

Telecon - Information Request, January 11, 2011 - Corifact

RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125385/0 Office: OBRR

Product:

Factor XIII Concentrate (Human)

Applicant:

CSL Behring GmbH

Telecon Date/Time: 11-Jan-2011, 03:15 PM Initiated by FDA? Yes

Telephone Number: -----(b)(6)-----

Communication Category:

1. Information Request

Author: NANNETTE CAGUNGUN

Telecon Summary:

FDA communicated clinical, statistical, and labeling comments.

FDA Participants: Daniela Vanco, Iftekhar Mahmood, Timothy Lee, Ze Peng, Renee Rees, Nannette Cagungun

Non-FDA Participants: David Desris, PharmD, Sr. Manager, Regulatory Affairs (CSL Behring LLC, US)

Paul Hartmann, RPh, Sr. Director, Regulatory Affairs (CSL Behring LLC, US)

Antoinette Mangione, MD, PharmD, Director, Clinical R & D (CSL Behring LLC, US)

Henry Foehl, PhD, Sr. Statistician, Clinical R & D (CSL Behring LLC, US)

Anne-Regine Herboth, Regulatory Affairs (CSL Behring GmbH, Marburg, Germany)

Christine Joch, MD, Sr. Manager, Clinical R&D (CSL Behring GmbH, Marburg, Germany)

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

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

The discussion ensued immediately following introductions.

FDA conveyed the following comments, questions, and recommendations.

Clinical Pharmacology:

1. Please include the PK data which is baseline unadjusted.

- CSL Behring (CSLB) indicated they submitted the rationale for not including unadjusted baseline PK data in the PI in their January 6, 2011 submission. They stated that if endogenous, half-life is over-estimated when the baseline is not adjusted. Clinicians might feel that there is a wider range of safety than what exists.

- FDA stated that clearance is more important than half-life.
 2. Please add 'years' to the statement as shown in bold:
*A 12-week prospective, open-label, multicenter pharmacokinetic and safety study was conducted in 7 females and 6 males with congenital FXIII deficiency, ranging in age from 5 to 42 **years** (3 children, 2 adolescents, 8 adults).*

- CSLB will make the change,

Clinical:

3. Please adjust the safety data (tables, graphs) to reflect the new total number of subjects, as of the 3-months safety update submission.
- CSLB stated that the updated safety data was submitted on November 17, 2010.
 4. FDA asked about the discrepancies in the numbers of total unique subjects in the clinical studies, as well as the total number of infusions administered. The specifics of the question would be later discussed by the statistician.
 5. FDA recommended that the Highlights section of the PI does not exceed the requirement of half a page. In case it needs to be expanded, CSLB should make a request to FDA as soon as possible. (in order that a waiver from the requirement can be made.)
 - CSLB acknowledged the comment.
 6. FDA pointed out that the language for thrombogenicity and immunogenicity should be strengthened in the PI. These two are serious adverse events, which have occurred during the clinical development of Corifact, and need to be described in more detail in the PI.
 7. FDA asked CSLB about the planned completion date for the PMR Phase 4 study, date of final study report submission, as well as the planned total number of subjects.
 - CSLB responded that the last patient will be treated on April 17, 2011, and the final study report will be completed by December 2011. Forty-three subjects were screened. Of these 43 subjects, two were screening failures and, forty-one subjects were treated.
 - CSLB stated they would submit the requested post-marketing information (i.e., dose, presence of diagnosis of Factor XIII deficiency and the exact number of thrombo-embolic events) on 3 subjects who experienced thrombo-embolic events on January 12, 2011. This will be followed by an amendment with responses to the additional questions raised during this telecon.

Statistics:

8. Please confirm the total number of infusions given. Section 2.5.5.2 states that 3284 doses were administered. Tables 2 (page 26) and 3 (page 27) in Section 2.7.4 of the Clinical Summary confirm the number as 3284, with 72 doses given for Study 3001 and 9 doses given for Study 3002. However, Table 10 in Section 12.1 in 5.3.5.4.2.2 indicates that 81 doses were given for Study 3001 and the data listing (da.xpt) for Study 3002 indicates that 5 doses were given.
 9. Please provide the number of doses administered for the studies in the original submission, the number of additional doses in the 3-month safety update, and the total number of doses.
- CSLB stated that they would clarify the number of doses given for Study 3001 and Study 3001.

10. Please confirm the total number of unique subjects. In the safety update, Section 2: Conclusion on page 50 states that the total number of unique subjects increased from 176 to 187. However, Section 1.1.2.1 states that 13 additional unique subjects entered Study 3001 and Section 1.1.3.1 states that 10 additional unique subjects entered Study 3002.

- CSLB referred FDA to the safety update submitted in November 2010. (FDA was later able to confirm CSLB's number of 187 unique subjects).

CMC

Regarding the 1.14.1.3 draft labeling text dated 6 January 2011:

11. On page 14 under 16.1 **How Supplied**, please replace IU with units.

12. Under 16.2 **Storage and Handling**, please revise the last sentence from the second paragraph to "The product must be used within 4 hours after reconstitution."

- FDA explained that if there is contamination during reconstitution, the bacterial load within the first 4 hours will still be acceptable.
- CSLB stated that reconstitution is done using aseptic techniques and the product should remain stable within (b)(4) hours after reconstitution based on their stability data.
- FDA pointed out that this is a safety issue related not only to the stability of the product but also its sterility at the time of administration. FDA asked CSL Behring to review PI's of other coagulation factor products to compare this time period. CSL Behring insisted that since the product will be reconstituted ----(b)(4)----- using aseptic techniques, there would be no chance of contamination. FDA asked CSL Behring to provide justifications in their response and FDA will consider them.

13. Under 11 **Description**, please add the following information to end of the second paragraph:

The potency expressed in units is determined using a Berichrom Activity assay referenced to the current International Standard for Blood Coagulation Factor XIII Plasma. Therefore, a unit herein is equivalent to an International Unit.

FDA stated that the questions discussed in today's telecon as well as labeling comments for the PI would be sent to CSLB tomorrow, January 12, 2011.

Toward the end of the meeting, FDA advised the applicant to ensure that they submit baseline adjusted as well as baseline unadjusted PK data in future BLAs.

The meeting ended.