Summary Basis for Regulatory Action

Date: 12/23/2016
From: Megha Kaushal, MD, Chair of the Review Committee
BLA/ STN#: 125566/51
Applicant Name: Baxalta
Date of Submission: 2/25/2016
PDUFA Goal Date: 12/25/2016
Proprietary Name/ Established Name: ADYNOVATE
Indication: Indicated in patients with congenital Hemophilia A for:
1) on-demand treatment and control of bleeding episodes and routine prophylaxis to reduce the frequency of bleeding episodes in children
2) perioperative management.
Recommended Action: **Approval** / Non Approval

Signatory Authorities Action:

Offices Signatory Authority:

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Megha Kaushal
Clinical Pharmacology Review	Iftekhar Mahmood
Statistical Review	Judy Li
CMC Review	Ze Peng
Pharmacology/ Toxicology Review	La'Nissa Brown-Baker
Pharmacovigilance/Epidemiology Review	Jane Baumblatt
Bioresearch Monitoring Review	Christine Drabick
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A

1. Introduction

Adynovate was approved in 2015 and is indicated in adolescents and adults with Hemophilia A for on-demand treatment and control of bleeding episodes and routine prophylaxis to reduce the frequency of bleeding episodes.

Baxalta submitted an efficacy supplement in support of the proposed labeling changes to expand the clinical indication to children (<12 years of age) for on-demand treatment and control of bleeding episodes and routine prophylaxis to reduce the frequency of bleeding episodes and for perioperative management. This submission includes and fulfills the postmarketing requirement to submit the final study report for the pediatric study and fulfills the second postmarketing requirement by submitting the interim report from the perioperative study. The revised labeling text incorporates changes based on these studies.

2. Background

ADYNOVATE is a PEGylated full-length recombinant FVIII (rFVIII) product manufactured by modifying the U.S.-licensed rFVIII product, ADVATE, with a 20-kDa branched polyethylene glycol (PEG) reagent. The U.S. licensed rFVIII bulk drug substance (BDS), ADVATE, is produced by recombinant DNA technology from Chinese hamster ovary (CHO) cells. The functional characteristics, *in vitro* potency in standard clotting assays, and the clinical hemostatic activity of ADYNOVATE are consistent with those of other human FVIII products, and enable the formation of a fibrin clot. The elimination half-life of ADYNOVATE is 14.3 hours compared to the half-life of the parent molecule ADVATE which is 10.4 hours. ADYNOVATE exhibits an extended terminal half-life through PEGylation of ADVATE, which reduces its binding to low density lipoprotein receptor-related protein (LRP1), the physiological clearance receptor of FVIII. As a result, ADYNOVATE is longer-acting and was developed for intravenous replacement therapy or prophylaxis on a less frequent basis than ADVATE in adult and adolescent patients with hemophilia A. This submission proposes to expand the current indications to a) on-demand treatment and control of bleeding and routine prophylaxis in children (<12 years of age) and b) for perioperative management in children and adults. The basis to support licensure for the proposed indications for ADYNOVATE are as follows: a) data from a phase 3 prospective uncontrolled multicenter pediatric study to evaluate the PK, efficacy, safety and immunogenicity of ADYNOVATE in 66 pediatric subjects (<12 years of age) to support routine prophylaxis (Study # 261202) b) data from 22 of 66 pediatric subjects who received ADYNOVATE for treatment of breakthrough bleeding episodes to support on-demand treatment and control of bleeding (Study #261202) and c) data from a phase 3 multicenter, open-label study of the efficacy and safety of ADYNOVATE in previously treated patients (PTPs) with severe hemophilia A undergoing surgical or other invasive procedures to support perioperative management (Study # 261204).

