



Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

January 8, 2008

Our STN: BL 125251/0

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Dr. Barbara Rangtiner
Oberlaaer Strasse 235
Vienna A-1100
Austria

Dear Dr. Rangtiner:

We have completed the review of your submission dated December 12, 2006 to your biologics license application (BLA) under section 351 of the Public Health Service Act for Coagulation Factor VIII/von Willebrand Factor Complex (Human), for the (b)(4) treatment of spontaneous and trauma-induced bleeding episodes (b)(4) of bleeding episodes in severe von Willebrand disease (VWD), and in mild and moderate VWD where use of 1-Desamino-8d-Arginine Vasopressin (DDAVP) treatment is ineffective or contra-indicated.

The following identifies the deficiencies and our comments and questions based on our review of your submission:

CLINICAL PHARMACOLOGY

1. Of the three assays used in pharmacokinetics (PK) studies the VWF:RCo is the most relevant functional assay. The PK data (plasma concentrations vs. time data) of Wilate generated by the current analytical method are not interpretable. It appears that the analytical method is not sensitive enough to appropriately detect Wilate concentrations (VWF:RCo) in plasma. According to you, the method is somewhat 'coarse' and the results are limited to one of a discrete series of possible concentrations, 1%, 6%, 12%, 24%, and 36%, etc. The result of this analytical method is that following administration to VWD patients measured plasma concentrations of VWF:RCo remain unchanged in many subjects during multiple sampling at different time points. Since these concentrations may not be accurate, the PK parameters may also be inaccurate. Thus, the PK parameters determined from the VWF:RCo assay are unreliable and cannot be used in the package insert for dosing recommendations. Therefore, FDA recommends that you develop a sensitive analytical method to measure the relevant concentrations of Wilate in plasma and then conduct a PK study of Wilate with a suitable sample size.
2. Even though the FVIII:C dose of Wilate is more than twice the dose of Humate-P in Study WIL-12, the AUC of FVIII:C for Humate-P is higher than the AUC of Wilate in all

VWD type patients. This result suggests that VWF in Wilate may be less able to stabilize FVIII:C. Please comment.

3. Two types of half-lives (terminal and average) have been described as PK parameters for Wilate and Humate-P in Study WIL-12. Please describe the method of calculation of average half-life and its significance. Is average half-life more relevant or meaningful than the terminal half-life?

CLINICAL

FDA requires both PK and clinical outcome data on hemostatic efficacy for approval of a VWF product as a replacement therapy for VWD. Studies supporting such an indication should have the patients dosed according to VWF:RCO potency and monitored using reliable assays for VWF:RCO activity.

You have defined the primary efficacy endpoints for the four VWD clinical studies supporting hemostatic efficacy (TMAE-105, -109, -104, and -106) based on PK data or plasma level parameters. The PK data in all your studies were generated by dosing based on VWF:RCO activity. In contrast, the clinical doses used in all these studies were based on FVIII:C activity. The information provided by you indicate that the ratio of VWF:RCO to FVIII:C varied from 0.6 to 1.1 in the clinical study lots. We have determined that the PK parameters obtained from VWF:RCO assays in your PK studies are not reliable (please see comment 1 above). Accordingly, your data generated on VWF:RCO plasma levels associated with the clinical information on hemostatic efficacy are not sufficiently reliable. Without reliable plasma level data on the active factor to be replaced, as measured by VWF:RCO, the guidance for dosing for Wilate in the clinical indications of VWD cannot be established at this time.

Pivotal studies in support of an indication must be designed with a clearly stated hypothesis and provide measures to minimize bias and uncertainty for product use and evaluation. There should be prospectively defined criteria for success or failure. None of the clinical studies submitted in this application meet these requirements.

Please conduct appropriate studies with adequate design to acquire efficacy data in support of the indications sought, taking into consideration the comments below on the deficiencies in the VWD clinical studies of the current submission. Please specify in the protocols, the analyses of efficacy as a function of dose administered and plasma levels of VWF:RCO achieved in the subjects treated for each indication in order to establish the intended effect of the product, as well as the dosing recommendations for labeling.

Comments Related To (b)(4) Treatment of Bleeding Episodes:

For the (b)(4) treatment of bleeding episodes, your studies were not adequately designed to provide data for drawing meaningful conclusions about effective use of your product at your proposed dosing regimens. The following are our comments:

