Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
From:	Graça Dores, MD, MPH Medical Officer, Analytic Epidemiology Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Bayer Healthcare, Inc
Product:	JIVI (Antihemophilic Factor (Recombinant), PEGylated-aucl)
STN:	125661/399
Indication:	Indicated for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for: (1) On-demand treatment and control of bleeding episodes; (2) Perioperative management of bleeding (3) Routine prophylaxis to reduce the frequency of bleeding episodes Limitation of Use: JIVI is not indicated for use in children <12 years of age, previously untreated patients, and treatment of von Willebrand disease.
Meeting Date:	Pediatric Advisory Committee Meeting, April 2021

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1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the initial approval of BLA 125661/0 for JIVI on August 29, 2018 in adults and adolescents (12 years of age and older) with Hemophilia A (congenital Factor VIII (FVIII) deficiency).

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

JIVI, damoctocog alpha pegol (BAY 94-9027) is a pegylated (PEG) 60 kDa (two 30 kDa PEG), B-domain deleted (BDD), recombinant (r) coagulation factor VIII (FVIII) conjugated protein. Prior to conjugation, the active protein is a rBDD human coagulation FVIII produced by recombinant DNA technology in baby hamster kidney (BHK) cells. There is no addition of any human- or animal-derived protein in the cell culture, purification, or pegylation processes used in the formulation of JIVI.

1.3 Regulatory History

JIVI was approved in the U.S. on August 29, 2018 for use in adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for: (1) On-demand treatment and control of bleeding episodes; (2) Perioperative management of bleeding; (3) Routine prophylaxis to reduce the frequency of bleeding episodes. JIVI was approved in Japan on September 21, 2018, in Canada on October 18, 2018, and by the European Medicines Agency (EMA) on November 22, 2018. JIVI has gained subsequent additional regulatory approvals worldwide.

2 MATERIALS REVIEWED

- FDA Adverse Event Reporting System (FAERS)
    - FAERS reports for JIVI during August 29, 2018 to September 30, 2020 (PAC review period)
- Manufacturer's Submissions
    - JIVI US package insert, dated 08/2018
    - Sponsor response to information request regarding dose distribution data, received November 2, 2020
    - Pharmacovigilance Plan, submitted July 25, 2018

    - All Periodic Adverse Drug Experience Reports (PADERs) and Periodic Benefit-Risk Evaluation Reports (PBRERs) included within PADERs covering the period since product approval (August 29, 2018) through September 25, 2020
- FDA Documents
    - JIVI Approval Letter for BLA 125661/0, dated August 29, 2018
    - Division of Epidemiology Pharmacovigilance Plan Review Memorandum for STN 125661/0
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for JIVI since licensure.

4 PRODUCT UTILIZATION DATA

Bayer Healthcare, Inc provided distribution data for the US and worldwide for the time interval August 29, 2018 to September 30, 2020, as specified in Table 1.

These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and **requires redaction** from this review.

Table 1: Distribution data for JIVI during August 29, 2018 to September 30, 2020

Geographic area	Distribution (IU) by Age group		PY of exposure[1]	
	12 to <18 years	≥18 years	12 to <18 years	≥18 years
US	(b) (4)			
Worldwide				

Abbreviations: IU, international units; PY, person-years.

[1] Patient-years of exposure = International units sold/annual dose per patient. The average annual dose per patient is based on the clinical trial data for patients ≥12 years where a mean annual consumption of 3,391.8 IU/kilogram was observed. Mean person-years of exposure is based on an average weight of 50 kilograms (patients 12 to <18 years of age) or 80 kilograms (patients ≥18 years of age). Person-years represents the estimated number of patients treated for an average of one year.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) for JIVI was submitted July 25, 2018. Table 2 describes the important identified risks, important potential risks, and missing information for JIVI.

The identified risk of development of FVIII inhibitors listed in Table 2 is common to this product class (class effect) and is a labeled AE for JIVI (US Product Information (USPI) section 5.2, Warnings and Precautions - Neutralizing antibodies). Closely related to this event is the development of anti-PEG antibodies that, similar to FVIII inhibitors, also result in lack of drug effect. Development of anti-PEG antibodies is related to the

composition of JIVI (PEG moiety) and is a labeled event (USPI section 5.3, Warnings and Precautions – Immune response to PEG). Hypersensitivity is an important identified risk that is common to the FVIII product class (recombinant or plasma-derived) and is a labeled event (USPI section 5.1, Warnings and Precautions – Hypersensitivity Reactions). In addition, hypersensitivity may arise due to an immune response to PEG.

