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

# MEMORANDUM

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| To: | Craig Zinderman, MD, MPH<br>Acting Director, Division of Epidemiology (DE)<br>Office of Biostatistics and Epidemiology (OBE),<br>Center for Biologics Evaluation and Research (CBER) |
| Through: | Meghna Alimchandani, MD<br>Associate Director for Medical Policy, OBE, CBER |
| From: | Firoozeh Alvandi, MD<br>Medical Officer, Pharmacovigilance Branch, DE, OBE, CBER |
| 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: | 125251/256 |
| Indication: | Use in children and adults with von Willebrand Disease for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding.<br><br>WILATE is not indicated for Hemophilia A. |
| Meeting Date: | Pediatric Advisory Committee Meeting, September 2019 |

## Contents

# 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 was the approval of an efficacy supplement, supplemental Biologics License Application (sBLA) 125251/139, for WILATE on August 5, 2015, to expand the clinical indication to include children with von Willebrand Disease (vWD).

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*

WILATE is a human plasma-derived, virus inactivated von Willebrand Factor/Coagulation Factor VIII Complex, supplied as a lyophilized powder for reconstitution for intravenous injection. WILATE is manufactured by Octapharma.

## *1.3 Regulatory History*

WILATE was first approved in the United States (US) on December 04, 2009, for treatment of spontaneous and trauma-induced bleeding episodes in patients with severe 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, the indication for WILATE was expanded to include use in children with vWD (Efficacy Supplement 125251/139).

**Current indication:** WILATE is indicated for use in children and adults with vWD for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding.

WILATE is <u>not</u> indicated for Hemophilia A.

# 2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for WILATE for dates August 05, 2015 to March 03, 2019 (PAC review period) and for December 04, 2009 to March 31, 2019 (historical review period)

- Manufacturer's Submissions
    - WILATE US package insert, dated August 2015
    - Letter regarding dose distribution data, received June 19, 2019
    - Pharmacovigilance Plan, Version 9, dated June 29, 2018
- FDA Documents
    - WILATE Efficacy Supplement Approval Letter for Submission Tracking Number (STN) 125251/139, dated August 05, 2015, and Revised Approval Letter dated August 21, 2015
    - Division of Epidemiology Pharmacovigilance Review Memorandum for STN 125251/139, dated June 12, 2015
- Publications (see Literature Search in Section 7)

## 3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for WILATE since licensure.

## 4 PRODUCT UTILIZATION DATA

Octapharma USA, Inc. provided distribution data for the US and worldwide for time intervals August 05, 2015 to March 31, 2019 and December 04, 2009 to March 31, 2019:

During the period of August 01, 2015 to March 31, 2019, there was a total of (b) (4) international units (IU) of WILATE distributed in the US, with an estimated (b) (4) IU used in the pediatric age group (18 years of age and younger). The worldwide distribution for the same period was a total of (b) (4) IU, with an estimated (b) (4) IU used in the pediatric age group (18 years of age and younger).

During the period of December 01, 2009 to March 31, 2019, there was a total of (b) (4) IU of WILATE distributed in the US, with an estimated (b) (4) IU used in the pediatric age group (18 years of age and younger). The worldwide distribution for the same period was a total of (b) (4) IU, with an estimated (b) (4) IU used in the pediatric age group (18 years of age and younger).

Per the sponsor, WILATE usage in the pediatric age group was calculated using the distribution of hemophilia patients by age as reported in the 2017 World Federation of Hemophilia (WFH) Annual Global Survey, and applying the percentage of patients in each age group to the total distributed amount. The sponsor used internal market

research data on the proportion of WILATE used for vWD and similarly applied the vWD age distributions from the WFH Report.

These estimates were 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*

The manufacturer's current Pharmacovigilance Plan (PVP) for WILATE is Version 9, dated June 29, 2018[1]. Table 1 describes the identified risks, potential risks and missing information for WILATE.

