Genentech
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Hemlibra® (emicizumab-kxwh) Update
March 28, 2018

Given the recent dialogue, we are reaching out to clarify the facts surrounding five people with hemophilia A with inhibitors to factor VIII who have passed away while receiving Hemlibra® (emicizumab-kxwh).

In 2015, Hemlibra pivotal clinical trials were initiated in people with hemophilia A with inhibitors. It was also made available through requests to Roche for compassionate use[1] as well as through expanded access protocols[2] in the U.S. and other countries. Data from the pivotal trials have demonstrated the positive benefit/risk profile of Hemlibra and have led to regulatory approvals for people with hemophilia A with inhibitors in the U.S.,[3] EU,[4] and other countries.

Since 2016, five adults with hemophilia A with inhibitors taking Hemlibra have passed away. One of the patients was enrolled in the HAVEN 1 clinical trial; one was in the U.S. expanded access program and three were receiving treatment through compassionate use requests. In each of these cases, the assessment of the treating physician or investigator was that the cause of death was unrelated to Hemlibra. Based on these assessments and the available information, these events do not change the currently known benefit/risk profile.

Upon learning of adverse events, rigorous assessment and reporting protocols are followed. If any adverse event in a person taking Hemlibra impacts the overall benefit/risk profile of the medicine, we will share this information as quickly as possible. Hemlibra's FDA-approved prescribing information remains the primary source of information on the safety and efficacy of the medicine. We are committed to providing timely and transparent updates on the safety profile of Hemlibra to health authorities, healthcare professionals and the hemophilia community.

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

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[1] The Genentech expanded access protocol, reviewed by the FDA, allowed U.S. patients who were not participating in a Hemlibra clinical trial but who met eligibility criteria similar to our key studies to have access to Hemlibra prior to approval.
[2] Compassionate use of Hemlibra is available on a case-by-case basis to eligible patients, following a request to Roche from their treating physician, if they have a serious or life-threatening condition, have exhausted all other treatment options and are unable to participate in a clinical trial.
[3] Hemlibra® (emicizumab-kxwh) is approved in the U.S. for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A with factor VIII inhibitors.
[4] Hemlibra® (emicizumab) is approved in the EU for routine prophylaxis of bleeding episodes in people with haemophilia A with factor VIII inhibitors. Hemlibra can be used in all age groups.

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.

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.

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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