Table 2: JIVI Safety Concerns and Planned Pharmacovigilance Actions[1]

Important Identified Risks	**Planned Pharmacovigilance Actions**
Development of FVIII inhibitors	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Loss of drug effect) **Additional pharmacovigilance activities** • Interventional post-marketing study to assess safety and efficacy of BAY 94-9027 • EUHASS registry
Hypersensitivity	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Hypersensitivity) **Additional pharmacovigilance activities** • Interventional post-marketing study to assess safety and efficacy of BAY 94-9027 • EUHASS registry
Clinical response characterized by lack of drug effect associated with anti-PEG antibodies	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Loss of drug effect) **Additional pharmacovigilance activities** • Interventional post-marketing study to assess safety and efficacy of BAY 94-9027
Missing Information	**Planned Pharmacovigilance Actions**
Potential long-term PEG-related adverse reactions	**Routine pharmacovigilance** • Follow-up questionnaire for adverse reactions (Renal Impairment) **Additional pharmacovigilance activities** • EUHASS registry
Use in patients with severe hepatic impairment	**Routine pharmacovigilance**
Use in patients with severe renal impairment	**Routine pharmacovigilance**
Use in elderly patients >65 years of age	**Routine pharmacovigilance**

Abbreviations: EUHASS, European Haemophilia Safety Surveillance System.
[1] There were no important potential risks identified; therefore, this category is excluded from the table.

These important identified risks will be monitored with routine safety surveillance (and questionnaires for selected AEs), including review of AE reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining.

5.2 Postmarketing studies

There are no postmarketing requirement (PMR) safety studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for JIVI; however, the sponsor is conducting a postmarketing study to assess the safety and efficacy of BAY 94-9027. This study is an ongoing phase IV, interventional, open label, non-controlled study of previously treated male patients ≥12 years of age with severe hemophilia A with a target of reaching a total of 200 patients achieving 100 exposure days (EDs) based on prior agreement with the EMA that a total of 200 patients need to complete 100 EDs. The sponsor is also submitting AE reports to The European Haemophilia Safety Surveillance System (EUHASS), an AE reporting system for Europe that involves prospective AE reporting in patients with hemophilia A and other rare inherited bleeding disorders.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for AE reports following the use of JIVI between August 29, 2018 (PAC trigger) to September 30, 2020. FAERS stores postmarketing AE and medication error reports submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every AE or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of AE reports for JIVI during the PAC review period are listed in Table 3. There were 48 US and 9 foreign reports for review period, August 29, 2018 to September 30, 2020.

Table 3: FAERS Reports for JIVI during August 29, 2018 to September 30, 2020 (PAC review period)[1]

Age	Serious non-fatal, US[2]	Serious Non-fatal, Foreign[2]	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	2	3	0	0	5	0	7	3
<12 years	0	0	0	0	3	0	3	0
12 to <18 years	2	3	0	0	2	0	4	3
≥18 years	22	3	0	1	8	0	30	4
Unknown	6	1	0	0	5	1	11	2
All ages	30	7	0	1	18	1	48	9

[1] Based on initial FDA received date.
[2] Serious non-fatal AEs include otherwise medically important conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.

6.2.1 Deaths

There was one death following JIVI during the PAC review period (foreign report). The fatal report was reviewed and is summarized below.

- A 57-year-old male with hemophilia (not further specified) on anti-retroviral therapy for human immunodeficiency virus infection, with a history of hepatitis, and longstanding thrombocytopenia had been previously treated with another FVIII product. In December 2019, approximately one month prior to his death, the patient started JIVI. The patient did not have optimal self-care habits (e.g., poor diet, lack of exercise). In late December 2019, the patient experienced upper abdominal pain radiating to his back, and he was evaluated at a health care facility. He was sent home from the facility and returned the next day in cardiopulmonary arrest and died. On autopsy, the cause of death was reported as gallbladder rupture and hemoperitoneum.

  Reviewer assessment: The underlying cause of death (gallbladder rupture) seems unlikely to be causally related to FVIII therapy (JIVI or prior FVIII product), and the switch in FVIII products prior to the patient's death is likely an incidental finding. In the setting of a ruptured gallbladder, hemoperitoneum would not be unexpected, although the latter also would have been influenced by the patient's FVIII level at the time of the incident. The presence of hemoperitoneum is confounded by the patient's underlying hemophilia and possible suboptimal compliance with FVIII therapy (as suggested in the report with respect to poor self-care) that may have resulted in a subtherapeutic FVIII level. While bleeding is included in the JIVI USPI and is confounded by indication for therapy, gallbladder rupture is not a labeled event.

