

From: Ward-Peralta, Cherie
Sent: Wednesday, June 03, 2015 11:45 AM
To: Fernandez, Alexander Maximilian (max.fernandez@baxalta.com)
Subject: STN 125577/0 - Information Request - Please respond by June 17, 2015

Our Reference: BL 125577/0

Baxter Healthcare Corporation
Attention: Maximilian Fernandez, PhD
June 3, 2015
Sent by email

Dear Dr. Fernandez:

We are reviewing your December 19, 2014, biologics license application (BLA) for von Willebrand Factor (Recombinant). We determined that the following information is necessary to continue our review:

Clinical/Package Insert

1. The draft label (section 2.1) indicates a requirement that "for each bleeding episode, administer the first dose of VONVENDI with ADVATE...if factor VIII levels are below 40%." This will require a delay until results of FVIII measurements are returned from the laboratory. Please modify to indicate if VONVENDI can be given alone in an emergency situation prior to establishment of baseline FVIII levels with ADVATE administration to follow if necessary.

Clinical Pharmacology

2. Study 070701:
 - a. Please provide the duration of drug infusion.
 - b. What analytical methods were used for PK studies for components of rVWF:rFVIII?
 - c. Please provide PK parameters of individual subjects and mean concentration-time plots for every moiety of rVWF:rFVIII. The plots you have provided (14.2.6-14.2.9) require proper adjustment of y-axis.
 - d. Please clarify the reason(s) for not reporting PK parameters for 2 IU/kg dose.
 - e. In Table 14.2.8 (PK of VWF:Ag), IR unit is reported as [(U/dL)/(U VWF:RCo/kg)]. Is it correct to report IR for VWF:Ag as VWF:RCo/kg? The same pattern was noted with VWF:CRB.
3. Study 071001:

- a. Please provide PK parameters for Factor VIII:C (single and multiple dose) as you have done for VWF:RCo, VWF:Ag, VWF:CB.
 - b. Please provide mean concentration-time plots for every moiety of rVWF:rFVIII (50 and 80 IU/kg dose).
4. Study 071104:
- a. Co-administration of rFVIII with BAX 111 did not improve the half-life of rFVIII at both 10 and 50 IU/kg BAX 111 dose. However, based on arithmetic mean, co-administration of rFVIII with BAX 111 at 50 IU/kg dose led to a 26% increase in the AUC of rFVIII and a decrease in clearance by 50%. Based on geometric mean, co-administration of rFVIII with BAX 111 at 50 IU/kg dose led to a 41% increase in the AUC of rFVIII and a decrease in clearance by 28%. This is a substantial change in the PK of rFVIII which may impact the dose of rFVIII if given with BAX 111 at 50 IU/kg dose. Please comment.

Sample and Reagent

5. Please provide 5 vials per lot of:
- a. 3 lots of Vonvendi [von Willebrand Factor (Recombinant)] at 650 IU/vial
 - b. 3 lots of Vonvendi [von Willebrand Factor (Recombinant)] at 1300 IU/vial

These lots should be representative of the manufacturing process to be used for lots intended for interstate commerce.

6. Reagents for test method CTP Doc.-ID VN1306081TB-CTP00.05, entitled, "Determination of Ristocetin Cofactor Activity according to (b) (4)

Please provide the following standards and reagents sufficient to perform 2 independent assays of each of the 6 lots requested.

(b) (4)

7. Please provide the most recent test results with the date of the test for each of the lots sent. The samples and reagents should be shipped to:

Josephine Resnick
Regulatory Coordinator
Food and Drug Administration

Center for Biological Evaluation and Research
Division of Biological Standards and Quality Control
10903 New Hampshire Avenue
WO75, G-717
Silver Spring, MD 20993-0002
Contact Marie Anderson at 240-402-6292 or Josephine Resnick at 240-402-7344
for questions on the shipment.

We request that these samples, reagents and documentation be sent at the latest by June 19, 2015, or notify CBER by then when the shipment can be expected.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by June 17, 2015 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

The action due date for this file is December 19, 2015.

Very Respectfully,

Cherie Ward-Peralta, M.S.

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