disorders can be treated with DDAVP, platelet transfusion or recombinant factor VIIa. In all cases antiplatelet drugs such as aspirin and anti-inflammatories should be avoided. **Management:** • Tranexamic acid and compression for minor bleeding • Platelet transfusions for more major bleeding • DDAVP and/or rFVIIa may be useful in some disorders **Specific conditions** **i. Bernard Soulier syndrome:** • Tranexamic acid • Treat with platelets **ii. Glanzmanns thrombasthenia:** • Tranexamic acid • DDAVP anecdotally beneficial (0.3mcg/kg) • Recombinant Factor VIIa 80-140mcg/kg. (may require NPPA) • Platelets for bleeding **iii. Platelet storage pool disorders:** • Tranexamic acid • Platelets for bleeding • DDAVP can be trialed
	Missing	International consensus recommendations on the management of people with hemophilia B (2022)[11]	**Factor product choice, switching and clinical indications** **Specific therapeutic agent laboratory monitoring considerations** **Pharmacokinetic (PK) considerations – modelling, predictions and dose optimization** **Inhibitor management and preparing for novel agents**

			Preparing for Gene therapy (GT)
	Missing	Emergency management in patients with hemophilia A and inhibitors on prophylaxis with emicizumab: AICE practical guidance in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET (2019)[12]	• **Guidance for the use of bypassing agents during prophylaxis with emicizumab** • **Management of inhibitor patients on emicizumab in the emergency unit** **Management of bleeding or suspicion of bleeding in inhibitor patients on emicizumab prophylaxis** **Management of surgery in inhibitor patients**
	Missing	Practical Guidance of the GTH Hemophilia Board on the Use of Emicizumab in Patients with Hemophilia A (2020)[13]	• Each Emicizumab administration needs to be recorded meticulously in a patient diary on every occasion. (100% agreement) • Every patient should maintain an emergency supply of FVIII or bypassing agents (BPAs) at their residence for addressing breakthrough bleeding episodes. (92.3% agreement, 7.7% limited agreement) • Hemorrhage management in individuals with hemophilia A, both with and without inhibitors, should be provided when there are applicable bleeding events or substantial injuries. (92.3% agreement, 7.7% limited agreement) • Patients under Emicizumab prophylaxis may not require treatment for every non-severe bleeding episode. (92.3% agreement, 7.7% limited agreement) c) Tranexamic acid can be applied either locally or systemically as needed.

			• In individuals with hemophilia A (PWHAs) who do not have inhibitors, clinically significant breakthrough bleeds should be managed with factor VIII (FVIII) treatment. (100% agreement) • In individuals with hemophilia A (PWHAs) who have inhibitors, recombinant factor VIIa (rFVIIa) should be the initial treatment choice for significant breakthrough bleeds. It's important to note that the prolonged use of activated prothrombin complex concentrate (aPCC) at doses exceeding 100 units per kilogram for more than 24 hours has been linked to an increased risk of thrombotic or thrombotic microangiopathy (TMA) events. (92.3% agreement, 7.7% limited agreement) g) If there is an inadequate clinical response to rFVIIa, FVIII can be considered as an option for patients with low FVIII inhibitor activity. h) Activated prothrombin complex concentrate (aPCC) should be reserved for situations where no other treatment options are available or effective. g) In minor surgery cases, additional FVIII treatment may not always be required, but patients should undergo clinical monitoring to detect any signs of abnormal bleeding. h) Surgical procedures categorized by bleeding risk have been managed successfully using standard

