Summary Basis for Regulatory Action Template

Date: April 13, 2018

From: Poornima Sharma M.D., Chair of Review Committee

STN#: 125577/118

Applicant Name: Baxalta

Date of Submission: June 16,2017

Goal Date: April 16, 2018

Proprietary Name/ Established Name: Vonvendi [von Willebrand factor (recombinant)]

Indication: Perioperative management of bleeding

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority:

Tejashri Purohit- Sheth , M.D./ Director/Division of Clinical Evaluation and Pharmacology/Toxicology/OTAT/CBER/FDA

- ☐ **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.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	N/A
Clinical Review(s) • *Clinical (product office)* • *Post marketing safety epidemiological review (OBE/DE)* • *BIMO*	Poornima Sharma April 13, 2018 Wambui Chege March 22, 2018 Christine Drabick February 14, 2018
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Shuya Lu March 15, 2018
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Theresa Chen
Clinical Pharmacology Review(s)	Iftekhar Mahmood February 27, 2018
Labeling Review(s) • *APLB (OCBQ/APLB)*	Kristine Khuc March 19, 2018
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	N/A
Advisory Committee summary	N/A

1. Introduction

Vonvendi is a human recombinant Von-Willebrand factor (VWF) and was approved for on-demand treatment and control of bleeding events in adults with Von-Willebrand disease (VWD) on December 8th, 2015.The product was given orphan designation in November 2010. Since Vonvendi is not exposed to plasma protease ADAMTS 13, it contains a higher proportion of hemostatically active high molecular weight multimers (HMWM) and ultra-large multimers (ULM) compared to plasma derived products. Unlike plasma derived von-Willebrand factor replacement therapy that contains Factor VIII, Vonvendi contains only VWF necessitating co-administration of exogenous Factor VIII for treatment of bleeding events.

This efficacy supplement seeks the additional indication of perioperative management of bleeding in patients with Von-Willebrand disease.

Study 071101 provided the primary evidence of efficacy for this indication, and was a Phase 3, prospective, single arm, multicenter study that assessed the efficacy and safety of Vonvendi (with/out recombinant Factor VIII; Advate) in the perioperative management of 15 adult subjects with severe Von-Willebrand disease that underwent major and minor elective surgeries. Safety was assessed based on an integrated assessment from Study 071101 and two additional trials: Study 070701, a Phase 1 trial evaluating PK, safety and tolerability of recombinant von-Willebrand factor / Factor VIII in severe VWD; and Study 071001, a Phase 3 trial to evaluating the PK, safety and efficacy of recombinant VWF factor/Factor VIII in the treatment of bleeding episodes in severe VWD.

This document summarizes the basis for approval of Vonvendi for perioperative management of bleeding and highlights key review issues. The review team recommends approval of this efficacy supplement for the expanded indication of perioperative management of bleeding, to include elective and emergency surgery.

2. Background

VWD is the most common inherited bleeding disorder in humans, most commonly inherited in an autosomal dominance pattern, with an incidence of approximately 1:1000 live births. The prevalence of symptomatic disease is estimated to be 1 case per 10,000 persons. It can involve quantitative (types 1 and 3) or qualitative (type 2) abnormalities in VWF. Type 1 VWD constitutes approximately 70-80% of cases; approximately 20% of cases are Type 2, and Type 3 is the rarest form of disease and constitutes approximately 1-5% of cases.

Von Willebrand factor (VWF) plays an important role in primary hemostasis by binding to both platelets and endothelial components, at sites of endothelial injury and between adjacent platelets in areas with high shear. It also contributes to secondary hemostasis by acting as a carrier protein for factor VIII. Deficiency of VWF can be associated with low levels of FVIII, and concurrent treatment with exogenous FVIII is sometimes required for hemostasis.

