



March 5, 2020

Dear Dr. Valentino and Ms. Meyers,

Thank you for reaching out to us regarding our decision to take back two specific lots of VONVENDI. You had a list of questions for us, and we have provided answers below. I would like to emphasize that we take your concerns seriously, we realize the importance of these medicines to the patient community, and we value any continued dialogue.

1. Please describe in chronological order the circumstances that occasioned the recall. i.e.,

- a. What was the date on which the affected lots were manufactured?**
- b. What was the date on which Takeda identified an issue with the affected lots?**
- c. On what date did Takeda send the affected lots to wholesalers or to other parts of the distribution channel?**

Here is a rough timeline of events that have occurred so far, from the time these lots were manufactured to now:

- **May 2019:** Each batch of VONVENDI (a batch is a quantity of vials produced at one time) is assigned a unique lot number to track its distribution following the completion of the manufacturing process. These two lots, numbered TVA19005AA and TVA19005AB, completed production in May of 2019.

These lots were manufactured following our standard process and were thoroughly tested and met all requirements to be distributed to patients, meaning they passed our standards for quality and safety.

- **July-December 2019:** These batches of VONVENDI were sent to pharmacies to be distributed to patients as needed. The treated patient population for Von Willebrand disease is small relative to the larger bleeding disorders community; therefore, these two lots of VONVENDI were distributed over a period of several months.
- **August 2019:** Takeda has rigorous procedures in place that ensure we are checking every step of our manufacturing methods. As part of routine activities at our manufacturing sites, we periodically test our processes. During a test in August, we observed that one step did not proceed as expected. We assessed this situation thoroughly and determined that there was no impact to these two VONVENDI lots, meaning they were manufactured properly. Takeda maintains a close working relationship with the FDA, and as part of our process we informed them of this observation.
- **January 2020:** Every two years the FDA conducts on-site inspections of pharmaceutical manufacturing sites as part of their efforts to support patients in the US. During their routine inspection of the VONVENDI manufacturing site in January, the FDA inspector reviewed the test of our process that was performed in August. The inspector provided feedback on how we could improve our approach. Consequently, Takeda decided to pull back any VONVENDI vials that had not been distributed from these two lots.



Our safety and quality testing demonstrated that these VONVENDI batches were safe for patient use. Therefore, they didn't meet the criteria for a patient-level recall, which would be used if the product could pose a risk to patients. As a result, we only asked pharmacies to return their medicine, and we did not ask patients to return their VONVENDI doses.

- **February 2020:** We shared our decision with the FDA, and after confirming our communications with the FDA, announced this action on February 25, 2020. No distribution of these VONVENDI lots has occurred since the decision to take them back from pharmacies was made.

2. Have any of the affected lots reached consumers?

Yes. Some medicine from these VONVENDI lots has reached consumers. Although there is no requirement for patients to return the medicine because it is safe to use, we've heard from you and from patients that they would like the opportunity to return medicine from these lots and have it replaced with medicine from different lots. Takeda is working to inform patients that we will replace any product they have on hand from these lots.

To determine if individual vials of VONVENDI came from these lots, the lot number can be found listed on the side of the VONVENDI vial or carton. If patients need assistance finding the lot number they can also call contact Takeda's Hematology Support Center Team at 888-229-8379, Monday - Friday from 8:30 a.m. to 8:00 p.m. Eastern Time.

For those patients who are concerned that they've already used medicine from these lots, we'd like to reiterate that they passed all safety and quality testing and are safe for use.

3. Takeda states that it "believes" there is no impact on "the sterility, quality, safety and potency" of the recalled product. What is the basis for that belief? The notice on your website says that Takeda has tested the affected product. Please elaborate on the tests conducted and the results of those tests.

Before we send any medicine to patients, we test it thoroughly and perform comprehensive quality assurance checks. These involve testing for sterility, appearance, potency and other aspects to ensure the medicine is effective and safe. The two lots of VONVENDI were produced using our standard process without any issues occurring and passed all testing and quality assurance requirements.

