SUPPLEMENT APPROVAL
PMR/PMC Fulfilled

December 22, 2016

OUR STN: BL 125566/51

Baxalta US Inc.
Attention: Arwa Shurrab
Associate Director, Regulatory Affairs
One Baxter Way
Westlake, CA 91362

Dear Ms. Shurrab:

We have approved your request dated February 24, 2016, to supplement your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (42 U.S.C. 262) for Antihemophilic Factor (Recombinant), PEGylated [ADYNOVATE], to expand the clinical indication of ADYNOVATE to include on-demand treatment and control of bleeding episodes in children (< 12 years of age), routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children (< 12 years of age), and perioperative management in adults and children.

The review of this supplement was associated with the following National Clinical Trial (NCT) numbers: NCT 01599819, NCT 01736475, NCT 01913405, NCT 01945593, NCT 02210091, NCT 02585960, and NCT 02615691.

We hereby approve the draft package insert labeling submitted under Amendment 20, dated December 22, 2016, and the draft carton and container labeling submitted on February 24, 2016.

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 your BLA, STN 125566, 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 & 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)).

Please submit an amendment to all pending supplemental applications for this BLA that include revised labeling incorporating a revised content of labeling that includes these changes.

FULFILLMENT OF POSTMARKETING REQUIREMENT

This submission fulfills your postmarketing requirements (PMRs) #1 and #2 identified in the November 13, 2015, approval letter for 125566/0. The requirement addressed in this submission is as follows:

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

We remind you that there are still one PMR (#3) and PMCs open:

PEDIATRIC REQUIREMENTS

Deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act

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

AGREED UPON POSTMARKETING COMMITMENTS

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

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 as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of the approval of this BLA until all Requirements and Commitments subject to the reporting requirements of section 506B of the Federal Food, Drug, and Cosmetic Act are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this 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 at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will include information contained in the above-referenced supplement in your BLA file. We recommend that you have a copy of this letter available for review at the time of FDA inspections.

Sincerely,

Wilson W. Bryan, MD
Director (Acting)
Division of Clinical Evaluation and
Pharmacology/Toxicology
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research