

This fax is regarding STN 125317/0



ceFACSIMILE TRANSMISSION RECORD

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FAX No.: 610-878-4182

To: David Desris, Regulatory Affairs

This Fax is regarding STN **125317/0** that was submitted to the agency on **18 July 2008** designated as n original BLA for the treatment of congenital fibrinogen deficiency. CBER has finished a preliminary review for the reference submissions and requests CSLB to provide responses to the following information request.

Please submit a response to this information request as an amendment to the file by **November 20, 2008.**

**Vasanth Kumar
Regulatory Project Manager
FDA/CBER/DBA/OBRR/RPMB**

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1. The pivotal clinical studies assessing the efficacy and safety of HFCEP were extremely restricted in size, limiting the ability to detect uncommon adverse events. Further, the population receiving the product after-licensure may differ from the population studied in pre-approval trials. In this case, a nearly identical product has been licensed and marketed previously in Europe, providing a larger exposed population than were available in clinical trials. Spontaneously reported AEs from this population are available for assessment of safety. You have reported a total of 48 adverse event reports for Haemocomplettan P since it began marketing in Europe (1986-2008), corresponding to one report for every 3,414 doses distributed. We concur this seems to be a relatively small crude number of AEs relative to the number of doses administered. However, to expedite review and assessment of potential safety risks identified in these reports, please submit a detailed line list of all AEs, including thromboembolic events and viral transmission, and any other relevant information. Please include the following variables for each report, if available: patient gender, age, indication for treatment, dose level and number of doses, time interval from treatment to onset of AE, AE terms and description of events, relevant concomitant medications or co-suspect products. Also, please describe the surveillance method by which these AE reports were collected: spontaneous, passive reporting, through a registry, active surveillance, or other methods.
2. Please submit both of the 5-year Periodic Safety Update Reports for Haemocomplettan P, along with the associated addendum reports. Please also summarize the types of patients (demographics and indications) who received the marketed product in Europe, if such data are available. Specifically, please address if the exposed population include elderly, pediatric, or other special populations.
3. Please submit a pharmacovigilance plan, per the ICH E2E Pharmacovigilance Planning guidance. The pharmacovigilance plan should summarize and address any safety concerns such as important identified risks, important potential risks, or important missing information. For Riastap, please include routine pharmacovigilance (i.e., compliance with applicable post-market reporting requirements under FDA regulations) and consider additional post-market actions (e.g., a patient registry) as needed to address the above concerns.
4. Please also submit any adverse event reports collected as part of clinical studies conducted in Europe for the indication of acquired hypofibrinogenemia.
5. Please note that --(b)(4)-- viral reduction factors obtained for two removal steps that are not --- (b)(4) --- will result in overestimation of viral clearance capacity of the manufacturing process and therefore, is not acceptable. Your first and second glycine precipitation steps (Stage 2 and Stage 4) have an ----- (b)(4) ----- mechanism for virus --- (b)(4) ----. Therefore, only one of these two steps should be considered in estimating the total log reduction of the manufacturing process. You may calculate the virus reduction factor by summing up individual claims for the combination of Stages 1+2, and 3 for the non-

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enveloped viruses (excluding Stage 4) and Stages 1, 3, and 4 for the enveloped viruses (excluding Stage 2).

6. Please exclude the value of the reduction factor for PRV (Cryoprecipitation; Stage 1) from the proposed overall mean virus reduction factor for HSV-1.
7. Please clarify your testing algorithm for the absence of HAV RNA in plasma that is used for the manufacture of Riastap.
8. Please revise the conformance lot protocols for Fibrinogen Concentrate (Human) to indicate a shelf life of 30 months. Please be informed that the FDA will accept a shelf-life of 30 months if no additional stability data are provided to extend it.
9. In consultation with CBER's Advertising and Promotional Labeling Branch (APLB), we have considered your proposed proprietary name RIASTAP and conclude that under 21 CFR Part 201 the proposed proprietary name is **acceptable with concerns** at this time. There is a potential risk that the medical community may confuse the name RIASTAP with other currently marketed products that sound or look like RIASTAP. We recommend that you use tall-man lettering (i.e. **RIAsTaP**) to mitigate potential risk of medication errors or that you submit one or two new names for FDA consideration.
10. Please revise the CLINICAL PHARMACOLOGY LABELING section as below:

12.3 Pharmacokinetics

~~A pharmacokinetic (PK) study evaluated the single-dose PK and compared the maximum clot firmness (MCF) before and after administration of Riastap™ in subjects with afibrinogenemia (see [Clinical Studies 141](#)).~~

A prospective, open label, uncontrolled, multicenter **pharmacokinetic study was conducted in** 5 females and 40 9 males **with congenital fibrinogen deficiency**, ranging in age from 8 to 61 years (2 children, 3 adolescents, 9 adults). Each subject received a single intravenous dose of 70mg/kg Riastap™. ~~The median dose was 77.0 mg/kg body weight (range 76.6 — 77.4 mg/kg) with a mean average infusion rate of 4.35 mL per minute. Blood samples were drawn was sampled from 15 subjects (14 evaluable) from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. was complete.~~ **The pharmacokinetic parameters of Riastap in patients with congenital fibrinogen deficiency are summarized in Table 2.**

No statistically relevant difference was observed between males and females for fibrinogen activity. Subjects less than 16 years of age (n=4) ~~had a lower median $t_{1/2}$, AUC, AUC for dose 70mg/kg and MRT and a higher median V_{ss} and CL~~ **had shorter half-life (69.9 ± 8.5) and faster clearance (0.73 ± 0.14) compared to subjects between >16 and 65 years of age.** The number of subjects less than 16 years of age in this study limits statistical interpretations. ~~Table 2 provides the PK results.~~

~~In addition,~~ The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-

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infusion. The ~~median~~ mean incremental IVR was 1.8 mg/dL (range 1.30 – 2.73 mg/dL) increase per mg/kg body weight. ~~with a mean of 1.8 mg/dL.~~

Table 2: Pharmacokinetic Parameters (n =14) for Fibrinogen Activity

Parameters	Mean ± SD
Half-life [hours]	78.7 ± 18.13 (55.73-117.26)
C _{max} [g/L]	1.4 ± 0.27 (1.00-2.10)
AUC for dose of 70 mg/kg [mg*hr/mL]	124.3 ± 24.16 (81.73-156.40)
Clearance [mL/h/kg]	0.59 ± 0.13 (0.45-0.86)
Mean residence time [hours]	92.8 ± 20.11 (66.14-126.44)
Volume of distribution at steady state [mL/kg]	52.7 ± 7.48 (36.22-67.67)

The values in the parenthesis are range

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12.4 Pharmacokinetics

A prospective, open label, uncontrolled, multicenter pharmacokinetic study was conducted in 5 females and 9 males with congenital fibrinogen deficiency, ranging in age from 8 to 61 years (2 children, 3 adolescents, 9 adults). Each subject received a single intravenous dose of 70mg/kg Riastap™. Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters of Riastap in patients with congenital fibrinogen deficiency are summarized in Table 2.

No statistically relevant difference was observed between males and females for fibrinogen activity. Subjects less than 16 years of age (n=4) had shorter half-life (69.9 ± 8.5) and faster clearance (0.73 ± 0.14) compared to subjects >16 years of age. The number of subjects less than 16 years of age in this study limits statistical interpretations.

The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The mean incremental IVR was 1.8 mg/dL (range 1.30 – 2.73 mg/dL) increase per mg/kg.

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