

April 14, 2020

To all HTC's, hemophilia treaters, physicians and other healthcare professionals,

We are reaching out to you to remind you about Hemlibra and its known interaction with certain laboratory assays. Some of these assays may be relevant to some individuals that are receiving Hemlibra and become infected with the novel coronavirus that causes COVID-19. Given that the physicians and laboratories treating COVID-19 patients may not be familiar with Hemlibra, we want you to be prepared to share this information in cases where it is relevant. The below information is in line with the approved U.S. Prescribing Information.

COVID-19 is caused by a novel coronavirus, therefore knowledge about how it may affect people with hemophilia A is not well understood. Severe COVID-19 patients with or without hemophilia may develop a COVID-19-associated coagulopathy resembling disseminated intravascular coagulation (DIC) as the condition progresses.

Importantly, Hemlibra is known to interfere with one-stage clotting assays, some of which are used to diagnose and monitor patients with DIC. The following table lists common coagulation assays that may be used to diagnose, monitor and manage patients with COVID-19-associated coagulopathy, whether these assays are affected by Hemlibra, and potential alternatives where applicable.

Analyte / Assay	Assay interference with Hemlibra?	Alternatives
aPTT	Yes (overestimate coagulation potential of Hemlibra)	For heparin monitoring: anti-Xa assay
PT	Yes (weak effect)	No mitigation required (small effect)
D-dimer	No	
Fibrinogen: Clauss method	No	
Fibrinogen: derived	Yes (weak effect)	No mitigation required (small effect); or use Clauss method
Protein C: chromogenic	No	
Protein C: aPTT-based	Yes (overestimate coagulation potential of Hemlibra)	Chromogenic protein C assay
Antithrombin activity	No	
Anti-Xa activity	No	
FVIII activity: aPTT-based	Yes (overestimate coagulation potential of Hemlibra)	Chromogenic FVIII assay (see below guidance)
FVIII activity: chromogenic bovine reagents	No	Does not detect Hemlibra, but allows measurement of endogenous or infused FVIII activity
FVIII activity: chromogenic human reagents	No	Responsive to Hemlibra, but may overestimate clinical hemostatic potential of Hemlibra

1. For additional information on effects and interferences of Hemlibra on coagulation assays, please refer to Adamkewicz, et al. *Thromb Haemost* 2019;119:1084–1093.
2. Please consult U.S. Prescribing Information for further information.

While this information is known within the hemophilia community, if an individual on Hemlibra seeks treatment due to symptoms of COVID-19 infection, we recommend the above table or information is communicated proactively to the treating healthcare provider to ensure they are aware of this information and to remind them to consult the U.S. Prescribing Information. The long half-life (~30 days) of Hemlibra should also be taken into consideration in the context of clinical management. Please consult U.S. Prescribing Information in all cases.

Additional Pharmacovigilance Reporting Request

Patient safety is Genentech's highest priority. At this time, the interaction between Hemlibra and the coagulopathy secondary to COVID-19 infection is unknown. We are committed to obtaining as much information as possible. We are closely monitoring the evolving COVID-19 situation and reviewing any information regarding COVID-19 infections in individuals receiving Hemlibra as it becomes available.

We encourage reporting all confirmed/suspected cases of COVID-19 in individuals receiving Hemlibra through the Genentech adverse event (AE) reporting line [(888) 835-2555] , and request that the reporter provide as many details as possible, including COVID-19 specific details such as:

- Patient demographics
- COVID-19 diagnostic test results
- Coagulation laboratory test results (D-dimer, platelets, PT/INR, fibrinogen, etc.) if applicable and imaging results as appropriate if thrombotic complications are suspected
- Concurrent or recent use of medications that may have an impact on hemostasis (e.g. replacement factor, FFP, low-molecular weight heparin, etc.)
- Assessment of causality
- Contact details to conduct follow up, as needed

You may find these additional resources useful:

- [NHF website](#)
- [HFA website](#)
- [ISTH COVID-19 Resource center](#)
- [WFH COVID-19 guidance](#)
- [World Health Organization's website.](#)
- [ASH COVID-19 resources](#)

In case of Hemlibra-related medical information inquiries you may contact our medical communications department at (800) 821-8590 or gene.com.

Adverse event reporting line: (888) 835-2555

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Hemlibra is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors.

Important Safety Information

Boxed WARNING: THROMBOTIC MICROANGIOPATHY and THROMBOEMBOLISM

Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of Hemlibra if symptoms occur.

Warnings and Precautions

- Laboratory coagulation test interference: Hemlibra interferes with activated clotting time (ACT); activated partial thromboplastin time (aPTT); and coagulation laboratory tests based on aPTT, including one-stage, aPTT-based single-factor assays; aPTT-based Activated Protein C Resistance (APC-R); and Bethesda assays (clotting-based) for factor VIII (FVIII) inhibitor titers. Intrinsic pathway clotting-based laboratory tests should not be used.

Most Common Adverse Reactions

The most common adverse reactions (incidence $\geq 10\%$) are injection site reactions, headache, and arthralgia.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see the Hemlibra full Prescribing Information for additional Important Safety Information, including **Boxed WARNING**.