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HEMOSTATIC REBALANCING THERAPY

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What are hemostatic rebalancing therapies?

Hemostatic rebalancing therapies belong to the non-factor therapy class and can be used to treat hemophilia A and hemophilia B, with and without inhibitors.

To understand how these medications work, we need to know more about how a blood clot forms. When we are injured, our body's natural system stops the bleeding through activation of the clotting factors already present in the blood and through thrombin generation. People with hemophilia have no or low levels of clotting factor VIII (hemophilia A), or factor IX (hemophilia B) and low thrombin generation, so their blood cannot clot effectively. In other words, in people with hemophilia, there is an imbalance between the factors that help the blood clot (clotting factors) and the factors that prevent clotting (anticoagulation factors).

Hemostatic Rebalancing Therapy

Rebalancing therapies help to restore this balance by decreasing the anticoagulation factor levels, which helps prevent bleeding events and restore normal blood clotting.

What are the different types of hemostatic rebalancing therapies?

Three hemostatic rebalancing therapies have been approved for use. They all have different mechanisms of action, indications, administration frequencies, risks, and benefits.

Concizumab[1] and marstacimab[3] are monoclonal antibodies that target a natural anticoagulation factor called *tissue factor pathway inhibitor* (TFPI). By inhibiting TFPI (also known as anti-TFPI) these medications increase thrombin generation and blood clotting in people with hemophilia A and B, with and without inhibitors.

Fitusiran[2] works differently. Fitusiran is a *small interfering RNA* (siRNA) that inhibits the production of another coagulant, antithrombin. This increases thrombin generation and results in increased blood clotting in people with hemophilia A and B, with and without inhibitors.

How is the mechanism of action of hemostatic rebalancing therapies different from other treatments for hemophilia?

The main treatment types for hemophilia are clotting factor replacement therapy, bispecific antibodies, re-balancing agents, and gene therapy. All these treatments help the blood clot more efficiently, but they all work in different ways.

Clotting factor replacement therapies temporarily increase factor levels by injecting the needed clotting factor protein directly into the blood of a person with hemophilia.

Bispecific antibodies are Y-shaped proteins that act as a bridge between factor IXa and factor X, which helps the blood to clot more efficiently. This antibody bridge mimics the function of the missing activated factor VIII (i.e., factor VIIIa-mimetic).

(continued)	Rebalancing therapies restore the disrupted balance between the levels of anticoagulation (i.e., anti-clotting) factors and clotting factors in the blood, thereby improving blood clotting. Gene therapy introduces a working copy of the missing clotting factor gene. Once the gene is introduced, the body can produce the missing protein and maintain adequate clotting factor levels, on its own, for an extended time.

TREATMENT WITH HEMOSTATIC REBALANCING THERAPIES

Who is eligible to use rebalancing agents?	Hemostatic rebalancing therapies are approved for people with hemophilia A and B, including those with inhibitors. The indications vary by product and regulatory agency. Generally, concizumab (Alhemo) is approved for use in people with hemophilia A or B with inhibitors who are 12 years of age and older; marstacimab (Hympavzi) is approved for use in people with hemophilia A or B without inhibitors who are 12 years of age and older; and fitusiran (Qfitlia) is approved for use in people with hemophilia A or B, with or without inhibitors, who are 12 years of age and older.
How are prophylactic rebalancing therapies administered?	Rebalancing therapies are administered by subcutaneous injection under the skin. The injection takes approximately one minute and can be done at home or at a clinic.
What is the treatment frequency for prophylaxis with hemostatic rebalancing therapies?	Prophylactic treatment with hemostatic rebalancing therapies is administered on a daily to bi-monthly basis and is determined by the medication type. Concizumab is administered daily, marstacimab is administered weekly, and fitusiran is administered every 1–2 months based on antithrombin activity.
Can hemostatic rebalancing therapies be used in combination with other hemophilia treatments?	In some cases, additional treatments (clotting factor replacement therapies or bypassing agents) may be required. It is important to discuss with your healthcare team how to treat breakthrough bleeding as the dosing of other therapies may need to be adjusted. Hemostatic rebalancing agents are not intended for episodic (on-demand) use to treat a breakthrough bleed.

