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 Deputy Director, DE, OBE, CBER
From:	Graça Dores, MD, MPH Medical Officer, Analytic Epidemiology Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	CSL Behring, LLC
Product:	AFSTYLA (antihemophilic factor (recombinant), single chain)
STN:	125591/244
Indication:	Indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes, • Routine prophylaxis to reduce the frequency of bleeding episodes, • Perioperative management of bleeding. Limitation of Use AFSTYLA is not indicated for the treatment of von Willebrand disease.
Meeting Date:	Pediatric Advisory Committee Meeting, April 28-29, 2020

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the post-marketing 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]. The trigger for this pediatric post-marketing safety review was the initial approval of AFSTYLA (CSL Behring) on May 25, 2016 for use in adults and children with hemophilia A (congenital Factor VIII deficiency).

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

1.2 Product Description

AFSTYLA (lonoctocog alfa) is a recombinant Factor VIII produced in Chinese hamster ovary (CHO) cells. It is a construct where the B-domain occurring in wild-type, full-length FVIII has been truncated, and four amino acids of the adjacent acidic a3 domain have been removed. AFSTYLA is expressed as a single chain FVIII molecule with covalent linkage between heavy and light chains, thereby keeping the molecule in the single chain form and resulting in increased stability and increased von Willebrand factor affinity. The post-translational modifications are comparable to those of endogenous FVIII.

AFSTYLA is purified in a multi-step process including two virus reduction steps, and no human or animal derived proteins are used in the purification or formulation processes. AFSTYLA is available as a preservative-free, sterile, non-pyrogenic, lyophilized powder that is reconstituted with sterile water for intravenous injection.

1.3 Regulatory History

AFSTYLA was approved in the U.S. on May 25, 2016 for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for (1) on-demand treatment and control of bleeding episodes, (2) routine prophylaxis to reduce the frequency of bleeding episodes, and (3) perioperative management of bleeding.
AFSTYLA is not indicated for the treatment of von Willebrand disease.

2 MATERIALS REVIEWED

- FDA Adverse Event Reporting System (FAERS)
    - FAERS reports for AFSTYLA during May 25, 2016 to August 31, 2019 (PAC review period)
- Manufacturer's Submissions

    - AFSTYLA US Prescribing Information (USPI), dated 9/2017
    - Pharmacovigilance Plan, Version 5, dated August 28, 2016
    - Periodic Adverse Drug Experience Reports (PADERs) and Periodic Safety Update Reports (PSURs) covering the period from May 25, 2016 to July 3, 2019
    - Sponsor response to information request regarding dose distribution data, received November 11, 2019
    - Labeling supplement for STN 125591/227
- FDA Documents
    - AFSTYLA Approval Letter for BLA 125591/0, dated May 25, 2016
    - Division of Epidemiology Pharmacovigilance Plan Review Memorandum for STN 125591/0, dated March 22, 2016
    - AFSTYLA Approval Letter for BLA 125591/59, labeling supplement to updated section 6.2 Adverse Reactions – Immunogenicity
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

Safety-related label changes during the review period included updated information regarding inhibitor development from completed clinical trials and an ongoing extension study.

FDA approved a labeling revision on September 14, 2017 to modify the language in the Adverse Reactions - Immunogenicity Section 6.2 of the USPI to include updated information on inhibitor development based on data from completed clinical trials in previously treated patients (PTPs) and updated information regarding inhibitor rate in previously untreated patients (PUPs) from an ongoing extension study. The Adverse Reactions and Immunogenicity section (section 6.2) was updated as follows: "Preliminary data from an actively enrolling clinical trial in previously untreated patients (PUPs) aged ≤5 years indicate that 6 of 15 treated subjects (40% with a 95% confidence interval of 16%, 68%) developed an inhibitor. Of these 6 subjects, 3 (50%) had peak inhibitor values in the high titer range, and 3 (50%) had peak values in the low titer range. Of the 6 subjects who tested positive for inhibitors, 5 subjects have remained in the trial and have continued treatment with AFSTYLA; 3 now have titer values in the low titer range and 2 experienced successful eradication of the inhibitor. No PTPs developed neutralizing antibodies (inhibitors) to Factor VIII or antibodies against CHO host cell proteins at any time during the completed clinical trials."

FDA is currently reviewing a proposed labeling revision submitted in July 2019, that aims to clarify the description of FVIII inhibitors and adds FVIII inhibition to the post-marketing experience section.