**Table 1: WILATE Safety Concerns and Planned Pharmacovigilance Actions[2]**

| **Identified Risks** | **Planned Pharmacovigilance Actions** |
|---|---|
| Inhibitory antibody formation | Routine surveillance |
| Hypersensitivity reactions | Routine surveillance |
| **Potential Risks** | **Planned Pharmacovigilance Actions** |
| Infectious pathogen transmission | Routine surveillance |
| Thromboembolic events | Routine surveillance |
| **Missing Information** | **Planned Pharmacovigilance Actions** |
| Safety in pregnancy | Routine surveillance |
| Safety in breast feeding | Routine surveillance |
| Safety in elderly | Routine surveillance |
| Safety in patients with renal impairment | Routine surveillance |
| Safety in patients with hepatic impairment | Routine surveillance |

*Inhibitory antibody*: Inhibitory (neutralizing) antibody formation is an identified risk (although no cases of inhibitory antibody formation were reported in the premarket

[1] WILATE Pharmacovigilance Plan, Version 9, dated June 19, 2018, WILATE Submission STN 125251/244 .1 Module 1.16.1 Risk Management.

[2] WILATE Pharmacovigilance Plan, Version 9.

safety database), which can result in decreased drug effectiveness, and is labeled under Warnings and Precautions (section 5) of the package insert.

*Hypersensitivity reactions:* WILATE is contraindicated for patients who have known anaphylactic or severe systemic reaction to plasma-derived products, any ingredient in the formulation, or components of the container. Hypersensitivity or allergic reactions have been observed after use of WILATE and is labeled under Warnings and Precautions (section 5) and Adverse Reactions (section 6) of the package insert.

*Thromboembolic events*: WILATE may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma von Willebrand Factor: Ristocetin Cofactor (vWF:RCo) and Factor VIII (FVIII) activities. Thromboembolic risk is labeled under Warnings and Precautions (section 5) of package insert.

*Infectious pathogen transmission*: There exists a theoretical risk of transmission of infectious agents as the product is made from human plasma, and this risk is labeled under Warnings and Precautions (section 5) of package insert. Parvovirus B19 positivity was reported in the premarket safety database but was not definitively attributed to WILATE.

The identified and potential risks listed in Table 1 are common to this product class and will be monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for WILATE.

# 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 between December 04, 2009 (initial licensure) to March 31, 2019, and August 05, 2015 (PAC trigger) to March 31, 2019. 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 AE reports for WILATE during the PAC review period are listed in Table 2 below and during the historical review period are listed in Table 3 below. There were 18 US and 15 foreign reports for review period August 05, 2015 to March 31, 2019. There were 23 US and 34 foreign reports for review period December 04, 2009 to March 31, 2019.

**Table 2: FAERS Reports for WILATE August 05, 2015 to March 31, 2019 (PAC review period)**

| Age | Serious non-fatal, US | Serious Non-fatal, Foreign | Deaths, US | Deaths, Foreign | Non-Serious, US | Non-Serious Foreign | Total, US | Total, Foreign |
|---|---|---|---|---|---|---|---|---|
| <18 years | 7 | 2 | 0 | 0 | 5 | 0 | 12 | 2 |
| ≥18 years | 2 | 10 | 0 | 2 | 3 | 0 | 5 | 12 |
| Unknown | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 |
| All ages | 9 | 13 | 0 | 2 | 9 | 0 | 18 | 15 |

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

**Table 3: FAERS Reports for WILATE December 04, 2009 to March 31, 2019 (Historical review period)**

| Age | Serious non-fatal, US | Serious Non-fatal, Foreign | Deaths, US | Deaths, Foreign | Non-Serious, US | Non-Serious Foreign | Total, US | Total, Foreign |
|---|---|---|---|---|---|---|---|---|
| <18 years | 10 | 4 | 0 | 0 | 5 | 1 | 15 | 5 |
| ≥18 years | 3 | 26 | 0 | 2 | 3 | 0 | 6 | 28 |
| Unknown | 1 | 1 | 0 | 0 | 1 | 0 | 2 | 1 |
| All ages | 14 | 31 | 0 | 2 | 9 | 1 | 23 | 34 |

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

#### 6.2.1 Deaths

There were 2 foreign deaths, both in adults, following WILATE during the review period from December 04, 2009 to March 31, 2019. All fatal reports were individually reviewed and are summarized below.

