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We recently learned that a patient in our Phase III HAVEN 2 clinical trial developed a neutralizing anti-drug antibody to HEMLIBRA. As with all therapeutic proteins, there is a potential for the development of anti-drug antibodies with HEMLIBRA, as indicated in the U.S. and EU HEMLIBRA product labels. For this patient, the anti-drug antibody resulted in reduced efficacy of HEMLIBRA. The patient and his family have decided to discontinue treatment with HEMLIBRA, and he will resume treatment with his previous medicine.

To date, more than 600 people with hemophilia A have been treated with HEMLIBRA worldwide, including in clinical trials. This is the first confirmed report of a detectable anti-drug antibody that has impacted the efficacy of HEMLIBRA in a person with hemophilia A. We continue to monitor for the development of anti-drug antibodies to HEMLIBRA in ongoing studies globally.

The development of anti-drug antibodies to HEMLIBRA is distinct from the development of inhibitors to factor VIII. Anti-drug antibodies to HEMLIBRA may affect whether the medicine works, but they do not change the severity of the underlying disorder. On the other hand, for the nearly one in five people with hemophilia A who develop inhibitors to factor VIII[1], the inhibitors not only affect the efficacy of factor VIII replacement therapies, but they can also affect any natural factor VIII in the body. Inhibitors to factor VIII put people with hemophilia A at greater risk for life-threatening bleeds or repeated bleeds that can cause long-term joint damage.

We are committed to providing timely and transparent updates about HEMLIBRA to health authorities, healthcare professionals and the hemophilia community. Should patients or caregivers have any questions about HEMLIBRA, we encourage them to speak with their treating physician.

HEMLIBRA U.S. Indication
HEMLIBRA is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.

Important Safety Information
HEMLIBRA increases the potential for blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow the healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule one should use. 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.

[1] https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html

HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to one's kidneys, brain, and other organs. Patients should get medical help right away if they have any of the following signs or symptoms during or after treatment with HEMLIBRA:
    - confusion
    - weakness
    - swelling of arms and legs
    - yellowing of skin and eyes
    - stomach (abdomen) or back pain
    - nausea or vomiting
    - feeling sick
    - decreased urination
- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in one's arm, leg, lung or head. Patients should get medical help right away if they have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:
    - swelling in arms or legs
    - pain or redness in the arms or legs
    - shortness of breath
    - chest pain or tightness
    - fast heart rate
    - cough up blood
    - feel faint
    - headache
    - numbness in the face
    - eye pain or swelling
    - trouble seeing

If aPCC (FEIBA®) is needed, patients should talk to their healthcare provider in case they feel they need more than 100 U/kg of aPCC (FEIBA®) total.

How should patients use HEMLIBRA?
HEMLIBRA may interfere with laboratory tests that measure how well blood is clotting and may cause a false reading. Patients should talk to their healthcare provider about how this may affect their care.

What are the other possible side effects of HEMLIBRA?
The most common side effects of HEMLIBRA include: redness, tenderness, warmth, or itching at the site of injection; headache; and joint pain.

Before using HEMLIBRA, patients should tell their healthcare provider about all of their medical conditions, including if they:

- are pregnant or plan to become pregnant. It is not known if HEMLIBRA may harm their unborn baby. Females who are able to become pregnant should use birth control (contraception) during treatment with HEMLIBRA.
- are breastfeeding or plan to breastfeed. It is not known if HEMLIBRA passes into a female's breast milk.

These are not all of the possible side effects of HEMLIBRA. Patients should call their doctor for medical advice about side effects.

Side effects may be reported to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Side effects may also be reported to Genentech at (888) 835-2555.

Please see the HEMLIBRA full Prescribing Information and the Medication Guide, including **Serious Side Effects**, for more important safety information.

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