Summary Basis of Regulatory Action (SBRA)

Date: July 7, 2015

From: Laurence Landow MD

BLA/ STN#: 125251/139

Applicant Name: Octapharma Pharmazeutika Produktionsges.m.b.H.

Date of Submission: October 8, 2014

PDUFA Goal Date: August 8, 2015

Proprietary Name/ Established Name: Wilate® / von Willebrand Factor/Coagulation Factor VIII Complex (Human)

Indication: Prevention of excessive bleeding during and after surgery in von Willebrand Disease (VWD) patients

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:
Paul D. Mintz, MD, Director
Division of Hematology Clinical Review, Office of Blood Research and Review

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

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

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

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Laurence Landow, M.D.
Clinical Pharmacology Review	Carl-Michael Staschen, M.D., Ph.D.
Statistical Review	Boris Zaslavsky, Ph.D., Dr.Sc.
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Bioresearch Monitoring Review	Inspections were not conducted for this supplement
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A
Epidemiology	Wambui Chege, M.D.

1. Introduction

Von Willebrand disease (VWD) is a congenital coagulation disorder that is due to a partial (Type 1, mild disease) or complete absence (Type 3, severe disease) of von Willebrand factor (VWF). A partial qualitative deficiency of VWF also exists (Type 2). VWF deficiency results in decreased FVIII-stabilizing capacity, as well as impaired platelet adhesion. The disease affects approximately 1% of the population with equal frequency among men and women, although women are more often symptomatic because of physiological events related to menstruation, pregnancy, and birth.

Octapharma's product, Wilate®, a plasma-derived product, was approved on December 4, 2009 for the treatment of spontaneous or trauma-induced bleeding episodes in patients with severe VWD, as well as patients with mild or moderate VWD in whom use of desmopressin is ineffective or contraindicated. A request for the surgical prophylaxis indication included in the original application was denied because of inadequate information to support efficacy.

This efficacy supplement seeks to provide adequate information to support use of Wilate® in adult and pediatric patients with VWD undergoing surgery. Data submitted to support this indication are derived from three uncontrolled, open-label, multicenter studies: a pivotal IND study (WIL-24) and a supportive non-IND study (WIL-14), both submitted for the first time; and a non-IND study (TMAE-104) that was included as part of the original 2006 BLA. In addition, Octapharma has submitted a Pediatric Assessment that aggregates safety and efficacy data collected from pediatric cohorts enrolled in these three studies. The applicant submitted this efficacy supplement on October 8, 2014.

2. Background

Three products are licensed for VWD patients undergoing surgery, but only Humate-P® is indicated for patients undergoing major surgery or in those with severe disease.

1. Humate-P® is indicated for adult and pediatric patients with VWD in the (1) treatment of spontaneous and trauma-induced bleeding episodes and (2) prevention of excessive bleeding during and after surgery. It is also indicated for patients with severe VWD and patients with mild to moderate VWD where the use of desmospressin is known or suspected to be inadequate.
2. Alphanate® is indicated for surgical and/or invasive procedures in adult and pediatric patients with VWD in whom desmopressin acetate (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.
3. DDAVP is indicated for patients with mild to moderate VWD (Type I) with Factor VIII levels greater than 5%. It is not effective in patients with severe (Type 3) VWD and is contraindicated in Type 2B VWD (increased affinity for platelet glycoprotein 1b) and contraindicated for other clinical reasons, e.g., creatinine clearance <50 mL/min, hyponatremia, or a history of hyponatremia. In addition, DDAVP can be associated with significant side effects.

Several months after Wilate® was approved, the applicant submitted a single-arm, phase 3 trial draft protocol (WIL-24) to support the surgical prophylaxis indication in adults and adolescents. The primary endpoint, hemostatic efficacy ("success"), was defined as a rating of excellent or good on a 4-point scoring system (i.e. excellent, good, moderate, none) as assessed independently by the surgeon at the end of surgery, and by the hematologist/investigator 24 hours after final infusion of product. All outcomes were

adjudicated *post hoc* by an Independent Data Monitoring Committee (IDMC). In situations where the IDMC's assessment differed from that of the surgeon and/or investigator-hematologist, the IDMC assessment took priority.

