

Summary Basis for Regulatory Action

Date: September 26, 2011

From: Ling Yang, M.D., Ph.D. Chair of the Review Committee

BLA/STN#: STN 125350/136

Applicant Name: CSL Behring

Date of Submission: December 8, 2010

PDUFA Goal Date: October 7, 2011

Proprietary Name/ Established Name: Hizentra™/ Immune Globulin Subcutaneous (Human), 20% Liquid

Indication: Treatment of Primary Immune Deficiency

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Howard Chazin MD, MBA for Basil Golding, M.D., _____

I concur with the summary review.

I concur with the summary review and include a separate review to add further analysis.

I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Specific documentation used in developing the SBRA	
Reviewer Name	Document(s) Date
Clinical Review	Ling Yang
Clinical Pharmacology Review	Iftekhar Mahmood
Statistical Review	Jiang Hu
CMC Review	Pei Zhang
Labeling (APLB)	Liza Stockbridge
RPM	Pratibha Rana

1. Introduction

Hizentra [Immune Globulin Subcutaneous (Human)] is a liquid immune globulin product containing 20% human IgG, and has been licensed for the treatment of primary humoral immunodeficiency (PI) by subcutaneous (SC) route of administration since March 2010. The initial approval was based on a pivotal study conducted in the United States.

CSL Behring (CSLB) submitted a supplement to Biologics License Application (BLA) STN 125350 on August 19, 2010 (STN 125350/103) to fulfill pediatric assessment requirement for subjects aged from 2 to less than 16 (deferral granted at time of approval, together with waiver for neonate and infant age groups), based on data from a European study (ZLB06_001CR). This supplement was approved on February 17, 2011 with labeling changes in Pediatric Use, Dosage and Administration, and Warning and Precautions sections.

CSLB submitted the current efficacy supplement to BLA STN 125350 on December 8, 2010 and referenced the clinical study report for the European study (ZLB06_001CR),

previously submitted and approved under STN 125350/103, and provided a revised draft package insert.

The submission is classified as an efficacy supplement because of clinical data, although no new clinical data are included in the submission.

2. Background

This submission is a Biologics License Prior Approval Supplement (PAS) from CSLB to BLA STN 12350 for Immune Globulin Subcutaneous (Human), 20% Liquid (Hizentra). In the current submission, CSLB referenced the clinical study report for their European study, ZLB06_001CR, previously submitted and approved under STN 125350/103, and provided a revised draft package insert.

Clinical study ZLB06_001CR was a phase 3, prospective, open-label, multicenter, single-arm study on efficacy and safety of Hizentra in 51 adult and pediatric subjects with PI, who had been treated previously with immune globulin intravenous (IGIV) every 3 or 4 weeks or with immune globulin subcutaneous (IGSC) weekly.

3. Chemistry, Manufacturing and Controls (CMC)

There were no new CMC changes.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical studies conducted.

5. Clinical Pharmacology

There were no new clinical pharmacology studies conducted.

6. Clinical/ Statistical

a) Clinical Program

The clinical program to support the proposed labeling changes consisted of one clinical study conducted in Europe, ZLB06_001CR.

Design: Study ZLB06_001CR, entitled “*A multicenter study of the efficacy, tolerability, safety, and pharmacokinetics of Immune Globulin Subcutaneous (Human) IgPro20 in subjects with primary immunodeficiency*” was a prospective, open-label, multicenter, single-arm study in 51 adult and pediatric subjects with PI, who had been treated previously with IGIV every 3 or 4 weeks or with IGSC weekly, to evaluate the efficacy and safety of Hizentra.

The study consisted of a 3-month wash-in/wash-out period followed by a 7-month efficacy period. During the efficacy period, subjects were treated with Hizentra at weekly intervals and visited the study site every 4 weeks for efficacy and safety evaluations. The initial weekly Hizentra dose was 100% of the subjects’ previous weekly equivalent IGIV or IGSC dose. Dose adjustments were performed during the wash-in/wash-out period at

the discretion of the investigator. In a PK substudy, PK assessments were performed during one treatment interval at steady-state (Week 28 ± 1).

Endpoints:

The primary efficacy endpoint of Study ZLB06_001CR was total serum IgG Ctrough values. Secondary efficacy endpoints included rates for serious bacterial infections, ((SBI), defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, or visceral abscess), all infections, antibiotic use, hospitalization due to infections, and days out of work, school, kindergarten, day care or inability to perform normal activities.

Safety endpoints were: rate, intensity, and relatedness of any adverse events (AEs) per infusion and subject; local tolerability of SC infusions; changes in routine laboratory parameters (hematology, serum chemistry, urinalysis) as compared to baseline assessments; vital sign changes before and after infusions at the study site, and physical examination at baseline and completion.

RESULTS:

Efficacy:

Of the 51 PI subjects screened, 46 subjects were treated with Hizentra during the efficacy period. For the 46 subjects in the efficacy analysis, the weekly mean dose in the efficacy period was 120.1 mg/kg (range 59 to 243 mg/kg), which was 104% of the previous weekly equivalent IGIV or weekly IGSC dose. The mean of individual median IgG Ctrough values increased from 7.49 g/L with the previous IgG therapy to 8.10 g/L during infusions 12 to 17.