1. 38-year-old female with vWD, and multiple pre-existing conditions (non-alcoholic liver disease, dyspnea, anti-nuclear antibodies, *E. coli* sepsis, fungal infection, anemia, hemorrhage, lung infiltrates, systemic lupus erythematosus, and diabetes mellitus) received recombinant FVIII (rFVIII) and WILATE. The patient was suspected of developing inhibitory Factor VIII antibodies and, per the report, "*experienced lack of effect in context of rFVIII therapy (which was failing despite high dosing)*." The patient died approximately 2 weeks after the last dose of WILATE. Cause of death was due to underlying pneumonia, sepsis, fungal infection, vWD, and multiorgan failure, per the report.
   *Reviewer comments*: There was no mention of von Willebrand Factor inhibitory antibody in the narrative, though the report states that Factor VIII inhibitory antibody development was suspected. Per the report, quality review and testing of WILATE batches found no deviations or anomalies pertaining to manufacturing or product quality.
2. 40-year-old male with type 3 vWD receiving treatment with WILATE developed spontaneous cerebral hemorrhage and died of hemorrhagic stroke.
   *Reviewer comments*: There was no information regarding any testing for antibodies to Factor VIII or to von Willebrand Factor. Per the report, quality review and testing of WILATE batches found no deviations or anomalies pertaining to manufacturing or product quality. Based on the available information, in this case hemorrhage/hemorrhagic stroke was likely confounded by underlying condition/indication.

### 6.2.2 Serious Non-fatal Reports

During the reporting period (December 04, 2009 to March 31, 2019), there were 45 serious, non-fatal reports; 14 of which involved pediatric patients. The most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for serious non-fatal reports are summarized in Table 4. The 14 (10 from the US and 4 foreign) serious non-fatal AEs reported in children are summarized below.

- 6 reports of AEs consistent with hypersensitivity reactions (flushing/redness, urticaria/rash, throat tightness, mouth edema, rash), hyperhidrosis, infusion related reaction, nausea, vomiting. Hypersensitivity reactions are labeled AEs that can occur with any factor replacement product, including WILATE.
- 3 reports of von Willebrand inhibition/inhibitory antibody, all in patients with type 3 vWD. Of these, 2 patients were described in a literature report[3]. Formation of inhibitory antibody to von Willebrand Factor is an expected/labeled AE associated with administration of von Willebrand Factor containing products, including WILATE.
- 2 reports of device related infection in patients with Hemophilia A and Factor VIII inhibitor, receiving WILATE as part of an immune tolerance study, both with underlying intravenous access device infection, unrelated to WILATE.

[3] Platt CD, D'Angelo L, Neufeld EJ, Broyles AD. Skin testing, graded challenge, and desensitization to von Willebrand factor (VWF) products in type III von Willebrand disease (VWD). *J Allergy Clin Immunol Pract*. 2016 Sep-Oct; 4(5): 1006-8).

- The remaining reports described sporadic events of Factor VIII inhibition (with no adverse event), epistaxis, and amnesia/memory loss (no further details provided).

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

| Preferred Term (PT) | Number of Serious Reports | Label* Status |
|---|---|---|
| Flushing | 10 | Labeled (5.1, 6.2) |
| Dyspnoea | 9 | Labeled (5.1,6.2) |
| Maternal exposure during pregnancy | 7 | Limited experience in pregnancy discussed in label (8.1) |
| Infusion related reaction | 6 | Unlabeled |
| Drug ineffective | 5 | Unlabeled |
| Nausea | 5 | Labeled (5.1,6.2) |
| Abortion spontaneous | 4 | Limited experience in pregnancy discussed in label (8.1) |
| Back pain | 4 | “Pain” Labeled (6.2) |
| Chest discomfort | 4 | Labeled (6.2) |
| Hypersensitivity | 4 | Labeled (4, 6, 6.1, 17) |
| Vomiting | 4 | Labeled (5.1, 6.2) |
| Von Willebrand’s Factor inhibition | 4 | Labeled (5.1, 5.3) |
| Chest pain | 3 | “Chest discomfort” and “chest tightness” are labeled (5.1,6.2,17); “pain” is labeled (6.2) |
| Haemoglobin decreased | 3 | “Low hemoglobin” and “anemia” due to surgical loss are discussed in the label as findings in clinical trials (14) |
| Hyperhidrosis | 3 | Unlabeled |
| Urticaria | 3 | Labeled (5.1,6, 6.1, 6.2, 17) |

*Label dated August 2015
Label Sections: 4 CONTRAINDICATIONS; 5.1 Hypersensitivity Reactions; 5.3 Neutralizing Antibodies; 6 ADVERSE REACTIONS; 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience; 8.1 Pregnancy; 14 CLINICAL STUDIES; 17 PATIENT COUNSELING INFORMATION.

