Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: Octapharma USA, Inc.

Product: Wilate (von Willebrand Factor/Coagulation Factor VIII Complex (Human))

STN: BL 125251/366

Indication: Wilate is indicated in children and adults with von Willebrand disease for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

Wilate is indicated in adolescents and adults with hemophilia A for:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes

Meeting Date: Pediatric Advisory Committee Meeting, September 2022

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1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents 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]. The trigger for this pediatric postmarketing safety review is the September 25, 2019, approval of an efficacy supplement, supplemental Biologics License Application (sBLA) 125251/244, to add an indication in adults and adolescents with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes and on demand treatment and control of bleeding episodes.

This memorandum documents FDA's complete 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

Wilate is a human plasma-derived, sterile, purified, double virus inactivated von Willebrand Factor/Coagulation Factor VIII Complex. Wilate is supplied as a lyophilized powder for reconstitution for intravenous injection.

1.3 Regulatory History

- On December 04, 2009, FDA approved Wilate original BLA 125251/0 for treatment of spontaneous and trauma-induced bleeding episodes in patients with severe Von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.
- On August 05, 2015, FDA approved sBLA 125251/139 to include an additional indication for the prevention of excessive bleeding during and after minor and major surgery in VWD patients. This was the trigger for a previous review for the PAC in 2019.[1]
- On September 25, 2019, FDA approved sBLA 125251/244 to add an indication in adults and adolescents with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes and on demand treatment and control of bleeding episodes. This is the trigger for the current review for the PAC.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Wilate during September 25, 2019, to April 30, 2022 (PAC review period)

[1] Safety and Utilization Review for the Pediatric Advisory Committee: Wilate; STN 125251/256

- Manufacturer's Submissions
  - Wilate U.S. package insert (USPI), updated November 20, 2019
  - Applicant response regarding dose distribution data, dated June 20, 2022
  - Risk Management Plan (RMP), version 9, dated June 19, 2018
  - Periodic safety reports
- FDA Documents
  - BLA 125251/244 Wilate Approval Letter, dated September 25, 2019
  - BLA 125251/244 Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA[2]

The U.S. and worldwide distribution data for Wilate during September 25, 2019, to April 30, 2022 (PAC review period):

U.S.:

A total of (b) (4) IU of Wilate has been distributed in the U.S. during October 01, 2019 to April 30, 2022, of which (b) (4) IU was in the patient age group ≤18 years of age, and (b) (4) IU was in the patient age group >18 years of age.

The sponsor also stated that in the U.S., 11.5% of treated patients had hemophilia A and 88.5% had VWD. Of these, 44% of patients with hemophilia A and 56% of patients with VWD were ≤18 years of age. Per the sponsor, "*the estimates do not take into account differences in doses or dosing frequencies between the different age groups, disease types, etc., and should therefore be interpreted with caution*."

NOTE: Per the sponsor, for administrative reasons, reporting period could not start exactly on September 25, 2019 and was instead set to October 01, 2019. Therefore the U.S. distribution data presented above is for the period of October 01, 2019 to April 30, 2022, to approximately match the PAC review period of September 25, 2019 to April 30, 2022.

Worldwide:

A total of (b) (4) IU of Wilate has been distributed worldwide during October 01, 2019 to April 30, 2022, of which (b) (4) IU was in the patient

[2] Distribution data is protected as confidential commercial information and may require redaction from this review.

age group ≤18 years of age, and (b) (4) IU was in the patient age group >18 years of age.

The sponsor also stated that globally, 35% of patients with hemophilia A and 24% of patients with VWD were ≤18 years of age.

NOTE: Per the sponsor, for administrative reasons, reporting period could not start exactly on September 25, 2019 and was set to October 01, 2019. Therefore, the worldwide distribution data presented above is for the period of October 01, 2019 to April 30, 2022, to approximately match the PAC review period of September 25, 2019 to April 30, 2022.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP) is the Risk Management Plan, version 9, dated June 19, 2018, which lists the important identified risks and important potential risks displayed in Table 1.