3. Chemistry Manufacturing and Controls (CMC)

No new CMC information was submitted and information provided in prior submissions adequately supports this submission.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology was submitted and information provided in prior submissions adequately supports this submission.

5. Clinical Pharmacology

No clinical pharmacology studies in the surgery setting were conducted with Wilate®. However, included in this application were two supportive clinical pharmacology studies (WIL-12 and WIL-21) that compared the pharmacokinetics (PK) of Wilate® and Humate-P® in VWD subjects. The studies were designed as prospective, randomized, controlled, open-label, and two-arm cross-over.

When administered in approximately equal doses, the VWF PK profiles (based on VWF:RCo assay) for Wilate® and Humate-P® showed no significant difference in mean terminal half-life (HL) for subjects diagnosed with VWD Type 3 (HL = 12 h) or Type 1 (HL = 13 h). For VWD Type 2 subjects, mean terminal HL was 18 h (range: 5 to 32 h) for Wilate® and 28 h (range: 6 to 76 h) for Humate-P®; the difference in mean HL is not statistically significant. No significant differences were noted in recovery, Cmax or AUC between Wilate® and Humate-P®.

The results are acceptable to this reviewer.

6. Clinical/ Statistical

a) Protocol Amendments – Study WIL-24

The original WIL-24 protocol was amended several times with FDA concurrence. The most noteworthy changes are presented below.

(i) Incorporation of an interim analysis into the statistical analysis plan after enrollment of 30 subjects, and implementation of early stopping rules for success.

An interim analysis was introduced after 30 procedures to test for early success with $\alpha = 0.005$. The study would be terminated early, and success claimed if the 99.5% confidence interval (CI) for the overall success rate excluded and was >0.70 (equivalent to ≥29 successes out of the 30 procedures). If success was not demonstrated after 30 procedures, the study was to continue to include a total of 41 procedures, and the final analysis was to use $\alpha = 0.045$, success being defined if the 95.5% CI for the overall success rate excluded and was >0.70. Seven or more failures would make it impossible to reach the criteria for success.

(ii) Recruitment of VWD Type 1 and Type 2 subjects into the study to enhance the enrollment rate.

(iii) Addition of an independent Data Monitoring Committee (IDMC) to adjudicate all outcomes.

Ultimate determination of success (hemostatic efficacy rating of excellent or good) was redefined so that in situations where differences existed between assessments made by the surgeon and/or investigator versus the IDMC, the IDMC's assessment would take priority.

b) Design Overview – Study WIL 24

WIL-24 was a prospective, multicenter, open-label, uncontrolled phase 3 study.

The Safety Population comprised 41 adult and pediatric (adolescent) subjects with VWD undergoing major or minor surgery. Eleven adult subjects were terminated prematurely due to Screening failure (N=9) or premature withdrawal (N=2), one at sponsor request for slow site enrollment and another at subject request. The remaining 30 subjects (28 individuals, 25 adults and 3 adolescents) included 2 adults who underwent additional procedures and were assigned different ID numbers. Most procedures were orthopedic or dental; obstetric/gynecological, gastrointestinal, ENT, and ophthalmologic procedures comprised the remainder. Of the 21 VWD Type 3 subjects, 17 underwent major surgery and 4 underwent minor surgery.

Past Medical History was remarkable for bleeding episodes that were of mild (N=6) or moderate (N=22) intensity and occurred approximately every month.

Demographic characteristics included a median age of 36 years (range: 12 to 74 years) with females (N=21) outnumbering males 2:1. The population was predominantly Caucasian (N=18) and Asian (N=11), with a noticeable underrepresentation of Black/African American (N=1) and Hispanics (N=0). Most subjects (N=21) had Type 3 disease (complete absence of von Willebrand factor, VWF); the remainder were Type 1 (partial quantitative VWF deficiency, N=7) or Type 2 (partial qualitative VWF deficiency, N=2).