None of the subjects had an SBI during the efficacy period. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.

Safety: See below, under section 7, Safety.

b) Pediatrics

The pediatric assessment of 23 children from 2 to 16 years of age (18 aged 2 to <12, and 5 aged 12 to <16) was included in this submission. A waiver for neonates and children up to 2 years of age had been granted previously.

7. Safety

51 subjects in the safety analysis received a total of 1831 infusions of Hizentra. The most common ARs experienced by 2 or more subjects were local reactions (25 [49%] subjects), headache (6 [11.8%] subjects), pruritus (4 [7.8%] subjects), pyrexia (3 [5.9%] subjects), fatigue (3 [5.9%] subjects), and rash, erythema, hypothermia, and abdominal discomfort (2 [3.9%] subjects each).

Three subjects withdrew from the study due to ARs of mild to moderate intensity. One subject experienced injection-site pain and injection-site pruritus; the second subject experienced injection-site reaction, fatigue, and feeling cold; and the third subject

experienced injection-site reaction and hypersensitivity. All reactions were judged by the investigator to be “at least possibly related” to the administration of Hizentra. The following sponsor table 4 from the European study and reproduced here from the Hizentra package insert summarizes the most frequent ARs (in 2 or more subjects) occurring during or within 72 hours after the end of infusion.

Incidence of Subjects with Adverse Reactions (ARs)* (Experienced by 2 or More Subjects) and Rate per Infusion, European Study

AR (≥2 Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=51)	Number (Rate†) of ARs (n=1831 Infusions)
Local reactions‡	24 (47.1)	105 (0.057)
Other ARs:		
Headache	9 (17.6)	20 (0.011)
Rash	4 (7.8)	4 (0.002)
Pruritus	4 (7.8)	13 (0.007)
Fatigue	3 (5.9)	5 (0.003)
Abdominal pain, upper	2 (3.9)	3 (0.002)
Arthralgia	2 (3.9)	2 (0.001)
Erythema	2 (3.9)	4 (0.002)
Abdominal discomfort	2 (3.9)	3 (0.002)
Back pain	2 (3.9)	2 (0.001)
Hematoma	2 (3.9)	3 (0.002)
Hypersensitivity	2 (3.9)	4 (0.002)

* Excluding infections.

† Rate of ARs per infusion.

‡ Includes infusion-related reaction; infusion-site mass; infusion/injection-site erythema, hematoma, induration, inflammation, edema, pain, pruritus, rash, reaction, swelling; injection-site extravasation, nodule; puncture-site reaction.

The proportion of subjects reporting local reactions decreased over time from approximately 20% following the first infusion to <5% by the end of the study.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling:

The original submission on December 8, 2010 and the amendment submission on March 31, 2011 included the revised package insert. Major revisions in labeling include changes to:

- Adverse Reactions section to include safety data of Study ZLB06_001CR
- Clinical Studies section to incorporate efficacy data of Study ZLB06_001CR
- Postmarketing Experience Section to incorporate postmarketing pharmacovigilance data

Other revisions in labeling include:

- Additional language regarding age range in the Indications and Usage section
- Update on thrombotic events (TE) associated with subcutaneous IG use in the Warnings and Precautions section
- Correction in the steps for product administration in the Dosage and Administration section
- Patient Counseling Information section

On June 22, 2011, FDA provided the revised package insert (revised by Dr. Hon-Sum Ko) and comments to CSLB. The major revisions were:

a. Efficacy: Section 14.2 “European Study”:

CSLB has been advised that the PK information to be provided in labeling for this study should be limited. The PK evaluation in study ZLB06_001CR was based on comparable IgG trough levels at steady state between Hizentra SC treatment and previous IG therapy (IGIV or IGSC). This is not a primary comparison recognized by FDA, as the Agency requires matching AUC for the investigational IGSC upon reaching steady state with the AUC obtained with previous IGIV treatment.

b. Safety: Section 6.1 “Adverse Reaction”

The Table submitted to summarize the most frequent AEs (experienced by at least 4 subjects), *irrespective of causality* during the European study was revised to add the number of AEs (such as pyrexia) the occurrences of which were truncated presumably as being associated with infections. The Table was further revised on August 31, 2011 to include ARs only.

On July 20, 2011, CSLB submitted the revised labeling in response to FDA’s comments. The submission also included a Postmarketing Safety Report for Hizentra in the US between 04 March 2010 and 15 May 2011. The safety report was submitted to support section 6.2 Postmarketing Experience, of the labeling. Postmarketing ARs reported included: infusions reactions such as swollen face or tongue, pharyngeal edema and thromboembolic events. The Postmarketing Experience section was revised according to FDA’s labeling guidance and comments were conveyed to CSLB on August 31, 2011.

On September 6, 2011, a teleconference was held between FDA and CSLB for clarification and further discussion of the labeling changes. On September 16, 2011, CSLB submitted the final labeling for approval.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of this supplement.

b) Risk/ Benefit Assessment

PK, efficacy, and safety data were found adequate to make a favorable decision concerning potential risk/benefit balance.

c) Recommendation for Postmarketing Risk Management Activities

There are no Postmarketing Risk Management Activities.

d) Recommendation for Postmarketing Activities

There are no Postmarketing requirements or commitments.