

**Mid-Cycle Review Memorandum
OBE/DE Review
for
Pharmacovigilance Planning**

Date: August 31, 2009

FDA STN: 125251/0

Sponsor: Octapharma Pharmazeutika

Product: WILATE, von Willebrand Factor/Factor VIII Concentrate (Human)

Indication: The application for approval of use in the United States is only for the treatment of patients suffering from von Willebrand disease.

To: Tomothy Lee, PhD, OBRR/DH/LH, BLA Chair

From: Jonathon Rose, MD, MPH
Medical Officer, Therapeutics and Blood Safety Branch (TBSB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE)

Through: Robert P. Wise, MD, MPH
Chief, OBE/DE/TBSB
Acting Deputy Director, OBE/DE

CC: None

Materials Reviewed: STN 125251/0 Modules 1 through 5; Submitted Pharmacovigilance Plan from the Sponsor

(Italics identify text copied from BLA documents.)

Introduction

OBE/DE/TBSB has completed a review of STN 125251/0, an original BLA application for WILATE. The purpose of this review is to identify potential safety issues that may need to be addressed through post marketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed.

Product Background

WILATE is a plasma-derived, stable, double virus inactivated, highly purified concentrate of freeze-dried active human coagulation factor VIII (FVIII) and von Willebrand factor (VWF) being developed for treatment of patients suffering from von Willebrand disease (VWD) -----(b)(4)-----. The application for approval of use in the United States is only for the VWD indication.

Sponsor's Proposed Indications

Von Willebrand Disease, in both adult and pediatric patients:

- A. In severe VWD: for the treatment ----(b)(4)---- of spontaneous and trauma-induced bleeding episodes
- B. In mild and moderate VWD: where use of DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contraindicated
- C. -----(b)(4)-----

Manufacturing

[WILATE] is prepared from cryoprecipitate harvested from fresh-frozen plasma collected in the US. By introducing new biotechnological methods and optimized chromatographic media into the WILATE manufacturing process, it has been possible to manufacture a preparation containing the FVIII/VWF complex in its native form and almost devoid of lower molecular weight proteins.

Epidemiology of von Willebrand Disease in the United States

Von Willebrand Disease is the most common bleeding disorder. The CDC reports that there is a prevalence of approximately 1-2% in the U.S. population. A 1993 study, which assumed an ethnically heterogeneous population, found a prevalence of 1.3% (J PEDIATR, 1993;123:893-8). Incidence data could not be found. An examination of raw patient encounter reporting data for 2001 through 2006 did not reveal a reliable pattern, so a conclusion about trend would not be reliable.

Similar Products or Alternative Therapies

Von Willebrand Disease Type 1 and Type 3 are associated with a quantitative deficiency of vWF, whereas Type 2 is a qualitative abnormality of vWF. Type 3 is the rarest and most severe. It also tends to be refractory to the most common therapy, DDAVP.

The mainstays of therapy for vWD are DDAVP, which induces secretion of both vWF and FVIII, and replacement therapy with vWF-containing plasma concentrates. The choice of treatment in any given patient depends upon the type and severity of vWD, the clinical setting, and the type of hemostatic challenge that must be met. Type 1 patients are most often treated with DDAVP alone, types 2A and 2B with a combination of DDAVP and a vWF-containing FVIII product, and type 2N and type 3 patients with vWF-containing concentrates. A previous history of trauma or surgery and the success of previous treatment are important parameters to include in the assessment of risk of bleeding. Prophylaxis generally is not used except in anticipation of hemostatic challenges, such as dental extractions, and in the most severe type 3 vWD patients who exhibit recurrent hemarthroses or gastrointestinal bleeding. (Williams Hematology - 7th Ed. (2006))

In addition, Alphanate (Antihemophilic Factor/von Willebrand Factor Complex (Human)) manufactured by Grifols Biologicals, Inc., is an alternative product to Wilate.

Pre-clinical Studies

No pharmacokinetic studies were performed in animals for WILATE itself, as pharmacokinetic studies with human proteins in animals are not predictive of the situation in humans. Animal experiments on pharmacodynamics would not add any further information. Single-dose toxicity studies in animals – the heterologous recipients – seem to be not very informative. Antibody formation and consequently occurrence of anaphylactic reactions are strong arguments against repeat dose toxicity studies for WILATE in animals. WILATE is well tolerated in humans, and further animal experiments are therefore not justified. Pregnancy Category C. Animal reproduction studies have not been conducted with WILATE. FVIII and VWF in Wilate are normal constituents of the human plasma and act like the endogenous FVIII/VWF.