Table 1: Wilate safety concerns

Important Identified Risks
• Inhibitor development in PUPs and PTPs with HA • Inhibitors against VWF • Hypersensitivity reactions, including anaphylactic reactions
Important Potential Risks
• Suspected transmission of pathogen infection • Cardiovascular events in HA patients and VWD patients at risk of thromboembolic events
Missing Information
• None

PUP: Previously Untreated Patients; PTP: Previously Treated Patient; HA: Hemophilia A; Von Willebrand factor (VWF); VWD: Von Willebrand Disease

The important identified and potential risks for Wilate listed in table 1 are common to the Von Willebrand factor (VWF) and factor VIII (FVIII) product class, and these risks are labeled events in the USPI.

- Neutralizing antibodies (inhibitors) to FVIII or VWF may occur and are described in the USPI under *Warnings and Precautions*.
- Hypersensitivity reactions may occur with Wilate and is described in the USPI under *Warnings and Precautions* and *Adverse Reactions*. Wilate is contraindicated (USPI, section *Contraindications*] in patients with known hypersensitivity reactions to human plasma-derived products, any ingredient in the formulation, or components of the container.
- The risk for thromboembolic events is described in the USPI under *Warnings and Precautions*, and the label directs healthcare providers to monitor plasma

levels of VWF:RCo and FVIII activities in patients receiving Wilate to avoid sustained excessive VWF and FVIII activity levels.

- Because this product is made from human blood, it may carry a risk of transmitting infectious agents, and this risk for transmissible infectious agents is described in the USPI under *Warnings and Precautions*. The risk that Wilate will transmit viruses has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses during manufacture.

The identified and potential risks for Wilate are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no ongoing or planned additional pharmacovigilance activities for Wilate, such as safety-related postmarketing requirement/commitment (PMR/PMC) studies or Risk Evaluation and Mitigation Strategy (REMS).

5.2 Postmarketing studies

There are no safety-related postmarketing requirement or commitment (PMR/PMC) studies for Wilate.

Study under the Pediatric Research Equity Act (PREA) are listed below:

- Deferred pediatric study under PREA for the treatment of hemophilia A in pediatric patients 1<12 years of age (WIL-30)
    - Final Protocol Submission: June 19, 2017
    - Study Completion Date: March 30, 2019
    - Final Report Submission: December 31, 2019

  Reviewer comments: The current status of this study is delayed and a PREA Noncompliance letter was issued on September 8, 2021.[3]

The applicant has fulfilled the pediatric study requirement for ages 12 to 18 years for this application.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Wilate received during September 25, 2019, to April 30, 2022 (PAC review period). 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

[3] Information on Postmarket Requirements and Commitments is available at https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

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 Wilate during the PAC review period are listed in Table 2. There were 21 U.S. and 12 foreign reports for review period September 25, 2019, to April 30, 2022 (PAC review period). Note that a comprehensive review of Wilate postmarketing data was previously presented to the PAC in 2019[4]. This memo will focus on the review period from September 25, 2019 (regulatory trigger for this PAC) through April 30, 2022 (data lock point).

Table 2: FAERS reports for Wilate during 9/25/2019 to 4/30/2022 (PAC review period)

Age (years)	Serious non-fatal, US	Serious non-fatal, foreign	Deaths, US	Deaths, foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18	8	6	0	0	3	0	11	6
≥18	4	6	0	0	2	0	6	6
Unknown	2	0	0	0	2	0	4	0
All	14	12	0	0	7	0	21	12

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

6.2.1 Deaths

During September 25, 2019, to April 30, 2022 (PAC review period), there were 0 (none) death reports

6.2.2 Serious Non-fatal Reports

During September 25, 2019, to April 30, 2022 (PAC review period), there were 26 serious, non-fatal reports; 14 of which involved pediatric patients.
Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) occurring in >1 serious non-fatal reports are summarized in Table 3. Note that a report may have one or more PTs.

