Summary Basis for Regulatory Action

Date	January 15, 2015
From	Daniela J. Vanco. M.D., Committee Chair
Subject	Summary Basis for Regulatory Action
BLA Supplement#	STN 125350/416
Applicant	CSLB Behring AG
Date of Submission	April 1, 2014
PDUFA Goal Date	January 30, 2015
Proprietary Name / Established (USAN) names	Hizentra/ Immune Globulin Subcutaneous (Human) 20% Liquid
Approved Indication	Treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older
Proposed Dosing	Weekly, biweekly and 2 to7 times a week
Recommended Action:	**Approval**
Signatory Authorities Action:	**Approval** **Paul Mintz_____** *Offices Signatory Authority:* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

Reviewer Names
Clinical Review: Daniela Vanco
Epidemiology: Wambui Chege
Clinical Pharmacology Review: Carl-Michael Staschen
Advisory Committee Transcript: Not applicable
Labeling (Advertising and Promotion): Lisa Stockbridge/Alpita Popat
Regulatory Project Manager: Pratibha Rana

1. Introduction

On April 1, 2014, CSL Behring (hereafter Applicant), submitted an Efficacy Supplement to Biologics License Application (BLA) STN 125350 for Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid (IGSC, hereafter Hizentra), seeking a frequent dosing regimen of 2 to 7 times a week and revision to the dose adjustment factor when switching from intravenous immune globulin (IGIV) to Hizentra, for the approved indication of Primary Humoral Immunodeficiency (PI) in adults and pediatric patients two years of age and older .

Hizentra was originally approved on March 4, 2010, for the treatment of PI for weekly subcutaneous (SC) administration. On February 17, 2011, the package insert was updated to include safety and efficacy information from a post-marketing phase 4 study in the pediatric age groups 2 to 16 (BLS 125350/103) for weekly dosing regimen.

On September 12, 2013, biweekly dosing regimen, (every two weeks) in both adults and pediatric patients two years of age and older was approved based on a pharmacometric [population-based pharmacokinetic (population PK)] modeling and simulation] data submitted in the Efficacy Supplement (BLS 125350/316). The PK modeling approach compared PK profiles for weekly IGSC and biweekly IGSC dosing in subjects with PI.

A covariate analysis showed that patient's gender had no statistically significant impact on the estimated PK parameters. The impact of patient's race on PK-results was not studied.

In the current supplement, the same pharmacometric approach was employed for frequent dosing option of 2 to 7 times per week, including revision of the dose adjustment factor from the current 1.53 to 1.37 when switching from IV to SC.

No new clinical data were submitted in support of the current efficacy supplements.

For the pharmacometric approach, data from four completed phase 3 studies (151 unique adults and 57 pediatric patients) were used to develop and evaluate population PK models with the goal of deriving the new dosing regimen of 2-7 times per week. This data was previously used for modeling and simulation to support the biweekly dosing regimen.

The new dosing regimen triggered Pediatric Research Equity Act of 2003 (PREA). Pediatric Review Committee (PeRC) PREA Subcommittee Meetings held on December 17, 2014, agreed with the review division's recommendations:

- To grant a partial waiver for pediatric studies for neonates and children up to 2 years of age, as the studies are impossible or highly impracticable to conduct.
- To allow the new dosing regimen for the pediatric patients 2 years of age and older.

Recommendation: It is recommended that this efficacy supplement be approved.

2. Background

Primary immunodeficiency includes a variety of disorders in which there is an intrinsic defect in the immune system that renders subjects more susceptible to infections. Immunoglobulin (IG) replacement therapy has been the standard treatment for PI since the early 1950s. The administration routes have evolved from intramuscular, intravenous to subcutaneous. The systemic adverse event (AE) rate of SC infusions is generally considered to be lower than that of IG administered intravenously, without compromising efficacy.

3. Chemistry Manufacturing and Controls (CMC)

There is no new CMC information submitted. Cross-reference to original BLA 125350/0.

