



August 22, 2019

Mr. Val Bias
Chief Executive Officer
National Hemophilia Foundation

Ms. Kimberly Haugstad
President & CEO
Hemophilia Federation of America

Dear Val and Kimberly,

We realize the recent recall of two lots of Kogenate® FS antihemophilic factor (recombinant) has caused concern within the hemophilia community and generated questions about the recall's potential impact on patient safety. We are committed to continuing to work with the community to monitor the situation and keep you updated. The following are responses to the questions raised in your letter received on August 14, 2019.

1. **In the physician letter, Bayer states that Jivi is not indicated for use in previously untreated patients (PUPs) or in children younger than 12. In your recent letter to us, you indicated that you have not received reports of any children under 12 taking the product. Are you asking medical professionals to proactively notify you of members of either group who may have been exposed to Jivi by virtue of these errors?**

On August 1, 2019, Bayer instructed our recall coordinator to inform our distribution partners to report if they have received recalled product from patients under 12 years of age. Since our initial letter, Bayer has received reports of patients under the age of 12 who did receive product from the recalled lots. We are currently in the process of evaluating these reports and any new reports that we receive. As this evaluation is ongoing, the number of cases being reported is continually changing. We will provide a summary report once our evaluation has been completed.

We encourage patients, caregivers and healthcare professionals to report cases of patients who have received the recalled lots, including those under the age of 12, to Bayer Medical Communications at 1-888-84-BAYER (1-888-842-2937).

2. **Please provide an update to us regarding adverse events reported to Bayer. In particular:**
 - a. **Have any allergic reactions been reported to Bayer related to use of the adulterated product?**
 - b. **Have any new instances of inhibitor been reported among patients exposed to the adulterated product?**
 - c. **Have any thrombotic events been reported to Bayer? The physician letter indicates that Jivi's longer half-life and more IUs per vial relative to Kogenate FS "may contribute to increased plasma levels for factor VIII. Elevated plasma levels of factor VIII may be associated with an increased risk of thrombosis, primarily in patients with vascular disease."**

As of August 19, 2019, Bayer has conducted a thorough review of all adverse events (AEs) reported to the company since the release of the affected Kogenate FS 2000 IU lots. To date, Bayer has not received any reports of allergic reactions or new instances of inhibitor formation related to use of affected lots. Whereas the Dear Healthcare Provider letter mentioned a reported case of myocardial infarction, to date, we have not received any other reports of thrombotic events.

Bayer Pharmacovigilance continues to assess all reports for AEs, including reports of bleeds.

Bayer continues to monitor and assess all incoming reports associated with this recall; the company will report cases to the FDA according to the Agency's regulatory requirements. As this evaluation is ongoing, the number of cases being reported is continually changing. We will provide a summary report once our evaluation has been completed.

3. **What is the potential impact for patients who utilize multiple vials for each infusion and may have used both Jivi and Kogenate FS at one time? For example, patients who are prescribed 3000IU of Kogenate may have actually taken 3000IU of Jivi in combination with another 1000IU vial of standard Kogenate. Typically, the two vials would have been mixed and drawn up into**

one syringe for infusion. Are there any known incompatibilities between the two products related to excipients or potential impact on the efficacy of the combined products?

The potential impact of combining a vial of 3000 IU Jivi antihemophilic factor (recombinant) PEGylated-aucl with a vial of Kogenate FS in the same syringe on product properties -- including composition, active pharmaceutical ingredients, and process-related impurities -- is unknown, as this has not been studied.

The following product characteristics are instructive with regards to excipients and the potential impact of combination:

- 1. Kogenate FS and Jivi are formulated using the same excipients. Thus, mixing vials of Jivi and Kogenate FS would not result in patient exposure to new excipients.*
- 2. Jivi 3000 IU contains a smaller quantity of each excipient than Kogenate FS 2000 IU and the potential reduction in excipient concentration is not expected to negatively affect the product.*
- 3. Combining vials of Jivi and Kogenate FS presumably would not result in detachment of the polyethylene glycol (PEG) moiety from Jivi or PEGylation of Kogenate FS, as stability studies done with lyophilized Jivi show no measureable loss in PEG under real-time storage conditions, and forced degradation studies of reconstituted drug product show no measureable loss of PEG over 16 hours at elevated temperature (40°C).*

4. **The physician letter indicated that “one patient who may have taken the suspect vials has reported a myocardial infarction.” This is extremely concerning, especially given the increased risk of thrombosis acknowledged in the letter. We require assurance that you will share more information about this situation and other adverse events as they become available to Bayer.**

The myocardial infarction mentioned in the Dear Healthcare Provider letter was reported by a patient to a specialty pharmacy and this pharmacy reported the case to Bayer in May 2019. This reported case prompted Bayer to attempt to contact the treating physician on numerous occasions prior to the recall, as per standard operating procedures. Following the recall, Bayer has made additional attempts to contact the treating physician. We have not received a response to these attempts therefore many relevant details are missing in this case.


