

**Final Review Memorandum
OBE/DE Review
for
Pharmacovigilance Planning**

Date: December 3, 2009, revised

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.

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

APPROVED
By Robert Wise at 11:41 am, Dec 03, 2009

APPROVED
By Rickey Wilson, MD, MS, JD at 5:38 pm, Dec 03, 2009

(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 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, no completed trial has involved 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 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; 45/2-20	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) 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

After discussions with Dr. Hon Sum Ko, an OBRR medical reviewer, I understand that (b)(4) may not be adequately supported by data. Although lack of effect can be both an efficacy and a safety issue, it is beyond the scope of this memorandum.

Newly Analyzed Studies

TMAE-103:

The study started in July 2002 and was completed in April 2007. This Phase III international, multicentre, prospective, non-controlled, open-labeled study was conducted in 8 centres in Germany, Russia, Belarus, Ukraine and Tatarstan.

The primary objective of the study was to assess the immunogenicity of WILATE in previously untreated patients (PUPs) by monitoring the levels of inhibitor against FVIII (by (b)(4) assay) every 3 to 4 exposure days until the 20th exposure day and thereafter every 10th exposure day or every 3 months, whichever was the soonest.

b(4)

When recovery data were analyzed according to whether or not the subject developed an inhibitor, a mean recovery of $1.36 \pm 0.41\%$ ($N= 57$) was found for subjects without inhibitors and $0.66 \pm 0.74\%$ ($N=21$) for subjects with inhibitors.

99.4% of cases the efficacy was considered to be good or excellent (99.8% when subjects with inhibitors were excluded). The most frequent reason for administration was for treatment of bleeding episodes (1.271 infusions on 1.020 exposure days)

b(4)

b(4)

Of important note is the fact that of the 28 subjects evaluable for safety: 26 (92.9%) experienced at least one adverse event (AE), and 11 of them (39.3% of the 28) experienced at least one serious adverse event (SAE). Half of the 28 subjects had asymptomatic seroconversions to Parvovirus B19, with no apparent clinical consequences. However, 8 of the 28 developed inhibiting antibodies to FVIII, which could have important implications for subsequent therapy.

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 catheter 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. *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 was provided, and the report failed to identify which individuals had which adverse event.

3. The remaining available PSUR's identified no new safety risks.

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)

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

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 event where a causal association with Wilate could not be ruled out. Such events could reflect suboptimal dosing, inhibiting antibodies (but none were detected in this trial), or potentially other factors that might lead to less than expected therapeutic effect of a product.

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 and those with Hemophilia A, while the 34 includes only individuals with VWD. (Although this ambiguity was identified in the mid-cycle review memorandum, it remains unresolved at this date.)

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 hematuria (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 validation 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. Although Octapharma suggests that "(n)ot 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," there was a case of right atrial thrombus attributed by the Investigator to have arisen from Vascuport infection.

Immunogenicity

Patients with type 3 VWD have the potential to develop antibodies against VWF. The clinical significance of these antibodies is not clear, but it is worth considering the sponsor's explanation, "*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)

Sponsor's Proposed Pharmacovigilance Plan (PVP)

The sponsor has identified three areas of potential 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 (e.g., in patients (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 these 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 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.*

Assessment and Recommendations

There are the main areas of potential 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 sought is for use in the pediatric population; and

In addition to the PVP plan provided by the sponsor we recommend:

1. Please define, capture, and submit any lack of effect events, especially ones related to the treatment of GI bleeding. This information should be reported under a separate section in the PSURs.
2. The BLA submitted does not provide any data to support the safety (or efficacy) of the product in children under 6 years old. Although we are very concerned about the lack of safety (and efficacy) data for use of the product in children under six years old, PREA regulations do not require that pediatric studies be conducted for orphan products unless a clear safety signal has been identified. In this case, since there is no data to that suggest a safety concern in this age group.