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 Associate Director for Medical Policy, OBE, CBER
From:	Wenyu Sun, MD, MPH Medical Officer, PVB, DE, OBE, CBER
Subject:	Adynovate Safety and Utilization Review for the Pediatric Advisory Committee
Sponsor:	Baxalta
Product:	Adynovate
STN:	BLA 125566/379
Indication:	Indicated in children and adults with hemophilia A (congenital factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Perioperative management • Routine prophylaxis to reduce the frequency of bleeding episodes
Meeting Date:	Pediatric Advisory Committee Meeting, April 2019

Contents

1 INTRODUCTION

1.1 Objective

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present 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]. This is the first such pediatric postmarketing safety review for Adynovate. The triggers for this pediatric postmarketing safety review were:

- Initial U.S. approval on November 13, 2015 for use in patients 12 years and older with congenital hemophilia A
- Efficacy supplement approval on December 22, 2016, to expand the clinical indication to include children <12 years of age with congenital hemophilia A

This memorandum documents FDA's evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

Adynovate is a recombinant full-length human coagulation factor VIII covalently conjugated with one or more molecules of polyethylene glycol (PEG). Its therapeutic activity is derived from its parent drug substance, Advate [Antihemophilic Factor (Recombinant)], produced by recombinant DNA technology from the CHO cell line. Adynovate is formulated as a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection.

1.3 Regulatory History

Adynovate was first approved in the United States for use in patients 12 years and older with congenital hemophilia A on November 13, 2015. On December 22, 2016, the indication was expanded to include use in children less than 12 years of age with congenital hemophilia A.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Adynovate for dates November 13, 2015 – August 31, 2018
- Manufacturer's Submissions
    - Adynovate U.S. package insert, dated 12/2016
    - Letter regarding dose distribution data, received October 29, 2018

    - Pharmacovigilance Plan (U.S), Version 2, dated February 5, 2016
- FDA Documents
    - Adynovate initial Approval Letter, dated November 13, 2015
    - Adynovate efficacy supplement Approval Letter, dated December 22, 2016
    - Division of Epidemiology Adynovate Pharmacovigilance Plan Review Memorandum, dated December 6, 2016
- Publications (see Literature Search in section 8)

3 LABEL CHANGES IN REVIEW PERIOD

The label was updated for use in children less than 12 years of age on December 22, 2016. There have been no label changes regarding safety since the PAC triggers.

4 PRODUCT UTILIZATION DATA

Baxalta provided distribution data for the U.S. and worldwide for November 1, 2015 through August 31, 2018:

U.S.: (b) (4)
Worldwide (outside U.S.): (b) (4)

The distribution data was provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

Baxalta's current Pharmacovigilance Plan (U.S.) for Adynovate is Version 2, dated February 5, 2016. There are no identified risks for Adynovate. Important potential risks and missing information for Adynovate are summarized in Table 1.

Table 1: Adynovate Safety Concerns

Identified Risks
None
Potential Risks
Inhibitor formation
Hypersensitivity reactions
Missing Information
No clinical data on use in patients ≥ 65 years of age
No clinical data on use in previously untreated patients (PUPs)
No clinical data on the use of ADYNOVATE for Immune tolerance induction (ITI)

There were no allergic/hypersensitivity reactions, none of the subjects developed inhibitory antibodies to factor VIII, and no persistent treatment-emergent antibodies to factor VIII, PEG factor VIII, or PEG were observed in the studies supporting initial approval [Summary Basis for Regulatory Action; STN 125566/0]. Other factor VIII products have historically had inhibitors develop in some treated patients, and inhibitor formation can be associated with lack of effect of the product. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with other recombinant antihemophilic factor VIII products, including the parent molecule, Advate.

The sponsor is conducting routine pharmacovigilance for Adynovate. The product does not have a safety postmarketing requirement (PMR) study or Risk Evaluation and Mitigation Strategy.

5.2 Postmarketing Studies

Ongoing and completed pediatric postmarketing studies for Adynovate are summarized in Table 2. The initial approval of Adynovate included Postmarketing Requirements (PMRs) for studies 261202, 261204 and 261303, under the Pediatric Research Equity Act (PREA) to evaluate the use of Adynovate in children.

Table 2: Adynovate Pediatric Postmarketing Studies

Postmarketing studies *[Initial approval letter, dated 13-Nov-2015]*	***Study Status***
Clinical study 261202 for on-demand treatment and control of bleeding episodes and routine prophylaxis to reduce frequency of bleeding episodes in pediatric patients ages 0 to <12 years (PREA PMR)	Completed. Study results supported approval of sBLA 125566/51 to expand use in children.
Clinical study 261204 for treatment of perioperative management of bleeding in pediatric patients ages 2 to <17 years (PREA PMR)	Completed. Study results supported approval of sBLA 125566/51 to expand use in children.
Clinical study 261303 for routine prophylaxis to compare the efficacy and safety of two different pharmacokinetics guided dosing regimens in pediatric patients ages 12 to <17 years (PREA PMR)	Ongoing *Study milestones:* Final Protocol Submission: September 08, 2015 Study Completion Date: December 31, 2018 Final Report Submission: September 30, 2019
Clinical study 261302 – 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 previously treated patients age 12 years and above (PMC)	Final Study Report is currently under FDA review. *Study milestones:* Final protocol submission date: July 22, 2015 Study/trial completion date: December 31, 2017 Final Report Submission date: September 30, 2018
Clinical study 261203 –A phase 3, multi-center, open label study to investigate safety and immunogenicity of ADYNOVATE in previously untreated patients. (PMC)	Ongoing. *Study milestones:* Final protocol submission date: December 31, 2015 Study/trial completion date: December 31, 2022 Final Report Submission date: September 30, 2023