			FVIII regimens without complications. f) Minor surgeries may not always require additional bypassing agent (BPA) treatment, but patients should be clinically monitored for any signs of abnormal bleeding. g) For major surgeries, preventive treatment with rFVIIa should be administered based on the bleeding risk associated with the surgery and the patient's clinical course. h) Inhibitor testing should be conducted before surgery to assess the possibility of using FVIII treatment in case of low or negative inhibitory activity. i) If rFVIIa proves to be insufficiently effective, the recommendations for second-line treatment align with those for bleeding management. *g)* Established ITI protocols, such as the Bonn protocol, have demonstrated effectiveness (60-80%) and safety. *h)* In patients who have received Emicizumab for less than six months, the use of activated prothrombin complex concentrate (aPCC) as a prophylactic agent during ITI should be avoided. • There are only limited case series where immune tolerance induction (ITI) protocols incorporating both FVIII and Emicizumab for prophylaxis have been employed. Consequently, there is insufficient evidence to provide recommendations regarding the specific

			indications, dosages, and durations for this combined approach of ITI with Emicizumab prophylaxis. (92.3% agreement, 7.7% limited agreement) • Emicizumab is approved for use in all age groups; however, its licensure for children relies on limited available data. Therefore, the decision to employ Emicizumab in very young children, especially those who are previously untreated (PUPs), should be made on a case-by-case basis, considering the individual patient's needs and circumstances. (92.3% agreement, 7.7% limited agreement)
	Missing	Nordic Guidelines on Acquired Hemophilia (2020)[14]	• Acquired hemophilia should be suspected in patients with prolonged APTT, but normal INR and signs of bleeding. Treatment of bleeding: • Bypassing agents are recommended for significant bleeds as first-line therapy. • Factor VIII concentrates in high dosages can be used as first line treatment in patients with AHA, if bypassing agents are not available and especially in patients with low antibody titres and if daily measurement of FVIII is possible. • Tranexamic acid can be used as concomitant treatment both in patients receiving bypassing agents and factor concentrates • Either factor concentrates or bypassing agents can be used as second line treatment. • Porcine FVIII is also used as second-line therapy.

			Eradication therapy: • Agents recommended include corticosteroids, azathioprine, cyclophosphamide, cyclosporine and rituximab

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Hemophilia

The following is the result of the PubMed search conducted for hemophilia A guideline search:

Query	Filters	Search Details	Results
((((((((((((((((((Hemophilia A[MeSH Terms]) OR (Hemophilia As[Title/Abstract])) OR (Hemophilia, Classic[Title/Abstract])) OR (Hemophilia[Title/Abstract])) OR (Hemophilia A, Congenital[Title/Abstract])) OR (Congenital Hemophilia A[Title/Abstract])) OR (Congenital Hemophilia As[Title/Abstract])) OR (Hemophilia As, Congenital[Title/Abstract])) OR (Classic Hemophilia[Title/Abstract])) OR (Classic Hemophilias[Title/Abstract])) OR (Hemophilias, Classic[Title/Abstract])) OR (Hemophilia[Title/Abstract])) OR (Autosomal Hemophilia A[Title/Abstract])) OR (As, Autosomal Hemophilia[Title/Abstr	Guideline, in the last 5 years	("hemophilia a"[MeSH Terms] OR "hemophilia as"[Title/Abstract] OR "hemophilia classic"[Title/Abstract] OR "Hemophilia"[Title/Abstract] OR "hemophilia a congenital"[Title/Abstract] OR "congenital hemophilia a"[Title/Abstract] OR (("Congenital"[MeSH Subheading] OR "Congenital"[All Fields] OR "congenitally"[All Fields]) AND "hemophilia as"[Title/Abstract]) OR (("hemophilia as"[All Fields] OR "hemophilia a"[MeSH Terms] OR "hemophilia a"[All Fields] OR "Hemophilia"[All Fields] OR "hemophilia as"[All Fields]) AND "Congenital"[Title/Abstract]) OR "classic hemophilia"[Title/Abstract] OR (("Classic"[All Fields] OR "classical"[All Fields] OR "classically"[All Fields] OR "classicals"[All Fields]	6

