DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 125566/0 **BLA APPROVAL**

Baxalta US Inc.
Attention: Mr. Erik Bjornson
One Baxter Way
Westlake Village, CA 91362

Dear Mr. Bjornson:

We have approved your biologics license application (BLA) for Antihemophilic Factor (Recombinant), PEGylated effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Antihemophilic Factor (Recombinant), PEGylated under your existing Department of Health and Human Services U.S. License No. 2020. Antihemophilic Factor (Recombinant), PEGylated is indicated in adolescent and adult patients (12 years and older) with hemophilia A (congenital factor VIII deficiency) for (1) on-demand treatment and control of bleeding episodes and (2) routine prophylaxis to reduce the frequency of bleeding episodes.

Under this license, you are approved to manufacture Antihemophilic Factor (Recombinant), PEGylated drug substance at your facilities. The final formulated product will be manufactured and filled at your (b) (4), and labeled and packaged at your facility. You may label your product with the proprietary name ADYNOVATE and will market it in a single-use vial containing nominally 250 international units (IU), 500 IU, 1000 IU, or 2000 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 which would have benefited from an advisory committee discussion.

The dating period for Antihemophilic Factor (Recombinant), PEGylated shall be 24 months from the date of manufacture when stored at +2 °C to +8 °C. During the shelf life, the product may be kept at room temperature (up to 30 °C) for a single period not exceeding one month. After storage at room temperature, the product must be used or discarded, and must not be refrigerated again. 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 when stored at . The expiration date for the packaged product, the lyophilized powder plus solvent, shall be dependent on the shortest expiration date of any component.

You currently are not required to submit samples of future lots of Antihemophilic Factor (Recombinant), PEGylated to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. 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.

You must submit information to your biologics license application 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, or in the manufacturing facilities.

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, packing, 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

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on FDA Form 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 & 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 an FDA Form 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 advertisement 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. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, 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

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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 are deferring submission of your pediatric studies for ages 0 to <12 years for this application because this product is ready for approval for use in adults and adolescents age 12 years and older, and the pediatric studies in patients age 0 to <12 have not been completed.

Three of your deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must

be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

1. Deferred pediatric study under PREA for the on-demand treatment and control of bleeding episodes and routine prophylaxis to reduce the frequency of bleeding episodes in pediatric patients ages 0 to <12 years (A phase 3 prospective, uncontrolled, multi-center study to evaluate PK, efficacy, safety, and immunogenicity of ADYNOVATE in pediatric previously treated patients (PTPs) less than 12 years of age [clinical study 261202]).

   Final Protocol Submission: July 22, 2015
   Study Completion Date: November 15, 2015
   Final Report Submission: June 30, 2016

2. Deferred pediatric study under PREA for the treatment of perioperative management of bleeding in pediatric patients ages two years to less than 17 years (A phase 3, prospective, open label, multi-center study of efficacy and safety of ADYNOVATE in the perioperative management of bleeding in PTPs age 2-75 years [clinical study 261204] – **PEDIATRIC COMPONENT ONLY**).

   Final Protocol Submission: July 22, 2015
   Study Completion Date: March 31, 2017
   Final Report Submission: December 31, 2017

3. Deferred pediatric study under PREA for routine prophylaxis to compare the efficacy and safety of two different pharmacokinetics (PK) guided dosing regimens in pediatric patients ages 12 to < 17 years (A phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of ADYNOVATE following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Hemophilia A [clinical study 261303] - **PEDIATRIC COMPONENT ONLY**).

   Final Protocol Submission: September 08, 2015
   Study Completion Date: December 31, 2018
   Final Report Submission: September 30, 2019

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated **"Required Pediatric Assessment(s)."**

We note that you have fulfilled the pediatric study requirement for ages 12 and older for this application. This product is appropriately labeled for use in ages 12 and older for these indications. Therefore, no additional studies for the indications of on-demand treatment and control of bleeding episodes or routine prophylaxis to reduce the frequency of bleeding episodes are needed in this pediatric group.

Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

AGREED UPON POSTMARKETING COMMITMENTS

We acknowledge your written commitments as described in your letter of October 06, 2015 as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

4. You have committed to conducting "A phase 3, prospective, open label, multi-center study of efficacy and safety of ADYNOVATE in the perioperative management of bleeding in PTPs age 2-75 years" [clinical study 261204] – **ADULT COMPONENT ONLY**.

   Final protocol submission date: July 22, 2015
   Study/trial completion date: March 31, 2017
   Final Report Submission date: December 31, 2017

5. You have committed to conducting "A phase 3b, prospective, open label, and multi-center continuation study of safety and efficacy of ADYNOVATE in the routine prophylaxis of bleeding to reduce the frequency of bleeding episodes in PTPs" age 12 years and above [clinical study 261302].

   Final protocol submission date: July 22, 2015
   Study/trial completion date: December 31, 2017
   Final Report Submission date: September 30, 2018

6. You have committed to conducting "A phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of BAX 855 [ADYNOVATE] following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Hemophilia A" [clinical study 261303] – ADULT COMPONENT ONLY.

   Final protocol submission date: September 08, 2015
   Study/trial completion date: December 31, 2018
   Final Report Submission date: September 30, 2019

7. You have committed to conducting "A phase 3, multi-center, open label study to investigate safety and immunogenicity of ADYNOVATE in previously untreated patients (PUPs)" [clinical study 261203]. This study will evaluate on-demand treatment and control of bleeding episodes in the setting of routine prophylaxis to reduce the frequency of bleeding episodes, as well as the perioperative management of bleeding.

   Final protocol submission date: December 31, 2015
   Study/trial completion date: December 31, 2022
   Final Report Submission date: September 30, 2023

Please submit clinical protocols to your IND 15299, with a cross-reference letter to this BLA, STN BL 125566/0. Submit correspondence, annual reports, and all study final reports to your BLA STN BL 125566/0. If the information in the final study report supports a change in the labeling, the final study report should be submitted as a supplement. We may also request a supplement if we think labeling changes are needed. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment - Protocol**
- **Postmarketing Study Commitment - Correspondence**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement contains Postmarketing Study Commitments – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report an **Annual Status Report of Postmarketing Study Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in the letter,
- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm). Please refer to the February 2006 *Guidance for Industry: Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf) for further information.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals,

complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely,

Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research