Patients with Type 3 VWD, severe Type 1 and Types 2A, 2B and 2M disease require replacement therapy with a VWF-containing product especially in the perioperative setting. Guidelines recommend administration of a loading dose to achieve a target peak plasma VWF:RCo (von-Willebrand ristocetin cofactor activity) and Factor VIII:C concentration of 100 IU/dl for major surgery and 50-60 IU/dl for minor surgery. A maintenance dose is recommended to keep trough VWF:RCo and Factor VIII:C levels at >50 IU/dl for the first 3 days postoperatively and >30 IU/dl after day 3 for major surgery. For minor surgery, it is recommended to keep the trough VWF:RCo and Factor VIII:C levels above 30 IU/dl in the immediate postoperative period. The duration of therapy in the postoperative period and the target trough levels are also dictated by the nature of the surgery.

Three plasma derived products: Alphanate, Humate P and Wilate are currently licensed in the United States for treatment of bleeding episodes in patients with von-Willebrand

disease. Vonvendi is the only recombinant VWF that is approved for on-demand treatment of bleeding in adults with VWD.

Human plasma derived VWF/FVIII (pdVWF/FVIII) products, Alphanate and Humate-P, are currently approved in the US for the perioperative management of patients with VWD. Alphanate is not indicated for Type 3 (severe) VWD patients undergoing major surgery. There are no recombinant products currently available for the perioperative management of VWD.

There was no pre-submission meeting for this efficacy supplement. Since this is an orphan designated product, it is not subject to PREA. No agreed iPSP was included in this submission.
This efficacy supplement was reviewed under PDUVA V program (10 month). The efficacy supplement review milestones are outlined below.

Milestone	Date
Received	June 16, 2017
Filed	August 15, 2017
Labeling target	March 17, 2018
PMC study target	March 17, 2018
Action due date	April 16, 2018

Based on the 6th Development Safety Update Report (DSUR,1July 2016- 30 June 2017), 93 subjects have been enrolled on clinical studies with Vonvendi. There are no safety concerns that have emerged from clinical studies or post marketing experience with Vonvendi.

The review team recommends approval of Vonvendi for the perioperative management of bleeding.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

The scope of the CMC review was limited to review of Section 11 of the package insert in which the applicant made some edits to the description of stabilizers and excipients that are contained in Vonvendi. CMC reviewed and approved these minor edits.

a) Product Quality –N/A

b) CBER Lot Release (only applicable for BLAs) N/A

c) Facilities review/inspection N/A

d) Environmental Assessment N/A

e) Product Comparability N/A

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Based on the results from Study Report Plac-Lab-12-12 (BAX 111: An *ex vivo* Human Placental Transfer Study), an *ex vivo* human cotyledon double perfusion model testing system showed that administration of rVWF up to concentrations of approximately 10 U of VWF:RCo/mL rVWF (500 U VWF:RCo/kg), did not transfer to the fetal circuit. However, the study was performed using full-term placenta, thus the placental transfer profile for first and second trimester placentas was not characterized. The materno-fetal diffusion distance has been reported to change significantly during pregnancy, and the expression of transporter proteins also changes during pregnancy. Therefore, the statement added by the applicant indicating that Vonvendi does not cross the human placental barrier based on this *ex vivo* placental perfusion model, should not be included in Section 13.1 ('Carcinogenesis, Mutagenesis, Impairment of Fertility') of the proposed label.

5. CLINICAL PHARMACOLOGY

In Study 071101, 11 out of 15 adult subjects underwent PK analysis with 50 IU/kg dose of Vonvendi. Loading and maintenance doses for subjects undergoing major surgery was based on IR (incremental recovery), and the half-life was determined by PK analysis. PK parameters were assessed by non-compartmental analysis. The mean IR for VWF: RCo was 1.96 (SD=.45) and half-life was 18 hours. Within 60 minutes' post infusion of Vonvendi, concentrations of VWF: RCo reached peak level and gradually declined over a period 72 hours post infusion. Overall, PK directed dosing of Vonvendi was effective in achieving target plasma levels of VWF: RCo during surgery and postoperatively.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

CLINICAL:

The clinical trial supporting the efficacy of Vonvendi for the perioperative management of VWD included 15 adult subjects with severe Von-Willebrand disease. Ten subjects underwent major surgeries and 5 subjects underwent minor surgeries. Major surgeries included major orthopedic, abdominal surgeries and complex dental extractions. All patients were administered a priming dose of Vonvendi 12-24 hours before surgery to increase Factor VIII levels into the target range. If target Factor VIII levels were not reached 3 hours prior to surgery despite administration of a priming dose, then Advate (recombinant Factor VIII) was administered in addition to Vonvendi preoperatively.