Wilate contains trace amounts of the chemicals tri(n-butyl)phosphate and Octoxynol (Triton X-100), which are used for solvent/detergent (S/D) viral inactivation during manufacturing. However, preclinical data revealed no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity and embryo-foetal development.

Market Experience

Note that the product has been approved for use in Europe, but not yet in the United States.

Experience in the treatment of pregnant or lactating women is not available. Likewise, there have been no completed trials involving children under six years of age. Clinical experience provides no hint for tumorigenic and mutagenic effects of human FVIII/VWF.

In February 2005, WILATE received marketing approval for the treatment of all types of VWD and hemophilia A in Germany. There were 2 spontaneously reported ADRs by June 2007 (non-serious hypersensitivity reactions).

According to the sponsor, *no new areas of concern beyond the safety information already included in the current product data sheet/label [have been] identified.*

Data Available for Safety

Ongoing Studies (copied and pasted from the BLA)

Study No.	Population; No. of patients enrolled/planned;	Design; Study Site; Location; Study Period;	Evaluation Criteria	Endpoints
WIL-14	inherited VWD, any type; 15/12-20 «6 years of age)	Prospective, open-label, non-controlled, Germany, Poland, France, Czech Republic Ongoing since Q2 2006	efficacy, immunogenicity, safety,	<i>Efficacy endpoints</i> assessment of bleeding episodes; incremental/absolute recovery of FVIII:C, VWF:RCo, VWF:Ag, VWF:CB. <i>Immunogenicity endpoints</i> Determination of inhibitors against VWF and FVIII. <i>Safety endpoints</i> adverse event monitoring, safety, laboratory parameters, physician's and patient's assessment of tolerability
WIL-15	inherited VWD, any type; 45/2:30	open, non-controlled, observational study; Germany; ongoing since Q1 2005;	efficacy safety optional: PK;	<i>Efficacy endpoints</i> Efficacy assessment of WILATE in bleeding episodes, ---(b)(4)----- ----- with percentage of "excellent/good" as primary endpoint. <i>Safety endpoints</i> Tolerability of injections with percentage of "excellent/good" and rate of ADR as endpoints
----- (b)(4) ----- ----- -----				
----- (b)(4) ----- ----- ----- ----- ----- ----- ----- ----- ----- -----				

-----~~(b)(4)~~-----

-----~~(b)(4)~~-----

-----~~(b)(4)~~-----

-----~~(b)(4)~~-----

Planned Studies

There are three planned studies. Two with efficacy end points, and one of these will also include “tolerability” as an end point. The third is a pharmacokinetic study.

Safety Database

The product has not been approved for use in the United States. All of the following data were obtained outside of the United States.

1. The Periodic Safety Update Report (PSUR) covering the period February 1, 2005 – July 31, 2005 reported the following:

Serious Adverse Events: 7 year old female with VWD type 3 experienced post-Wilate prophylaxis prolonged bleeding at a catheterization insertion site and required hospitalization.

The TMAE-104 was reported as follows: 37 enrolled, with 35 adverse events in 8 patients. These included asymptomatic B19 seroconversion in a 7 year old (no gender provided); and, the Wilate batch was also found to be positive for B19.

The TMAE-106 was reported as follows: 22 year old female experienced an *allergic reaction*, and a 60 year old (no gender provided) experienced asymptomatic B19 seroconversion.

2. The PSUR covering the period August 1, 2005 – January 31, 2006 reported no new adverse or serious adverse events.

3. The PSUR covering the period February 2006 (no day provided) – July 31, 2006 reported no new adverse or serious adverse events.

4. *Fourth Adverse Experience Report* covering the time period February 3, 2008 until June 1, 2008 reported the following:

Adverse Events: 1. Hypersensitivity; 2. Rash
Serious Adverse Events: Factor VIII inhibition

All were deemed expected by the sponsor and according to the label. They involved three individuals, but no gender or age were provided and the report failed to identify which individuals had which adverse event.

Note: I am unable to locate PSURs for periods between August 1, 2006 and January 31, 2008.

Adverse Events

There have been five completed studies with a total of 160 individuals. There have been a total of 231 adverse events in 43 individuals with VWD -----(b)(4)-----
-----.

The following adverse events were reported by the sponsor and considered related to Wilate for the VWD indication:

- Dizziness (n=2)
- Headache
- Dyspnoea
- Abdominal discomfort
- Nausea
- Dysgeusia
- Vertigo
- Rash
- Urticaria (n=2)
- Anemia
- Parvovirus
- B19 serology positive (n=4)
- Hypersensitivity

Note that the above is from the draft labeling text (BLA section 1.14.1.3), but elsewhere in the BLA additional serious adverse events are reported (BLA section 2.7.4). These are described below.