6.2.2 Serious, Non-fatal Reports

During the PAC review period, there were 37 serious, non-fatal reports; 5 of which involved pediatric patients. The most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for all serious non-fatal reports (with a frequency of >2 reports) are summarized in Table 4.

Table 4: Top preferred terms (PTs) for serious, non-fatal reports

Preferred Term (PT)	Number of Serious Reports	Label[1] Status
Hemarthrosis[2]	16	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Hemorrhage[2]	10	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Spontaneous hemorrhage[2]	3	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Joint injury	3	Not labeled

[1] Label dated 08/2018 (and section(s), if applicable). Includes label sections with PT and related terms (e.g., hemarthrosis, hemorrhage, and bleeding are considered related terms). Label sections include: 1 (Indications and Usage), 2.1 (Dose), 5.2 (Neutralizing Antibodies), 5.4 (Monitoring Laboratory Tests), 14 (Clinical Studies), and 17 (Patient Counseling Information).
[2] PT represents an AE that is confounded by indication for use (also reflected in label status).

Most reported MedDRA PTs are labeled events. The PTs “hemarthrosis,” “hemorrhage,” and “spontaneous hemorrhage” are related terms and confounded by indication for treatment. Joint injury (often associated with accidental injury or trauma) is often included in AE reports due to this event precipitating hemarthrosis or hemorrhage and is not typically an AE causally associated with FVIII therapy.

The 5 (2 US and 3 foreign) serious, non-fatal AE reports describing children are summarized below. Three reports describe hypersensitivity reactions; one of which was associated with anti-PEG antibodies. Immune response to PEG can manifest with symptoms of hypersensitivity and/or loss of drug effect. Two other reports describe episodes of bleeding/hemarthrosis. The AEs of hypersensitivity, anti-PEG antibodies, and bleeding/hemarthrosis are included on the USPI.

- 16-year-old male was found to have a suboptimal rise in FVIII level when measured 30 minutes after JIVI infusion. There was suspicion of anti-PEG (anti-drug) antibodies. After <20 EDs, the patient experienced hemarthrosis and was switched back to his prior FVIII product. JIVI was discontinued. While the report indicates that anti-PEG antibodies should be measured, it is uncertain whether this testing was done, and no anti-PEG antibody results are provided.

- 12-year-old male experienced a hypersensitivity reaction after the fourth exposure to JIVI which was characterized by tachycardia, increased blood pressure, and dizziness. Signs and symptoms resolved spontaneously. Upon re-administration of JIVI the patient had no symptoms but had a minimal increase in FVIII level and a rapid decline in FVIII level after infusion. The patient was

switched back to his prior FVIII product. Subsequent results of testing revealed the presence of anti-PEG-(IgM) antibodies.

- 15-year-old male experienced a mild allergic reaction after 4 doses of JIVI characterized by mydriasis, malaise, feeling abnormal, feeling hot, ocular hyperemia and rash. JIVI was discontinued.
- 14-year-old male sustained a hip fracture and required an increase in dose/frequency of JIVI. He later sustained elbow trauma and required additional JIVI to control bleeding.
- 15-year-old male experienced hemarthroses of the knee requiring additional JIVI to control symptoms.

6.2.3 Non-serious Reports

During the reporting period, there were 19 non-serious reports; 5 of which involve pediatric patients (5 US and 0 foreign). The top PTs for non-serious reports are summarized in Table 5. No other PTs appear in more than 2 reports.

Table 5: Top preferred terms (PTs) for non-serious reports, all ages

Preferred Term (PT)	Number of Non-serious Reports	Label[1] Status
Product administered to patient of inappropriate age	4	Labeled (1, 8.4, 17)
Off label use	4	Not labeled (by definition)
Limb injury	3	Not labeled

[1] Label dated 08/2018 (and section(s), if applicable). Includes label sections with PT and related terms. Label sections include: 1 (Indications and Usage), 8.4 (Pediatric Use), and 17 (Patient Counseling Information).

Among reports with specified patient age, pediatric non-serious reports appearing in more than 2 reports include the PTs product administered to patient of inappropriate age (n=3) and off label use (n=3).

The PTs “product administered to patient of inappropriate age” and “off label use” describe events in patients 11 (n=2) and 1.8 (n=1) years of age, and one report (n=1) describes these events in a patient of unspecified age. These PTs relate to the age-specific indication of JIVI that is intended for use in individuals 12 years of age or older. These reports did not describe any other AE.