This supplemental BLA was reviewed under the PDUFA V program and the review milestones for this BLA are listed as follows:

Milestone	**Date**
Received	February 25, 2016

Filing date	April 7, 2016
Mid-cycle communication	July 21, 2016
Late cycle meeting (external)	Cancelled
Advisory Committee	Waived
Action Due	December 25, 2016

3. Chemistry Manufacturing and Controls (CMC)

ADYNOVATE (Antihemophilic Factor, Recombinant, PEGylated) is an extended half-life recombinant human coagulation factor VIII (Antihemophilic Factor Recombinant; rFVIII) modified with polyethylene glycol (PEG) and expressed in Chinese Hamster Ovary (CHO) cells. The mean number of PEG moieties per rFVIII molecule is (b) (4) ADYNOVATE is manufactured using Baxter's Antihemophilic Factor (Recombinant) which is also the active substance in Baxter's licensed product ADVATE. ADYNOVATE is manufactured by covalently binding a branched PEG reagent with a molecular weight of 20 kDa to ADVATE. No human or animal materials are employed during the manufacturing process of ADYNOVATE.

No new CMC data were submitted with this supplement.

Please refer to the original BLA/SBRA including the CMC Review Memo for further details including Product Quality, CBER Lot Release, Facilities Review and Inspection and Environmental Assessment.

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data were submitted with this supplement. Please see Pharmacology/Toxicology review memo from the original BLA for complete details.

5. Clinical Pharmacology

Study Title: A Phase 3 prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity of ADYNOVATE (pegylated full-length Recombinant FVIII) in previously treated pediatric patients with severe hemophilia A.

This was a Phase 3, prospective, uncontrolled, multi-center, open-label study to investigate pharmacokinetics (PK), hemostatic efficacy, safety, and immunogenicity in at least 60 pediatric previously treated patients (PTPs) with severe hemophilia A. In this study, the PK of ADYNOVATE was also compared with ADVATE. However, this summary describes only the PK assessment of ADYNOVATE.

A total of 31 subjects (14 children <6 years of age (1-5 years) and 17 children 6 -<12 years of age (6-11 years)) were in the PK analysis. There were 21 Caucasians, 5 Asians, 3 African Americans and 2 Hispanics in the study. The subjects received a single infusion of 60 ±5 IU/kg ADYNOVATE. The PK parameters of ADYNOVATE were estimated by sparse blood sampling (4 blood samples (one sample pre-infusion) were taken at different times

from each subject). FVIII activity was measured using a one-stage clotting assay as the primary assay and a chromogenic assay to provide supportive data.

A nonlinear mixed effects model was used to develop a population PK model for ADYNOVATE to estimate individual PK parameters by empirical Bayesian estimates from the model. A 1-compartment model (27 models were tested with different covariates such as age, weight, VWF) was found to be suitable to estimate the PK parameters for both one-stage and chromogenic assay. Non-compartmental analysis was also used to estimate PK parameters. The results are summarized below.

In a one-stage clotting assay, the clearance of ADYNOVATE was approximately 14% higher in children <6 years of age than children 6 to <12 years of age. Volume of distribution at steady state (V_{ss}) of ADYNOVATE was comparable between children <6 and 6 to <12 years of age. Despite sparse sampling, V_{ss} and clearance values of ADYNOVATE were comparable between population and non-compartmental analysis. The half-life and mean residence time (MRT) of ADYNOVATE were 11.8 ± 2.4 and 17.0 ± 3.5 hours, respectively, in children <6 years of age. In children 6 to <12 years of age, half-life and MRT of ADYNOVATE were 12.4 ± 1.7 and 17.8 ± 2.4 hours, respectively. Both half-life and MRT of ADYNOVATE should be interpreted with caution since these parameters were estimated based on sparse sampling.

In the chromogenic assay, the clearance of ADYNOVATE was approximately 15% higher in children <6 years of age than children 6 to <12 years of age. Volume of distribution at steady state of ADYNOVATE was about 15% higher in children <6 years of age than children 6 to <12 years of age. The half-life and mean residence time (MRT) of ADYNOVATE were 13.0 ± 8.7 and 18.7 ± 12.6 hours, respectively in children <6 years of age. In children 6 to <12 years of age, half-life and MRT were 11.9 ± 2.6 and 17.2 ± 3.7 hours, respectively. Both half-life and MRT of ADYNOVATE should be interpreted with caution since these parameters were estimated based on sparse sampling.