[4] Safety and Utilization Review for the Pediatric Advisory Committee: Wilate; STN 125251/256

Table 3: Most frequently reported PTs for serious reports

Preferred Term (PT)	Number of reports	Label status
Dyspnea	6	Labeled (6.2)
Anaphylactic reaction	5	Labeled (4, 5.1, 5.3)
Flushing	4	Labeled (5.1)
Chest pain	3	Unlabeled - Chest discomfort (6.2) / chest tightness (5.1)
Hemorrhage	3	Unlabeled
Infusion related reaction	3	Unlabeled – label cautions to observe for symptoms during infusion; lists infusion site burning and stinging (5.1)
Loss of consciousness	3	Unlabeled
Nausea	3	Labeled (5.1)
Abdominal pain	2	Labeled (6.2)
Anxiety	2	Unlabeled
Back pain	2	Unlabeled ("Joint pain" Labeled 18)
Chest discomfort	2	Labeled (6.2)
Dizziness	2	Labeled (6, 6.1)
Fall	2	Unlabeled
Feeling hot	2	Unlabeled
Gastrointestinal hemorrhage	2	Unlabeled
Headache	2	Labeled (5.1, 6.1)
Pallor	2	Unlabeled
Urticaria	2	Labeled (6, 6.1)

Wilate U.S. package insert (USPI), updated November 20, 2019

Reviewer comments: Most reported PTs are labeled events or consistent with an already labeled event. The unlabeled PT of anxiety is non-specific and was reported in the context of labeled PTs typically associated with anaphylaxis (anaphylaxis itself being a labeled PT). The unlabeled PT for loss of consciousness was associated with syncope and presyncope states/symptoms (such as pallor, feeling hot, sweating), or reported with possible hypersensitivity reaction/symptoms. The unlabeled PT of infusion related reaction was reported in the context of hypersensitivity (labeled PT) reactions. Other unlabeled PTs listed consisted of PTs/AEs related to underlying conditions and patient factors, such as hemorrhage, hemorrhage associated with fall, and gastrointestinal hemorrhage.

Of the 14 serious non-fatal reports involving pediatric patients, eight reports consisted of adverse events biologically or mechanistically unlikely related/unrelated to the product, and likely related to the underlying condition, patient-related factors, or administration issues (e.g. hemorrhage (including epistaxis), arthralgia, joint injury, hemorrhage or other AE related to fall/trauma, user error/wrong technique use, inability to access the vein, treatment noncompliance).

The other six serious, pediatric reports were consistent with hypersensitivity and anaphylactic reactions, and infusion related reactions (e.g. urticaria, flushing, dyspnea, pharyngeal swelling, nausea, vomiting, pallor, tachycardia).

Reviewer comments: Review of these reports did not raise new safety concerns. Most of the unlabeled AEs were in the context of accompanying labeled AEs or the underlying condition. Hypersensitivity reactions can be seen in patients with previous exposure to other vWF/FVIII products, and anaphylactic reactions have been associated with presence of anti-vWF antibodies in patients with type III vWD.

6.2.3 Non-serious Reports

During September 25, 2019, to April 30, 2022 (PAC review period), there were 7 non-serious reports; 3 of which involved pediatric patients. There were no PTs occurring in >1 non-serious reports. All PTs in the non-serious reports are listed in Table 5.

