

Memorandum of Filing: BLA STN125350/0, CSLB's Immune Globulin Subcutaneous (Human) 20%, IgPro20, 5. 10, -(b)(4)-, and 20 mL Solutions

DATE: June 10, 2009

FROM: Hon-Sum Ko, Medical Officer, CBER/DH/CRB, HFM-392

THROUGH: Nisha Jain, Acting Chief, CBER/DH/CRB, HFM-392

TO: The File for BLA STN 125350

SUBJECT: Filing of Original BLA: IgPro20, IGSC 20% Solution (CSL-Behring)

Brief Description of BLA Submission

This submission for a liquid IGSC 20% formulation from CSL-Behring, has been submitted electronically via the Gateway in Global Submit Review, and is in the ICH Common Technical Document (CTD) format, with five modules.

Module Information

- | | |
|---|---------------------------|
| 1 | Administrative/Labeling |
| 2 | Overviews and Summaries |
| 3 | Quality |
| 4 | Nonclinical study reports |
| 5 | Clinical study reports |

The indication in the proposed package insert is “the treatment of primary immunodeficiency (PI).”

Modules 1 and 2 (Administrative/Labeling information and Overviews and Summaries, respectively) appear to contain the required information for review.

- The proposed labeling (package insert) conforms to the PLR format under 21 CFR 201.57 (71 FR 3922-3997; January 24 2006), and has been provided in both annotated and clean versions (in Sections 1.14.1.2 and 1.14.1.3, respectively). The EDR contains a Microsoft Word file of the clean (not annotated) package insert, as well as SPL.
- Financial certification and disclosure information (Form 3454 on Study ZLB04_009CR) have been submitted in Module 1, Section 1.3.4. The applicant certifies that there has been no arrangements where the compensation could have been affected by the outcome of the study.
- In Module 1, Section 1.9, CSLB requests:
 - Waiver of pediatric studies for neonates and children up to 2 years of age – reasons cited: studies are impossible or highly impracticable.Ten subjects in Study ZLB04_009CR were aged 16 or under (3 children and 7 adolescents). There were no apparent differences in the safety and efficacy profiles vs adults, and no pediatric-specific dosing requirements were observed to achieve the desired serum IgG levels.

Comment It may be insufficient for 3 children and 7 adolescent subjects in the database to adequately establish pediatric use, especially in the children subpopulation.

However, CSLB will have data from at least 23 patients (18 children and 5 adolescents) from their European study that can be used to support use in those subpopulations. A deferral request for data submission on children and adolescents would be recommended.

Modules 3 and 4 will be reviewed by the CMC and Pharm/Tox Reviewers, respectively.

Module 5 contains the clinical study reports, and will be reviewed by me as the Clinical Reviewer, and by the Statistical (Dr. J. Hu), the Pharmacokinetics (Dr. I. Mahmood), and the BIMO (Dr. B. Kannan) Reviewers.

Clinical Module (Module 5)

The clinical module contains the clinical study reports for these trials:

- **ZLB04_008CR**. A single-center, randomized, 4-way cross-over, assessment-blinded trial to investigate the local tolerability of a newly developed subcutaneous immunoglobulin G with different concentrations in comparison to Vivaglobin®.
- **ZLB06_003CR**. A single-center, randomized, single-blind, 2-way cross-over study to compare the safety of intravenous (IV) administration of 10% (IgPro10, Privigen®) and 20% (IgPro20) liquid human immunoglobulin
- **ZLB04_009CR**. A phase III open-label, prospective, multicenter study of the efficacy, tolerability, safety, and pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 in subjects with primary immunodeficiency (PID).

This module consists of the following sections

| <u>Volume(s)</u> | <u>Information</u> |
|-------------------------|---|
| 5.2 | List of clinical studies |
| 5.3.3 | Human PK and tolerability study reports ZLB04_008CR and ZLB06_003CR |
| 5.3.5 | Clinical study report of ZLB04_009CR |
| 5.3.7 | Case report forms and case report tabulations |
| 5.4 | Literature references |

Comments

1. The required material has been submitted in full in electronic format. The submission is legible and well organized. The required information for conducting a substantive BLA clinical review appears to have been included in this submission. The definitions in the datafiles have been provided.