EFFICACY OF HEMOSTATIC REBALANCING THERAPIES

How will clotting factor levels be affected?	Hemostatic rebalancing therapies will not change the clotting factor levels. Studies show that the effect of hemostatic rebalancing therapies is similar to having mild hemophilia.
How will hemostatic rebalancing therapies affect my annual bleed rate?	Any form of regular prophylactic treatment is likely to reduce your annual bleed rate. All three hemostatic rebalancing therapies are effective for bleed prevention when used prophylactically. In clinical trials for concizumab, people with hemophilia A or B with inhibitors who received concizumab prophylaxis had an annual bleed rate of 1.7 compared to 11.8 for people using on-demand bleed management. In clinical trials for marstacimab, people with hemophilia A or B who used marstacimab prophylaxis had an annual bleed rate of 3.2 compared to 38 for people using on-demand bleed management. Similarly, in clinical studies for fitusiran, people who used fitusiran prophylaxis had an annual bleed rate of 3.1 compared to 31 for people using on-demand bleed management.

SAFETY OF HEMOSTATIC REBALANCING THERAPIES

What are the possible side effects of hemostatic rebalancing therapies?	Side effects vary by the product. The most common side effects of concizumab are reactions related to the injection.[1] Other reported side effects include joint pain (arthralgia), upper respiratory tract infection, and headache.
Are there any known serious side effects?	Thromboembolic events (blood clots in the veins or arteries), which can be dangerous and life-threatening have been reported in patients taking rebalancing therapies and are a known risk associated with all three products. It is important to discuss with your healthcare team how you will treat bleeding, injury, and/or surgery while taking hemostatic rebalancing therapies. Fitusiran also has a risk of acute and recurrent gallbladder disease and hepatotoxicity. Blood tests will be used to monitor liver and gallbladder function for at least 6 months after initiating treatment or after a dose increase. Hypersensitivity reactions are a potential serious side effect for concizumab and marstacimab. Additionally, marstacimab may cause fetal harm based on its mechanism of action. Women who are or may become pregnant should be advised of the potential risks. Women should use contraception during treatment with marstacimab and for at least 2 months after their last dose.

MONITORING AND FOLLOW-UP AFTER HEMOSTATIC REBALANCING THERAPY TREATMENT

How often will you need follow up and monitoring with hemostatic rebalancing therapies?	As with all hemophilia treatment classes, regular monitoring by your healthcare team is recommended. Follow up may be more frequent when switching to a new medication. Clinical review should be conducted every 6 months and as needed.
What will happen in the event of a bleed, injury, or surgery?	In the event of a bleed, injury, or planned surgical procedure, additional therapies may be required and your options should be discussed with your healthcare team.

HEMOSTATIC REBALANCING THERAPY TREATMENT IN CHILDREN AND ADOLESCENTS

Are hemostatic rebalancing agents approved for use in children and adolescents?	All hemostatic rebalancing agents are approved for use in adolescent patients who are aged 12–18 years.
Are there any special considerations for treating children with hemostatic rebalancing agents?	The safety and efficacy of hemostatic rebalancing therapies are generally the same between adults and pediatric patients older than 12 years. The safety and efficacy have not been established in patients aged less than 12 years.

1 Product Monograph for Alhemo. Health Canada, 2023.
2 ClinicalTrials.gov. Ongoing Phase 3 studies for Fitusiran: NCT03974113, NCT03754790, and NCT05662319.
3 ClinicalTrials.gov. Ongoing Phase 3 studies for Marstacimab: NCT05611801, NCT05145127, and NCT03938792.

Last reviewed: March 2025
This is a living document that will be updated with new evidence twice per calendar year. The cutoff dates are January 31 and July 31, with updates taking place in the following month(s). Any new evidence after these cutoffs will be included in the next update.