4. Bleeding episodes were not clearly defined in the VWD studies of this submission. The number of infusions per episode and the duration of treatment within any episode are defined by the length of the "episode" arbitrarily assigned by the patient or Investigator. Without an appropriate definition to be used consistently by all Investigators and patients in all the studies, the number of infusions and duration of treatment are subject to bias.
5. The 4-point VRS grading scale used by Investigators and patients for clinical efficacy evaluation is inadequately defined.
 - a. It would be appropriate to have more precise language separately for bleeding episodes. b(4) For instance, the definition of good includes the term "oozing" which would not be expected to occur with spontaneous or trauma-induced bleeding in soft tissue or joints. Bleeding into the joint should be classified according to swelling and pain, not visible oozing. In addition, the definitions should not include the term to be defined, e.g., the term "moderate" should not be used to define moderate severity. The lack of definition for bleeding episode severity (minor, moderate, severe) in the protocols makes interpretation of the dosing data difficult. Your study protocols did not include appropriate instructions to Investigators and study subjects in the grading of severity, taking into consideration the quantity and rapidity of blood loss, as well as the significance of the bleeding location.
 - b. The term "additional product" for the grades "good" and "moderate" can be misleading to patients and Investigators. You have affirmed in previous communications that "additional product" refers to a non-Wilate product. However, in Study WIL-14 (protocol but not data included in this submission), the definition used instead for "additional product" is "additional injections of IMP (investigational medicinal product) or other styptic treatment." It is difficult to expect consistency in applying the current 4-point VRS without additional clarification to the patients and Investigators, including:
 - definition and criteria for using "additional product",
 - a time-frame before the use of the "additional product", and
 - differences between "hemostasis achieved" (as in excellent) in contrast to "adequate control of bleeding" (as in good).
 - c. In contrast to the 4-point scale efficacy rating for each infusion, an overall assessment termed "outcome" was recorded for each bleeding episode in Studies TMAE-109, -104 and -106, with gradings of "recovered", "ongoing" and "unknown." This parameter is unclear, because in the absence of a definition for "bleeding episode", its duration may be adjusted to fit the outcome, hence making the terms "recovered" and "ongoing" rather indistinct, depending on how the "episode" has been recorded.
6. The differentiation of bleeding episodes into "minor", "moderate" and "severe" was not defined in the study protocols (also see comment 5.a). The instructions given to patients to grade severity were not provided. In proposed labeling, bleeding episodes were divided

into “minor” and “major” for the purpose of dosing. As the term “minor” may carry different meaning in the clinical trials vs. that in the proposed dosing recommendations for dose labeling, potential confusion may result from extrapolating the clinical trials doses to labeling recommendations.

7. In your submission, the VWD study protocols provide for the administration of product based on FVIII content, and only general dosing guidelines were provided. As stated before, as replacement therapy for VWD, it is appropriate to dose according to VWF:RCO activity. This may also mitigate underdosing arising from the variability in the ratio of VWF:RCO: FVIII:C in the product lots.
8. For the VWD studies in this submission, the recommended dosing intervals are usually once daily or every other day, whereas you propose dosing every 12 to 24 hours in the package insert. Please explain the dosing differences between the protocol requirements and what was actually done in the studies. The dosing interval should be based on the pharmacokinetics of the active entities to be replaced.
9. For the VWD studies in this submission, the guidelines for repeating the use of the test product, as well as criteria for administering rescue products and/or blood transfusions have not been included.

10.

(b)(4)

11. We note that the doses used for bleeding episodes in the VWD studies on Wilate appear to be lower than those reported in the literature for other products and the labeled recommendations of the U.S. licensed product for bleeding episodes in VWD. Since there are only limited data provided on VWF:RCO plasma levels attained after Wilate infusion in the treatment of bleeding episodes, and their measurement accuracy is in question, the dosing information derived from the treatment of bleeding episodes of VWD patients in the clinical studies (which mirrors those in the proposed package insert) may result in underdosing for the bleeding episodes. Please comment

(b)(4)

Page 5 redacted for the following reason:

(b)(4)

(b)(4)

Additional Clinical Comments:

20. Although the protocols in your VWD studies suggest analysis using an intent-to-treat approach, you have actually excluded subjects with major protocol violations in the actual analysis. Please ensure that analyses will be based on the intent to treat principle. Please also ensure that all subjects enrolled into the study have the diagnosis of VWD confirmed prior to entry, and the method for administration of Wilate standardized across study centers.
21. Please provide (a) the instructions for patients and Investigators for using the tolerability assessment instrument in the form of a 4-point scale in your clinical studies of VWD (b)(4) and (b) validation of this instrument. In your future studies please include appropriate criteria for assignment to the grades of this scale.
22. Please provide a cross-study analysis of subjects, who participated in more than one VWD clinical study, to include, but not be limited to the following :
 - a. changes in disease manifestation pattern, such as severity and location of bleeding, and
 - b. changes in the pattern of product use, such as dosing, concomitant medications, routine prophylaxis vs. treatment, etc.

Please also address the selection bias for enrolling patients who participate in more than one study.

23. With respect to dosing in the proposed package insert we have the following preliminary comments:
 - a. Please explain why the dosing recommendations in the proposed package insert are not consistent with those in the clinical studies:
 - The clinical studies use FVIII:C activity for dosing whereas labeling uses VWF:RCO activity.
 - The proposed labeling recommendations include use of loading and maintenance doses, which were not in the protocols of the VWD trials.
 - The distinction of "minor" and "major" bleeding episodes is different from the grading for bleeding severity in the VWD trials, which use scores of "minor", "moderate", and "severe".
 - b. Please explain the following in the proposed package insert:
 - (b)(4)
 - the basis of the dosing intervals in the labeling recommendations.