2. The clinical safety and efficacy data in this application are based on trials in primary humoral immunodeficiency patients; these trials being conducted under BB-IND -(b)(4)-, with guidance from FDA.

3. For AE datafiles, there should be columns relating to (a) infusion start time, (b) infusion end time, (c) whether event is between start time and within 48 hours of end of the infusion, and (d) whether event is between start time and within 72 hours of end of the infusion.

Conclusion and Recommendation

1. This application is fileable.

2. To the applicant:

- To facilitate reviewing the submission, please submit electronic files in Microsoft Word for Sections 1 to 13 of each clinical study report (ZLB04_009CR, ZLB04_008CR, and ZLB06_003CR) in Microsoft Word.
- Please provide an additional xpt file for adverse events showing (a) start time of immediate preceding infusion, (b) end time of immediate preceding infusion, (c) whether the event started between start time and within 48 hours of end of the infusion, and (d) whether event started between start time and within 72 hours of end of the infusion.
- Please provide your rationale why 10 pediatric subjects' data are sufficient to support use of IgPro20 in children and adolescents. Since you will have additional data from European studies that include children and adolescents, please request a Deferral for submission of data on these pediatric subpopulations in accordance to PREA requirements.

**Appendix. Checking Refuse-to-file Conditions under SOPP 8404 and 21
CFR601.2: Clinical Section for BLA STN 125350/0**

CBER's SOPP 8404 - Basis for a BLA RTF

| | |
|--|----|
| Administrative incompleteness of an application (i.e., clear omission of information or sections of information required). | No |
| Scientific incompleteness of an application (i.e., omission of critical data, information or analyses needed to evaluate safety, purity and potency or provide adequate directions for use [21 CFS 601.2]). The concept of "potency" of a biological product includes clinical evidence of effectiveness, demonstrated by adequate and well-controlled clinical trial(s) or acceptable alternative scientific methods. | No |
| Inadequate content, presentation, or organization of information in an application such that substantive and meaningful review is precluded (e.g., illegibility; failure to translate portions of the application into English; data tabulations (line listings) or graphical displays that are uninterpretable; failure to reference the location of individual data and records in summary reports; absence of protocols for clinical trials; omission of critical statistical analyses or the analysis of a study as planned in the protocol (as opposed to a different, post-hoc analysis); or due to technically deficient electronic submission (1). | No |

21 CFR 601.2 Requirements

| <u>A RTF decision may be made in the absence of any of the following:</u> | |
|--|--|
| <ul style="list-style-type: none"> • A full description of manufacturing methods. • Data establishing stability of the product through the dating period. • Identification by lot number and submission of sample (s) representative of the product to be introduced or delivered for introduction into interstate commerce. • Summaries of results of tests performed on the lot(s) represented by the sample(s). • Specimens of the labels, enclosures, and containers, and if applicable Medication Guide, proposed to be used for the product. • An environmental assessment or claim for exclusion with supporting information;. • List of all manufacturing sites, including contract facilities. | Defer to CMC Reviewers |
| <ul style="list-style-type: none"> • Data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets prescribed standards of safety, purity and potency [The concept of "potency" of a biological product includes a demonstration of clinical potency, i.e., effectiveness]. | Present for clinical studies |
| <ul style="list-style-type: none"> • Financial certification or disclosure statements, or both, for clinical investigators as required by 21 CFR Part 54. | Present |
| <u>The following statements should be included in the application (as appropriate) with respect to the requirement to submit data derived from nonclinical laboratory and clinical studies</u> | |
| <ul style="list-style-type: none"> • For each non-clinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance. | Defer to Non-clinical Reviewer |
| <ul style="list-style-type: none"> • A statement with regard to each clinical investigation involving human subjects that it either was conducted in compliance with the requirements in 21 CFR Part 56, or was not subject to such requirements in accordance with 21 CFR 56.104 and 56.105 and was conducted in compliance with requirements for informed consent in 21 CFR Part 50. | Included in Section 5 of each study report are statements on IRB review and informed consent |