Hizentra is a 20% immunoglobulin, liquid formulation of human immunoglobulin containing 250 mmol/L L-proline and ≤30 mg/L polysorbate 80 at a pH of 4.8 for subcutaneous infusion using an infusion pump. Hizentra is manufactured from large pools of human Source Plasma or recovered plasma by a combination of cold alcohol fractionation, octanoic acid precipitation, and anion exchange chromatography. The manufacturing process of Hizentra is identical to the manufacturing process of its parent product Immune Globulin Intravenous (Human), 10% Liquid, Privigen (BLA STN 125201, licensed on July 26, 2007) up to the active substance solution step of Privigen (IgPro10-SOL). After production of the active substance solution IgPro10-SOL and pre-formulation, the protein solution is concentrated to the final protein concentration of 20%, resulting in Hizentra, whereas Privigen is concentrated to a final protein concentration of 10%.

Hizentra is formulated with 250 mmol/L of L-proline (used as a stabilizer) and 10-30 mg/L polysorbate 80, and trace amounts of sodium, has pH of 4.6 to 5.2. It does not contain any sucrose or preservatives. The product is stable at room temperature (up to 25 ^{O}C) for up to 30 months.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical data submitted in this efficacy supplement. Cross-reference to BLA STN 125350/0.

5. Clinical Pharmacology

5.1 Mechanism of Action

Hizentra supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents.

5.2 Pharmacokinetics (*For the full Clinical Pharmacology review, please see Dr. Carl-Michael Staschen's memo.*)

The objective of this submission was to use population PK based modeling and simulation techniques to seek approval for Hizentra to:

- Allow for more frequent SC dosing of Hizentra compared to weekly SC administration and
- Allow to switch from IGIV (Privigen) to biweekly or more frequent dosing of Hizentra SC with an alternative IV: SC Dose Adjustment Coefficient (DAC) of 1:1.37 (as opposed to currently approved 1:1.53).

Methods:

Modeling

Human Immune Globulin serum concentration data consisting of > 3800 samples from 151 adult and pediatric subjects with PI (four phase 3 studies) were analyzed by nonlinear mixed effects modeling. All study subjects in the analysis data set were on IgG treatment prior to and during all study periods. The resulting final model was a two-compartment PK model that included bodyweight effects on clearance and volume of distribution of the central compartment.

Results:

1. Simulation of Exposure Metrics (more frequent SC vs. weekly SC)
   Based on population PK simulations, it was shown that for the same total weekly SC maintenance dose, administering SC infusions
   - daily
   - 2 times per week,
   - 3 times per week,
   - 5 times per week (daily for 5 days)

   produced similar exposures, with overlapping steady-state concentration time profiles and similar AUC0-7days, Cmax, and Cmin values compared to weekly SC-infusions.

2. Simulation of Exposure Metrics with varying DACs
   Population PK simulations showed that biweekly or more frequent SC dosing with DACs of 1:1.37 or greater maintained AUC0-28days and Cmin above 90% of values observed with IV dosing. DAC of 1.37 is appropriate for switching from Privigen IV to Hizentra SC dosing.

6. Clinical Program

There were no new clinical data submitted in this efficacy supplement. The safety/efficacy results for support of US Hizentra approval are cross-referenced to BLA 125350/0 and BLS 125350/103 (*see Dr. Hon-Sum Ko's clinical reviews*).

The Applicant is using population PK based modeling and simulation techniques to seek approval for frequent dosing of Hizentra.

Four phase 3 studies were used for PK modeling:

- **ZLB04_009CR:** Pivotal phase study for US licensure conducted under IND 13201: "A Phase III Open-Label, Prospective, Multicenter Study on the Efficacy, Tolerability, Safety and Pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 (Hizentra) in Subjects with Primary Immunodeficiency (PID)." Forty-nine subjects, ages 2 to 75 years, with PI were treated with Hizentra. Ten out of 49 were pediatric patients, 3 children (ages 2 to < 12) and 7 adolescents (ages 12 to <16) were included (cross-reference to BLA STN 125350/0).
- **ZLB03_002:** Pivotal trial for Privigen (CSLB's licensed IGIV), multicenter, open-label, single-arm, prospective study with PI patients. All subjects had been on regular IGIV replacement therapy at least 6 months prior to participating in the study.
- **ZLB05_006:** Multi-center, US open-label, single-arm prospective extension study to ZLB03_002.
- **ZLB06_001:** Multi-center, European open-label, single-arm prospective study on PI subjects who had been on regular IGIV or IGSC replacement therapy at least 6 months prior to participating in the study.