Table 5: Most frequently reported PTs for non-serious reports

Preferred Term (PT)	Number of reports	Label status
Chest discomfort	1	Labeled (6.2)
Condition aggravated	1	Unlabeled
Epistaxis	1	Unlabeled
Eye swelling	1	Unlabeled - "Swelling" Labeled (18)
Hemarthrosis	1	Unlabeled
Heart rate decreased	1	Unlabeled
Heart rate increased	1	Tachycardia Labeled (5.1)
Hyperhidrosis	1	Unlabeled
Infusion related reaction	1	Unlabeled – label cautions to observe for symptoms during infusion lists infusion site burning and stinging (5.1)
Internal hemorrhage	1	Unlabeled
Malaise	1	Unlabeled
Paresthesia oral	1	Unlabeled
Rash	1	Labeled (18)
Transfusion reaction	1	Unlabeled
Vision blurred	1	Unlabeled
Visual impairment	1	Unlabeled
Weight increased	1	Unlabeled

Wilate U.S. package insert (USPI), updated November 20, 2019

Reviewer comments: No nonserious PTs were reported in more than 1 report. The PTs reported consisted mostly of unlabeled PTs related to the patients' underlying conditions (i.e., confounding by indication), or are consistent with an already

labeled event. No new safety concerns were identified from review of non-serious reports.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Wilate were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis as of June 05, 2022. 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. 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) run identified 10 PTs with a disproportional reporting alert and are listed in Table 6 below:

Table 6: Data mining results with data lock point of June 05, 2022

Preferred Term (PT) with EB05>2	Number of reports	Label status
Anaphylactic reaction	9	Labeled (4, 5.1, 5.3)
Chest discomfort	8	Labeled (6.2)
Chest pain	12	Unlabeled - Chest discomfort (6.2) / chest tightness (5.1)
Dyspnea	24	Labeled (6.2)
Flushing	17	Labeled (5.1)
Hyperhidrosis	6	Unlabeled
Infusion related reaction	12	Unlabeled – label cautions to observe for symptoms during infusion lists infusion site burning and stinging (5.1)
Maternal exposure during pregnancy	7	Limited experience in pregnancy in label (8.1)
Tachycardia	8	Labeled (5.1)
Von Willebrand's factor inhibition	6	Labeled “Inhibitor antibodies” (5.1) / “Neutralizing antibodies to….vWF” (5.3)

Wilate U.S. package insert (USPI), updated November 20, 2019

Reviewer comments: Most of these events are labeled events which also appeared among the most frequently reported PTs and are discussed in Section 6.2 of this memo. The unlabeled PT of hyperhidrosis is non-specific and occurred in 6 reports received between 2017 and 2020. Review of these reports found that this PT was reported in the context of a variety of events (labeled and unlabeled) that can be associated with sweating, such as hypersensitivity reactions, vomiting, nausea, loss of consciousness/syncope/ presyncope states, and does not raise new safety concerns.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Wilate 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 U.S. National Library of Medicine's PubMed.gov database on June 07, 2022, for peer-reviewed literature, with the search term "Wilate" and published dates between September 25, 2019 and April 30, 2022, retrieved 1 publication relevant to safety information for Wilate. [5]

Table 7: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Sholzberg M, Khair K, Yaish H, Rodgers G, Cruz MS, Mejía CM, Čermáková Z, Matino D, Teitel J, Barrie A, Werner S, Prondzinski MVD. Real-World Data on the Effectiveness and Safety of wilate for the Treatment of von Willebrand Disease. *TH Open*. 2021 Jul 4;5(3):e264-e272.	The authors concluded that in the real world setting, WILATE was safe, well tolerated, and effective for prevention of bleeding in both the adult and pediatric patient population, with no findings of thrombotic events or unexpected adverse drug reactions.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Wilate does not indicate any new safety concerns. The PAC review was initiated due to the September 25, 2019, approval of an efficacy supplement to add an indication in adults and adolescents with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes and on demand treatment and control of bleeding episodes. There were no deaths.

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 Wilate.

[5] Search strategy: To limit search to WILATE and avoid non-specific publications regarding von Willebrand Disease, non-specific von Willebrand Factor, FVIII, and FVIII related disorders, the search strategy in PubMed consisted of specifying ((Wilate) NOT (factor VIII) NOT (von Willebrand factor))