Approximately 1-2 hours prior to incision, a loading dose of product was infused, followed by 2 (or more) maintenance infusions every 12 hours postoperatively as needed to control hemostasis. Dose titration was based on the type of surgery (major, minor, gastrointestinal procedures) and expected blood loss. The size of the loading dose was based on in vivo recovery (IVR) for VWF:RCo, VWF:Ag and FVIII:C calculated at a central laboratory from blood samples collected at the Screening/Baseline visit following administration of a 60 IU VWF:RCo/kg BW (labeled potency) dose. Results were reported as (IU/dL)/(IU/kg). The IVR value for VWF:RCo was used to determine the recommended loading and maintenance doses, and communicated to the study site prior to the start of the procedure.

Hemostatic efficacy, the primary endpoint of the study, was assessed by the surgeon at the conclusion of surgery, and by the investigator-hematologist at 24 hours following completion of the final maintenance dose, using a prospectively defined 4-point scoring system (excellent, good, moderate, none) in which "success" was defined as a rating of excellent or good. All outcomes were adjudicated post hoc by an independent Data Monitoring Committee (IDMC). In situations where the IDMC's assessment differed from that of the surgeon and/or investigator-hematologist, the IDMC assessment took priority.

The study was terminated prematurely after the planned interim analysis found that the success rate (29/30 procedures rated excellent or good) exceeded the prespecified stopping threshold of ≥25/30 successful procedures (rate of success: 0.967; CI 0.784 to 1.000). Only one procedure, lumbar laminectomy in a VWD Type 1 Caucasian male adult, was judged as a failure. Treatment was successful in 100% of minor surgeries and 95.2% of major surgeries (1 failure, lumbar laminectomy). Success rates were 100% in VWD Type 3 and Type 2 subjects, and 85.7% in Type 1 subjects (1 failure in the same subject). See Table 1, below for a summary of these results.

In terms of breakdown by demographics, successful outcomes were reported in 89% of males and 100% of females; 94% of Caucasians, 100% of Asians and 100% of Blacks; and 100% of subjects aged 12-17 years, 96% of subjects aged 18-65, and 100% of subjects aged >65 years.

Table 1: Success Rate by Surgery Severity (upper panel) and VWD Type (lower panel)

Efficacy	**Minor (n=9)**		**Major (n=21)**		**All Procedures (n=30)**	
	n (%)	98.75% CI	n (%)	98.75% CI	n (%)	98.75% CI
Success	9 (100)	0.569, 1.000	20 (95.2)	0.704, 1.000	29 (96.7)	0.784, 1.000
Failure	0		1 (4.8)		1 (3.3)	

Efficacy	**VWD Type 1 (7)**		**VWD Type 2 (n=2)**		**VWD Type 3 (n=21)**	
	n (%)	98.75% CI	n (%)	98.75% CI	n (%)	98.75% CI
Success	6 (85.7)	0.328, 0.999	2 (100)	0.079, 1.000	21 (100)	0.785, 1.000
Failure	1 (14.3)		0		0	

n=number of surgical procedures

Adapted from WIL-24 Final Study Report, Tables 16 and 17

c) Pediatric Assessment - Studies WIL-24, WIL-14, TMAE-104

The supplement also included a final study report for study WIL-14, study TMAE-104 and a Pediatric Assessment.

WIL-14 was a prospective, multicenter, open-label, uncontrolled study in children (N=15) <6 years of age. The primary objective was to assess hemostatic efficacy of the product when administered either for (a) spontaneous/post-traumatic bleeding (N=8) or (b) surgical prophylaxis (N=7). Children in the surgical prophylaxis subgroup were aged 0 to <2 (N=3) and 2 to <6 (N=4) years, and underwent 9 procedures (major: n=3; minor: n=6). Hemostatic efficacy was rated as excellent or good in 100% of cases.

TMAE-104 was a prospective, multicenter, open-label, uncontrolled study in adult and pediatric subjects undergoing surgery. The primary objective was to assess plasma levels of FVIII:C, VWF:Ag, VWF:CB and VWF:RCo as surrogate markers of efficacy (clinical efficacy was a secondary endpoint). Children in the surgical prophylaxis subgroup were aged 6 to <12 years (N=3). Hemostatic efficacy was rated as excellent or good in 100% of cases.

