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CHAPTER 1 Recommendation on the Use and Management of Anti-Tissue Factor Pathway Inhibitors in Hemophilia

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TOPIC 1: Concizumab-mtci (Alhemo®) for treatment of hemophilia A or B ≥ 12 years of age WITH or WITHOUT inhibitors

BACKGROUND

- Concizumab is a monoclonal antibody that binds to the Kunitz-2 domain of tissue factor pathway inhibitor (TFPI). The reduction of TFPI inhibitory activity allows for sufficient activated factor X (FXa) production by the activated factor VII (FVIIa)-tissue factor complex to achieve hemostasis. Concizumab was shown to be safe and effective in adults and children 12 years and older with hemophilia A or B with or without inhibitors.[1-4]

RECOMMENDATION 1.1

- Concizumab may be considered for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with hemophilia A or B with or without inhibitors.
- REMARK: Concizumab is administered once daily via a multi-use subcutaneous route with a pen injector and uses weight-based dosing.
- REMARK: Concizumab is administered as a loading dose of 1 mg/kg on day 1, followed by an initial daily maintenance dose of 0.2 mg/kg starting on day 2. Maintenance doses may need to be adjusted based on monitoring of concizumab plasma concentrations. The first concizumab level should be obtained after 4 weeks and before 8 weeks of stable maintenance treatment. As real-world experience grows, laboratory monitoring guidance may need to be adjusted. Please refer to prescribing information for additional information.[9]

- REMARK: Concizumab may cause elevation of fibrin D-dimer and Prothrombin fragment 1+ 2, but it does not affect standard coagulation laboratory assays such as PT/INR and aPTT
- REMARK: When changing from other products to concizumab, the half-life of the previous products should be considered to ensure complete wash-out. For example,12 hours for recombinant FVIIa (rFVIIa), 48 hours for activated prothrombin complex concentrate (aPCC), 24 hours for standard half-life (SHL) factor VIII (FVIII) or factor IX (FIX) product. There is no data on changing from FVIII mimetic therapy or antithrombin knockdown therapy to concizumab. The complete washout period for emicizumab is six months. After discontinuing fitusiran, the duration of persistent antithrombin activity < 60% (non-negligible impact on anticoagulation) is also approximately six months. As the compendium of approved novel agents for treatment of hemophilia grows, the half-life and washout periods of each therapeutic must be considered when transitioning to concizumab for prophylaxis.
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RECOMMENDATION 1.2

- Concizumab is used for prophylaxis, not for treatment of bleeding episodes.
- REMARK: PwH receiving concizumab prophylaxis should have treatment plan management of breakthrough bleeding episodes in consultation with their hemophilia treatment center (HTC).
- REMARK: When giving bypassing agents (recombinant factor VIIa, aPCC), for treatment of breakthrough bleeding episodes in patients on concizumab, the lowest-approved dose and dose interval in the product label should be used The maximum dose of aPCC to be used is a maximum single dose of 50 IU/kg and a maximum of 100 U/kg within 24 hours.
- REMARK: FVIII and FIX products can be given for treatment of breakthrough bleeding episodes in patients on concizumab, and the lowest possible effective dose should be used
- REMARK: Surgical management of patients on concizumab: Given limited experience in the perioperative setting, it is generally recommended to pause concizumab at least 4 days prior to major surgery. Concizumab may be resumed 10 – 14 days after surgery with the same maintenance dose without a loading dose. Concizumab may be continued for management of certain minor surgeries/procedures.

RECOMMENDATION 1.3

- Patients should be educated on the risk, signs, and symptoms of thromboembolic events.
- REMARK: treatment should be interrupted if symptoms of thrombosis occur. Venous and arterial thromboembolic events were reported in 1.9% (6/320) patients, all of whom had other risk factors for thromboembolism. Three of these events occurred in March 2020, leading to a temporary pause of the clinical trials program. The dose of concizumab was lowered and the monitoring protocol was enhanced. No further thromboembolic events occurred after this change. Risk factors for thromboembolism include use of high or frequent doses of breakthrough bleed treatment and conditions in which tissue factor is overexpressed, such as crush injury, cancer, disseminated intravascular coagulation, atherosclerotic disease, septicemia.
- REMARK: Concomitant use of systemic antifibrinolytic agents has not been studied and should generally be avoided. Topical use of antifibrinolytics may be considered.

FUTURE RESEARCH NEEDS:

- The safety and efficacy of concizumab use in patients receiving ongoing immune tolerance induction (ITI) have not been established, therefore shared decision making should be implemented to discuss risks and benefits of continued ITI treatment if concizumab is initiated.
- There is no data on the optimal approach to safely switch from a FVIII mimetic or other rebalancing agent (i.e., fitusiran) to concizumab.
- Optimal surgical management of patients on concizumab is not known.
- The safety of concomitant use of systemic antifibrinolytic therapy in patients on concizumab has not been determined.
- There is no safety data on the use of concizumab in pregnancy or lactation.
- Safety and efficacy have not been established in patients <12 years old
- Establishing long-term safety and efficacy surveillance, reporting of adverse effects, and research collaborations for monitoring are encouraged. This includes registry enrollment and open-label extensions of ongoing phase III and future phase IV clinical trials.

