

Mid-Cycle Communication Telecon

Application type: Original BLA
Tracking number: STN 125574/0
Product name: Antihemophilic Factor (Recombinant)
[Kovaltry]
Proposed Indication: For use in adults and children with hemophilia A for: (1) Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes; (2) Control and prevention of bleeding episodes; and (3) Peri-operative management (surgical prophylaxis)
Applicant: Bayer HealthCare LLC
Meeting date & time: 11 June 2015, 1:00 pm - 2:00 pm
Committee Chair: Natalya Ananyeva, PhD
RPM: Pratibha Rana, MS

Purpose: To provide an update on the review status of the BLA

FDA Attendees:

Pratibha Rana, MS, Regulatory Project Manager
Natalya Ananyeva, PhD, CMC/Product Reviewer, Chair of the Review Committee
Megha Kaushal, MD, Clinical Reviewer
Patrick Zhou, Independent Assessor, Eastern Research Group (ERG)

Bayer Attendees:

Joseph Scheeren, PharmD, Senior Vice President, Head of Global Regulatory Affairs
Gerhard Schlueter, PhD, Vice President, Head of Specialty Medicine, Global Regulatory Affairs
Chi Li, PhD, MBA, Senior Director, Head of Hematology and Neurology Group, Global Regulatory Affairs
Vicki Chen, MS, Associate Director, Global Regulatory Affairs - Hematology and Neurology
Mark Goldman, MS, Deputy Director, Global Regulatory Affairs - CMC
Lisa Michaels, MD, Vice President, Head of Hematology, Global Clinical Development
Monika Maas Enriquez, MD, Global Clinical Leader, Global Clinical Development
Inge Ivens, PhD, DABT, Deputy Director, Global Toxicology
Steve Garger, Director, Global Biological Development
Thomas Bamberger, PhD, Director, Product Supply
Anita Shah, PhD, Senior Director, Global Clinical Science

Discussion Summary:

1. To date, no significant issues have been identified by the Review Committee except for a major safety concern on the development of inhibitory antibodies to Kovaltry in

previously untreated patients (PUPs), and the use of chromogenic substrate (CS) assay for potency assignment. Additional information will also be requested with regard to CMC, pharmacological and clinical data (specified in item # 4).

2. A GMP inspection of the Bayer, (b) (4) facilities was performed on (b) (4). The Review Committee will assess the outcome of the inspection to determine if a separate pre-license inspection is warranted. Bayer should submit a plan to resolve the observations cited in Form FDA 483, with completion dates for each item, to the lead inspector within 15 business days from the inspection close-out date.

Additional discussion:

Bayer confirmed that the resolution plan will be submitted within the specified timeframe.

3. Responses to *Information Requests* dated 27 February, 19 March, 14 April, 16 April, 4 May, 11 May, and 29 May 2015 were received, and are under review.
4. Requests for additional information will be communicated to Bayer by the end of June 2015 regarding the following disciplines:
 - CMC: information on the control of critical steps and intermediates and assessment of criticality of process parameters; justification of re-processing; and validation of analytical procedures
 - Toxicology: justification of your program for leachables/extractables
 - Clinical Pharmacology: significant differences were noted between pharmacokinetic parameters generated with the One-Stage Clotting (OC) and CS assays in the Leopold 1 study. PK results based on the OC assay are missing in the Leopold Kids study.
 - Clinical/Statistical: additional information from study results and re-analysis (currently partial) of the clinical data from the Leopold 1, Leopold 2 and Leopold Kids studies
 - CDRH: information on the qualification of reconstitution devices (sent on 9 June 2015).

Additional discussion:

On 11 June 2015 just prior to this teleconference, Bayer e-mailed the FDA a document entitled “Chromogenic Substrate Assay for Release of BAY 81-8973”. According to this document, neither the annualized bleeding rate (ABR) during routine prophylactic dosing nor the incremental recovery (both related to clinical outcome) showed significant differences, when the patients were dosed based on either the CS or OC assays.

FDA acknowledged that FDA reviewers had also found this document in Section 2.3.R of the BLA, and will consider it during the review. Since Bayer had used a cross-over dosing design, FDA sought clarifications on how the ABRs were actually determined and

compared, and requested additional analyses of the data, which will be specified in an upcoming Information Request (IR).

Bayer also stated in the e-mail that a field study to compare the performance of the OC and CS assays was completed and the final study report will be provided.

5. A major safety concern is on the development of inhibitory antibodies to Kovaltry in PUPs in the ongoing Leopold Kids study (4 out of 13 patients, 30.8%), which is at the higher level of the known range. This concern is also based on recent publications suggesting an increased risk of inhibitor development in PUPs with severe hemophilia A after treatment with Kogenate FS when compared to Advate, and the similarity between Kovaltry and Kogenate FS. The feasible program for prospective risk management is currently under consideration by the Review Committee. At this time, the Review Committee does not think that a Risk Evaluation and Mitigation Strategy (REMS) is required.

Additional discussion:

In response to Bayer's inquiry, FDA stated that recommendations on prospective risk management will be detailed in an IR from the Epidemiology reviewer.

6. At this time, the Review Committee cannot accept the CS assay for potency assignment of Kovaltry because the pharmacokinetic and clinical data do not appear to support the comparability of the CS and OC assays (refer to item # 4). Further discussions will be needed on the choice of the primary assay for potency assignment for Kovaltry.

Additional discussion:

This topic was discussed under item # 4. FDA also informed Bayer that after receiving the IRs, Bayer may request a teleconference if clarifications are needed.

7. This BLA will not be presented at the *Blood Products Advisory Committee* meeting.
8. The *Late-Cycle Meeting* is scheduled for Tuesday, 22 September 2015 at 1:30 pm - 3:00 pm, and the format of the meeting will be determined at a later date.

END