6.1 Pediatrics

At the time of the original BLA (125350/0) approval, the Applicant was required to conduct a post-marketing pediatric deferral study. Additional safety and efficacy data in children and adolescents were collected in then ongoing clinical study in Europe (ZLB06_001CR), entitled, "A multi-center study of the efficacy, tolerability, safety, and pharmacokinetics of Immune Globulin Subcutaneous (Human) IgPro20 in subjects with primary immunodeficiency".

The study evaluated Hizentra in 51 subjects, ages 3 to 60 with PI, 23 of 51 were pediatric subjects, represented in the subgroups:

- 18 Children (ages >2 to ≤12)
- 5 Adolescents (ages >12 to ≤16)

The study was completed and the final clinical study report for ZLB06_001CR was submitted on August 19, 2010 (BLS 125350/103), which was approved on February 17, 2011, resulting in labeling changes to include the pediatric population 2 years of age and older.

7. Safety

Safety Conclusions:

PK modeling was used to support a new frequent dosing regimen. As PK modeling cannot model/predict safety (local and systemic), safety was extrapolated from the previous clinical trials, which were conducted in support of weekly administration, as well as assessed from postmarketing safety data.

Data from the US and European pivotal studies showed no unexpected safety concerns outside of the spectrum of those known and labeled for immune globulins. The most

common adverse reactions observed in ≥5% of study subjects were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain. No consistent trends of different ARs, including rates or severity of ARs of local reactions, by age subgroup or by Hizentra dose within the range of doses tested, were observed in Hizentra studies.

OBE's data mining of the FAERS showed no unexpected events: adverse reactions reported following use of Hizentra fall into broad categories - Infusion Site Reactions and Infections, the first recognized and labeled as expected, the latter is expected due to the condition itself. *(For the full pharmacovigilance review, please refer to Dr. Wambui Chege's memo.)*

Overall, in the clinical studies, as well as since its licensure in 2010, Hizentra has shown acceptable safety profile.

Simulations of the frequent dosing regimens showed that Cmax is comparable with weekly and bi-weekly administration and remains markedly lower than the levels achieved with IGIV products. Adverse effects arising from the systemic exposure of the frequent administration of Hizentra are therefore not expected to differ from the already labeled ARs for the weekly and bi-weekly administration. The volumes and rates remain unchanged in the proposed new label. The recommended maximum volume per site is up to 25 mL, as well as the rate of infusion (per site and overall maximum flow rate of 25mL/hour). The more frequent doses of Hizentra may result in increased frequency of injection site reactions however; the new dose adjustment coefficient (decreased from 1.53 to 1.37) will reduce the overall volumes injected.

The labeling instructs to space apart and to change the injection sites with each administration.

Hizentra is approved for pediatric patients two years of age and older. The injection site reactions in the youngest population were of concern due to their relatively small body surface area. However; no pediatric-specific dose requirements are necessary to achieve the desired serum IgG levels. As for all age groups, dosing for pediatric subjects is based on body weight and the labeling clearly instructs that dosing is titrated to patient's clinical response.

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 final labeling was negotiated and agreed upon with the Applicant.

11. Recommendations and Risk/ Benefit Assessment

11.1 Recommended Regulatory Action

The CBER review committee recommends approval of this BLA Efficacy Supplement.

11.2 Risk/ Benefit Assessment

There are currently no concerns regarding the risk/benefit ratio. Although with the frequent dosing more injection site reactions are to be anticipated, the new decreased dose adjustment coefficient will reduce the overall volumes injected.

Thromboembolic events (TEEs) have been described after the administration of both IGIV and IGSC products, including Hizentra. Measures to mitigate the risk of TEE following use of Hizentra are highlighted in the label as box warning.

There is no evidence to suggest that the safety profile of frequent dosing is likely to be qualitatively different from that of already approved.

Overall, the alternative more frequent regimen will give a wider range of dosing options (from daily up to bi-weekly) based on individual patient's needs/preferences

11.3 Recommendation for Postmarketing Activities

No postmarketing study has been proposed by the sponsor to evaluate the safety of the frequent dosing regimen and the available data do not warrant one. In the current Pharmacovigilance Program, TEEs are not listed as a potential risk but rather an Important Identified Risk, along with the local reactions, for which the sponsor plans routine pharmacovigilance. The sponsor will submit annual reports for serious AEs for two years.