

From: Rana, Pratibha
Sent: Friday, March 02, 2012 2:10 PM
To: 'Matthew Vaughn'
Subject: STN 125389/0 Information Request

Dear Matt,

This is regarding your BLA submission STN 125389/0 for Immune Globulin Intravenous (Human). FDA continues with the review of the referenced submission and requests BPC to provide the following information.

1. The FDA appreciates the commitment *to collect and analyze spontaneously reported pharmacovigilance data to specifically examine at-risk populations which were studied in small numbers or excluded from pre-marketing safety studies (children, adolescents, pregnant or lactating women, elderly) and report these results in PSURS.* (See Biotest-IgIV BLA, 1.16.2 Risk Management Plan p.2)
2. The FDA appreciates the commitment to *submit to the FDA all spontaneously reported hypotension events, including non-serious, as expedited reports for the first 3 years of marketing in the U.S.* (Biotest BLA, 1.16.2 p.2)
3. **Comments regarding the proposed Biotest-IgIV Post-Market Observational Safety Study – Hypotension**

A 2-arm study utilizing a comparator group is a reasonable design to assess hypotension risk. It is difficult to make specific, substantive comments, as the outline provided is brief and has few details. In preparing the study protocol, please address the following areas:

Study Population

The outline indicates that PIDD patients are the desired population, as this is the indication for Biotest-IgIV.

- a. Please clarify the study population in terms of inclusion and exclusion criteria.
 - Please clarify if there will exclusion criteria regarding history factors such as hypo- or hyper-tension, a history of liver disease and/or a history of renal disease.
- b. Please identify the infusion service providers involved in the study, when selected. Please elaborate on how the choice of infusion service providers will impact the study population
- c. Please comment on whether study patients will be new IgIV users, current IgIV users, or both. Please discuss the rationale for this choice and how it will impact the comparator group.

Study Design / Analysis Plan

- a. A comparator study design is useful, given the lack of an adequate comparator in the published literature. The null hypothesis currently states that Biotest-IgIV will be “comparable” to other products for the frequency of hypotension, hepatic, and renal impairment. Please modify the null hypothesis to clarify “comparable” and state the statistical methods that will be used to accept or reject the null hypothesis.

- b. Please elaborate on the comparator group product(s). Please explain the rationale for the product(s) selected. Comparator group products should be currently licensed polyvalent IgIVs. Only patients receiving an Ig intravenously should be included (some products are licensed for both IV and subcutaneous use).
- c. Please specify the methods that will be used to ensure the Biotest-IgIV group and comparator groups are similar. Please discuss if matching will be used or a regression analysis will be performed.
- d. Please submit a detailed statistical analysis plan with the study protocol. Please elaborate on the reasons, advantages, and disadvantages of the selected analytic plan. Please consider designing the study to detect a relative risk of 2.0, powered at 80%. FDA considers a single, end of study analysis to be appropriate (as opposed to sequential analyses).
- e. Please clearly state the primary endpoint. Since hypotension is an acute event, the primary endpoint should focus on hypotension occurring in the acute setting (within 4 hours of infusion completion or a similarly short timeframe). It is acceptable to collect and analyze data collected at a variety of time points, including 72 hours, but the primary endpoint should analyze hypotensive events occurring during and shortly after infusion.
- f. Please change the definition of hypotension to include a decrease of 30mmHg **or** a SBP less than 90mmHg **and** clinical symptoms of hypotension.

Data Collection

- a. Please identify the study investigators and elaborate on their role in the study; please state who will adjudicate cases and whether they are blinded to the product brand name. (b)(4)
 (b)(4) Please provide any details currently available and additional information as arrangements are finalized.
- b. Please elaborate on the personnel who will conduct the 72 hour follow-up telephone interviews. The schedule specifies that each patient will have a past medical history taken. If this medical history is collected using a standard form, please provide a copy.
- c. Please describe the “standard data collection scheme for Adverse Drug Reactions and Temporally Associated Adverse Events (ADR/TAAE)” described in the Biotest PASS outline (p.2/5). Please provide a copy of the “standardized checklist” which will be used during the 72 hour telephone follow-up.
- d. Please add “name of product administered” and “route” to the IgIV Administration section of the schedule.
- e. Please specify the frequency of vital sign measurements (including blood pressure) during IgIV infusions. Please specify when blood pressure measurements will be taken following an infusion rate change and how long blood pressure will be monitored following the completion of the infusion.

Reporting

- a. Progress on this post-market study should be provided in the quarterly PSURs. The number of patients enrolled in each arm (in the most recent quarter and cumulatively), the number of adverse events seen in each arm (in the most recent quarter and cumulatively),

the sponsor's assessment of the data to date, and any difficulties encountered in conducting the study should be provided in each interim report. These updates in the quarterly PSURs do not need to contain any statistical analysis of the data in order to avoid the statistical issues related to multiple testing.

- b. A final report on the study should be completed and submitted within 6 months of the last patient completing the study.

4. Comments regarding the proposed Biotest-IgIV Post-Market Observational Safety Study – Hepatic and Renal Failure

- a. Please specify the normal values for transaminases and creatinine which will be used to define hepatic and renal impairment.
- b. Please clarify if the past medical history will specifically include questions regarding a history of liver or kidney disease. If so, please provide a copy of the questions or the form that will be used.

Please submit a response to this request to as many items as an amendment to the file by March 12, 2012 and the rest by March 19, 2012.

Thank you.

Pratibha Rana

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