- [REDACTED]
- [REDACTED] (b)(4)

- c. Please also note that under "DOSAGE AND ADMINISTRATION" in the Highlights section of the package insert, there is no indication on which coagulation factor activity the dosing should be based (FVIII:C or VWF:RCO). This should be clarified.

24. Please provide the case report forms and all investigations including those in the hospital records for Patient (b)(6) in Center 5 in Study TMAE-104, during his serious adverse event of right atrial thrombus.
25. The mean incremental recovery of VWF:RCO from the European VWD clinical studies (1.5 – 1.9%/IU/kg) is higher than that in the U.S. PK study (WIL-12) (1.1 – 1.2 %/IU/kg). Please address this difference, especially in terms of the issues relating to VWF:RCO assay as discussed above under the section on Clinical Pharmacology and its impact on dosing.
26. You have an ongoing study with data collection in pediatric patients having VWD. In your response to this letter, please update your Pediatric Plan, and data pertaining to pediatric subjects for the proposed package insert, if such data become available.
27. [REDACTED] (b)(4)

CMC

28. Please establish as a release specification the ratio of VWF:RCO to Factor VIII clotting activity, and propose an acceptance criterion based on your manufacturing and clinical experiences. The proposed ratio of (b)(4) ratio is acceptable at this time but should be re-evaluated annually and if possible tightened as more information is available.
29. Regarding the determination of residual moisture in the final drug product:
 - a. The specification for inter-method correlation of (b)(4) does not reflect your experience in practice with $r = 0.98$. Please comment.
 - b. It is noted that in the calibration, results from 13 spectra were rejected as outliers out of (b)(4) spectra obtained from (b)(4) samples. Please describe the criteria for outlier rejection.

- c. Please support the correlation between the (b)(4) and (b)(4) procedures by more extensive testing of different samples (vials) from the same lot by the two techniques. Precision by each technique would include vial-to-vial variability, but would provide information as to the relative accuracy of each technique in establishing a value for residual moisture content for a given lot.
 - d. The (b)(4) determination of water in a solid must be calibrated with reference to the (b)(4) procedure. Please establish the (b)(4) procedure as the "reference" or official regulatory method, and the (b)(4) method as an "alternate" method for routine lot release.
30. Since you currently use recovered plasma frozen within (b)(4) after collection and recovered plasma frozen within (b)(4) after collection for the production of Wilate, please stipulate in the biologics license application that only U.S. recovered plasma under these two categories, and U.S. Source Plasma, will be used for the manufacture of Wilate lots to be distributed to the U.S. market.
31. You have indicated in your amendment submitted on November 13, 2007 that potency values of Wilate lots generated using an automated VWF:RCO assay method are lower than those derived using a manual assay method. In a survey conducted by the North American Specialized Coagulation Laboratory Association in 2004, 51% of laboratories use aggregometry to determine VWF:RCO activity, while 42% use an automated method and 6% use an ELISA method. The trend is likely to be moving towards automation.
- a. Please describe how you would address the discrepancies in VWF:RCO values derived from the different methods when physicians will depend on VWF:RCO values generated from clinical laboratories.
 - b. We obtained VWF:RCO values that were lower than the labeled potency values when conformance lots were assayed in our laboratory using an automated method. Please propose a plan to reconcile such differences to minimize failure of Wilate batches through the lot release program.
32. Under section 3.2.P.5.5 of your BLA submission, the ratio between the various VWF parameters, VWF:Ag, VWF:RCO, and VWF:CB of the conformance lots is quite consistent and close to 1. However, in the pharmacokinetics (PK) studies, these ratios did not follow a particular pattern, and clearly diverged from 1. For example, the PK profile following VWF:RCO is different from that following VWF:Ag, indicating that these parameters were affected differently *in vivo*. Please comment on these discrepancies with reference to the structure of the VWF molecule in Wilate. In particular, please explain this difference in the context of the observation that VWF multimers in Wilate consist of (b)(4) VWF subunits while those in plasma and Humate-P have (b)(4) VWF subunits.

33. Please provide data to demonstrate that the final Wilate product reconstituted with (b)(4) 0.1% polysorbate 80 solvent at the end of its dating period still meets specifications.
34. Please provide updated stability data in your response to this action letter.
35. Please provide an updated development report as the one enclosed under section 3.2.P.2.7 of your BLA submission regarding Pharmaceutical Development.

We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the final proposed labeling.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in the FDA *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products* dated February, 2000 (<http://www.fda.gov/cber/gdlns/mfpdufa.pdf>). For details, please also follow the instructions described in CBER's SOPP 8101.1: *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* (http://www.fda.gov/cber/reg_sopp/81011.htm).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Regulatory Project Manager, Franklin T. Stephenson, at (301) 827-6165.

Sincerely yours,



Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research