4 PRODUCT UTILIZATION DATA

As noted in the AFSTYLA USPI, dosing is based on the clinical indication (e.g., routine prophylaxis, management of bleeding), FVIII activity starting level and desired level, patient weight, and severity of bleeding (if any). The indication for AFSTYLA and severity of bleeding (if applicable) in turn determine the frequency of administration. CSL Behring, LLC provided estimated AFSTYLA exposure data for the US and worldwide (Table 1).

Table 1: Estimated US and Worldwide AFSTYLA Exposure, May 26, 2016 to August 31, 2019*

Patient Age	US		Worldwide	
	Standard Doses	Patient-years	Standard Doses	Patient-years
<18 years	8,984	58	29,878	192
≥18 years	25,455	245	84,654	814

* Courtesy of CSL Behring, LLC. The estimated exposure (i.e., number of standard doses distributed) was calculated by (b) (4). An estimated standard dose is the (b) (4). Patient-years was estimated based on the (b) (4).

The US exposure data calculations are based on distribution data for May 26, 2016 to August 31, 2019 and the following assumptions:

(b) (4)

For individuals <18 years of age:

(b) (4)

(b) (4) = 8,984 standard doses

(b) (4)

= 58 patient-years

For individuals ≥18 years of age:

(b) (4)

= 25,455 standard doses

(b) (4)

= 245 patient-years

5 PHARMACOVIGILANCE PLAN AND POST-MARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) for AFSTYLA is Version 5, dated May 12, 2017. Table 2 describes the important identified risks, important potential risks and missing information for AFSTYLA.

Table 2: AFSTYLA Safety Concerns and Planned Pharmacovigilance Actions

Important Identified Risks	**Planned Pharmacovigilance Actions**
Hypersensitivity and anaphylactic reactions	- Routine pharmacovigilance, including additional follow-up and specific follow-up questionnaire - CSL627_3001 extension study
Development of inhibitors	- Routine pharmacovigilance, including additional follow-up and specific follow-up questionnaire - CSL627_3001 extension study (including planned enrolment of PUPs in this study)
Important Potential Risks	**Planned Pharmacovigilance Actions**
Clinical impact of non-inhibitory anti-drug antibodies (ADAs)	- Routine pharmacovigilance - CSL627_3001 extension study

Dosing errors based on assay type (chromogenic (ChS) vs. one-stage (OS)) used for monitoring of FVIII levels	- Routine pharmacovigilance - CSL627_3001 extension study
Development of antibodies against CHO host cell proteins	- Routine pharmacovigilance - CSL627_3001 extension study
Missing Information	**Planned Pharmacovigilance Actions**
Experience of inhibitor formation in PUPs	- Routine pharmacovigilance, including additional follow-up and specific follow-up questionnaire - CSL627_3001 extension study (including planned enrolment of PUPs in this study)
Experience in pregnancy and lactation, including labor and delivery	- Routine pharmacovigilance, including additional follow-up and pregnancy follow-up questionnaire
Experience in geriatric patients (65 years and older)	- Routine pharmacovigilance, including additional follow-up

The CSL627_3001 extension study mentioned in the PVP is an ongoing multicenter, open-label, phase 3 extension study that is investigating the safety and efficacy of AFSTYLA for prophylaxis and on-demand treatment of bleeding episodes in at least 200 PTPs with severe congenital hemophilia A and previous exposure to FVIII products who achieve at least 100 exposure days (EDs) to AFSTYLA in this study, as well as in PUPs with no previous exposure to any FVIII product who achieve at least 50 EDs on AFSTYLA in this study. A substudy (open to PUPs who develop an inhibitor to AFSTYLA) is investigating the use of AFSTYLA in immune tolerance induction (ITI) therapy.

Development of anti-factor VIII antibodies is a well-established potential AE associated with FVIII products (class effect) and a labeled AE for AFSTYLA (USPI section 5.2, Warnings and Precautions - Neutralizing antibodies). PUPs have a higher risk of developing anti-FVIII antibodies than PTPs, particularly within the initial 50 EDs.[1] The USPI (section 6.2 Immunogenicity) includes preliminary data from an ongoing clinical trial of PUPs (CSL627_3001) 5-years of age or younger and reports FVIII inhibitor formation rate of 40% (6 of 15 treated children) [95% confidence interval (CI): 16% - 68%]. These results are in contrast to the pre-approval clinical trials of AFSTYLA that included 98 PTPs <18 years of age, none of whom developed FVIII inhibitor (USPI sections 6.2, 8.4).

The identified and potential risks listed in Table 2 are common to this product class and will be monitored with routine safety surveillance, including review of AE reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no post-marketing commitment or requirement (PMC/PMR) safety studies or Risk Evaluation and Mitigation Strategy (REMS) for AFSTYLA.