Loading and maintenance doses for Vonvendi and Advate were based on protocol specified perioperative target peak and trough levels and individual PK data.

The primary efficacy end-point was overall hemostatic efficacy (intraoperative and postoperative) assessed 24 hours after the last perioperative dose of Vonvendi or at completion of the Day 14 visit, whichever occurred earlier using a 4-point rating scale. The intraoperative hemostatic efficacy assessment was made by the surgeon and the postoperative assessment was made by the hematologist. Final adjudication of the efficacy was made by the hematologist. Severity of bleeding observed during surgery, need for additional hemostatic medications and postoperative bleeding were considered in the assessment of overall hemostatic efficacy. These observations were compared to expected rates in a hemostatically normal subjects undergoing the same surgery. Preoperatively, the surgeon predicted intraoperative blood loss for each subject. This predicted blood loss was compared to the actual blood loss for each subject and was considered in the overall efficacy assessment. An outcome of good or excellent was considered as successful.

Key issues identified during this review are summarized below. Although the rating scales were similar for intraoperative and postoperative assessments, inter reader discrepancies are expected. The protocol did not provide information as to how intra and postoperative hemostatic efficacy ratings were factored into the overall hemostatic efficacy rating. The clinical review team determined that the overall hemostatic efficacy would be based on the lowest score attained from both assessments as both intra and postoperative hemostasis should meet defined threshold for a successful outcome. The clinical reviewer compared the actual blood loss to predicted blood loss for each surgery as a key indicator of intraoperative hemostasis. In addition, postoperative hemoglobin, surgical drain outcomes, wound hematomas and duration of treatment were also considered in the efficacy assessment.

The FDA review team downgraded overall hemostatic efficacy in 3 major surgeries and intraoperative hemostatic efficacy in 2 major and 1 minor surgeries. In addition, overall and intraoperative hemostatic efficacy for two surgeries (both major) was upgraded from good to excellent based on FDA analysis. (Please see Section 6.1.11 efficacy analysis; BLA clinical review memo for details).

Hemostatic efficacy of 1 major surgery (knee replacement surgery) was initially downgraded to moderate (failure) based on significantly increased intraoperative blood loss compared to predicted blood loss. However, based on discussions with the applicant during labeling negotiations, overall and intraoperative hemostatic efficacy for this subject was changed from moderate (failure) to good (success). This subject underwent knee replacement surgery with a tourniquet resulting in minimal blood loss (20 ml) during surgery, but with an additional 490 ml blood loss immediately post-surgery from the surgical drain output. The predicted blood loss of 50 ml outlined in the Case Report Form was not an accurate reflection of the typical blood loss seen with this type of surgery. Total blood loss for this subject (510 ml) was compared to blood loss reported for unilateral knee replacement surgery in literature (median intraoperative blood loss up to 600 ml), and was found to be consistent with expected blood loss in this type of

procedure. As such, FDA updated the assessment of hemostatic efficacy in this subject from moderate to good.

In 40% (4/10) of major surgeries and 80% (4/5) of minor surgeries, Vonvendi was administered based on post priming VWF:RCo levels, and as such lower loading doses were required compared to the protocol prespecified loading dose. No difference in clinical efficacy or safety was noted in this subgroup of subjects compared to rest of study population that were treated with protocol specified dose.

Hemostatic efficacy of Vonvendi administered with Advate during major and minor surgery was confirmed. The success rate for overall and intraoperative hemostatic efficacy for all 15 surgeries (10 major and 5 minor) was 100% (90% CI 81.9-100). The study did not have predefined criteria for success. However, an overall hemostatic efficacy of 100% compares favorably with historically reported hemostatic efficacy of 71% -96% with plasma derived VWF concentrates in perioperative prophylaxis of VWD patients.

Statistical Summary:
Statistical review of Study 071101 concurs with the clinical review. The hemostatic efficacy analysis was conducted in 15 subjects, which was the full analysis data set. There was no prespecified criterion for study success and descriptive statistical analysis was used for the primary and secondary efficacy analyses. Overall, 15/15 (100%) subjects had successful outcomes with a 90% CI of 81.9-100.