Bleeding appears to be both the most common and most serious adverse event deemed to be associated with Wilate in the individuals with the VWD indication.

Most common adverse events (BLA section 2.7.4 pg. 7):

Gastrointestinal: including 41 episodes (BLA section 2.7.4.2.1.1 pg. 73) or 34 episodes (BLA section 2.7.4.2.1.3 pg.75) of GI hemorrhage. There appears to be a contradiction in the number being reported. It is possible that the 41 includes both individuals with VWD -----(b)(4)-----, while the 34 includes only individuals with VWD.

The GI hemorrhage events also included one death. According to the information provided by the sponsor, it appears that the Wilate was used as attempted treatment after the bleeding had started rather than before the bleed began. This does not rule out the theoretical possibility that the Wilate may have somehow exacerbated the bleed.

Other bleeding (BLA section 2.7.4.2.1.3 pg.75) included epistaxis (n=6), melena (n=14), ulcer hemorrhage (n=1), *mouth hemorrhage* (n=1), and heamaturia (n=2). This makes a total of 51 GI bleeds involved with the VWD indication.

Frequency of Treatment Related Adverse Events, by System Organ Class (All Studies) (MEDDRA primary system organ class MEDDRA preferred term, as provided by the sponsor):

Blood and Lymphatic System Disorders Any Event 1: Anaemia 1
Immune System Disorders Any Event 1: Hypersensitivity 1
Psychiatric Disorders Any Event 1: Sleep Disorder 1
Nervous System Disorders Any Event 5: Headache 2, Dizziness 2, Dysgeusia 1
Ear and Labyrinth Disorders Any Event 1: Vertigo 1
Respiratory, thoracic and mediastinal any event 1: Disorders Dyspnoea 1,
Gastrointestinal Disorders Any Event 2: Abdominal discomfort 1, Nausea 1
Skin and Subcutaneous Tissue Disorders Any Event 5: Rash 1, Urticaria 2, Pruritus 2
General disorders and administration any event 2: Site conditions Pyrexia 2
Investigations Any Event 4: Parvovirus B19 Serology Positive 4

Pharmacovigilance Planning

Summary of Safety Issues

Viral and Prion:

There have been multiple instances of asymptomatic parvovirus B19 seroconversions. None required medical intervention. This is in spite of following:

Two specific virus inactivation steps, i.e. the S/D treatment and terminal dry-heating, are part of the production process of WILATE. Furthermore, the protein precipitation and chromatographic steps included remove pathogens such as the prion causing vCJD and nonenveloped viruses. All steps have been validated for their ability to inactivate/removes pathogens in conformity with the note for guidance on such studies. The results of the virus and prion validations studies are summarized in Module 3.2.A.2.5. ...[it] seems prudent to maintain an adequate warning statement for parvovirus B19 in the package insert.

Thrombogenicity

Venous thromboembolic events have occurred in individuals with VWD. Wilate causes an increase in FVIII and VWF and therefore may theoretically contribute to these events. Nevertheless, the sponsor reports that, *Not one single thrombotic event has been observed with WILATE during extensive repeated dosing, either during the major surgical procedures or in patients under long-term prophylactic treatments.*

Immunogenicity

Some patients with type 3 VWD who received Wilate have developed antibodies against VWF. The clinical significance of these antibodies is not clear, but it is worth considering that *The incidence of anti-VWF antibodies is thought to be similar to that reported for haemophilia B, or about 1.5–3%. VWD patients with alloantibody inhibitors directed against VWF may rarely experience serious, potentially life-threatening anaphylactic reactions when treated with VWF/FVIII concentrates.* (Manucci's 2009 update - Haemophilia. 2009 Sep;15(5):1154-8 - on p. 1156)

Bleeding

While Wilate is intended to be beneficial in stopping bleeding, and the indication sought is for a population in which bleeding is a primary issue of concern, of the 160 clinical trial patients (treated with Wilate for a definite or potential bleeding diathesis), 31.9% developed any bleeding adverse or serious adverse event where a causal association with Wilate could not be ruled out.

Sponsor's Proposed Pharmacovigilance Plan (PVP)

The sponsor has identified three areas of safety concern specific to Wilate that will be subject to a PVP: pathogen safety, for which the sponsor plans to provide the available pathogen safety data from ongoing clinical trials and from the post-marketing surveillance in the PSURs; thrombogenicity in VWD, for which the sponsor plans to evaluate the risk in the ongoing VWD studies in patients at risk -----(b)(4)----- and to monitor viral safety within the framework of post-marketing surveillance; and, “*insufficient information on children with VWD*”, for which the sponsor plans to study the tolerability and efficacy in children < 6 years of age with VWD in a clinical study (WIL-14).

