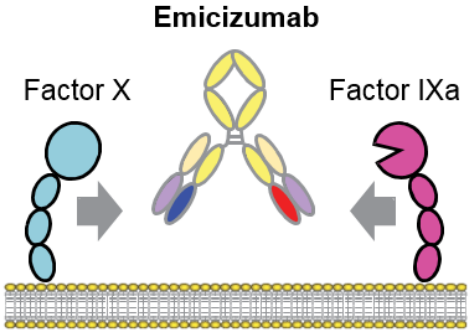
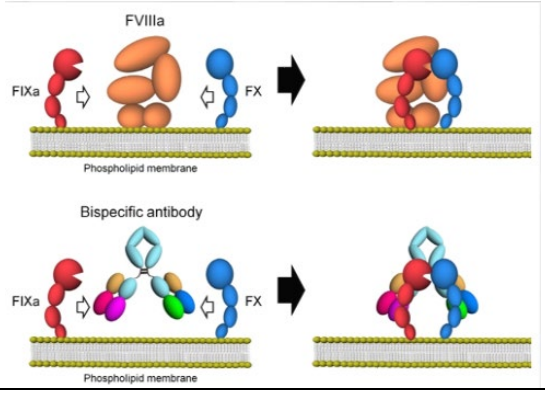
THIS INFORMATION ON HEMLIBRA WAS PROVIDED TO THE SOCIETY BY THE INDIANA COMPREHENSIVE CARE CENTRE IN THE USA

Mechanism of Action

QUESTION	INFORMATION
What is Hemlibra?	Hemlibra is an antibody that is made in the laboratory. It is made to be "like" a human antibody. It has two binding sites; one that recognizes and binds to factor IXa and one that recognizes and binds to factor X. This is why it is called a humanized monoclonal bispecific antibody. 
How does Hemlibra work?	Hemlibra binds factors IXa and X and brings them together. This is the normal function of factor VIII once it is activated (FVIIIa). 

<table>
<tr><td></td><td>Therefore, Hemlibra substitutes for factor VIII and can work when FVIII is absent or in the presence of an inhibitor.</td></tr>
<tr><td>How does Hemlibra work if an inhibitor is present?</td><td>FVIII inhibitors are antibodies that people make that are directed against the missing clotting factor; the body recognizes FVIII as “foreign” or “different” than themselves. These antibodies “inhibit” the ability of infused FVIII to work. Inhibitors do not recognize Hemlibra as the structure of Hemlibra is not FVIII. Therefore, Hemlibra can work the same way if the patient has or does not have an inhibitor.</td></tr>
<tr><td>Is Hemlibra Factor VIII?</td><td>No. Hemlibra is a man-made antibody that binds and pulls two clotting factors together (FIXa & FX) so clotting can occur when needed.</td></tr>
<tr><td>Can Hemlibra be given to treat a bleed?</td><td>No. You need a steady state level of Hemlibra to prevent bleeding episodes. Hemlibra greatly decreases the number of bleeding episodes a patient, either with or without inhibitors, experience. However, patients can still bleed and therefore another hemostatic agent is needed at the time of a bleeding event.
More Hemlibra will not treat a bleeding event.
Starting Hemlibra at the time of a bleed will not treat that bleeding event.
The product needed for a bleeding event depends upon whether the patient has an inhibitor, the inhibitor titer and the severity of the bleeding event. For routine bleeding events:
FVIII with an inhibitor: Treat breakthrough bleeds with NovoSeven at a starting dose up to 90 micrograms/kg/dose. Less doses may be required than if the patient was not taking Hemlibra
FVIII without an inhibitor: Use the previous FVIII product taken by the patient before Hemlibra was started. Use the same dose as dictated by the type of bleed as the IHTC previously recommended. The length of therapy may not be as prolonged as before the Hemlibra was used.</td></tr>
<tr><td>How is Hemlibra different than Factor VIII?</td><td>
<table>
<tr><th></th><th>HEMILBRA</th><th>FVIII /FVIIIA</th></tr>
<tr><td>Half-life</td><td>28.3 – 34.4 days</td><td>8-12 hours</td></tr>
<tr><td>Coagulation factor</td><td>No</td><td>Yes</td></tr>
<tr><td>Recognized by inhibitor</td><td>No</td><td>Yes</td></tr>
<tr><td>On-Off Mechanism</td><td>No</td><td>Yes</td></tr>
<tr><td>Needs to be activated</td><td>No</td><td>Yes</td></tr>
<tr><td>Binding Affinity</td><td>Low</td><td>High</td></tr>
<tr><td>Administered</td><td>Under the skin (Sub-Q)</td><td>Intravenously (IV)</td></tr>
</table>