Comparison of clearance across age:
The clearance of ADYNOVATE in children <6 years of age, children 6 to <12 years of age, adolescents (12 to <18 years), and adults was 3.53 ± 1.29, 3.11 ± 0.76, 2.73 ± 0.93, and 2.27 ± 0.84 mL/hour per kg, respectively. Compared with adults the clearance of ADYNOVATE in children <6 years of age and children 6 to <12 years of age is 55% and 37% higher, respectively. The higher clearance of ADYNOVATE on per kg body weight basis requires a higher dose of ADYNOVATE in children <12 years of age than in adults.

Dosing Recommendation in Children:
In children 2 to <6 years and 6 to <12 years, the clearance of ADYNOVATE based on per kg body weight is 55% and 37% higher, respectively, than adults. This indicates that children <12 years of age will require higher dose of Adynovate than adults. The applicant, however, suggests a starting dose of Adynovate of 40 IU/kg and a maximum dose of 60 IU/kg in children <12 years of age. The starting adult dose of Adynovate is 40 IU/kg and a maximum dose of 50 IU/kg. This proposal of the applicant is not acceptable in light of the substantial difference in the clearance of Adynovate between adults and children as well as Adynovate

dose given in clinical trials to children <12 years of age. Children 2 to <6 years of age were given an Adynovate dose ranging from 43 IU/kg to 73 IU/kg. Children 6 to <12 years of age received an Adynovate dose ranging from 42 IU/kg to 81 IU/kg. The following Table summarizes the number of subjects receiving different Adynovate doses in clinical trials.

Dose (IU/kg)	Number of subjects	Number of subjects
	2 to <6 years (n= 32)	6 to <12 years (n = 34)
<50	7 (22)	9 (26)
≥50-55	9 (28)	14 (41)
≥60	8 (25)	6 (18)
>55	16 (50)	11 (32)

Based on the clearance of Adynovate in children and a starting dose of 40 IU/kg in adults, a starting dose of 60 IU/kg and 55 IU/kg is projected in children 2 to <6 years and 6 to <12 years of age, respectively. The data in the above Table also indicate that 72% of the children 2 to <6 years of age required an Adynovate dose ≥50 IU/kg of which 50% required a dose >55 IU/kg and 25% required a dose of >60 IU/kg. Similarly, 74% children 6 to <12 years of age required an Adynovate dose ≥50 IU/kg of which 32% required a dose >55 IU/kg and 18% required a dose of >60 IU/kg. Considering these data FDA recommends that:

A starting dose of 55 IU/kg Adynovate be administered to children <12 years of age with a maximum dose of 70 IU/kg twice weekly.

6. Clinical/ Statistical

a) Clinical Program

To support licensure for the proposed indications, the clinical development program for ADYNOVATE included data from a phase 3 prospective uncontrolled multicenter study to evaluate the PK, efficacy, safety and immunogenicity of ADYNOVATE in 66 pediatric subjects (<12 years of age) to support routine prophylaxis and on-demand treatment from breakthrough bleeds and from the phase 3 multicenter, open label study of efficacy and safety of ADYNOVATE in previously treated patients (PTPs) with severe hemophilia A undergoing surgical or other invasive procedures to support perioperative management.

The pediatric study had two age-dependent cohorts: subjects below 6 years (n=32) and those 6 to 12 years of age (n=34). Subjects received twice-weekly prophylactic treatment with 50 ±10 IU/kg of ADYNOVATE over a period of 6 months or at least 50 exposure days (EDs), whichever occurred last. A subset of subjects (12 evaluable) within each age cohort underwent a PK evaluation prior to the start of prophylactic treatment. The primary objective was to assess the incidence of FVIII inhibitory antibodies (≥0.6 Bethesda units [BU] using the (b) (4) Bethesda assay). No subject developed inhibitory antibodies to FVIII. The adverse event (AE) profile is consistent with that previously observed in adults and adolescents. The total median annualized bleeding rate (ABR) was 2

with an Interquartile Range (IQR) of [0, 3.9] with twice weekly dosing of 50±10 IU/kg of ADYNOVATE.