All PTs occurring with a frequency >2 reports are shown in Table 4. Most reported MedDRA PTs are labeled events or consistent with an already labeled event. Infusion related reaction may occur during or after infusion of the product, – common PTs seen in association with infusion related reaction include, but are not limited to hypersensitivity signs and symptoms, flushing, erythema, dyspnea, and/or hemodynamic related changes including hyper- or hypotension. “Drug ineffective” is not an adverse event, and may be associated with inhibitory antibody, which is labeled, or other underlying or confounding factors such as inadequate dosing. The PTs “Erythema” and “Feeling Hot” are non-specific symptoms that may be related to labeled PTs for hypersensitivity reactions, flushing, or urticaria. Hyperhidrosis is a non-specific event. Decreased hemoglobin resulting from bleeding is confounded by the indication/ underlying disease. “Exposure during pregnancy” is not an adverse event and there is no contraindication to use in pregnancy specified in the WILATE label (please see additional discussion of this PT in section 6.3 of memo). Other PTs associated with serious AE reports were associated with 2 or less reports. Unlabeled AEs/PTs were confounded by concomitant or underlying conditions and/or accompanied labeled AEs and did not raise new safety concerns.

### 6.2.3 Non-serious Reports

During the reporting period, there were 10 non-serious reports; 6 of which involved pediatric patients (5 US and 1 foreign). The top PTs for non-serious reports include dyspnea and flushing. No other PTs appeared in more than 2 reports. Pediatric non-serious reports included mild allergic/hypersensitivity reactions (urticaria, dyspnea, erythema, feeling hot, flushing), increased blood pressure, diarrhea, contusion, pain in extremity, and oxygen saturation decreased. These PTs were generally similar to those seen with serious reports, and each of them only appeared in one or a few reports. Unlabeled AEs/PTs were confounded by concomitant or underlying conditions and/or accompanied labeled AEs and did not raise new safety concerns.

## *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 of April 28, 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) run identified the preferred terms (PTs) summarized in Table 5, with a disproportional reporting alert. Note that a report may have one or more PTs. (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 with data lock point of April 28, 2019**

| Preferred Term (PT) with EB05>2 | Number of Reports | Label* Status |
|---|---|---|
| Dyspnoea | 12 | Labeled (5.1,6.2) |
| Flushing | 11 | Labeled (5.1, 6.2) |
| Maternal exposure during pregnancy | 7 | Limited experience in pregnancy discussed in label (8.1) |
| Infusion related reaction | 6 | Unlabeled |
| Von Willebrand's Factor inhibition | 4 | Labeled (5.1, 5.3) |

*Label dated August 2015
Label Sections: 5.1 Hypersensitivity Reactions; 5.3 Neutralizing Antibodies; 6.2 Postmarketing Experience; 8.1 Pregnancy

Most of these events appeared among the most frequently reported PTs and are discussed in Section 6.2. Maternal exposure during pregnancy is not an adverse event and there is no contraindication to use in pregnancy. Per section 8.1 of the label, "*There is no data with WILATE use in pregnant women to inform a drug-associated risk. WILATE was given to four subjects during labor and delivery in one clinical study. In this study all procedures were uneventful*." Review of the 7 reports found 3 cases of abortion, of which, 1 case was due to Parvovirus B19 [testing of WILATE found results within normal limits (low level Parvovirus B19 in pools, acceptable per manufacturer]; 1 case occurred in a patient with previous abortions who received WILATE and experienced hypersensitivity reaction from which she recovered, and 2 months later, had a spontaneous abortion; and 1 case was due to hemorrhage which is confounded by indication (test for von Willebrand Factor inhibitor was negative). Other cases of maternal exposure during pregnancy were associated with infusion reactions (2 cases) and/or hypersensitivity reactions (2 cases).