Hemlibra is different than factor and the “on-off mechanism” or “needs to be activated” concept isn’t viewed in the same way. With a long half-life, you can’t turn it off, however you don’t need to. Hemlibra is available in the blood ready to work when needed (when upstream clotting factor activation due to a bleed being present somewhere in the body).</td></tr>
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<table>
<tr><td>What is the half-life of Hemlibra?</td><td>The half-life of Hemlibra is about one month, ~30 days.</td></tr>
<tr><td>If a patient stops using Hemlibra, how long does it take to get out of their system?</td><td>The half-life is about 30 days. That means for Hemlibra to be completely out of a patient's system will take months. Therefore, standard coagulation assays will be inaccurate for months even through the patient no longer has an adequate level of Hemlibra to protect against bleeding.</td></tr>
<tr><td>How does Hemlibra affect the coagulation assays?</td><td>Hemlibra interferes with the usual clotting tests: it makes them look normal.
<table>
<tr><th colspan="2">Coagulation test results affected and Unaffected by Hemlibra</th></tr>
<tr><th>RESULTS AFFECTED BY HEMLIBRA</th><th>RESULTS UNAFFECTED BY HEMLIBRA</th></tr>
<tr><td>Activated partial thromboplastin time: aPTT</td><td>Bethesda assays (bovine chromogenic) for FVIII inhibitor titers</td></tr>
<tr><td>Bethesda assays (clotting-based) for FVIII inhibitor titers: BU or NBU</td><td>Thrombin time: TT</td></tr>
<tr><td>One-stage, aPTT based, single-factor assays</td><td>One-stage, prothrombin time (PT)-based, single-factor assays</td></tr>
<tr><td>Activated clotting time: ACT</td><td>Chromogenic-based single-factor assays other than FVIII</td></tr>
<tr><td></td><td>Immuno-based assays, (i.e. ELISA, turbidimetric methods)</td></tr>
<tr><td></td><td>Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210</td></tr>
</table>

You can measure infused FVIII when a patient is on Hemlibra with a bovine chromogenic assay.
You can look for an inhibitor with a bovine chromogenic based modified Bethesda Assay.
Do not order a standard FVIII assay for any reason as it will return with very high spurious levels of FVIII which are meaningless.
</td></tr>
<tr><td>Is Hemlibra removed by dialysis or plasmapheresis?</td><td>Hemlibra is a large molecule with a molecular weight of 145.6 KDaltons so that it is not likely removed by dialysis.
Plasmaphereses can lower Hemlibra levels.</td></tr>
<tr><td>If you give factor VIII replacement on top of Hemlibra, are the effects on coagulation additive?</td><td>No, as the binding affinity of FVIII is much higher than that of Hemlibra.
FVIII dose (80% correction) + Hemlibra (~equivalent FVIII activity 10-30%) ≠ FVIII activity of 90-110%

Because Hemlibra is always there and working, less FVIII overall dosing may be required (meaning perhaps the length of therapy).
We need more data on this issue and need to learn from our patients' experiences.</td></tr>
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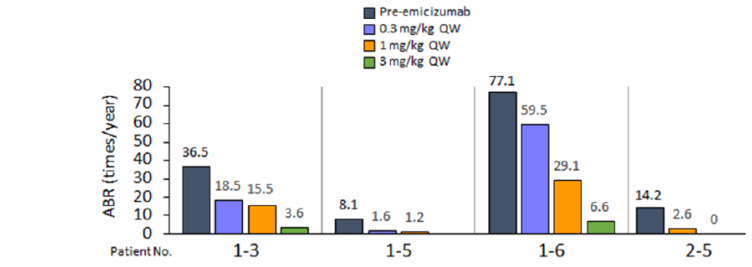
STORAGE, DOSING AND ADMINISTRATION

