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 Product Safety, Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE)
From:	Kerry Welsh, MD Medical Officer, Analytic Epidemiology Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Bayer HealthCare, LLC
Product:	KOVALTRY (antihemophilic factor (recombinant))
STN:	125574/394
Indication:	Indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes KOVALTRY is not indicated for the treatment of von Willebrand disease.
Meeting Date:	Pediatric Advisory Committee Meeting, April 2020

Contents

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 125574/0 for KOVALTRY on March 16, 2016 in adults and children with hemophilia A (congenital Factor VIII 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

Kovaltry, Antihemophilic Factor (Recombinant), is a recombinant human DNA sequence derived, full length Factor VIII concentrate. Like Kogenate FS, Kovaltry uses sucrose as a stabilizer for the final product and is synthesized in modified baby hamster kidney cells (BHK). However, unlike Kogenate FS, the BHK cell line used in the manufacturing of Kovaltry has been modified to include the gene for human heat shock protein 70 (HSP70(b)(4)).

1.3 Regulatory History

Kovaltry was approved in the U.S. on March 16, 2016 for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Kovaltry is not indicated for the treatment of von Willebrand disease.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
  - FAERS reports for KOVALTRY during March 16, 2016 to August 31, 2019 (PAC review period)
- Manufacturer's Submissions
  - KOVALTRY US package insert, dated March 18, 2016 (STN125574/2.0)
  - Sponsor response to information request regarding dose distribution data, received October 30, 2019 (STN125574/394.1)
  - Pharmacovigilance Plan, dated January 23, 2015 (STN125574/0.1)

    - Request for PMC extension, dated March 16, 2018 (STN125574/357)
    - Response to Information Request (PMC), dated October 25, 2019 (STN125574/357.2)
    - Periodic safety reports
- FDA Documents
    - KOVALTRY Approval Letter for BLA 125574/0, dated March 16, 2016
    - Division of Epidemiology Pharmacovigilance Plan Review Memorandum for STN 125574/0, dated December 7, 2015
    - Extension of Postmarketing Commitments Memo for STN125574/357, dated January 2, 2019
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

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

4 PRODUCT UTILIZATION DATA

Bayer HealthCare, LLC provided distribution data for the US and worldwide for time intervals March 16, 2016 to August 31, 2019:

Patient Age Group	U.S. Distribution Data (IU)	Worldwide Distribution Data (IU)
< 18 years	(b) (4)	
≥ 18 years		
All		

IU = International Unit

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

Prior investigations estimated that previously untreated patients (PUPs) make up 2.58% of the hemophilia A population and previously treated patients (PTPs) comprise 97.4%; the average annual consumption of recombinant FVIII was estimated as 48,600 IU per PUP and 148,700 IU per PTP based on a meta-analysis of recombinant FVIII use in international multi-center prospective trials (1, 2). Based on these rates and the amount distributed in the U.S., the number of patients exposed to Kovaltry in the U.S. from the time of FDA licensure on March 16, 2016 to August 31, 2019 is estimated as (b) (4) PUPs and (b) (4) PTPs for a total of (b) (4) patients.

The estimate of the number of patients is an approximation because all distributed doses may not have been administered to patients. Dose adjustment, baseline FVIII

levels, indication, and off-label use may impact this estimation. Additionally, the calculations of estimated patient use included multiple sources from both U.S. and international data.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) for KOVALTRY is dated January 23, 2015. Table 1 describes the important identified risks, important potential risks, and missing information for KOVALTRY.

Table 1: KOVALTRY Safety Concerns and Planned Pharmacovigilance Actions

Important Identified Risks	**Planned Pharmacovigilance Actions**
1) Development of FVIII inhibitors 2) Hypersensitivity	• Routine pharmacovigilance and cumulative review in each Periodic Benefit-Risk Evaluation Report (PBRER) • Enhanced data collection with targeted follow-up questionnaires to be used in spontaneous cases and in post-marketing studies and clinical trials o Registries/post-authorization safety studies in EUHASS* and PedNet** (study #14149 and study #15689) o Clinical trials (Leopold Kids Part B, Leopold Kids extension, and Leopold IV)
Important Potential Risks	**Planned Pharmacovigilance Actions**
Cardiovascular risk	• Routine pharmacovigilance and cumulative review in each PBRER • Analyses of data from the existing EUHASS registries (post-authorization safety studies)
Missing Information	**Planned Pharmacovigilance Actions**
Not applicable	

* EUHASS: European Haemophilia Safety Surveillance System
**The European Paediatric Network for Haemophilia Management and the PedNet Haemophilia Registry

