

Clinical Review Memorandum

Date: September 26, 2011
To: To File (BLA STN 125350/136)
From: Ling Yang, Medical Officer, HFM-392
Through: Nisha Jain, Branch Chief, HFM-392
CC: Pratibha Rana, RPM, HFM-370
Applicant: CSL-Behring
Product: Immune Globulin Subcutaneous (Human), (IGSC, 20%; IgPro20)
Trade Name: Hizentra®
Received Date: December 8, 2010
PDUFA Goal Date: October 7, 2011
Indication: Treatment of Primary Immune Deficiency
Subject: Final Review of Supplement

EXECUTIVE SUMMARY

CSL Behring submitted an “efficacy” supplement to Biologics License Application (BLA) STN 125350 on 08 December 2010, 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 efficacy supplement because of clinical data, although no new data are included in the submission.

On March 31, 2011, CSLB submitted an Amendment to the Supplement with additional changes to the draft 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 minor 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

During the review process, FDA and CSLB communicated multiple times to finalize the package insert.

CONCLUSION AND RECOMMENDATION

- The data from Study ZLB06_001CR support the proposed labeling revision.
- This supplement is recommended for approval.

2. CLINICAL REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition Studied:

Primary humoral Immunodeficiency (PI)

2.2 Available Treatments for Proposed Indication

Current treatment of PI is replacement therapy with human immune globulin products, usually administered intravenously (IV). There are four marketed products in the U.S. that allow for subcutaneous (SC) route of administration: Vivaglobin (CSL-Behring), Hizentra (CSL-Behring), Gamunex-C (Talecris) and Gammagard Liquid (Baxter).

2.3 Safety and Efficacy of Pharmacologically Related Products

The safety profile and effectiveness of human immune globulin products for replacement therapy of PI have been well documented for the IV preparations. Immune globulin products for SC use have similar efficacy as the IV preparations with adequate dosing. SC immune globulin differs from IV immune globulin in the safety profile, as there is greater tendency for local infusion site reactions, but lower likelihood of severe systemic reactions.

2.4 Previous Human Experience with the Product (including Foreign Experience)

- Hizentra has been licensed in the U.S. for SC route of administration for the treatment of PI since March 4, 2010
- CSLB submitted a supplement (STN 125350/103) on August 19, 2010 to fulfill pediatric assessment requirement for subjects aged 2 to <16 (deferral granted at time of approval, together with waiver for neonate and infant age groups), based on data from a study in Europe (ZLB06_001CR). This supplement was approved on February 17, 2011 with labeling changes from the additional pediatric data.
- Hizentra Postmarketing Safety Report was submitted on July 20, 2011 per FDA's request. The report included safety data received by CSLB pharmacovigilance for Hizentra in the US between March 4, 2010 and May 15, 2011. The report included the line listing of all 584 suspected adverse reaction (AR) cases reported and a summary tabulation. (Details see section 8 "Postmarketing Experience").

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

- Data from a European study (ZLB06_001CR) for subjects aged 2 to <16 was submitted on August 19, 2010 as supplement (STN 125350/103) to fulfill pediatric assessment requirement. The supplement was approved on February 7, 2011 with labeling changes from the pediatric data.
- On March 31, 2011, CSLB submitted a revise package insert to include the approved changes from the previous supplement in the current "efficacy" supplement.

2.6 Other Relevant Background Information

- Upon approval of the above labeling supplement (STN 125350/103), CSLB has updated the draft label for the current “efficacy” supplement, to include the approved changes from the previous supplement in a submission dated March 31, 2011 (STN 125350/136/4).
- On July 20, 2011, CSLB submitted the revised package insert in response to FDA’s mid-cycle review comments and revised package insert sent on June 22, 2011. The submission also includes postmarketing Safety Report for Hizentra in the US between 04 March 2010 and 15 May 2011. The safety report is to support section 6.2 of the package insert.

3. Chemistry, Manufacturing and Controls (CMC)

- There are no new CMC changes.

4. Nonclinical Pharmacology/Toxicology

The product used in the European study is the same as CSLB’s marketed Hizentra. There are no new nonclinical studies conducted.

5. Clinical Pharmacology

There are no new clinical pharmacology studies conducted.

6. Clinical

- The clinical program to support the proposed labeling changes consisted of one clinical study conducted in Europe, ZLB06_001CR.
- Data from study ZLB06_001CR was submitted on August 19, 2010 as BLA supplement (STN 125350/103). The supplement was approved on February 7, 2011 with labeling changes from the pediatric data. (For detail of the study, please see Dr. Hon-Sum Ko’s review of STN 125053/103).

