September 27, 2019
Bayer Pharmacovigilance Summary
Kogenate FS Recall Safety Assessment

Background
On July 19, 2019, Bayer voluntarily recalled two lots of Kogenate® FS antihemophilic factor (recombinant) 2000 IU vials in the United States to the patient level. Certain vials from these two lots that were labeled as Kogenate FS actually contained the FVIII hemophilia A treatment, Jivi® antihemophilic factor (recombinant) PEGylated-aucl 3000 IU. The U.S. is the only country where affected products were distributed. The affected lots (27118RK and 27119CG) were distributed from February 5, 2019 to July 15, 2019 from Bayer's distribution sites in Berkeley, CA and Shawnee, KS.

A total of 10,678 vials of the two recalled lots of Kogenate FS (#27118RK and #27119CG) were distributed, of which 986 were mislabeled as Jivi. Bayer voluntarily recalled both lots in their entirety in the interest of patient safety, and to ensure that any potentially impacted product was removed from the market and that patients and their healthcare providers were alerted. Importantly, vials of Kogenate FS that were not associated with the affected lot numbers (27118RK and 27119CG) were not impacted and could continue to be used without interruption. There were no lots of Jivi or Kovaltry® antihemophilic factor (recombinant) product affected by this recall.

Bayer Pharmacovigilance Analysis
As a result of the labeling mix-up leading to the recall, on July 18, 2019 Bayer Pharmacovigilance performed a safety assessment for all cases reported between January 31, 2019 and July 17, 2019, consistent with the potential dissemination period of the affected batches. One case report was found in this review of data received up until the recall decision that could potentially be related to the affected batches. This case was reporting a myocardial infarction (MI) reported by a patient to a specialty pharmacy and this pharmacy reported the case to Bayer in May 2019. This report prompted Bayer Pharmacovigilance to contact the treating physician. Attempts were made to obtain additional information from the treating physician about this event, including any confirmation of the MI, as per standard operating procedures. Unfortunately, no such information was received. Following commencement of the recall, Bayer made additional attempts to contact the treating physician, both by phone and registered mail. Despite numerous follow-up attempts, no medical confirmation of the myocardial infarction or any other medical history has been obtained from the treating physician.

In addition to the routine monitoring process for all hemophilia products, Bayer Pharmacovigilance has conducted a thorough review of all adverse events reported to the company since the initiation of the product recall through the first two weeks of September.
Since initiation of the recall, Bayer has received 61 reports of patients who state that they received vials from recalled Kogenate FS lots. This is in addition to the one case report identified at the time of the recall decision. Of this number, 43 reported no adverse events. Of these, 5 were reports of patients under the age of 12 years, also with no adverse events reported. There were 9 cases reporting bleeding events of which 7 were spontaneous bleeding events, 1 was a traumatic bleed and 1 was procedure related. Upon analysis, these events appear to be most likely due to the underlying disease state. All other cases described adverse events that are typically not related to Factor VIII replacement therapy.

It should be noted, that in all cases mentioned above, it is unknown if the actual product administered was Kogenate FS or the mislabeled product Jivi.

There have been no reports of allergic or hypersensitivity reactions or new instances of inhibitor formation related to the use of affected lots. Other than the one reported case of medically unconfirmed myocardial infarction referenced above, Bayer has not received any other reports of thrombotic events.

Bayer continues to monitor and assess all incoming adverse event reports associated with this product and will continue to report all adverse event cases to the FDA according to FDA regulatory requirements.

Description of Pharmacovigilance Case Report Analysis Process
The Bayer Pharmacovigilance department receives safety information, including adverse events, from a variety of sources, including patients, health care professionals, clinical trial data, the medical information call center, specialty pharmacies, sales representatives and literature searches, each of which has the potential to create an individual safety case. Each case is entered into the Bayer safety database and processed by a qualified and highly trained pharmacovigilance professional following comprehensive internal procedures, which are in line with the US FDA regulations.

Assessment typically includes the following:

- References for administration and identification purposes, including who reported the information
- Characteristics of the patient concerned

- Description of the adverse events (onset dates, treatment, outcome)
- Results of clinical tests and procedures
- Relevant medical history and concomitant medications
- Characteristics (dosing information, indication, route of administration, lot number and expiration date) of the medicinal product in question
- Narrative style summary of the case
- Causality Assessment – whether or not an adverse drug reaction is suspected due to the administered product based on the following considerations:
    - The chronology or association in time (or place) between drug administration and the adverse event
    - Current knowledge of the nature and frequency of the adverse reaction due to the suspect molecule; or the pharmacology
    - Medical or pharmacologic plausibility based on signs and symptoms, laboratory tests, pathological findings, and mechanism of action
- Likelihood or exclusion of other causes for the same adverse events; often the underlying disease condition, concurrent conditions/co-morbidities or concomitant medication. If information is missing from the initial safety report and is needed to complete the assessment of the case, Pharmacovigilance will follow up with the patient's treating physician via phone calls and/or letters to obtain the necessary information, such as lab tests, medical confirmation of the reported adverse event(s), outcome, causal relationship between the product and adverse event(s), etc. If we don't have the name of the treating physician, we will follow up with the patient (or reporter of the safety report) to try to obtain this information. Several follow-up attempts may be made in order to try to obtain this additional information to complete the assessment of the case.

Cases are reported to the FDA and other health authorities either as an expedited report or as part of an aggregate report, based upon pharmacovigilance policies, health authority regulations, and regulatory agency guidance documents.

Each case becomes part of Bayer's safety dataset for that medicinal product. Aggregate data are systematically analyzed by our Benefit Risk Management organization for safety issues and assessed for benefit versus risk on an ongoing basis throughout the product's life cycle. Safety findings are addressed in order to mitigate risk. This may include changes in proposed labeling or implementation of a risk mitigation plan.