



Our STN: BL 125661/0

**BLA APPROVAL**  
August 29, 2018

Bayer Healthcare LLC  
Attention: Michelle Meng, PhD  
100 Bayer Boulevard  
Whippany, NJ 07981

Dear Dr. Meng:

Please refer to your Biologics License Application (BLA) for Antihemophilic Factor (Recombinant), PEGylated-aucl dated August 30, 2017, received August 30, 2017, submitted under section 351(a) of the Public Health Service Act (PHS Act).

## LICENSING

We have approved your BLA for Antihemophilic Factor (Recombinant), PEGylated-aucl effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Antihemophilic Factor (Recombinant), PEGylated-aucl under your existing Department of Health and Human Services U.S. License No. 0008. Antihemophilic Factor (Recombinant), PEGylated-aucl is indicated for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for: on demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01184820, NCT01580293, and NCT01775618.

Under this license, you are approved to manufacture Antihemophilic Factor (Recombinant), PEGylated-aucl at your Bayer Healthcare LLC facility in (b) (4). The diluent, Sterile Water for Injection (sWFI), will be manufactured at (b) (4) and at Bayer (b) (4). You may label your product with the proprietary name JIVI and market it in single-use vials containing nominally 500 international units (IU), 1000 IU, 2000 IU, or 3000 IU of Factor VIII potency per vial.

We did not refer your application to the Food and Drug Administration Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

## DATING PERIOD

The dating period for Antihemophilic Factor (Recombinant), PEGylated-aucl shall be 24 months from the date of manufacture when stored at +2°C to +8°C. During the dating period, the drug product may be stored at temperatures up to +25°C for a single period of up to 6 months, or up to (b) (4) for a single period of 3 months. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4). Within this period, the drug substance may be stored for up to (b) (4) at (b) (4).

### **FDA LOT RELEASE**

You are not currently required to submit samples or protocols of future lots of Antihemophilic Factor (Recombinant), PEGylated-aucl to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

### **BIOLOGICAL PRODUCT DEVIATIONS**

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Document Control Center  
10903 New Hampshire Ave.  
WO71-G112  
Silver Spring, MD 20993-0002

### **MANUFACTURING CHANGES**

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Antihemophilic Factor (Recombinant), PEGylated-aucl, or in the manufacturing facilities.

### **LABELING**

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be

reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft package insert labeling submitted as Amendment 55, dated August 28, 2018 and the draft carton and container labeling submitted as Amendment 51, dated August 9, 2018.

Please provide your final content of labeling including the carton and container labels in Structured Product Labeling (SPL) format. All final labeling should be submitted as Product Correspondence to this BLA 125661 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Document Control Center  
10903 New Hampshire Ave.  
WO71-G112  
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

#### **ADVERSE EVENT REPORTING**

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format – Postmarketing Safety Reports* at

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369.pdf> and FDA's Adverse Event reporting System website <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>.

## **PEDIATRIC REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirements for all relevant pediatric age groups for this application.

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

## **POST APPROVAL FEEDBACK MEETING**

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Wilson W. Bryan, MD  
Director  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research