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TOPIC 2: Marstacimab-hncq (HYMPVAZI®) for treatment of hemophilia A or B WITHOUT inhibitors

BACKGROUND

- Marstacimab-hncq is a human monoclonal immunoglobulin G1 antibody binding to the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI). The reduction of TFPI inhibitory activity allows for sufficient FXa production by the FVIIa-tissue factor complex to achieve hemostasis. Marstacimab is approved for routine prophylaxis to prevent or reduce bleeding episodes in adults and children 12 years of age and older with hemophilia A or B WITHOUT inhibitors. Phase 1 and 2 clinical studies revealed reduction in total bleeds, spontaneous bleeds, treated bleeds, and joint bleeds.[1-3]

RECOMMENDATION 2.1

- Marstacimab may be considered for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with hemophilia A or B without inhibitors.
- REMARK: Marstacimab is administered once per week via a single dose prefilled syringe or a fixed dose prefilled pen .

- REMARK: The loading dose is 300 mg administered subcutaneously. One week after the loading dose is administered, a maintenance dose of 150 mg every week via subcutaneous route should be initiated. In persons weighing ≥ 50 kg with inadequate control of bleeding events, maintenance dosing can be increased to 300 mg weekly subcutaneously.
- REMARK: Marstacimab may cause elevation of fibrin D-dimer and Prothrombin fragment 1+ 2, but it does not affect standard coagulation laboratory assays such as PT/INR and aPTT
- REMARK: Prophylactic factor replacement should be discontinued prior to initiation of marstacimab. The half-life of the previous product should be considered, for example 12-24 hours for SHL FVIII or FIX product, 18-104 hours for extended half-life (EHL) FVIII and FIX products, and 47 hours for ultra-EHL FVIII product BIVV001 (Altuviiio®). There is no data on changing from emicizumab to concizumab. The complete wash-out period for emicizumab is 6 months. There is also no data on changing to marstacimab from antithrombin knockout product fitusiran, which has a complete washout period of 6 months for antithrombin level to return to >60%. As the compendium of approved novel agents for treatment of hemophilia grows, the half-life and washout periods of each therapeutic must be considered when transitioning to marstacimab for prophylaxis.

RECOMMENDATION 2.2

- Marstacimab is used for prophylaxis, not for treatment of bleeding episodes.
- REMARK: FVIII and FIX products can be given for treatment of breakthrough bleeding episodes in patients on marstacimab, and the lowest possible effective dose should be used.
- REMARK: Marstacimab should be discontinued prior to major surgery. A participant underwent knee replacement surgery and marstacimab was paused around the time of surgery.[1] The half-life of marstacimab is 7-10 days and the washout period is ~1 month.
- REMARK: There is limited experience with use of marstacimab in acute severe illness, pausing marstacimab therapy may be considered based on individual thromboembolic risk.

RECOMMENDATION 2.3

- Patients should be educated on the risk, signs, and symptoms of thromboembolic events.
- REMARK: Marstacimab treatment should be interrupted if symptoms of thrombosis occur. In the BASIS long-term extension study, one case of spontaneous (non catheter-related) venous thrombosis occurred in a 24-year-old male with hemophilia A who was heterozygous for Factor V Leiden and had additional lifestyle risk factors (sedentary, alcohol consumption, smoking) and family history of coronary disease. Marstacimab therapy was discontinued, and the patient was treated with anticoagulation and coagulation factor concentrates.[5] Risk factors for thromboembolism include use of high or frequent doses of breakthrough bleed treatment and conditions in which tissue factor is overexpressed, such as crush injury, cancer, disseminated intravascular coagulation, atherosclerotic disease, septicemia.
- REMARK: Concomitant use of systemic antifibrinolytic agents has not been studied and should generally be avoided. Topical use of antifibrinolytics may be considered.

FUTURE RESEARCH NEEDS:

- The safety and efficacy of marstacimab use in patients receiving ongoing ITI have not been established, therefore shared decision making should be implemented to discuss risks and benefits of continued ITI treatment if marstacimab is initiated.
- There is no data on optimal approach to safely switch from a FVIII mimetic or antithrombin knockdown product fitusiran (Qfitlia™) to marstacimab.
- Optimal surgical management of patients on marstacimab is not known.
- The safety of concomitant use of systemic antifibrinolytic therapy in patients on marstacimab has not been determined.
- There is no safety data on the use of marstacimab in pregnancy or lactation.
- Safety and efficacy have not been established in patients <12 years old.
- Safety and use of marstacimab in mild and moderate hemophilia A or B without inhibitors have not been evaluated in clinical trials
- Establishing long-term safety and efficacy surveillance, reporting of adverse effects, and research collaborations for monitoring are encouraged. This includes registry enrollment and open-label extensions of ongoing phase III and future phase IV clinical trials.

KEYWORDS: marstacimab-hncq, concizumab-mtci, anti-tissue factor pathway inhibitor

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