4. Takeda indicated to the FDA that it would conduct a pharmacy-level recall.

a. Please define a "pharmacy-level recall" and why this is an appropriate level of recall in this instance.

A pharmacy-level recall is intended for products that do not meet certain FDA requirements. This means the concerns are not related to safety or quality, but to a range of other issues such as process errors or labeling errors. Because our safety and quality testing demonstrated these doses of VONVENDI were safe for patient use, we decided this was the most appropriate course of action.

b. Does a pharmacy-level recall mean that patients may not be identified and/or notified of the recall?

Although there is no requirement for patients to return medicine because it is safe to use,



we've heard from you and from patients that they would like the opportunity to return medicine from these lots and have it replaced with medicine from different lots. Takeda is working to inform patients that we will replace any product they have on hand from these lots. We are using our website and will be leveraging the Plasma Protein Therapeutics Association (PPTA) Patient Safety Notification System to make patients aware of the situation and to let them know Takeda will replace any product they have on hand from these two lots.

c. How many patients received the affected lots?

VONVENDI is sold through distributors, specialty pharmacies and hemophilia treatment centers (HTCs). The records for individual patients are not shared with the company. We have contacted all of these customers and are in the process of replacing any VONVENDI doses they may have in their possession. We are also informing patients through our website and the Patient Safety Notification system.

d. If patients have received any of the affected lots, how are they supposed to learn of that?

e. How and to whom should patients return the product?

We are informing patients through our website and the Patient Safety Notification system. Although there is no requirement for patients to return medicine from these lots because it is safe to use, we've heard from you and from patients that they would like the opportunity to return medicine from these lots and have it replaced with medicine from different lots. Takeda is working to inform patients that we will replace any medicine they have from these lots.

Patients who have product from the identified lots may contact Takeda's Hematology Support Center Team at 888-229-8379, Monday - Friday from 8:30 a.m. to 8:00 p.m. Eastern Time.

To determine if individual doses of VONVENDI come from these lots, the lot number can be found listed on the side of the VONVENDI vial or carton. If patients need assistance finding their lot number, they can call Takeda's Hematology Support Center Team.

f. Can Takeda accurately and definitively track who and where the affected product was distributed?

Yes. Takeda knows exactly which specialty pharmacies, distributors, wholesalers and hemophilia treatment centers have received product. We are working with these customers directly to replace product and support patients who would like to do the same.

5. Have all specialty pharmacies been notified? Have pharmacies been provided with instructions on how and where to return affected product?

Yes, Takeda has notified all customers who have received affected product. We have provided them instructions and materials to return product.

6. Have all affected products been returned to Takeda? If not, in what timeframe do you expect that this will occur?

No, we are in the process of replacing all unused product from these two lots. Recall mailings, including instructions to return product, have been sent to all customers that received these two lots of VONVENDI. Takeda will closely monitor all returns and expects that they will be received



in the coming days.

7. **Does Takeda intend to inform PPTA's Patient Safety Notification System of the recall?**
Yes, at the request of the NHF and HFA, we are working actively with the PPTA and will be immediately leveraging their safety notification system for Von Willebrand Disease patients.
8. **Have any adverse events (including breakthrough bleeding) been reported to Takeda?**
There have been no reported adverse events, including breakthrough bleeding, submitted to Takeda for these two lots. Takeda will continue to monitor all reports of adverse events for VONVENDI.

Over the course of the last several weeks we've been in close contact with physicians and patients as well as your organizations. We understand your concerns and apologize for any alarm and confusion that this situation may have caused the bleeding disorders community. We understand how important these medicines are to patients' health, and we are committed to providing products and service of the highest standards.

If you would like to contact us or have any additional questions or concerns, please don't hesitate to contact me directly. Patients in your community may reach out to Takeda's Hematology Support Center Team at 888-229-8379, Monday - Friday from 8:30 a.m. to 8:00 p.m. Eastern Time.

Sincerely,

A handwritten signature in blue ink that reads "Ramona Sequeira".

Ramona Sequeira
President, US Business Unit