

Mid-Cycle Review Clinical Memorandum on BLA STN125251

INTRODUCTORY STATEMENT

H. S. Kim

REVIEWED

By Han-Sum Kim at 8:50 am, Aug 03, 2007

Subject: This is an original submission [STN 125251] to market Wilate (Human Coagulation Factor VIII and von Willebrand Factor) from: Octapharma Pharmazeutika Produktionsges.m.b.H. A-1100 Vienna Austria, Europe

Review committee: Members and their respective divisions:

- Franklin Stephenson of DBA
- Nancy Kirschbaum of DH
- Ifekhar Mahmood of DH
- Paul Buehler of DH
- Jessica Kim of DB/OBE
- Solomon Yimam of DIS/OCBQ
- James Crim of DMPQ/OCBQ
- Janie Russell of DMPQ/OCBQ

Milestones: Milestones from RMS-BLA are as follows:

- Application received 12/12/06
- First Committee meeting 1/4/07
- Filing meeting 1/26/07
- Deficiencies identified 1/26/07
- Filing action 2/11/07
- Day 90 meeting 3/14/07
- Mid-cycle meeting 5/11/07
- First action 10/12/07

BACKGROUND

This memo summarizes the status of the clinical review of BLA STN 125251 submitted by Octapharma AG to include evaluation of the clinical data for the support of marketing of Octapharma AG's Wilate (Human Coagulation Factor VIII/von Willebrand Factor). Based on this review, this Reviewer's current assessment of the application is given in the following sections.

SUMMARY OF CLINICAL REVIEW

The BLA submission for Wilate is to support licensure of this product for the following indication:

- WILATE is indicated in adult and pediatric patients for the treatment (b)(4) of spontaneous and trauma-induced bleeding episodes in severe VWD, and in mild

and moderate VWD where use of DDAVP (1-deamino-8-D-arginine vasopressin/desmopressin) treatment is ineffective or contra-indicated. (b)(4)

(b)(4)

The dosing recommendations are as follows:

- Minor hemorrhages: loading dose 20-40 IU/kg, maintenance dose 20-30 IU/kg every 12-24 hours;
- Major hemorrhages: loading dose (b)(4) 60 IU/kg, maintenance dose 20 (b)(4) IU/kg every 12-24 hours;

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

The dosage should be adjusted according to the extent and location of the bleeding: (b)(4)

(b)(4) In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

The Dosage and Administration section in the proposed package insert (Section 2) begins with: "Each vial of WILATE contains the labeled amount in International Units (IU) of factor VIII (FVIII) activity measured with the chromogenic assay (FVIII:C) and von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo)", followed by more detailed elaborations of the dosing scheme (based on above) and administration methods.

The clinical studies to support this application are summarized in the following Table.

Clinical Studies to Support Von Willebrand Disease Indication

Study ID & Title Product Batches Used & Strength (IU FVIII)	Population (N= patients in study; n=new individual)	Design/Dose Sites/Location Time frame	Efficacy Endpoints
TMAE-105. Pharmacokinetic properties, safety and efficacy of WILATE in patients with Inherited von Willebrand disease Batches 942 014 180 at 1000 IU 943 015 180 at 1000 IU 948 016 180 at 500 IU 948 018 180 at 500 IU	Inherited VWD, any type; not responding to DDAVP N=14; n=14 8M/6F Ages 13-64; m=36	Phase 2, open, uncontrolled, Safety-efficacy-PK study/ 1: 50 IU VWF:RCo/ kg single iv injection 2: 7 dose regular iv injection or continuous infusion (surgery) 2-centers/Poland & Bulgaria Dec 99 – Jul 00	Primary. <ul style="list-style-type: none"> • PK profile (AUC, AUC_{norm}, T_{1/2}, MRT, Vd, CL) for VWF:Ag, VWF:CB, VWF:RCo • plasma levels of FVIII:C Secondary. <ul style="list-style-type: none"> • PK profile (C_{max} & T_{max}) for VWF:Ag, VWF:CB, VWF:RCo, • recovery of FVIII:C, VWF:Ag, VWF:RCo • plasma levels of VWF:Ag, VWF:CB, VWF:RCo • bleeding time • multimeric pattern • Investigator overall efficacy assessment
TMAE-109. Clinical study to investigate efficacy and safety of human Factor VIII/VWF TMAE SEC in patients with inherited von Willebrand disease. Phase 2 study	Inherited VWD, any type; not responding to DDAVP N=16; n=5 10M/6F	Phase 2, open, uncontrolled, Safety-efficacy study/ 7 dose regular iv injection or continuous infusion (surgery)	Primary. <ul style="list-style-type: none"> • plasma levels of FVIII:C, VWF:Ag, VWF:RCo Secondary. <ul style="list-style-type: none"> • bleeding time • multimeric patterns