act])) OR (Autosomal Hemophilia As[Title/Abstract])) OR (Hemophilia A, Autosomal[Title/Abstract])) OR (Hemophilia As, Autosomal[Title/Abstract])) OR (Factor VIII Deficiency[Title/Abstract])) OR (Factor 8 Deficiency, Congenital[Title/Abstract])) OR (Factor VIII Deficiency, Congenital[Title/Abstract])) OR (Deficiency, Factor VIII[Title/Abstract])		OR "classics"[All Fields]) AND "Hemophilias"[Title/Abstract]) OR (("Hemophilia"[All Fields] OR "hemophilia a"[MeSH Terms] OR "hemophilia a"[All Fields] OR "Hemophilia"[All Fields] OR "haemophilias"[All Fields] OR "Hemophilias"[All Fields]) AND "Classic"[Title/Abstract]) OR "Hemophilia"[Title/Abstract] OR "autosomal hemophilia a"[Title/Abstract] OR ("autosomal hemophilia"[Title/Abstract]) OR (("Autosomal"[All Fields] OR "autosomally"[All Fields] OR "autosome"[All Fields] OR "autosomes"[All Fields] OR "autosomic"[All Fields] OR "autosomical"[All Fields]) AND "hemophilia as"[Title/Abstract]) OR (("Hemophilia"[All Fields] OR "hemophilia a"[MeSH Terms] OR "hemophilia a"[All Fields] OR "Hemophilia"[All Fields] OR "haemophilias"[All Fields] OR "Hemophilias"[All Fields]) AND "a autosomal"[Title/Abstract]) OR (("Hemophilia"[All Fields] OR "hemophilia a"[MeSH Terms] OR "hemophilia a"[All Fields] OR "Hemophilia"[All Fields] OR "haemophilias"[All Fields] OR "Hemophilias"[All Fields]) AND "as	

		autosomal"[Title/Abstract]) OR "factor viii deficiency"[Title/Abstract] OR (("factor viii"[MeSH Terms] OR ("Factor"[All Fields] AND "VIII"[All Fields]) OR "factor viii"[All Fields] OR "factor 8"[All Fields]) AND "deficiency congenital"[Title/Abstract]) OR (("factor viii"[MeSH Terms] OR ("Factor"[All Fields] AND "VIII"[All Fields]) OR "factor viii"[All Fields]) AND "deficiency congenital"[Title/Abstract]) OR "deficiency factor viii"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

The following is the result of the PubMed search conducted for hemophilia A guideline search:

Query	Filters	Search Details	Results
((((((((((((((((Hemophilia B[MeSH Terms]) OR (Bs, Hemophilia[Title/Abstract])) OR (Hemophilia Bs[Title/Abstract])) OR (Deficiency, Factor IX[Title/Abstract])) OR (Deficiencies, Factor IX[Title/Abstract])) OR (Factor IX Deficiencies[Title/Abstract])) OR (Factor IX Deficiency[Title/Abstract])) OR (Hemophilia B Leyden[Title/Abstract])) OR (Hemophilia B(M[Title/Abstract]))) OR (Hemophilia Bs (M[Title/Abstract]))) OR (Plasma Thromboplastin Component	Guideline, in the last 5 years	((((((((((((((((Hemophilia B[MeSH Terms]) OR (Bs, Hemophilia[Title/Abstract])) OR (Hemophilia Bs[Title/Abstract])) OR (Deficiency, Factor IX[Title/Abstract])) OR (Deficiencies, Factor IX[Title/Abstract])) OR (Factor IX Deficiencies[Title/Abstract])) OR (Factor IX Deficiency[Title/Abstract])) OR (Hemophilia B Leyden[Title/Abstract])) OR (Hemophilia B(M[Title/Abstract]))) OR (Hemophilia Bs (M[Title/Abstract]))) OR (Plasma Thromboplastin Component Deficiency[Title/Abstract])) OR (F9	1