6.1 STUDY DESIGN

6.1.1 Objectives

- To assess the efficacy, tolerability, safety, and pharmacokinetics (PK) of Hizentra in subjects with primary immunodeficiency (PI), including a health-related quality of life (HRQL) assessment
- The IgPro20 dose should result in sustained IgG trough levels (C_{trough}) comparable to the previous IgG treatment

6.1.2 Design Overview:

- 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*” is a prospective, open-label, multicentre, 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 and followed by a 7-month efficacy period. During the efficacy period, subjects were treated with Hizentra at weekly intervals and visited study site every 4 weeks for efficacy and

6.1.3 Population: Adult and pediatric subjects with PI

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Hizentra (IgPro20) was administered as SC infusion at weekly intervals by the subject or parent/guardian (after a training period at the study site) for at total of approximately 10 months.
- The initial weekly IgPro20 dose was 100% of the subjects' previous weekly equivalent IGIV or IGSC dose. Dose adjustments could be performed during the wash-in/wash-out period at the discretion of the investigator.

6.1.5 Sites and Centers: 16 centers at multi-countries

6.1.6 Surveillance/Monitoring

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

6.1.7 Endpoints:

- The primary efficacy endpoint was total serum IgG Ctrough values.
- Secondary efficacy endpoints included rates for serious bacterial infections (SBI; defined as bacterial pneumonia, bacteraemia/septicaemia, 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.
- PK endpoints were area under the concentration-time curve (AUC), maximum concentration (C_{max}), and time point of C_{max} of total IgG; serum concentrations of IgG subclasses, specific IgGs, and L-proline.
- HRQL endpoints were the influence of SC treatment on HRQL was assessed using validated HRQL questionnaires. Baseline and follow-up questionnaires completed by the subject (or parent/guardian).
- Safety endpoints were rate, intensity, and relatedness of any AEs per infusion and subject; local tolerability of SC infusions; changes in routine laboratory parameters as compared to baseline assessments; vital sign changes before and after infusions at the study site, and physical examination at baseline and completion.

6.1.8 Statistical Considerations & Statistical Analysis Plan

- The primary analysis was a descriptive comparison of 6 consecutive IgPro20 IgG Ctrough values per subject (before Infusions 12 to 17) with IgG Ctrough values obtained prior to the first IgPro20 infusion, in the ITT population.
- Further efficacy and safety data were analyzed descriptively.
- PK parameters were derived by non-compartmental analysis and summarized descriptively.
- Changes in HRQL scores compared to baseline were analyzed descriptively, including median changes and confidence intervals.

6.2 RESULTS:

6.2.1 Population Enrolled and Analyzed

- Planned enrolment: 51 subjects (18 children aged < 12 years, 5 adolescents aged 12 to <16)
- Planned enrolment for PK sub-study: Approximately 25 subjects
- Actual enrolment/all treated (AT) population: 51 subjects
 - Intention-to-treat (ITT) population (treated in the efficacy period): 46 subjects
 - Per-protocol efficacy (PPE) population: 34 subjects
 - Per-protocol PK (PPK) population: 23 subjects
 - Full HRQL population (baseline and ≥ 1 follow-up assessment): 48 subjects
 - Discontinued: 8 subjects

6.2.2 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.
- None of the subjects had an SBI during the efficacy period, resulting in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.
- One subject developed an SBI (pneumonia) during the wash-in/wash-out period (annual rate: 0.03 SBIs/subject/year for the full evaluation period; upper 99% confidence limit: 0.192) and her subsequent pneumonia in the efficacy period was not counted as a separate episode.

6.2.3 Safety:

- 51 subjects in the safety analysis received a total of 1831 infusions of Hizentra. 48 (94.1%) subjects experienced ARs occurring during or within 72 hrs of ending an infusion.
- 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),

- Seven SAEs (diarrhea, pneumonia x 2 events, pyrexia, bronchiolitis, appendicitis and sciatica) occurred in 5 subjects (9.8%). All were assessed by the investigator as unrelated to the study drug. Two of the SAEs occurred during or within 72 hrs after the end of an infusion (appendicitis and sciatica). Two SAEs were severe in intensity (pneumonia and appendicitis), 4 SAEs were moderate in intensity (pneumonia, pyrexia, bronchiolitis, and sciatica), and one SAE was mild in intensity (diarrhea).
- Three subjects withdrew from the study due to ARs. One subject experienced injection-site pain and injection-site pruritus; one subject experienced injection-site reaction, fatigue, and feeling cold; and one 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.