Pharmacovigilance:
Key identified risks of Vonvendi include thromboembolic events, the development of neutralizing antibodies against VWF, and hypersensitivity reactions. Based on the review of safety data from three completed studies included in the safety database for Vonvendi (see Section 7), a post marketing safety study is not indicated. FDA recommends routine pharmacovigilance, including adverse event reporting under 21CFR 600.80. In addition, the sponsor has two ongoing clinical trials that will collect additional safety data for Vonvendi. The first trial is in the pediatric population (0 to <18 years) and evaluates the use of Vonvendi for on-demand treatment of bleeding and perioperative management. The second trial will collect safety data in adults requiring routine prophylaxis. If concerns arise from surveillance activities or from further clinical studies, then the risk management strategy will be amended to address any newly identified concerns.

BIMO:
CBER BIMO issued inspection assignments covering three clinical sites. The BIMO inspections at two clinical sites did not reveal problems that would impact the data submitted in this application. The inspection of a third site outside of the United States was cancelled due to failure to obtain an entry visa.

b) Pediatrics

As an orphan designated product, Vonvendi is not subject to PREA, and as such, no agreed iPSP was included or required with this submission. (b) (4)

Other Special Populations

Not applicable.

7. SAFETY

The safety database was comprised of 80 unique subjects with VWD treated with Vonvendi in three trials; Studies 070701,071001 and 071101.Table 1 outlines the studies included in the safety database. The age range for subjects treated in all 3 trials was 18-70 years. Only one subject ≥ 65 years was enrolled in the surgical study, Study 071101. Eighty-eight percent (88.8%) of subjects were White, 11.3% were Asian. One subject was Hispanic. Gender distribution was similar in all three trials.

Table -1 Summary of Studies included in Safety Database

Study Number	Study Design	Subjects in safety database
070701	Phase 1, multicenter, randomized, controlled, prospective, dose escalation trial evaluating PK, and safety of Advate and Vonvendi in severe VWD.	31
071001	Phase 3, open label study to assess PK and efficacy of Vonvendi and Advate for on-demand treatment of bleeding episodes in adults with VWD.	37
071101	To assess hemostatic efficacy and safety of Vonvendi with or without Advate in adults with severe VWD undergoing elective surgery	15

None of the subjects treated with Vonvendi in the three clinical trials developed neutralizing inhibitors to VWF. One subject treated in Study 071101 developed a low titer (1:80) binding antibody to VWF on postoperative Day 7 that remained positive upon study completion. This subject did not develop any clinical sequela from the low titer binding antibody. Two subjects from Study 070701 had high titer binding anti-VWF antibodies that were present prior to treatment with Vonvendi. No treatment related significant increase in antibody titer against VWF was observed after exposure to Vonvendi. Despite having low exposure to Vonvendi, these subjects did not demonstrate any evidence of bleeding or change in their clinical condition.

Overall, three SAEs in 2 subjects were reported that were attributed to Vonvendi. These are outlined below.

A single subject treated with Vonvendi and Advate in Study 071101, developed proximal lower extremity deep vein thrombosis postoperatively after hip replacement surgery. She had additional risk factors including obesity and major orthopedic surgery. Thromboembolism is a known class effect of VWF/FVIII replacement products especially in the perioperative setting. The expected nature of the thromboembolic event observed in this study is the basis for not recommending a post marketing study.

One subject enrolled in Study 071001 developed an infusion reaction with Vonvendi, manifesting as chest pain and tachycardia (two SAEs) that resolved with supportive care. He subsequently withdrew from Study 071001. Information about this SAE is already incorporated in the label. Other adverse events that are felt to be related to Vonvendi include nausea, dizziness, infusion site reaction, transient and mild T wave changes on EKG. No deaths occurred in these trials.

Overall, no new safety concerns have been identified, the safety data summarized above supports approval of Vonvendi for the perioperative management indication.