Development of FVIII inhibitors. Inhibitor (neutralizing) antibody formation is an identified risk, which can result in decreased drug effectiveness. Neutralizing antibodies are also a labeled complication under the Warnings and Precautions (section 5) of the package insert. Additional data on this known safety concern is being collected from postmarketing commitment (PMC) studies; preliminary data on inhibitor development

from these studies is included in the package insert, section 6 Adverse reactions – Immunogenicity. The LEOPOLD Kids Extension Study has 82 patients enrolled, 67 of which have completed the extension study with at least 100 exposure days; there is one inhibitor case of a 13-year-old previously treated patient who developed an inhibitor after 550 exposure days. An interim safety update (dated August 24, 2015) for Part B of the LEOPOLD Kids study, where only previously untreated patients (PUPs) are enrolled, showed that 6 out of 14 PUPs (42.8%) developed inhibitors to FVIII (> 0.6 BU/mL), among whom three (3/14, 21.4%) had high titers (≥ 14 BU/mL) detected at 6, 10, and 37 exposure days; these interim results are included in Section 6.1 of the package insert. This cluster of cases led to a temporary suspension of enrollment in the study. An evaluation by the sponsor did not identify an underlying cause for the observed cluster of inhibitor cases. Enrollment in LEOPOLD Kids part B was resumed in September 2017. In response to an Information Request, dated October 25, 2019, the sponsor provided the following update for this study, which has now completed enrollment: The LEOPOLD Kids Part B study has (b) (4) since the last update provided on November 2, 2018. The data for the LEOPOLD Kids Part B is currently being analyzed and Bayer plans to submit the clinical study report (b) (4).

Hypersensitivity. Kovaltry is contraindicated in patients who have a history of hypersensitivity reactions to the active substance, to any of the excipients, or to mouse or hamster proteins. Hypersensitivity or allergic reactions have been observed after use of Kovaltry and are labeled under Warnings and Precautions (section 5) and Adverse Reactions (section 6) of the package insert.

Cardiovascular risk. Hemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-hemophilic patients when clotting has been normalized by treatment with Factor VIII. Cardiovascular risk is labeled under Warnings and Precautions (section 5) of the package insert.

The identified and potential risks listed in Table 1 are common to this product class and will be monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for KOVALTRY.

5.2 Postmarketing Studies

The two studies listed in the PVP are postmarketing commitments (PMCs) and are listed on the approval letter for Kovaltry. The two PMCs including study milestones are listed below.

PMC#1: “Bayer HealthCare LLC commits to collecting additional safety and efficacy information of KOVALTRY in patients with hemophilia A in a clinical study in 25 previously untreated patients under Protocol 13400 “A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 (KOVALTRY) in children with severe haemophilia A under prophylaxis therapy”

- Final protocol submission: December 20, 2010 (completed)
- Study/Clinical trial completion: February 28, 2019
- Final Report submission: August 31, 2019

Revised dates for PMC #1:

- Study/Clinical trial completion: February 28, 2021
- Final Report submission: August 31, 2021

PMC#2: “Bayer HealthCare LLC commits to collecting additional safety and efficacy information of KOVALTRY in patients with hemophilia A in an extension clinical study under Protocol 13400 “A multicenter Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 (KOVALTRY) in children with severe haemophilia A under prophylaxis therapy”

- Final protocol submission: December 20, 2010 (completed)
- Study/Clinical trial completion: December 31, 2020
- Final Report submission: June 30, 2021

Revised dates for PMC#2:

- Study/Clinical trial completion: December 31, 2022
- Final Report submission: June 30, 2023

On November 16, 2018, the sponsor submitted a request for extension for both PMC #1 and #2 to STN125574/357. The reason for the delay was a cluster of inhibitor development in consecutively newly treated subjects that resulted in cessation of enrollment from December 2016 to September 2017 (please see section 5.1 of memo). The preliminary data on inhibitor development from these studies are in the product label. Due to the safety concern, there was staggered enrollment which did not achieve the same enrollment rate prior to the temporary recruitment halt. The sponsor’s proposed extension dates were considered acceptable according to a product office memo dated January 2, 2019.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of KOVALTRY between March 16, 2016 (PAC trigger) to August 31, 2019. FAERS stores postmarketing adverse events and medication errors 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 adverse event 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 KOVALTRY during the PAC review period are listed in Table 2 below. There were 47 US and 72 foreign reports for review period March 16, 2016 to August 31, 2019.

Table 2: FAERS Reports for KOVALTRY during March 16, 2016 to August 31, 2019 (PAC review period)

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious Foreign	Total, US	Total, Foreign
<18 years	1	23	0	0	5	1	6	24
≥18 years	15	26	1	1	6	1	22	28
Unknown	15	14	0	6‡	4	0	19	20
All ages	31	63	1	7	15	2	47	72

Note: Serious non-fatal adverse events include otherwise medically important conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.
‡One of the six subjects of unknown age has an approximate age of “50s” and another subject has an approximate age of in the “60s” according to the case narratives.