QUESTION	INFORMATION
What is the recommended dose for Hemlibra?	Everyone who starts Hemlibra uses the same loading dose schedule of 3mg/kg/week for 4 doses. After these 4 doses, the dosing continues to be weight based and there are options for frequency of dosing on maintenance: ▪ Q week is 1.5 mg/kg ▪ Q 2 weeks is 3 mg/kg ▪ Q 4 weeks is 6 mg/kg
What happens if my weight changes; does my dose need to be changed?	It may, which is one reason why you need to be seen regularly to check your clinical status and weight to determine if a dose change is required.
Is there a difference in the dosing for obese patients?	It is weight based so the dose is higher if the patient is obese, but dosing is the same mg/kg.
What are the vial sizes for Hemlibra?	30 mg (BLUE), 60 mg (MAGENTA), 105 mg (GREEN) and 150 mg (BROWN)
Do all of the Hemlibra vials have the same concentration?	No 3 vials have the same concentration and can be mixed together (60 mg, 105 mg and 150 mg) as they have the same concentration (150 mg/ml) while one vial (30 mg vial) has a different concentration (30mg/ml).
What are the differences between loading dose and maintenance dose?	The loading dose is 3 mg/kg once weekly for 4 weeks; you will then start the maintenance dosing. Maintenance dosing is based upon the frequency of administration.
Can you increase the maintenance dose based upon patient response/number of breakthrough bleeding episodes?	The safety, efficacy, and pharmacokinetics of Hemlibra prophylaxis in patients with hemophilia A with and without FVIII inhibitors were evaluated in 4 Phase 3 clinical trials (HAVEN 1, HAVEN 3, and HAVEN 4 [in adult and adolescent patients], and HAVEN 2 [an ongoing pediatric study]). In these studies, patients were eligible for Hemlibra dose up-titration to 3 mg/kg once weekly (QW) for suboptimal bleeding control. • In HAVEN 1, 2 patients had up-titration of their Hemlibra maintenance dose from 1.5 mg/kg QW to 3 mg/kg QW. Preliminary results showed both patients experienced improved efficacy following up-titration. • In HAVEN 2, no patient had undergone dose up-titration as of the last interim analysis.

	• In HAVEN 3, 5 patients had up-titration of their Hemlibra maintenance dose from 1.5 mg/kg • QW to 3 mg/kg QW. • In HAVEN 4, no patient had undergone dose up-titration at the primary analysis. During the Phase 1/2 study, which evaluated the effect of Hemlibra in patients with hemophilia A with and without inhibitors, Hemlibra dose escalation was permitted during the extension phase up to 3 mg/kg QW for suboptimal bleeding control. • A total of 4 patients experienced dose escalation. Up-titration of the Hemlibra dose in these patients resulted in further reductions in annualized bleeding rates. **Figure 1: Annualize Bleeding Rates in 4 Patients who Experienced Dose Up-Titration*[13]**  Duration of dosing 0.3 mg/kg QW: 45 weeks; 96 weeks; 12 weeks; – 1 mg/kg QW: 27 weeks; 44 weeks; 25 weeks; 74 weeks 3 mg/kg QW: 72 weeks; –; 72 weeks; 38 weeks Notes: *Patients 1-3, 1-5, and 1-6 were enrolled in the C-1 cohort and initiated Hemlibra at 1 mg/kg at Week 0, followed by a maintenance dose at 0.3 mg/kg once weekly. Patient 2-5 was enrolled in the C-2 cohort and initiated Hemlibra at 3 mg/kg at Week 0, followed by a maintenance dose of 1 mg/kg once weekly. Abbreviations: ABR=annualized bleeding rate; QW=every week.
Can I round up or save some left over product in the vial for the next dose?	No; discard any unused Hemlibra. In addition, discard Hemlibra if not used immediately.
What if the maximum volume per syringe for each injection?	2 ml
Will my dose be any different if I infuse every 2 weeks or every 4 weeks?	Yes, Dosing is weight based and based upon the frequency of administration on maintenance: ▪ Q week is 1.5 mg/kg ▪ Q 2 weeks is 3 mg/kg

	▪ Q 4 weeks is 6 mg/kg
I am on every 4 weeks injection but think I am bruising more. Can I inject more frequently, for example, weekly?	Yes but you need to come in. The level of Hemlibra obtained falls within the same range when injected weekly versus every 4 weeks but the absolute peak and trough are slightly higher and lower respectively with every 4 weeks dosing. It is OK to change the frequency of injection, and go to weekly but need to keep close contact with the patient and consider ADA evaluation. [ADA = anti-drug antibodies]
What supplies do I need to administer this medication?	Alcohol swab; gauze; 1, 2 or 3 ml syringe; 18 gauge transfer needle; 26 gauge needle for injection; sharps disposal container.
How long should it be out of the refrigerator before I inject?	15 minutes
What injection sites do I use for administration?	Abdomen (2 inches from your belly button), thighs or upper arms
What angle should I use for injection?	45-90 degrees
Do I pinch the skin or hold flat?	Pinch the skin, insert the needle, let go of the skin then inject.
Do I have to store Hemlibra in the refrigerator?	It can be at room temperature for up to 7 days. If stored in the refrigerator it is good until the expiration date.
How long can the unused vial of Hemlibra be out of the refrigerator?	It can be at room temperature for up to a total of 7 days maximum. The total of 7 days could be a combination of being at room temperature on different days.
I left Hemlibra in my hot car. Can I still use it?	A Hemlibra vial cannot be placed at a temperature above 86° F.