Fifteen surgeries were performed in 15 subjects in the interim analysis of the surgical study. Eleven surgeries were major and 4 were minor. The dose of ADYNOVATE to be administered depended on the type of the surgery performed and the intensity of the hemostatic challenge. Perioperative hemostatic efficacy was rated as excellent (blood loss less than or equal to that expected for the same type of procedure performed in a non-hemophilic patient, and required blood components for transfusions less than or similar to that expected in non-hemophilic population) for all 15 procedures. The intraoperative efficacy was rated as "excellent" (blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic patient) for all 15 procedures, and postoperative efficacy (on postoperative Day 1, i.e., the day following the day of surgery) was rated as "excellent" for all 11 major surgeries, and 2 of 3 minor surgeries; efficacy in one minor surgery was rated as "good." Postoperative blood loss was observed in 5 major surgeries. Although 3 subjects had an overall perioperative blood loss in the range of 1210 mL to 1430 mL, none of them exceeded the maximum predicted perioperative blood loss of 1500 mL for major surgeries. No deaths and no related serious adverse events occurred. ADYNOVATE was shown to be safe and well tolerated and demonstrated hemostatic efficacy in both major and minor surgeries, although there was a limited amount of subjects in this study.

b) Pediatrics

Compared with adults the clearance of ADYNOVATE in children <6 years of age and children 6 to <12 years of age is 55% and 37% higher, respectively. The higher clearance of ADYNOVATE on per kg body weight basis requires a higher dose of ADYNOVATE in children <12 years of age than in adults and is addressed in the labeling of this product.

This supplement was presented to the Pediatric Review Committee (PeRC) on October 19, 2016. The PeRC concurred that the product has been fully assessed in patients 1 year to <18 years.

7. Safety

In the Pediatric study, ADYNOVATE was safe and well tolerated in 66 treated subjects. None of the subjects developed anti-FVIII inhibitory antibodies. There was no death in this study. No serious adverse events (SAEs) were assessed by the investigator or the sponsor as related to ADYNOVATE treatment. There were no thrombotic AEs or AEs considered allergic reactions.

During treatment, 156 AEs (of which 152 were non-serious) occurred in 43 (65.2%) subjects. One AE in one subject was assessed by the investigator as related to ADYNOVATE, but was judged as not related by the sponsor. Four SAEs were reported in three subjects: three SAEs were of moderate severity (febrile neutropenia, pancytopenia and acute gastritis); one SAE

was severe (abdominal pain). The most frequently reported AEs were infections and infestations followed by GI disorders and administration-site conditions.

In the surgery study, fourteen AEs were reported for five subjects. Six AEs were of moderate severity, four were considered severe and four as mild. All AEs were judged by the clinical reviewer to be unrelated to the study drug.. None of the subjects developed inhibitory antibodies to FVIII. One subject had positive IgG binding antibody to FVIII at the termination visit, which was negative at screening. There were no thrombotic events or allergic reactions related to the study agent.. There were no deaths.

8. Advisory Committee Meeting

The Division of Clinical Evaluation and Pharmacology/Toxicology Clinical Review in the Office of Tissues and Advanced Therapies (OTAT) reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not needed as the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

9. Other Relevant Regulatory Issues

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There were no other relevant regulatory issues.

10. Labeling

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) were reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective.

Final versions of the product labeling (FPI) and labels submitted to the BLA on December 9, 2016 (Package Insert) and were considered acceptable. A copy of FPI is attached.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action
The CBER review committee recommends approval of this BLA.

b) Risk/ Benefit Assessment
The benefits of ADYNOVATE for the proposed indications are considered to outweigh the risks.

c) Recommendation for Postmarketing Risk Management Activities

No new postmarketing risk management activities are recommended related to the current supplement. See postmarketing activities related to the original application, as described below.

d) Recommendation for Postmarketing Activities

As per the review of this efficacy supplement, the applicant has fulfilled the following postmarketing requirements (PMRs):

PMRs:

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]).

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**).

The following PMR and (postmarketing commitments) PMCs have not been fulfilled:

PMR

1) 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).**

PMCs:

1) "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**.

2) "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].

3) "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.

4) “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.