6.2.1 Deaths

There were eight deaths following KOVALTRY during the PAC review period. There were no pediatric deaths. The fatal reports were individually reviewed and are summarized below.

1. An adult patient of unknown age started Kovaltry in August 2017. Death from an unreported cause occurred in November 2017.

2. A male patient in his 60s on Kovaltry experienced hepatitis of an unreported type. The patient died due to progression of hepatitis.

3. A male patient of unknown age on Kovaltry experienced hepatic cirrhosis, which was the reported cause of death.

4. A patient of unknown age receiving Kovaltry and residing in a nursing home died. The cause of death was reported as “natural causes.”

5. A patient of unknown age on Kovaltry died of “natural causes” in a hospital setting.

6. A patient in his 50s receiving Kovaltry died of hepatic cancer.

7. A 64-year-old male patient experienced an out of hospital cardiac arrest. The patient died during hospitalization for the event.

8. An 85-year-old male with a history of cerebral infarction was receiving Kovaltry and experienced cerebral haemorrhage, which was the reported cause of death.

Most death reports contained minimal case details and several patients had other diagnoses that may have contributed to the fatal episodes. The role of Kovaltry and causality assessment was limited by paucity of information provided in these death reports.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 94 serious, non-fatal reports; 24 of which involved pediatric patients. The most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for serious non-fatal reports are summarized in Table 3.

Table 3: Top preferred terms (PTs) for serious non-fatal reports

Preferred Term (PT)	Number of Serious Reports	Label* Status
Haemarthrosis	25	Unlabeled
Haemorrhage	20	Unlabeled
Anti Factor VIII Antibody Positive	10	Labeled (5.2, 6.1)
Arthralgia	6	Unlabeled
Drug Ineffective	6	Unlabeled
Headache	3	Labeled (6, 6.1)
Spontaneous Haemorrhage	5	Unlabeled
Cerebral Haemorrhage	4	Unlabeled
Muscle Haemorrhage	4	Unlabeled
Pain	4	Unlabeled
Traumatic Haemorrhage	4	Unlabeled
Anti Factor VIII Antibody Increased	3	Labeled (5.2, 6.1)
Contusion	3	Unlabeled

Fall	3	Unlabeled
Haemorrhagic Diathesis	3	Unlabeled
Head Injury	3	Unlabeled
Joint Range of Motion Decreased	3	Unlabeled
Joint Swelling	3	Unlabeled
Malaise	3	Unlabeled
Pyrexia	3	Labeled (6, 6.1)
Vomiting	3	Unlabeled

*Label dated 03/2016
Label Sections: 5.2 Neutralizing Antibodies; 6 Adverse Reactions; 6.1 Clinical Trials Experience

All PTs occurring with a frequency >2 reports are shown in Table 3. Most unlabeled PTs are related to typical hemophilia disease complications such as “haemarthrosis”, “haemorrhage”, “arthralgia”, “spontaneous haemorrhage”, “cerebral haemorrhage”, “muscle haemorrhage”, “pain”, “traumatic haemorrhage”, “contusion”, “haemorrhagic diathesis”, “head injury”, “joint range of motion decreased”, and “joint swelling”; as hemophilia is a chronic coagulation disorder that often results in bleeding, these PTs are related to the patient’s underlying condition instead of the administered product. Anti factor VIII antibodies are a labeled complication of all Factor FVIII products. “Drug ineffective” is not an adverse event and may be associated with inhibitory antibody, which is labeled, or other underlying or confounding factors such as inadequate dosing. The PTs “fall”, “malaise”, “pyrexia”, and “vomiting” are non-specific events.

The 24 (1 from the US and 23 foreign) serious non-fatal AEs reported in children are summarized below:

- 19 reports of bleeding episodes and associated complications. Four of the patients in these reports were also reported to have anti-factor VIII antibodies.
- 2 reports of anti-factor VIII antibodies without a concurrent bleeding episode
- The remaining reports described sporadic events of lethargy, vomiting and diarrhea, and appendicitis.

6.2.3 Non-serious Reports

During the reporting period, there were 17 non-serious reports; 6 of which involved pediatric patients (5 US and 1 foreign). The top PTs for non-serious reports include headache and rash. No other PTs appeared in more than 2 reports. Pediatric non-serious reports included headache, abdominal pain, coagulation factor VIII level decreased, therapeutic product ineffective, tension headache, rash, and skin disorder. These PTs were generally similar to those seen with serious reports and each of them only appeared in one or a few reports. Unlabeled AEs/PTs were confounded by concomitant or underlying conditions and/or accompanied labeled AEs and did not raise new safety concerns.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of KOVALTRY were disproportionally reported compared to all products in the FAERS

database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis of October 6, 2019. 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 4, with a disproportional reporting alert. Note that a report may have one or more PTs. (Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 4: Data mining results