The PT “limb injury” describes accidents (trauma) that resulted in limb injury or contusion, of which one report specified use of an additional dose of JIVI. In none of the accidental injuries was JIVI causally implicated in the injury.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of JIVI were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure (August 29, 2018) through the data lock point (September 30, 2020) for the data mining analysis of October 19, 2020. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified the preferred terms (PTs) summarized in Table 6, with a disproportional reporting alert. The overall analysis (all ages) was adjusted for FDA year, gender, and 11 age groups; the age-stratified analyses were adjusted for FDA year, gender, and 4 age groups. Note that a report may have one or more PTs. (Disproportional reporting alert is defined as an EB05 $\geq$2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 6: Data mining results with data lock point of September 30, 2020

Age group[1] and Preferred Term (PT) with EB05 $\geq$2	**Number of Reports**	**Label[2] Status**
All ages		
Hemarthrosis[3]	12	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Hemorrhage[3]	8	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Limb injury	4	Not labeled
Product administered to patient of inappropriate age	4	Labeled (1, 8.4, 17)
Spontaneous hemorrhage[3]	3	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
<12 years		
Product administered to patient of inappropriate age	3	Labeled (1, 8.4, 17)
12 to <18 years		
Hemarthrosis[3]	2	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
<18 years		
Product administered to patient of inappropriate age	3	Labeled (1, 8.4, 17)
$\geq$18 years		
Hemarthrosis[3]	10	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Hemorrhage[3]	6	Labeled (1, 2.1, 5.2, 5.4, 14, 17)
Limb injury	4	Not labeled
Spontaneous hemorrhage[2]	3	Labeled (1, 2.1, 5.2, 5.4, 14, 17)

[1] Age groups are not mutually exclusive (i.e., reports specifying a patient age that is <18 years are included in one of two age groups: "<12 years" or "12 to <18 years"; both of these age groups are also included within the "<18 years" age group analysis). These age groups reflect important considerations related to the product indication for use (<12 vs. $\geq$12 years) and those relevant to the Pediatric Advisory Committee (<18 years vs. $\geq$18 years).

[2] Label dated 08/2018 (and section(s), if applicable). Includes label sections with PT and related terms (e.g., hemarthrosis, hemorrhage, and bleeding are considered related terms). Label sections include: 1

(Indications and Usage), 2.1 (Dose), 5.2 (Neutralizing Antibodies), 5.4 (Monitoring Laboratory Tests), 8.4 (Pediatric Use), 14 (Clinical Studies), and 17 (Patient Counseling Information).
[3] PT represents an adverse event that is confounded by indication for use (also reflected in label status).

Except for the PT "limb injury", the remaining MedDRA PTs identified in overall and age-stratified data mining analyses are labeled events. The PTs "hemarthrosis," "hemorrhage," and "spontaneous hemorrhage" are related terms and confounded by indication for treatment. Joint injury is often included in AE reports due to this event (often associated with accidental injury or trauma) resulting in subsequent hemarthrosis or hemorrhage. Joint injury, *per se,* is typically not an AE causally associated with FVIII therapy. The PT "product administered to patient of inappropriate age" reflects the age-specific indication for JIVI (indicated for individuals 12 years of age or older).

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for JIVI were reviewed. The AEs reported were consistent with those seen in FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on [November 9, 2020], for peer-reviewed literature, with the search term "JIVI" and "SAFETY" and dates from licensure (August 29, 2018) to date of search (November 9, 2020), retrieved one publication pertaining to safety. No new safety concerns for JIVI were identified in the review of this publication summarized in Table 7. The results described in the publication were previously reviewed by FDA as part of the JIVI BLA (125661/0) submission.

Table 7. Literature review of JIVI and safety

Publication	Authors' Safety Conclusion
Ivens IA, Banczyk D, Gutberlet K et al. Nonclinical Safety Assessment of a Long Acting Recombinant PEGylated Factor Eight (BAY 94-9027) With a 60 kDa PEG. Toxicol Pathol. 2019 Jul;47(5):585-597.	This nonclinical toxicology safety study of JIVI included a 2-week intravenous infusion in rats and rabbits (doses 75, 750, or 2250 IU/kg administered every other day), juvenile toxicity study in rats, and 26-week chronic study in rats. There was no PEG detected in choroid plexus or other areas of the brain, cerebrospinal fluid, or in spleen or kidneys. No findings related to PEG-60-Mal-Cys were observed. No safety findings were identified in these short- and long-term animal studies.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance AE reports, the sponsor's periodic safety reports, and the published literature for JIVI does not indicate

any new safety concerns. The PAC review was initiated due to initial approval of JIVI in adults and adolescents (12 years of age and older) on August 29, 2018. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of JIVI.