The Pediatric Assessment comprised aggregate data from the pediatric surgical cohorts enrolled in WIL-24 (N=3), WIL-14 (N=7), and TMAE-104 (N=3), the last included as part of the original BLA, representing subjects aged 12 to <16; divided into the following age cohorts, 0 to <2, 2 to <6, and 6 to <12 years of age.. Hemostatic efficacy was rated as excellent or good in 100% of cases. Six subjects experienced 19 unrelated SAEs that

included bleeding events (e.g., hematemesis, hemarthrosis) as well as non-bleeding events (e.g., catheter sepsis, head trauma, torticollis, synovitis, device-related infection).

7. Safety – Study WIL-24

There were no reports of death, thromboembolic events, accumulation of VWF or FVIII:C, or positive testing for VWF inhibitors at Screening or on Day 30 in Study WIL-24.

Two unrelated bleeding SAEs (vaginal hemorrhage and hematemesis) in two subjects and one unrelated wound infection AE of severe intensity in a third were reported. The two bleeding SAEs were almost certainly unrelated to Wilate exposure based on the elapsed time from last maintenance treatment to onset of event (11 and 9 days), as both subjects had been discharged from the hospital in stable condition. A causal association between Wilate and wound infection is unlikely given known postmarketing safety data.

The incidence of AEs was similar across demographic subgroups, reported in 67% of males (N=9) and 72% of females (N=21); 79% of Caucasians (N=18), 69% of Asians (N=11) and 0% of Blacks (N=1); and 67% of subjects aged 12-17 years (N=3), 74% of subjects aged 18-65 years (N=25), and 50% of subjects aged >65 years (N=2).

Mild-moderate intensity AEs (n=118), most commonly procedural pain, nausea and vomiting and assessed as "unlikely related" or "not related" by the applicantwere reported in 29 subjects (70.7%). Five subjects experienced mild-moderate intensity AEs "probably related" by the applicant to Wilate® and clinically manifest by anxiety, chest discomfort, hypersensitivity, hypertension, and hypotension. Three of these AEs were classified as "temporally-related" hypersensitivity reactions (within 24 hours) and required medical intervention. This reviewer agrees that such events are not unexpected since hypersensitivity reactions have been reported with other plasma-derived products.

Table 2: Number of Subjects in the Safety Population (N=41) Experiencing Adverse Events

Classification	All Subjects (%)
Adverse event	29 (70.7)
Serious adverse event	2 (4.9)
Related adverse events	5 (12.2)
Severe intensity adverse event	1 (2.4)
Adverse event leading to discontinuation of Wilate®	2 (4.9)
Adverse event leading to death	0

Adapted from WIL-24 Final Study Report, Table 25

8. Advisory Committee Meeting

There were no issues for the Blood Products Advisory Committee to address.

9. Other Relevant Regulatory Issues

Pharmacovigilance plan: no new safety concerns have been identified in the latest postmarketing surveillance report. FDA's Division of Epidemiology in the Office of Biostatistics and Epidemiology is in agreement with the sponsor's plan for ongoing routine surveillance and completion of four postmarketing studies to evaluate safety and efficacy. Available safety data do not substantiate a need for a postmarketing requirement study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS).

10. Labeling

The Advertising and Promotional Labeling Branch (APLB) was consulted and provided input with respect to physician labeling, as well as carton/container labeling. All issues raised by the APLB reviewer and the clinical reviewer have been addressed by the applicant.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The clinical reviewer recommended approval of STN125251/139.

b) Risk/ Benefit Assessment

All VWD patients undergoing surgery, especially those with severe deficiency of VWF (Type 3), are at increased risk of bleeding during and after surgery. Data from pivotal trial WIL-24, assessed by an IDMC, indicated that Wilate® reduced surgical bleeding in adult and adolescent VWD subjects undergoing surgery; data from studies conducted in the pediatric population aged 0-12 years supported this conclusion. Safety concerns, such as thromboembolism, coagulation factor accumulation, and inhibitor formation were not observed in the pivotal trial, and hypersensitivity reactions were mild to moderate in intensity. The aggregate data indicate Wilate® is an acceptable alternative to Humate-P®, currently the only product indicated for VWD patients undergoing surgery.

c) Recommendation for Postmarketing Risk Management Activities

A PMR or REMS is not recommended by the clinical reviewer.

d) Recommendation for Postmarketing Activities

The applicant's plan for ongoing surveillance and completion of ongoing postmarketing studies to evaluate safety and efficacy is sufficient.