5. **What is Bayer’s plan to monitor and notify the bleeding disorders community about any potential immediate and long-term health consequences that may be associated with the use of the adulterated product? There is considerable and reasonable concern among affected patients and caregivers as well as the broader bleeding disorders community about this situation, which will last beyond the immediate recall.**

We understand the community’s concern and are committed to full and transparent communication on all matters related to the recall issue now and in the future. Bayer monitors and evaluates its products on an ongoing basis for any potential safety signals. Bayer’s Pharmacovigilance division has reviewed all available data and has not detected any new safety signals related to the affected lots. Bayer will inform the community and the FDA of any potential safety signals that emerge through continued monitoring.

Kind regards,



Paul Bedard
Senior Vice President, Specialty Franchise



Juan Nadal, M.D. on behalf of Aleksandra Vljajnic, M.D., MBA
Vice President, U.S. Medical Affairs

Kogenate® FS antihemophilic factor (recombinant)

Indications and Important Safety Information

Indications

Kogenate® FS Antihemophilic Factor (Recombinant) is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A.

Kogenate FS is used to treat and control bleeding in adults and children with hemophilia A. Your healthcare provider may give you Kogenate FS when you have surgery.

Kogenate FS can reduce the number of bleeding episodes in adults and children when used regularly (prophylaxis). Kogenate FS can reduce the risk of joint damage in children without pre-existing joint damage when used regularly.

Kogenate FS is not used to treat von Willebrand disease.

Important Safety Information

You should not use Kogenate FS if you are allergic to rodents (like mice and hamsters) or are allergic to any ingredients in Kogenate FS.

Tell your healthcare provider if you have been told you have heart disease or are at risk for heart disease.

You could have an allergic reaction to Kogenate FS. Call your healthcare provider right away and stop treatment if you get rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headed, dizziness, nausea or a decrease in blood pressure.

Your body can make antibodies, called “inhibitors,” against Kogenate FS, which may stop Kogenate FS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

Other common side effects of Kogenate FS are local injection site reactions (pain, swelling, irritation at infusion site) and infections from implanted injection device. Tell your healthcare provider about any side effect that bothers you or does not go away.

Call your healthcare provider right away if bleeding is not controlled after using Kogenate FS.

For important risk and use information, please see [full prescribing information](#).

Jivi® antihemophilic factor (recombinant) PEGylated-aucl

Indications and Important Safety Information

INDICATIONS

- Jivi is an injectable medicine used to replace clotting factor (Factor VIII or antihemophilic factor) that is missing in people with hemophilia A.
- Jivi is used to treat and control bleeding in previously treated adults and adolescents (12 years of age and older) with hemophilia A. Your healthcare provider may also give you Jivi when you have surgery. Jivi can reduce the number of bleeding episodes in adults and adolescents with hemophilia A when used regularly (prophylaxis).
- Jivi is not for use in children below 12 years of age or in previously untreated patients.
- Jivi is not used to treat von Willebrand disease.

IMPORTANT SAFETY INFORMATION

- You should not use Jivi if you are allergic to rodents (like mice and hamsters) or to any ingredients in Jivi.

- Tell your healthcare provider about all of your medical conditions that you have or had.
- Tell your healthcare provider if you have been told that you have inhibitors to Factor VIII.
- Allergic reactions may occur with Jivi. Call your healthcare provider right away and stop treatment if you get tightness of the chest or throat, dizziness, decrease in blood pressure, or nausea.
- Allergic reactions to polyethylene glycol (PEG), a component of Jivi, are possible.
- Your body can also make antibodies, called “inhibitors,” against Jivi, which may stop Jivi from working properly. Consult your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to Factor VIII.
- If your bleeding is not being controlled with your usual dose of Jivi, consult your doctor immediately. You may have developed Factor VIII inhibitors or antibodies to PEG and your doctor may carry out tests to confirm this.
- The common side effects of Jivi are headache, cough, nausea, and fever.
- These are not all the possible side effects with Jivi. Tell your healthcare provider about any side effect that bothers you or that does not go away.

For additional important risk and use information, please see full [Prescribing Information](#).