PMC: postmarketing commitment study

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following use of Adynovate between November 13, 2015 (initial approval) – August 31, 2018. 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 adverse event reports for Adynovate during the review period are listed in Table 3 below. There were 60 U.S. and 39 foreign reports.

Table 3: FAERS Reports for Adynovate [November 13, 2015 – August 31, 2018]

Age	Serious non-fatal US	Serious non-fatal Foreign	Total serious non-fatal	Deaths US	Deaths Foreign	Total Deaths	Non-serious US	Non-serious Foreign	Total Non-serious	Total US	Total Foreign	Total
< 18	3	7	10	0	0	0	3	0	3	6	7	13
≥ 18	24	15	39	0	6	6	13	0	13	37	21	58
Unknown	9	9	18	1	2	3	7	0	7	17	11	28
All Ages	36	31	67	1	8	9†	23	0	23	60	39	99

*Serious non-fatal adverse events (AEs) include Otherwise Medically Important Conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.
†Follow-up on one death report showed that the patient did not receive Adynovate.

6.2.1 Deaths

There were no pediatric deaths. All 9 fatal reports were individually reviewed. Of note, additional follow-up information received for one of the reports revealed that the suspect products did not involve Adynovate. Thus, there were a total of 8 cases of death following use of Adynovate. Case narratives are summarized below:

1. An 81-year-old man in Japan with a history of Myelodysplastic syndrome (MDS) and hemophilia A had been receiving Adynovate. Approximately a year later, the patient died from progression of the pre-existing condition of MDS.
2. A 75-year-old man in Japan with a history of hemophilia A had been receiving Adynovate. One month later, the patient experienced melena. Approximately one month after onset of melena, the patient died due to aspiration pneumonia.
3. A 67-year-old man in Japan with a history of Hemophilia A had been receiving Adynovate. Approximately one month later, the patient fell at home and experienced femur fracture. A few days later, the patient died of aspiration pneumonia.
4. A 67-year-old man in Japan with a history of Hemophilia A, HCV hepatic cirrhosis and hepatocellular carcinoma had been receiving Adynovate for 3 months. He developed liver abscess and died.

5. A 68-year-old man in Japan with a history of Hemophilia A received Adynovate and died due to severe infectious disease.
6. A male patient in Japan in his 60s with Hemophilia A and hepatic cirrhosis received Adynovate on an unknown date for hemorrhage. The patient died due to lasting diarrhea secondary to hepatic cirrhosis.
7. A 42-year-old man in Japan received treatment with Adynovate on an unknown date. Adynovate was discontinued for unspecified reasons. Approximately two months after Adynovate was discontinued, the patient died at home and the cause of death was unclear. Hemorrhage of digestive tract was suspected.
8. A male patient (age not reported) in the United States received therapy with Adynovate, Recombinate and Advate for an unknown indication. On an unreported date, the patient's mother reported he had died. The cause of death was unknown.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 67 serious non-fatal reports, 10 of which involved pediatric patients (<18 years of age). These 10 cases were individually reviewed. The 10 pediatric SAE reports included one duplicate report, thus yielding 9 unique serious pediatric cases. In two cases, the SAEs involved bleeding episodes (spontaneous breakthrough bleeding; unspecified hemorrhage) and were confounded by indication/underlying disease. Three cases involved factor VIII inhibitor development (two patients received immune tolerance induction therapy and inhibitors resolved, and one case was associated with a false positive result for inhibitors). Narratives for the remaining cases are summarized below:

- A 13-year-old male who received Adynovate for hemophilia A had a hypersensitivity reaction. He experienced red swollen face, blue fingers, red chest, cold body, headache and low blood sugar in 50s. He was admitted to the hospital overnight for observation and all events resolved and he was discharged. Hypersensitivity reaction can occur after Adynovate, and is labeled in the Warnings and Precaution section of the package insert.
- A 3-year-old patient in Colombia experienced headache, decreased oxygen saturation, tachycardia and hypothermia on an unknown date. The latency between the administration of Adynovate and onset of events was unknown.
- An 8-year-old male patient in the United States had fever and headache after infusion with Adynovate. He had a positive bacterial blood test. The patient had a port for his infusion, and it was determined that port was infected.
- A 12-year-old male patient in Japan experienced contusion, limb and forearm fracture when on Adynovate for hemostasis. He recovered from these events.