Deficiency[Title/Abstract])) OR (F9 Deficiency[Title/Abstract])) OR (Deficiencies, F9[Title/Abstract])) OR (Deficiency, F9[Title/Abstract])) OR (F9 Deficiencies[Title/Abstract])) OR (Christmas Disease[Title/Abstract])) OR (Disease, Christmas[Title/Abstract])) OR (Hemophilia B[Title/Abstract])) OR (Hemophilia Bs[Title/Abstract])		Deficiency[Title/Abstract])) OR (Deficiencies, F9[Title/Abstract])) OR (Deficiency, F9[Title/Abstract])) OR (F9 Deficiencies[Title/Abstract])) OR (Christmas Disease[Title/Abstract])) OR (Disease, Christmas[Title/Abstract])) OR (Hemophilia B[Title/Abstract])) OR (Hemophilia Bs[Title/Abstract])	

Query	Filters	Search Details	Results
((((((((((((((((((((Factor XI Deficiency[MeSH Terms]) OR (Deficiency, Factor Eleven[Title/Abstract])) OR (Deficiencies, Factor Eleven[Title/Abstract])) OR (Factor Eleven Deficiencies[Title/Abstract])) OR (Factor 11 Deficiency[Title/Abstract])) OR (Factor Eleven Deficiency[Title/Abstract])) OR (Plasma Thromboplastin Antecedent Deficiency[Title/Abstract])) OR (Hemophilia C[Title/Abstract])) OR (Rosenthal's Syndrome[Title/Abstract])) OR (Rosenthal's Syndromes[Title/Abstract])) OR (Rosenthals Syndrome[Title/Abstract])) OR (Syndrome, Rosenthal's[Title/Abstr	Guideline, in the last 5 years	("factor xi deficiency"[MeSH Terms] OR (("deficiences"[All Fields] OR "Deficiencies"[All Fields] OR "Deficiency"[MeSH Subheading] OR "Deficiency"[All Fields] OR "deficient"[All Fields] OR "deficients"[All Fields]) AND "factor eleven"[Title/Abstract]) OR (("deficiences"[All Fields] OR "Deficiencies"[All Fields] OR "Deficiency"[MeSH Subheading] OR "Deficiency"[All Fields] OR "deficient"[All Fields] OR "deficients"[All Fields]) AND "factor eleven"[Title/Abstract]) OR (("factor xi"[MeSH Terms] OR ("Factor"[All Fields] AND "XI"[All Fields]) OR "factor xi"[All Fields] OR ("Factor"[All Fields] AND "Eleven"[All Fields]) OR	0

act])) OR (Rosenthal Syndrome[Title/Abstract])) OR (Rosenthal Syndromes[Title/Abstract])) OR (Syndrome, Rosenthal[Title/Abstract])) OR (Deficiency, Factor 11[Title/Abstract])) OR (Deficiencies, Factor 11[Title/Abstract])) OR (Factor 11 Deficiencies[Title/Abstract])) OR (Deficiency, Factor XI[Title/Abstract])) OR (Deficiencies, Factor XI[Title/Abstract])) OR (Factor XI Deficiencies[Title/Abstract])		"factor eleven"[All Fields]) AND "Deficiencies"[Title/Abstract]) OR "factor 11 deficiency"[Title/Abstract] OR (("factor xi"[MeSH Terms] OR ("Factor"[All Fields] AND "XI"[All Fields]) OR "factor xi"[All Fields] OR ("Factor"[All Fields] AND "Eleven"[All Fields]) OR "factor eleven"[All Fields]) AND "Deficiency"[Title/Abstract]) OR "plasma thromboplastin antecedent deficiency"[Title/Abstract] OR "hemophilia c"[Title/Abstract] OR "rosenthal s syndrome"[Title/Abstract] OR (("Rosenthal"[All Fields] OR "Rosenthal's"[All Fields]) AND "Syndromes"[Title/Abstract]) OR ("Rosenthals"[All Fields] AND "Syndrome"[Title/Abstract]) OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "Syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Rosenthal's"[Title/Abstract]) OR "rosenthal syndrome"[Title/Abstract] OR "rosenthal syndromes"[Title/Abstract] OR (("syndrom"[All	

		Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "Syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Rosenthal"[Title/Abstract]) OR (("deficiences"[All Fields] OR "Deficiencies"[All Fields] OR "Deficiency"[MeSH Subheading] OR "Deficiency"[All Fields] OR "deficient"[All Fields] OR "deficients"[All Fields]) AND "factor 11"[Title/Abstract]) OR (("deficiences"[All Fields] OR "Deficiencies"[All Fields] OR "Deficiency"[MeSH Subheading] OR "Deficiency"[All Fields] OR "deficient"[All Fields] OR "deficients"[All Fields]) AND "factor 11"[Title/Abstract]) OR (("factor xi"[MeSH Terms] OR ("Factor"[All Fields] AND "XI"[All Fields]) OR "factor xi"[All Fields] OR "factor 11"[All Fields]) AND "Deficiencies"[Title/Abstract]) OR "deficiency factor xi"[Title/Abstract] OR "deficiencies factor xi"[Title/Abstract] OR "factor xi deficiencies"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm for Hemophilia A

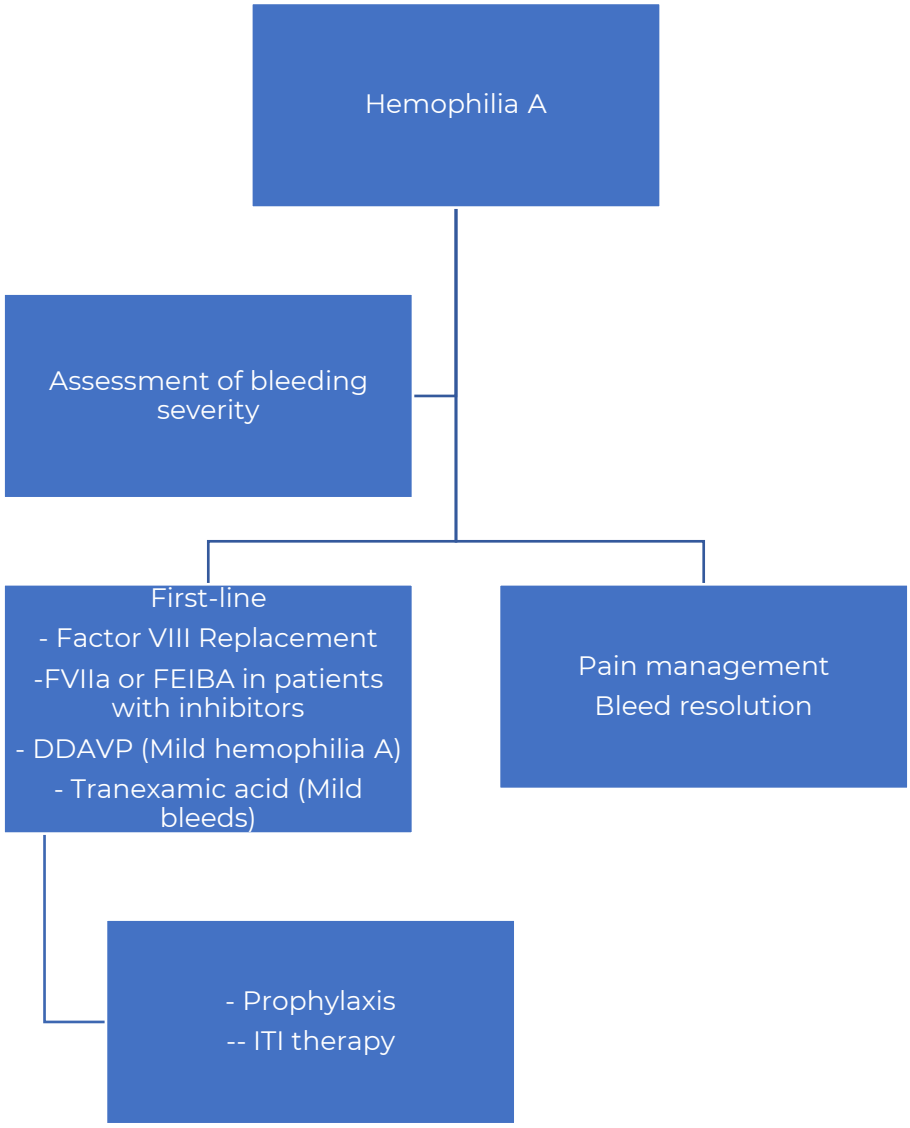

Figure 2. *Treatment Algorithm for the Management of Hemophilia A*[6,7,12,13]

