



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #267
(Replaces Document #241)

**MASAC RECOMMENDATION CONCERNING PROPHYLAXIS FOR
HEMOPHILIA A AND B WITH AND WITHOUT INHIBITORS**

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on March 11, 2022, and adopted by the NHF Board of Directors on April 27, 2022.

In view of the demonstrated benefits of prophylaxis begun at a young age in persons with hemophilia A or B (PwH), MASAC recommends that prophylaxis be considered standard of care therapy for individuals with severe hemophilia A or B (factor VIII or factor IX <1%) including those with inhibitors. Prophylactic therapy may also be considered for PwH with moderate and mild hemophilia with a severe phenotype. Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding). Efficizumab has led to a reconsideration of prophylaxis, regarding initiation age, dose intensity and target levels. See below and MASAC Recommendation #268 for more details.

The World Federation of Hemophilia provides detailed recommendations regarding prophylaxis. MASAC endorses these recommendations.

In particular:

- 1) Prophylaxis should be initiated at an early age, ideally before age 3 years and prior to the second joint bleed; prophylaxis may be considered within the first six months of life to reduce occurrence of intracranial hemorrhage (see section on emicizumab prophylaxis for hemophilia A)
- 2) Prophylaxis should be individualized (by dose and or frequency adjustment) and sufficient to prevent all bleeds at all times
- 3) Options for prophylaxis include plasma-derived or recombinant standard half-life factor, extended half-life factor and non-factor replacement (Table 1).

See Appendix for additional considerations for PwH and their families when considering prophylaxis.

Table 1. Options for prophylaxis are detailed in Table 1.

	Hemophilia A	Hemophilia B	Hemophilia A with inhibitor	Hemophilia B with inhibitor
Factor VIII replacement	X			
Factor IX replacement		X		
Bypassing agents (BPA)			X	X
Emicizumab	X		X	

Factor prophylaxis

There are several strategies to prophylaxis with considerations related to age of initiation, choice of product, frequency of administration, and venous access.

Age of prophylaxis initiation depends on clinical course, venous access, and goals of treatment. Optimal outcomes are associated with young age at initiation.

Several factor replacement products are approved for prophylaxis in PwHA and PwH B without inhibitors. Options include both plasma-derived and recombinant factor replacement. Recombinant products include both standard half-life and extended half-life products. As the only approved non-factor replacement product, emicizumab is a humanized monoclonal bispecific antibody, which is approved for prophylaxis in individuals of all ages with hemophilia A with and without inhibitors (MASAC Recommendation #258). In some cases, bypassing agents (FEIBA, rFVIIa) may be used for prophylaxis in patients with inhibitors, but for hemophilia A and inhibitors this strategy is less effective than emicizumab prophylaxis.

Central venous access devices (such as implanted port-a-cath) may be utilized to improve venous access and facilitate regular infusions. However, central venous catheters may be complicated by infections and thrombosis.

There are different treatment strategies for factor prophylaxis based on dose and frequency and may be individualized to the patient. Dosing and frequency may be individualized/tailored guided by PK studies (e.g., WAPPS-Hemo).

Factor prophylaxis

Standard half-life factor prophylaxis for hemophilia A is typically administered 2-4 times per week while extended half-life factor prophylaxis is typically administered 1-3 times per week. Goals of therapy include trough factor levels of at least 1% (>3%-5% or higher if feasible) and minimal to no spontaneous bleeding. Dosing and frequency may be individualized based on pharmacokinetic (PK) studies. Recognizing the power of WAPPS-Hemo in creating individualized PK estimates from sparse samples, the American Thrombosis and Hemostasis Network (ATHN) has integrated WAPPS-Hemo into ATHN Systems. Providers can now submit PK requests through the ATHN Systems interface. Being able to submit WAPPS-Hemo PK

requests directly from ATHN Systems streamlines the data entry process. In addition, the PK estimates generated through WAPPS-Hemo can be used to enrich the ATHN dataset for those individuals who opt-in to sharing their data.

For SHL and EHL FVIII prophylaxis, morning dosing may be ideal in prevention of potential bleeding events occurring typically during the day while the dose timing may not be relevant for most EHL FIX products.

Prophylaxis may be initiated with a dose-escalation strategy, starting at once weekly dosing, and then increasing as needed based on bleed frequency.

Emicizumab prophylaxis for hemophilia A

After the initial four weekly loading doses of emicizumab, dose frequency for maintenance may be every 1, 2 or 4 weeks for a total of 6 mg/kg/month. No laboratory-based assays are currently approved for monitoring response to emicizumab. Emicizumab, as the first approved non-factor replacement, has led to a reconsideration of how we define prophylaxis, regarding initiation age, dose intensity and target levels (see MASAC Recommendation #268 for more details). The goals for emicizumab prophylaxis remain like that of factor prophylaxis in that a regular administration of a prophylactic hemostatic agent should be considered as early as feasible to prevent the long-term complications of musculoskeletal bleeding and allow the patient to lead a physically active life approaching the quality of life of an unaffected individual.