The sponsor has developed generic PVP procedures that appear to apply to more than just Wilate, but has identified specific action plans for three areas of concern:

1. Pathogen safety:

The sponsor reports that in the ongoing and future clinical studies, the viral safety will be assessed by monitoring of viral markers for HIV, HBV, HCV, HAV, and B19 at baseline and at pre-defined intervals post-infusion. Case safety reports of suspected pathogen transmissions derived from post-marketing safety surveillance will be processed according to *internal procedures and regulatory requirements*.

2. Thrombogenicity in VWD:

Case safety reports of suspected thromboembolic events from post-marketing safety surveillance will be processed according to *internal procedures and regulatory requirements*. MedDRA search will be done when PSURs are required and will search using the phrase, “Embolic and thrombotic events”.

3. “*Insufficient information on children with VWD*”:

The sponsor proposes to continue the clinical study WIL-14, a *prospective clinical trial to assess the efficacy and tolerability of WILATE for -----(b)(4)----- treatment of bleedings, -----(b)(4)-----, in children <6 years of age*.

Questions for Post-licensure Pharmacovigilance:

I am unable to locate PSURs for periods between August 1, 2006 and January 31, 2008. Please provide them if they are not in the BLA.

Please clarify the following adverse and serious adverse event data: Gastrointestinal: including 41 episodes (BLA section 2.7.4.2.1.1 pg. 73) or 34 episodes (BLA section 2.7.4.2.1.3 pg.75) of GI hemorrhage. There appears to be a contradiction in the number being reported. It is possible that the 41 includes both individuals with VWD -----(b)(4)-----, while the 34 includes only individuals with VWD.

Assessment and Recommendations

There are four main areas of safety concern: pathogen safety as evidenced by asymptomatic seroconversion for B19 Parvovirus; thrombogenicity in VWD, possible by the mechanism of action of the product; “*insufficient information on children with VWD*” when one of the indications being sought is for the product to be used in a pediatric population; and bleeding, given the disproportionate number of adverse events involving bleeding where a causal association with Wilate could not be ruled out.

In addition to the PVP plan provided by the sponsor:

1. A study should assess GI bleeding, especially hemorrhages, to discern the temporality of the product’s use relative to these bleeds. The study could be prospective or active surveillance for two years and reported in its own section in future PSURs.
2. Please submit (or indicate where in the BLA they can be found) the PSURs for periods between August 1, 2006 and January 31, 2008 for evaluation.
3. The BLA submitted does not provide any data to support the safety (or efficacy) of the product in children under 6 years old. We feel great concern over this lack, because off-label use in young children would be possible. Therefore, the product should be expressly labeled as not for use in children under 6 years old.
4. Periodic testing of Wilate batches for the presence of Parvovirus B19 may provide information that will help to control this apparent contamination.
5. Please provide the narratives for all adverse events and serious adverse events that involved bleeding. Please evaluate them and indicate under which of the following circumstances the product was administered to each patient: on demand, prophylaxis, not an acute bleed, acute bleeding, major surgery, minor surgery, or combined surgery.

Letter Ready Comments

There are four main areas of safety concern including: pathogen safety as evidenced by asymptomatic seroconversion for B19 Parvovirus; thrombogenicity in VWD, possible by the mechanism of action of the product; “*insufficient information on children with VWD*” when one of the indications being sought is for the product to be used in pediatric population; and bleeding, given the disproportionate number of adverse and serious adverse events involving bleeding where a causal association with Wilate could not be ruled out.

1. Please provide a detailed plan to assess GI bleeding, especially hemorrhages, to discern the temporality of the product’s use relative to these bleeds. The study can be prospective study or active surveillance for two years and reported in its own section in future PSURs.
2. Please supply PSURs for periods between August 1, 2006 and January 31, 2008, or indicate where they are in the BLA.
3. We are very concerned about the lack of safety (and efficacy) data for use of the product in children under six years old.
4. Please provide a detailed plan for ongoing testing of Wilate batches for the presence of Parvovirus B19, and assure that the results will be reported in all future PSURs.
5. Please provide the narratives for all adverse events and serious adverse events that involved bleeding. Please evaluate them and indicate under which of the following circumstances the product was administered to each patient: on demand, prophylaxis, not an acute bleed, acute bleeding, major surgery, minor surgery, or combined surgery.