The most frequently reported MedDRA preferred terms (PTs) for serious non-fatal reports among all ages are summarized in Table 4. (Note that a report may have one or more PTs.)

Table 4: Top preferred terms (PTs) for serious non-fatal reports

Preferred Term (PT)	No. of Reports	Label Status
Haemorrhage	34	Unlabeled*
Factor VIII inhibition	12	Labeled (Warnings and Precautions)
Haemarthrosis	11	Unlabeled*
Headache	5	Labeled (Adverse Reactions)
Pain	3	Labeled (Chest Pain)
Pallor	3	Unlabeled
Back pain	2	Unlabeled
Chest pain	2	Labeled
Flushing	2	Labeled (Adverse Reactions)
Gingival bleeding	2	Unlabeled*
Hyperhidrosis	2	Unlabeled
Musculoskeletal discomfort	2	Unlabeled
Spinal pain	2	Unlabeled
Subcutaneous haematoma	2	Unlabeled*

*confounding by indication

Most reported MedDRA PTs are labeled events or consistent with an already labeled event. The unlabeled PTs for Haemorrhage, Haemarthrosis, Gingival bleeding, and Subcutaneous haematoma are confounded by indication/underlying disease (hemophilia A). Other unlabeled PTs (pallor, back pain, musculoskeletal discomfort, hyperhidrosis) are non-specific events. No other PTs appeared in more than 2 reports.

6.2.3 Non-serious Reports

During the reporting period, there were 23 non-serious reports, with 3 of those involving patients <18 years old. The top PTs for non-serious reports include Pruritus (N=3), Arthralgia (N=2), Coagulation factor VIII level increased (N=2), Infusion related reaction (N=2) and Tinnitus (N=2). No other PTs appeared in more than 2 reports.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Adynovate were disproportionally reported compared to other products in the FAERS database. Data mining covers the entire postmarketing period for this product, from

initial licensure through the data lock point of October 2, 2018 for the data mining analysis. 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 Trade (S) run identified four PTs with a disproportional reporting alert for Adynovate, summarized in Table 6. (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 5: ***Data mining results***

Preferred Term (PT) with EB05>2	No. of Reports	Label Status
Haemorrhage	40	Unlabeled*
Haemarthrosis	14	Unlabeled*
Factor VIII inhibition	12	Labeled (Warnings and Precautions)
Contusion	7	Unlabeled*

*The unlabeled PTs are confounded by indication/underlying disease, hemophilia A.

6.4 Periodic Adverse Experience Reports (PAERs)

The manufacturer's postmarketing periodic safety reports for Adynovate covering the PAC review period 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 10/18/2018, for peer-reviewed literature published between November 13, 2015 – August 31, 2018, with the search term "Adynovate" or "BAX" and "safety" retrieved 4 articles on human safety. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety issues for Adynovate were identified in these articles.

Table 6: *Literature Review*

Article	Safety Conclusion
Nogami K et al. Efficacy and safety of full-length pegylated recombinant factor VIII with extended half-life in previously treated patients with hemophilia A: comparison of data between the general and Japanese study populations. Int J Hematol. 2017 Nov; 106(5):704-710.	This article reported similar safety profile between the overall population and the Japanese subpopulation. The proportion of bleeds reported as excellent or good was 94.9% (149/157) in the overall population, whereas that in the Japanese subpopulation was 92.3% (12/13). No factor VIII inhibition or anaphylactic reaction was reported in the Japanese subpopulation.
Mullins ES et al. Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A. Haemophilia. 2017 Mar;23(2):238-246.	This article concluded twice-weekly prophylaxis with Adynovate was safe in pediatric previously treated patients (PTPs) with severe hemophilia A. Overall, no subject developed factor VIII inhibitors or persistent binding antibodies that affected safety or efficacy. No adverse reactions occurred.
Brand B et al. Efficacy and safety of pegylated full-length recombinant factor VIII with extended half-life for perioperative haemostasis in hemophilia A patients. Haemophilia. 2016 Jul;22(4):e251-8.	This phase 3 surgery study demonstrated that Adynovate was safe in patients with severe hemophilia A undergoing surgery. No related adverse events, allergic reactions, thrombotic events, nor signs of immunogenicity in terms of induction of binding antibodies to factor VIII, PEG or PEG VIII, or factor VIII inhibitors were observed.
Konkle BA et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood. 2015 Aug 27;126(9):1078-85.	This phase 1 study concluded that Adynovate was safe for on-demand treatment and prophylaxis administered twice weekly in patients with hemophilia A. No factorVIII inhibitory antibodies or safety signals were identified.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the manufacturer's periodic safety reports, and the published literature for Adynovate does not indicate any new safety concerns. This PAC review was initiated due to the initial approval in patients 12 years and older, and subsequent expansion of use to include patients less than 12 years of age. In general, very few adverse events were reported in the pediatric age group (<18 years) during the review period. There were no reports of pediatric death. 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 Adynovate.