In implementing factor prophylaxis, consideration of dose intensity and timing are clearly defined. There is no defined optimal timing of emicizumab prophylaxis other than prior to age 3 years of age and/or a second joint bleed, like that recommended for factor primary prophylaxis. Prevention of early life bleeding including mitigation of the risk of intracranial hemorrhage may be possible if emicizumab prophylaxis is implemented prior to 6 months of age. Additional data will be needed to determine whether emicizumab prophylaxis implemented early in life (prior to age 3 years of age) can further reduce the chance of hemarthropathy.

Bypassing agent (BPA) prophylaxis

Although long term data on emicizumab prophylaxis in PwHA and inhibitors is lacking, the mitigation of bleeding is clearly superior compared to bypassing agent prophylaxis. There are situations in which BPA prophylaxis can be considered. There are currently three approved products on the market for treatment of acute bleeding events for those with hemophilia A or B with inhibitors. rFVIIa promotes coagulation via tissue factor dependent and independent pathways and includes both eptacog alfa and eptacog beta. rFVIIa may be used for prophylaxis in PwHA and inhibitors and PwHB and inhibitors particularly those with a hypersensitivity to FIX. The role of eptacog alfa in preventing bleeding events in PwHA and inhibitors (without emicizumab) has been investigated while no data exists for eptacog beta in this setting. aPCC (activated prothrombin complex concentrates) contain mostly non-activated clotting factors (II, IX and X) but also activated VII and can also be considered for PwHA and inhibitors and PwHB with inhibitors (without a hypersensitivity reaction to FIX) as a primary prophylactic agent. The inhibitor titer may rise in those with hemophilia B and inhibitors since the product contains FIX.

Adherence with prophylaxis should be monitored. Options for monitoring include self-report,

electronic diaries, and pharmacy reports. VERITAS-Pro is a validated instrument for assessment of adherence of prophylaxis with factor prophylaxis.

Regular surveillance and utilization of a multidisciplinary team approach are critical to ensuring adherence to a mutually decided prophylactic regimen. Because of inevitable changes to physical activity and risk of traumatic bleeding, a patient's prophylactic regimen may need to change seasonally and throughout their lifespan.

Shared decision-making tools are available to help guide health care professionals and patients to guide decision-making about prophylaxis. These tools should be updated based on new product availability.

Further research is encouraged to evaluate:

- 1) the optimal strategies for prophylaxis, especially in young children to prevent bleeding as well as inhibitor formation
- 2) the optimal use of prophylaxis in patients undergoing immune tolerance induction
- 3) laboratory-based assays which may correlate with clinical response to emicizumab

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Appendix to MASAC Recommendation #267:

The National Hemophilia Foundation encourages PwH and their families to consider these recommendations within the context of comprehensive care, which emphasizes patient and family involvement in the decision-making process, based on a thorough discussion of the risks and benefits – medical, social, psychological, and economic – of such care. Thus, in considering prophylaxis, the NHF encourages PwH and their families to examine the following issues with their medical team:

- A. For parents of infants and young children with severe hemophilia who are being considered for prophylaxis, the following issues should be considered:
 - 1. Need for regular infusions or injections versus joint damage and other morbidities associated with hemophilic bleeding.
 - 2. Potential quality of life and mental health implications.
 - 3. Potential costs and reimbursement implications.
 - 4. Requirement for frequent venous access, often necessitating use of a central venous access device (such as a surgically implanted port).
 - 5. Potential complications of such central venous access devices (see MASAC Recommendation #115 regarding central venous access devices).
 - 6. Possibility of other benefits and complications not yet identified.

- B. If prophylaxis is being considered for an older child, adolescent, or adult, the following issues should be considered:
 - 1. Current joint damage and what can reasonably be expected from prophylaxis.
 - 2. Those considerations listed under A. above.

- C. If prophylaxis is selected as the therapeutic regimen of choice, the responsibilities and potential risks and benefits for the individual and the family need to be clearly delineated. The following points should be included in discussions held with patients and families:
 - 1. Frequency of infusion or injection.
 - 2. Quality of life and mental health implications.
 - 3. Standard care for the central venous access device, if utilized, that the family must follow.
 - 4. Frequency of follow-up.
 - 5. Statement of indications to alter or discontinue the protocol.
 - 6. Occurrences that prompt an immediate physician or nurse contact.
 - 7. Essential need for periodic follow-up education.
 - 8. A statement of continued risk of bleeding with trauma and surgery.
 - 9. An acknowledgement that there may be benefits and risks not yet identified.

- E. Once prophylaxis is begun, individuals may need to continue this therapy for life. Reasons to discontinue prophylaxis include:
 - 1. For factor prophylaxis: development of an inhibitor (lack of response to factor VIII or IX).
 - 2. Patient preference with physician concurrence.