6 ADVERSE EVENT REVIEW

6.1 Methods

FAERS was queried for AE reports following the use of AFSTYLA between May 25, 2016 (PAC trigger) and August 31, 2019 (inclusive). FAERS stores post-marketing AE and medication error reports 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 AE 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 AE reports for AFSTYLA during the PAC review period are listed in Table 3. There were 20 US and 14 foreign reports for review period May 25, 2016 to August 31, 2019.

Table 3: FAERS Reports for AFSTYLA during May 25, 2016 to August 31, 2019 (PAC review period)*

Age	Serious, Non-fatal		Deaths		Non-Serious		Total	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<18 years	6	7	0	0	2	0	8	7
≥18 years	3	2	0	1	2	1	5	4
Unknown	2	2	0	0	5	1	7	3
All ages	11	11	0	1	9	2	20	14

* Search criteria: Initial FDA received date = 05/25/16 – 08/31/19, drug role = suspect. Serious non-fatal AEs include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability, or otherwise medically important conditions.

6.2.1 Deaths

During the PAC review period, there was one adult death following receipt of AFSTYLA. There were no pediatric deaths. The fatal report was reviewed and is summarized below.

Death case (PTs – tongue hematoma, anti-factor VIII antibody-positive):
An 80-year-old male diagnosed with mild congenital hemophilia in 2017 received AFSTYLA for urgent orthopedic surgery (hip fracture) in 2018. After 1 month, the

patient was evaluated in the hospital for a tongue and arm hematoma that developed after a fall. The PTT ratio was 2.5 and Hgb was 6.0g. The patient died on the following day due to cardiac arrest (per the death certificate), and the physician thought the patient had an ischemic cerebrovascular accident. Only one inhibitor test was done the day the patient was evaluated for the fall, and it confirmed the presence of an inhibitor (4.7 BU). The physician did not think that the death was due to bleeding because hemoglobin had stabilized with transfusion therapy, AFSTYLA, and recombinant FVII (90 mcg/kg every 6 hours).

Other than the episode described above, the prior therapy administered (if any) for hemophilia was not well described. The patient's past medical history included elective tonsillectomy in 2017 (associated with bleeding), carotid endarterectomy in 2011 for carotid stenosis (no complications), diabetes, and cognitive impairment due to severe atherosclerosis.

Reviewer comment: This patient had a clinical diagnosis of congenital hemophilia established in 2017 when he would have been in his late 70s. While mild congenital hemophilia may manifest clinically later in life, other diagnostic considerations include acquired hemophilia A due to a spontaneously occurring inhibitor and acquired or congenital von Willebrand disease that can mimic hemophilia A and similarly manifest later in life. Given that there was no FVIII inhibitor level obtained at time of diagnosis (the only inhibitor level was recorded one day prior to death), it is not possible to determine when the inhibitor developed. While it is possible that the FVIII inhibitor may have been related to AFSTYLA therapy, the details in the report and surgical history raise the possibility of a low-titer, spontaneously acquired FVIII inhibitor being present even prior to AFSTYLA being administered. The fact that this patient underwent carotid endarterectomy in 2011 without bleeding and tonsillectomy in 2017 with associated bleeding suggests the possibility that a low-grade, spontaneously acquired inhibitor developed after 2011 but prior to the surgery in 2017 (the report is limited by lack of details on transfusion history). Without a pre-treatment FVIII inhibitor level at the time of diagnosis of hemophilia, it is difficult to implicate AFSTYLA as the causal agent in inhibitor development. Nevertheless, the development of a FVIII inhibitor is a known AE associated with FVIII products (class effect), and inhibitor development is a labeled event for AFSTYLA.

By description, this patient had an adequate response to AFSTYLA at the time of the hip fracture repair and did well clinically for one month with no bleeding episodes reported until he had a traumatic fall. It seems unlikely that the tongue hematoma was related to AFSTYLA, and more likely that it was related to the fall (e.g., patient bit his tongue). Recombinant FVII, which was likely used as a bypassing agent to circumvent the FVIII inhibitor, may also have played an important role in the death of this patient. FVII is known to be thrombogenic[2] and may have incited a thrombotic cerebrovascular or cardiovascular event or pulmonary embolism leading to death in this 80-year-old male with risk factors for vascular disease.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 22 serious, non-fatal reports; 13 of which involved pediatric patients. The most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for all serious, non-fatal reports (with a frequency >2 reports) are summarized in Table 4.