<u>Batches</u> 007 002 180 at 500 IU 011 005 180 at 1000 IU 017 007 180 at 1000 IU 038 008 180 at 500 IU	Ages 14-83; m=37	2-centers/Poland & Bulgaria Aug 00 – May 01	<ul style="list-style-type: none"> Investigator overall efficacy assessment
WIL-12. A prospective, randomized, controlled, open-labeled, two-arm cross-over study investigating the pharmacokinetic properties of WILATE and Humate-P® in subjects with inherited von Willebrand disease <u>Batches</u> 435 005 181 at 500 IU	Inherited VWD, any type n=22 8M/14F Ages 12-68; m=34	Phase 2, open, randomized, controlled, X-over, Safety-efficacy-PK study/ <u>≥40 IU VWF:RCo/ kg iv bolus injection</u> 6-centers/US Jun 05 – Apr 06	<u>Primary.</u> <ul style="list-style-type: none"> In vivo 1% of WILATE, calculated for FVIII:C, VWF:Ag, VWF:CB, VWF:RCo <u>Secondary.</u> <ul style="list-style-type: none"> Other PK parameters Incremental recovery of FVIII:C, VWF:RCo, VWF:Ag, & VWF:CB multimeric patterns
TMAE-104. International clinical study to investigate the safety and efficacy of WILATE in subjects with inherited von Willebrand disease <u>Batches</u> 23 batches including – 435 005 181 at 500 IU (as in WIL-12) & 5 other batches used in TMAE-106 (see below)	Inherited VWD, any type; not responding to DDAVP N=35; n=31 14M/21F Ages ≥6 - ≤85	Phase 3, open, uncontrolled, Safety-efficacy study/ <u>? dose regular iv injection or continuous infusion (surgery)</u> Multicenter/Europe Started Q1 2002	<u>Primary.</u> <ul style="list-style-type: none"> Plasma levels of FVIII:C, VWF:Ag, VWF:CB, VWF:RCo <u>Secondary.</u> <ul style="list-style-type: none"> bleeding time investigator and/or patient overall efficacy assessment of overall clinical efficacy
TMAE-106. Pharmacokinetic properties, safety and efficacy of human Factor VIII TMAE-SEC in patients with inherited von Willebrand disease, Phase II study <u>Batches</u> 038 008 180 at 1000 IU* 204 001 181 at 500 IU* 249 010 181 at 500 IU* 318 001 181 at 1000 IU 337 005 180 at 500 IU* 436 006 181 at 500 IU* 450 008 181 at 1000 IU (* = batches also used in TMAE-104)	Inherited VWD, any type; not sufficiently responding to DDAVP n=13 3M/10F Ages ≥12 - ≤85	Phase 2, open, uncontrolled, Safety-efficacy-PK study/ <u>1: 50 IU VWF:RCo/ kg single iv injection</u> <u>2: ? dose regular iv injection or continuous infusion (surgery)</u> Multicenter/Germany Started Q1 2002	<u>Primary.</u> <ul style="list-style-type: none"> PK profile (AUC, T½, MRT, Vd_{ss}, CL) for VWF:Ag, VWF:CB, VWF:RCo plasma levels of FVIII:C <u>Secondary.</u> <ul style="list-style-type: none"> Incremental recovery of FVIII:C, VWF:RCo, VWF:Ag plasma levels of VWF:Ag, VWF:CB, VWF:RCo bleeding time closure time multimeric patterns Investigator overall efficacy assessment
WIL-14. Clinical study to investigate the efficacy, safety and immunogenicity of Wilate in children < 6 years of age with inherited von Willebrand disease. A Phase 2 study <u>Batches (?)</u>	Inherited VWD, any type; known or suspected to be inadequate for DDAVP treatment N=20 planned n=5 (enrolled) Age ≤6	Phase 2, open, uncontrolled, Safety-efficacy-immunogenicity study/ <u>? dose regular iv injection or continuous infusion (surgery)</u> Multicenter/Germany & Poland Started Apr 2006	<u>Primary.</u> <ul style="list-style-type: none"> Efficacy in: b(4) treatment of bleeding episodes; no. of bleedings, amt of IMP reqd, no. exposures to stop bleeds, assessment of response to treatment of bleeding episodes Overall efficacy 4-point verbal rating scale

* Immunogenicity & safety evaluated by inhibitors vs VWF and FVIII, AEs, vital signs, lab parameters, viral safety

Status of Clinical Review

Clinical review has been initiated, and several discussions between this Reviewer, the Statistical Reviewer and the Clinical Pharmacology Reviewer have led to the identification of areas to be focused on.

Input from Drs. Toby Silverman, Ross Pierce, Nisha Jain, and Kaushik Shastry have also been obtained with respect to the clinical data standard of licensure of similar products (CSL Behring's Humate-P® and Grifols' Alphanate®). These will be applied to the review of the Wilate BLA.

Due to competing priorities, the clinical review for the Wilate BLA has not been completed as of this date (5/9/07). Completion of this review is projected to be around the first week of June 2007.

DEFICIENCIES

- Identify show-stoppers
- Other deficiencies

No comments at this time.

ACTION ITEMS

State proposed course of action according to the severity of deficiencies, such as:

- The deficiencies are so significant that a complete response (CR) letter may be warranted.
- The deficiencies may be addressed during the review cycle, so an information request (IR) letter should be issued to the applicant.
- There is no apparent significant deficiency, so the review committee should proceed with the approval process, e.g., compliance check, labeling review, and summary basis of approval.

RESERVED

STRATEGIES

- a. Identify issues that could prevent approval.
- b. Identify any informational requests.
- c. Identify any problems.
- d. A plan to discuss how to address any problems.

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