8. ADVISORY COMMITTEE MEETING

An Advisory Committee Meeting was not convened for the discussion of this submission as the product has been approved for another indication (on-demand treatment and control of bleeding) and other products Alphanate and Humate P) are approved for the peri-operative management of patients with von Willebrand's disease, and no significant issues of safety or efficacy were encountered during the course of the review.

9. OTHER RELEVANT REGULATORY ISSUES

N/A

10. LABELING

The review committee negotiated revisions to the package insert (PI), including the Dosage and Administration, Clinical Studies, Adverse Events, and Immunogenicity Sections. The following highlights the key labeling issues that were addressed.

1. Section 2, Dosage and Administration:
    - Dosing guidelines were added for emergency surgical procedures as the applicant is seeking approval of expanded indication of elective and emergency surgery. This section provides the option of weight based

dosing for Vonvendi and recombinant Factor VIII if baseline VWF: RCo and Factor VIII:C is not available in the setting of emergency surgery.

- Instructions were added for calculation of incremental recovery for Vonvendi.
- Instructions were added for dose calculation of recombinant Factor VIII
- Clarification was added regarding the timing of collection of baseline VWF: RCO for dose calculation with respect to priming dose. This was felt necessary as 40% of subjects undergoing major surgery and 80% of subjects undergoing minor surgery were treated with lower than protocol specified Vonvendi dose as post priming VWF:RCo was used for dose calculation.

2. Section 14; Clinical studies:
   Efficacy data from the study was updated to reflect the analysis of the FDA review team. Based on discussions with the applicant during labeling negotiations, FDA changed the hemostatic efficacy assessment for one subject undergoing major surgery from moderate (failure) to good (success). Please see Section 6; clinical for details. Overall and intraoperative hemostatic efficacy of Vonvendi was 100% ({90% CI 81.9-100%}. For all surgeries, overall hemostatic efficacy with an excellent outcome was changed from 73.3% to 60% and good outcome was changed from 26.7% to 40% based on FDA analysis. The intraoperative hemostatic efficacy was also modified based on FDA analysis. This was changed from 86.7% to 73.3% for excellent outcome and from 13.3% to 26.7% for good outcome.

3. Section 6; Adverse Events
   Deep vein thrombosis was added as an adverse event considered related to Vonvendi based on FDA analysis.

4. Section 6.2; Immunogenicity
   The label was updated to include information about 2 subjects treated in Study 070701 with pre-existing high titer antibodies to VWF who had a decreased exposure to Vonvendi. (For details, see Section 7; Safety).

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) were reviewed, commented on, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. APLB recommendations included formatting, organization of subsections and use of active voice in the label.

All issues were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee recommends approval of this efficacy supplement. The clinical trial data from Study 071101 provides substantial evidence of effectiveness and supports a favorable benefit/risk determination for the use of Vonvendi in the perioperative management of bleeding in patients with VWD.

b) Risk/ Benefit Assessment

Availability of recombinant VWF for perioperative prophylaxis will be beneficial as it is not associated with the risk of transmission of blood borne pathogens. Unlike other plasma derived VWF concentrates, Vonvendi does not contain Factor VIII, which decreases the risk of increased Factor VIII plasma activity with repeated administrations that are required postoperatively. Increased Factor VIII activity may be associated with increased risk of thromboembolism.

The key risks of Vonvendi include thromboembolism and neutralizing antibodies to VWF. Overall 1 /80 subjects treated in clinical trials with Vonvendi developed thrombosis in the postoperative setting. This patient had an additional risk factor of obesity. Thrombosis is a known adverse event of VWF replacement therapy especially in the postoperative setting. This risk can be mitigated with postoperative thromboprophylaxis. Neutralizing antibodies are not described with Vonvendi.

Overall the benefits described above, outweigh the risks related to Vonvendi for the proposed indication.

c) Recommendation for Postmarketing Activities

The Pharmacovigilance Plan proposed by the sponsor is adequate. The available data do not indicate a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a post marketing commitment (PMC) or a required post marketing (PMR) study that is specifically designed to evaluate a safety concern as a primary endpoint. The two planned post marketing clinical efficacy trials listed in the PVP will collect additional safety data and add to the overall clinical safety dataset for Vonvendi.