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

Preferred Term (PT)	Number of Serious Nonfatal Reports	Label* Status
Hemorrhage†	5	Labeled (1, 2.1, 5.2, 5.3, 6.1, 12.2, 14)
Anti-factor VIII antibody positive	4	Labeled (5.2, 5.3, 6.1, 6.2, 17)
Factor VIII inhibition	3	Labeled (5.2, 5.3, 6.1, 6.2, 17)
Hemarthrosis†	3	Labeled (specifically 2.1, but all sections referring to "hemorrhage" are applicable)

*Label dated 9/2017 (and section(s), if applicable). Includes label sections with PT and related PTs. Label sections include: 1 (Indications and Usage), 2.1 (Dosing Guidelines), 5.2 (Neutralizing Antibodies), 5.3 (Monitoring Laboratory Tests), 6.1 (Clinical Trials Experience), 6.2 (Immunogenicity), 12.2 (Pharmacodynamics), 14 (Clinical Studies), and 17 (Patient Counseling Information).
† PT represents AE that is confounded by indication for use (also reflected in label status).

Most reported MedDRA PTs are labeled events. The PTs "anti-factor VIII antibody positive" and "factor VIII inhibition" are related terms. Inhibitor formation is a class effect for all FVIII products and is a labelled event for AFSTYLA. The PTs "hemorrhage" and "hemarthrosis" are related terms and confounded by indication for treatment. Other PTs were reported for sporadic events, and no other PTs appeared in more than 2 reports.

The case narratives for the 13 serious, nonfatal pediatric reports (6 from the US and 7 foreign) were individually reviewed. Seven cases that reported FVIII inhibitor development (of which five described subjects in post-marketing clinical trials) are summarized as follows:

- 1-year-old male PUP developed an inhibitor and experienced bleeding episodes; received immune tolerance induction (ITI), and inhibitor was eradicated.
- 1-year-old male PUP developed new-onset low-titer inhibitor; initially asymptomatic but later experienced bleeding after lip surgery.
- 31-month-old male PUP developed inhibitor with subsequent traumatic bleed; he continued AFSTYLA (no change in dose) and did well without further bleeding.
- 2-year-old minimally treated male experienced three bleeds and inhibitor. detected (peak level 15.7 BU/ml); received ITI, and inhibitor was eradicated.
- 7-year-old male PTP developed transient low-titer inhibitor.

- 6-month-old male PUP developed new onset, low-titer inhibitor; clinically asymptomatic.
- 12-month-old male PUP developed a spontaneous hematoma and high-titer inhibitor (>300 BU/ml), and AFSTYLA was stopped; after 6 months the inhibitor decreased (<10 BU/ml). ITI was planned once the inhibitor level further decreased.

In three other cases, the serious, nonfatal AEs involved bleeding episodes (muscle hemorrhage; hemorrhage; hemarthrosis) and were confounded by the indication for treatment (hemophilia A). Narratives (and associated PTs) for the remaining three cases are summarized below:

- PT - therapeutic response delayed:

  A 17-year-old male with severe hemophilia A was found to have a delay in FVIII recovery time (time from AFSTYLA infusion to peak FVIII level). The reporter subsequently changed the laboratory testing of FVIII to a clot-based assay. During this time, the patient did not have any bleeding and treatment remained unchanged. The finding was incidentally discovered by a pharmacist during routine surveillance.

- PTs - feeling hot, hypersensitivity, pruritus, pyrexia, spontaneous hemorrhage, temperature intolerance, urticaria:

  A 14-month-old Caucasian male with hemophilia A and no prior history of allergic reactions or hypersensitivity was treated in a European country (with the exception of treatment received during holiday travel outside of the country; the product received was not specified) with a FVIII product for approximately 5 months prior to start of AFSTYLA. AFSTYLA prophylaxis (twice weekly) was initiated beginning at the age of 6 months. The patient's mother reported an episode of constant spontaneous bleeding, heat sensitivity, fever up to 40˚C 1-2 days after AFSTYLA administration, and an episode of allergic reaction associated with feeling of heat, hives, urticaria, and itching 1-2 days after AFSTYLA administration. There was no change in AFSTYLA dose or frequency. The treating physician could not confirm the reported AEs. The physician indicated that the patient did not exhibit any symptoms of anaphylaxis. The patient was monitored for 2 hours after AFSTYLA administration, and blood pressure, heart rate, and respiratory rate had always been normal. All treatment (except for that received during holiday travel) had been delivered at the same facility. The physician indicated that treatment with AFSTYLA would continue without pre-medication.

