NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #271
(Replaces Document #233)

MASAC RECOMMENDATION ON ADMINISTRATION OF INHIBITOR BYPASSING AGENTS IN THE HOME FOR PATIENTS WITH HEMOPHILIA AND 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.

Background

Persons with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) have frequent bleeding episodes that can be treated or prevented by infusion of the missing clotting factor (factor VIII or factor IX, respectively) or prevented with a non-factor replacement agent such as emicizumab. The most serious adverse event for patients with hemophilia A or B is the development of inhibitors, which are antibodies that neutralize infused factor VIII or factor IX so that the factor concentrate cannot stop the bleeding. This can lead to serious, even fatal bleeding episodes.

Management of Bleeding using an inhibitor bypassing agent (BPA), namely FEIBA (Anti-Inhibitor Coagulant Complex) or recombinant FVIIa (rFVIIa) product (NovoSeven RT or SEVENFACT) may be indicated in the setting of acute injury, bleeding, and around the time of surgery. These products may also be used for prophylaxis either alone or in combination with immune tolerance induction (ITI). These agents promote thrombin generation even in the absence of FVIII or FIX activity. Table 1 lists the individual product characteristics. Please review MASAC Document #272 for more details on dosing.

Table 1. Characteristics of bypassing agents

Medication	Indication	Storage	Dosing	Side effects
FEIBA, plasma-derived*	Control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B with inhibitors	Room temperature, 36-77 F	Intravenous; dose and frequency depend on bleed severity and response to treatment; every 6-12 hours Prophylaxis dose is 85 units/kg daily (not while on emicizumab)	Allergic reactions (more common than with recombinant products) Thrombotic events* Thrombotic microangiopathy*

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NovoSeven, recombinant (eptacog alfa)[#]	Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors	Room temperature, 36-77 F	Intravenous; dose and frequency depend on bleed severity and response to treatment; every 2-6 hours	Allergic reactions Thrombotic events[#]
SEVENFACT, recombinant (eptacog beta)[@]	Treat and control bleeding episodes in 12 years and older with hemophilia A or B with inhibitors	Room temperature, 36 to 86 F	Intravenous; dose and frequency depend on bleed severity and response to treatment; every 2-6 hours	Allergic reactions Thrombotic events[@]

PwH and inhibitors may be treated with emicizumab to prevent bleeding. Emicizumab is a factor VIII mimetic that is given subcutaneously. It is not indicated to treat acute bleeding events, and additional hemostatic agents are typically indicated for injury, bleeding, and around the time of surgery. Thrombotic events (TE) and thrombotic microangiopathy (TMA) have occurred in patients with hemophilia A and inhibitors on emicizumab when receiving aPCCs in excess of 100 U/kg/24 hours for 24 hours or more. *Thrombotic events have been reported when used (without emicizumab) alone in high doses (200 U/kg/day) and/or in patients with thrombotic risk factors. Specific recommendations for bleed management are provided in MASAC Document #268. In general, recombinant FVIIa (either eptacog alfa or beta) is favored over FEIBA to avoid TE and TMA.

[#] Serious arterial and venous thrombotic events following administration of NOVOSEVEN RT have been reported (without concurrent emicizumab).

[@] Serious arterial and venous thrombotic events may occur following administration of SEVENFACT.

Rationale for Home Therapy

PwH and inhibitors have better outcomes when they are taught to infuse with BPA in the home (home therapy).

PwH and inhibitors are at higher risk for life-threatening bleeding episodes thus need to be treated within a few hours, however many patients live more than 3 hours from their hemophilia care providers and emergency room providers. Home administration of inhibitor bypassing agents facilitates mitigation of a potentially life-threatening bleeding episode limiting the extent. Moreover, when BPA are prescribed for prophylaxis or ITI home administration of BPA allows patients to adhere the treatment.

Good adherence to prophylaxis plus speedy treatment of trauma and bleeding episodes will optimize outcomes for these patients by preventing serious joint damage or, in the case of limb or head trauma, permanent morbidity or mortality. Thus, in principle, being able to infuse inhibitor bypassing agents in a person with inhibitor in the home may be life- and limb-saving.

Persons with hemophilia and inhibitors have better outcomes when they are taught to infuse with factor concentrate products in the home (home therapy).

PwH and inhibitors should receive coordinated care from their regional Hemophilia Treatment Center (HTC) with a regularly updated tailored bleed management plan. HTC physicians and nurses should teach patients and family members how to mix and administer factor concentrates, including inhibitor bypassing agents, in a sterile manner, either by peripheral vein infusion or central venous catheter. HTC staff should also teach patients and family members to recognize early signs and symptoms of potential reactions and adverse effects to these products and whom to call for any questions. Patients and family members should also be instructed under which circumstances they should call the HTC immediately for advice regarding symptoms of serious bleeding episodes or management of a particular injury.

Therefore MASAC recommends that:

1. PwH and inhibitors should be prescribed the appropriate inhibitor bypassing agents to be administered in the home to treat or prevent bleeds associated with a personalized bleeding management plan.
2. PwH and inhibitors and/or their family members should be instructed in how to mix and administer inhibitor bypassing agents in a sterile manner in the home.
3. PwH and inhibitors and/or their family members should be educated about signs and symptoms of serious bleeding episodes and when to call their HTC care providers.
4. PwH and inhibitors and/or their family members should be educated about potential adverse effects of bypassing agents.
5. PwH and inhibitors and/or their family members should be given emergency contact numbers for HTC staff during regular hours and for 24-hour emergency on-call staff after hours.
6. Any adverse reaction should be reported to the HTC. In addition, adverse reactions may be reported to the pharmaceutical company and to the FDA at www.fda.gov/medwatch.

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