Preferred Term (PT) with EB05>2	Number of Reports	Label* Status
Anti factor VIII antibody increased	3	Labeled (5.2, 6.1)
Anti factor VIII antibody positive	12	Labeled (5.2, 6.1)
Haemarthrosis	26	Unlabeled
Haemorrhage	21	Unlabeled
Muscle haemorrhage	4	Unlabeled
Spontaneous haemorrhage	5	Unlabeled

*Label dated 03/2016
Label Sections: 5.2 Neutralizing Antibodies; 6 Adverse Reactions; 6.1 Clinical Trials Experience

Most of these events appeared among the most frequently reported PTs and are discussed in Section 6.2. Anti factor VIII antibodies are a labeled complication of all factor VIII products. The remaining PTs are associated with underlying hemophilia disease, which is a chronic disorder of coagulation that results in episodes of bleeding.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for KOVALTRY were reviewed. The adverse events 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 October 24, 2019, for peer-reviewed literature, with the search term "KOVALTRY" and "SAFETY" limited by human species, and dates from licensure (March 16, 2016) to date of search (October 24, 2019), retrieved six publications pertaining to safety. No new safety concerns for KOVALTRY were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
BAY 81-8973, a full-length recombinant factor VIII: Human heat shock protein 70 improves the manufacturing process without affecting clinical safety Enriquez MM, Thrift J, Garger S, and Katterie Y. *Protein Expression and Purification;* 2016 v127: 111 – 115 doi: 10.1016/j.pep.2016.07.009	This review article discusses the use of human heat shock protein 70 (HSP70) in BAY 81-8973 (Kovaltry). The authors concluded that the use of human HSP70 gene resulted in a cell line with higher yields of expressed FVIII with improved pharmacokinetics. The authors did not identify any safety issues of the product from data collected from the LEOPOLD clinical trial program.
Analysis of the Japanese subgroup in LEOPOLD II: a phase 2/3 study of BAY 81-8973, a new recombinant factor VIII product Fujii T, et al. *Int J Hematol*; 2017 v105: 280 – 285 doi: 10.1007/s12185-016-2133-9	This analysis focused on the Japanese subjects enrolled in LEOPOLD II treated with BAY 81-8973. There were no differences in the safety, efficacy, or pharmacokinetics between Japanese and other subjects. None of the Japanese subjects in this analysis developed inhibitors. The authors concluded the data support the use of the product in Japanese subjects.
BAY 81-8973, a full-length recombinant factor VIII: manufacturing processes and product characteristics Garger S, et al. *Haemophilia*; 2017 v23: e67 – e68 doi: 10.1111/hae.13148	This review article discusses the manufacturing process of BAY 81-8973. The authors conclude the product characterization data show expected protein profiles and posttranslational modifications that may have patient benefits.
BAY 81-8973 safety and efficacy for prophylaxis and treatment of bleeds in previously treated children with severe haemophilia A: results of the LEOPOLD Kids Trial Ljung R, et al. *Haemophilia*; 2016 v22: 354 – 360 doi: 10.1111/hae.12866	This study describes the results of 51 boys aged ≤ 12 years with severe haemophilia A that received prophylaxis with BAY 81-8973. No patient developed FVIII inhibitors. Prophylaxis with BAY 81-8973 reduced bleeds in patients with severe haemophilia and was well-tolerated.
Safety and efficacy of BAY 81-8973 for surgery in previously treated patients with haemophilia A: results of the LEOPOLD clinical trial programme Oldenburg J, et al.	This study reports 11 patients that underwent 13 surgeries and were treated with BAY 81-8973. All surgeries achieved good hemostasis without bleeding related complications.

Publication	Authors' Safety Conclusion
Haemophilia; 2016 v22: 349 – 353 doi: 10.1111/hae.12839	
Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial Saxena K, et al. *Haemophilia*; 2016 v33: 706 – 712 doi: 10.1111/hae.12952	This study included 62 patients that received BAY 81-8973 prophylaxis. The product was effective in preventing and treating bleeding episodes. No inhibitors developed and the authors concluded the safety profile was similar to other recombinant FVIII products.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for KOVALTRY does not indicate any new safety concerns. The PAC review was initiated due to initial approval of KOVALTRY in adults and children on March 16, 2016. There were no pediatric deaths. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of KOVALTRY.

REFERENCES

1. Soucie JM, Evatt B, Jackson D *et al* Occurrence of Hemophilia in the United States *Am J Hem* (1998) 59:288-294
2. Ewenstein BM, Gomperts ED, Pearson S *et al* Inhibitor development in patients receiving recombinant factor VIII (Recombinate rAHF/Bioclate®): a prospective pharmacovigilance study. *Hemophilia* (2004) 10:491-498