- PTs - muscle twitching, seizure-like phenomenon, somnolence:

  A 14-year-old female with mild factor VIII deficiency and a cardiac abnormality ("10 cm hole in heart") taking "many" unspecified medications received AFSTYLA pre-operatively for open heart surgery. After the first

dose of AFSTYLA, the patient was slow to awaken post-operatively and experienced facial twitches (like seizures). A computerized tomography scan and neurology checks were unremarkable. The following day, the patient was doing well.

6.2.3 Non-serious Reports

During the reporting period, there were 11 non-serious reports, of which two involved pediatric patients (2 US and 0 foreign). The top PTs for all non-serious reports are summarized in Table 5, and most reported MedDRA PTs represent labeled events. Other PTs were reported for sporadic events, and no other PTs appeared in more than 2 reports.

Table 5: Top preferred terms (PTs) for non-serious reports, all ages

Preferred Term (PT)	Number of Non-serious Reports	Label* Status
Depression	2	Not labeled
Headache	2	Not labeled
Vomiting	2	Not labeled

*Label dated 9/2017.

Among the pediatric, non-serious reports, one included the unlabeled PT, “limb discomfort,” to describe the non-specific event of the patient’s “foot bothering him.” Foot pain could be related to trauma, bleed, or other event and is potentially confounded by the indication for AFSTYLA.

The second case reported unlabeled PTs for “depression,” “aggression,” and “disease recurrence.” The PTs “aggression,” “depression,” and “disease recurrence” were derived from a single report of a 13-year-old male with history of depression and aggression that developed when he immigrated to another country. His symptoms were described to be related to bullying that the patient experienced in school. The depression resolved on antidepressant therapy, but the patient’s mother noted that depression and aggression returned after starting AFSTYLA, with signs being most notable the day after infusion. The PTs “depression” and “aggression” are not labeled terms. However, it is well documented in the literature that many patients with hemophilia may be affected by anxiety, depression, and other mental health conditions related to having a chronic condition and being limited in some physical activities, so as to avoid trauma and ensuing bleeding episodes.[3-5] Based on this information, it is difficult to implicate a causal role for AFSTYLA given that there might be other confounding situational factors accounting for the increase in symptoms. The PT “disease recurrence” in this report referred to the patient’s depression.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of AFSTYLA were disproportionally reported compared to all products in the FAERS database (Table 6). Data mining covers the entire post-marketing period for this product, from initial licensure through the data lock point for the data mining analysis of August 31, 2019. 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 Product Name (S) (v2) run identified the PTs summarized in Table 6, with a disproportional reporting alert. Note that a report may have one or more PTs (disproportional reporting alert is defined as an EB05 $\geq$2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). Most of these events appeared among the most frequently reported PTs and are discussed in Section 6.2.

Table 6: Data mining results with data lock point of August 31, 2019

Preferred Term (PT) with EB05 $\geq$2	Number of Reports	Label* Status
All ages		
Anti-factor VIII antibody positive	5	Labeled (5.2, 5.3, 6.1, 6.2, 17)
Hemorrhage†	5	Labeled (1, 2.1, 5.2, 5.3, 6.1, 12.2, 14)
Hemarthrosis†	4	Labeled (specifically 2.1; but all sections referring to "hemorrhage" are applicable)
Age <18 years		
Anti-factor VIII antibody positive	3	Labeled (5.2, 5.3, 6.1, 6.2, 17)
Age $\geq$18 years		
(No PTs with EB05 $\geq$2)	~	~

~ = not applicable.
*Label dated 9/2017 (and section(s), if applicable). Includes label sections with PT or related PTs. Label sections: 1 (Indications and Usage), 2.1 (Dosing Guidelines), 5.2 (Neutralizing Antibodies), 5.3 (Monitoring Laboratory Tests), 6.1 (Clinical Trials Experience), 6.2 (Immunogenicity), 12.2 (Pharmacodynamics), 14 (Clinical Studies), 17 (Patient Counseling Information).
† PT represents AE that is confounded by indication for use (also reflected in label status).

6.4 Periodic safety reports

The manufacturer's post-marketing periodic safety reports for AFSTYLA were reviewed. The AEs 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 November 1, 2019 for peer-reviewed literature, with the search terms "AFSTYLA" and "SAFETY"

limited by human species, and dates from licensure (May 25, 2016) to date of search (November 1, 2019), retrieved 0 publications pertaining to safety.

8 CONCLUSION

This post-marketing pediatric safety review of passive surveillance AE reports, the sponsor's periodic safety reports, and the published literature for AFSTYLA does not indicate any new safety concerns. The PAC review was initiated due to initial approval of AFSTYLA in adults and children on May 25, 2016. There were no pediatric deaths. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of AFSTYLA.

10 REFERENCES

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