*Reviewer comments:* Review of these cases does not raise new safety concerns. Patients with vWD are at risk for bleeding and for spontaneous abortions. According to a publication based on a pilot study in a single center, in women with vWD disease, the rate of pregnancy loss (spontaneous abortion) was 25% compared with 16.0% in women without vWD (p=.28) [4]. A 2018 review article by Reynen, et. al. stated that it is not clear if there is an increased risk of spontaneous abortion in patients with vWD, although acknowledging that this patient population is at increased risk of bleeding and

[4] Skeith L, Rydz N, O'Beirne M, Goodyear D, Li H, Poon MC.Pregnancy loss in women with von Willebrand disease: a single-center pilot study. *Blood Coagul Fibrinolysis*.2017;28:393-397.

thus at increased risk of postpartum hemorrhage [5]. Per a publication[6] assessing self-reported abortions, excluding induced terminations between 1990-2011, and without specific mention of association with vWD or other underlying conditions, the risk of pregnancy loss was 19.7% (with 13.5% risk of early pregnancy loss).

### *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 US National Library of Medicine's PubMed.gov database on May 09, 2019, for peer-reviewed literature, with the search term "WILATE" and "SAFETY" limited by human species, and dates from licensure (December 04, 2009) to date of search (May 09, 2019), retrieved 5 publications pertaining to safety. No new safety concerns for WILATE were identified in the review of these publications, summarized in the table below:

[5] Reynen E, James P. Von Willebrand Disease and Pregnancy: A Review of Evidence and Expert Opinion. *Semin Thromb Hemost*. 2016;42:717-723.

[6] Rossen LM1, Ahrens KA2, Branum AM3. Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. *Paediatr Perinat Epidemiol*. 2018;32:19-29.

| Publication | Authors' Safety Conclusion |
|---|---|
| Batty P, Chen YH, Bowles L, Hart DP, Platton S, Pasi KJ. Safety and efficacy of a von Willebrand factor/factor VIII concentrate (Wilate®): a single centre experience. *Haemophilia*. 2014;20:846-53. | Review of efficacy and safety of WILATE use at one center between January 03, 2007 and January 05, 2012, in 54 adult patients. The authors concluded that WILATE was safe and effective in adults with vWD. |
| Khair K, Batty P, Riat R, Bowles L, Burgess C, Chen YH, Hart D, Platton S, Pasi J, Liesner R. Wilate use in 47 children with von Willebrand disease: the North London paediatric haemophilia network experience. *Haemophilia*. 2015;21:e44-50. | Study of safety, efficacy, and tolerability of WILATE in 47 children with vWD within the North London Paediatric Haemophilia Network. The authors concluded that WILATE is well tolerated, safe, and effective when administered for on-demand use, and/or prophylactically, in neonates, children and adolescents. |
| Srivastava A, Serban M, Werner S, Schwartz BA, Kessler CM; Wonders Study Investigators. Efficacy and safety of a VWF/FVIII concentrate (wilate®) in inherited von Willebrand disease patients undergoing surgical procedures. *Haemophilia*. 2017;23:264-272. | Prospective, open label study of efficacy and safety of WILATE in maintaining hemostasis in 28 patients undergoing 30 surgical procedures (including 21 major surgeries). The authors concluded that WILATE was safe and effective in the prevention and treatment of bleeding in patients with vWD undergoing surgery. |
| Nowak-Göttl U, Krümpel A, Russo A, Jansen M. Efficacy and safety of Wilate in paediatric VWD patients under 6 years of age - results of a prospective multicentre clinical study including recovery information. *Haemophilia*. 2013;19:887-92. | Prospective, open label study of 15 pediatric patients ≤6 years of age who received WILATE for either prophylaxis, on demand treatment or for treatment in surgical procedures. The authors concluded that WILATE is effective, safe, and well tolerated in these patients. |
| Windyga J, von Depka-Prondzinski M; European Wilate® Study Group. Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery. *Thromb Haemost*. 2011;105:1072-9. | Review of four prospective, open label, uncontrolled, nonrandomized, phase II/III clinical trials of WILATE used perioperatively for hemostasis in 32 patients (including adults and children) undergoing 57 surgical procedures. The authors concluded that WILATE is effective, safe, and well tolerated in the perioperative management of hemostasis/bleeding in patients with vWD. |

## 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 approval of WILATE in pediatric patients on August 05, 2015. 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 WILATE.