Appendix E. Treatment Algorithm for Hemophilia B

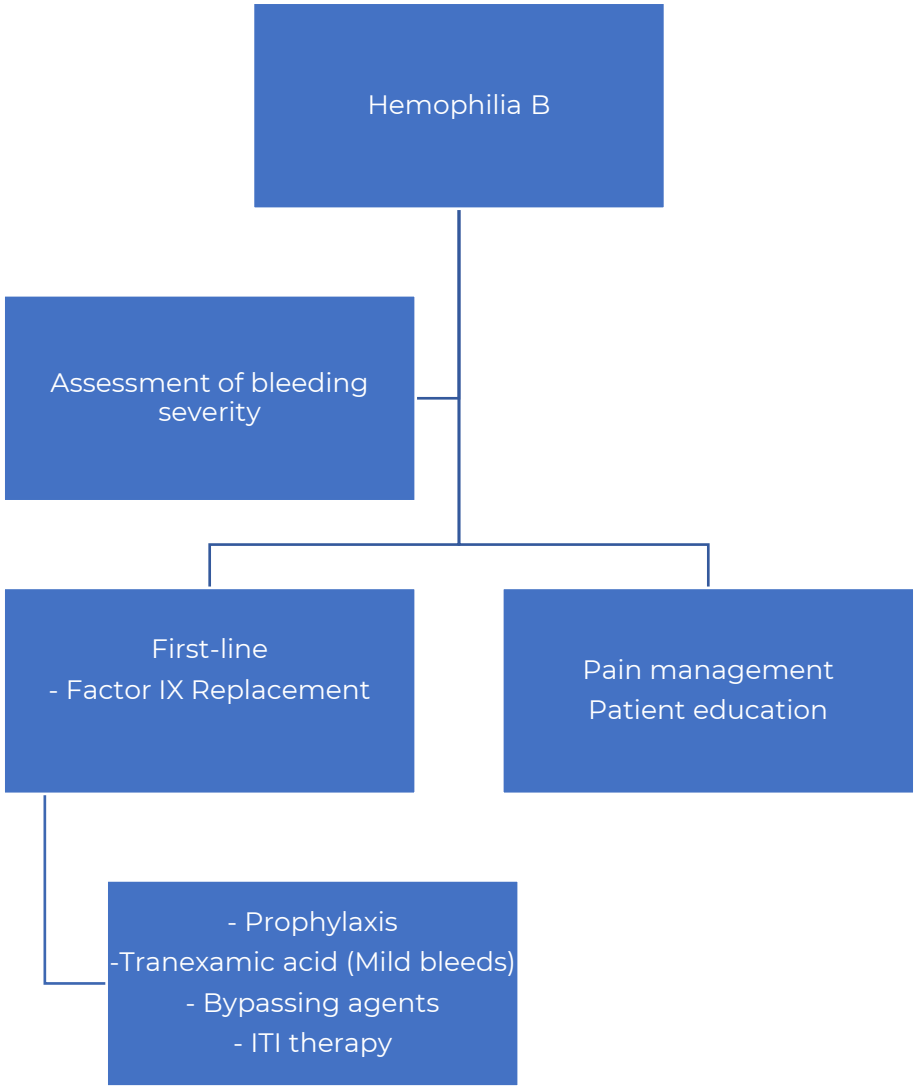

Figure 3. *Treatment Algorithm for the Management of Hemophilia B*[6–8,11]