7. Special Population

7.1 Pediatric Use and PREA Consideration

- 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 submission 125350/103. A waiver for neonates and children up to 2 years of age had been granted previously.
- During the review of 125350/103, the pediatric assessment and the labeling changes were presented to the PeRC on December 15, 2010. The Committee agreed that the PMR for PREA deferral has been fulfilled with labeling changes.
- Subgroup analysis by age for incidence of subjects with adverse reactions

Category	Number of Subjects (%)			
	Total (N=51)	2 to < 12 years (N=18)	12 to < 16 years (N=5)	16 to < 65 years (N=28)
Subjects with ARs within 72 hours	48 (94.1)	17 (94.4)	5 (100)	26 (92.9)

8. Postmarketing Experience

- CSLB submitted Hizentra postmarketing Safety Report on July 20, 2011 per FDA’s request on June 22, 2011. The report includes the line listing of all suspected ARs cases received by CSLB Pharmacovigilliance for Hizentra in the US between the approval of Hizentra on March 4, 2010 and May 15, 2011 and a summary tabulation. Sixty-three (63) of the 584 case reports were serious.
- The data came from the following sources:
 - Spontaneous reports (primarily from health professionals)
 - Reports from patients and other consumers
 - Other sources (e.g. reports received from licensors-licensees, from special registries)
- CSLB stated that 2,950,512 kg corresponding to 295,051 estimated standard doses (ESD) of 10 g had been distributed and this equals to 1 spontaneous report per 505 applications.
- The safety report is to support section 6.2 “Postmarketing Experience” of the package insert.

8.1 Summary of the Reported Cases:

431 (25 were serious) of the 584 cases are covered by the safety profile of Hizentra known from clinical studies conducted by CSLB or from the experience of other IGIV products:

- Generalized reaction: 218. The main symptoms were: headache, fatigue, nausea, pain, diarrhea, chills, vomiting, abdominal discomfort (including abdominal pain, abdominal distension), chest discomfort (including chest pain), pyrexia, dizziness, migraine, malaise, changes in blood pressure, arthralgia, myalgia, back pain and tachycardia.
- Local reaction at injection site/infusion site: 144. The main symptoms at the injection site were: erythema, pain, swelling, itching, mass, irritation, hematoma, induration, warmth, rash and edema.
- Allergic reactions: 69. The main symptoms were: pruritus, rash, dyspnea, urticaria and hypersensitivity reaction (including anaphylactic/anaphylactoid reaction). No report of “anaphylactic shock” was received.

153 (38 were serious) of the 584 cases were not covered by the safety profile of Hizentra and were assessed as unexpected. Thirty-eight (38) of these were serious.

Analysis of Cases Reported:

- 16 Cases: Asthenia, Sinusitis, Cough
- 13 Cases: Oropharyngeal pain
- 10 Cases: Swelling face
- 9 Cases: Upper respiratory tract infection, Paraesthesia
- 8 Cases: Swollen tongue, Urinary tract infection, Anxiety
- 7 Cases: Respiratory tract infection, Pharyngeal edema
- 6 Cases: Feeling abnormal, Pneumonia, Joint swelling, Throat irritation, Psoriasis,
- 5 Cases: Bronchitis, Weight increased
- 4 Cases: Facial pain, Gait disturbance, Infection, Decreased appetite, Lethargy, Asthma, Paranasal sinus hypersecretion
- 3 Cases: Ear pain, Eye pruritus, Ear infection, Infusion site infection, Dehydration, Muscle spasms, Hyperaesthesia, Sleep disorder, Respiratory tract congestion, Dry skin, Skin discoloration
- 2 Cases: Palpitations, Tinnitus, Eye pain, Constipation, Gingival hyperplasia, oral abscess, Gingival hyperplasia, Eye infection, Pharyngitis streptococcal, Sepsis, Weight decreased, Fluid retention, Muscle tightness, Muscular weakness, Dygeusia, Neuralgia, Insomnia, Urinary incontinence, Epistaxis, Nasal congestion, Throat tightness, Alopecia, Night sweats
- 1 Case: Lymphadenopathy, Thrombocytopenia, Atrial fibrillation, Bradycardia, Vertigo, Asthenopia, Blindness transient, Conjunctival granuloma, Dark circles under eyes, Excessive eye blinking, Eye swelling, Foreign body sensation in eyes, Lacrimation increased, Mydriasis, Ocular hyperaemia, Vision blurred, Visual acuity reduced, Visual impairment, Dental plaque, Dry mouth, Fecal incontinence, Flatulence, Gingival swelling, Lip swelling, Tongue discoloration, Tongue ulceration, Exercise tolerance decreased, Feeling jittery, Hunger, Inflammation, Irritability, Hepatic steatosis, Candidiasis, Cellulitis, Cystitis, Gastroenteritis E. coli, Herpes zoster, Laryngitis, Nasopharyngitis, Pneumonia streptococcal, Rhinitis, Skin infection, Sputum purulent, Viral infection, Vulvovaginal mycotic infection, Accidental overdose, Fall, Incorrect route of drug administration, Medication error, ALAT increased, ASAT increased, Blood alkaline phosphatase increased, Blood sodium decreased, Blood sodium increased, Blood thyroid stimulating hormone decreased, Heart rate decreased, Heart rate irregular, Sputum abnormal, Acidosis, Gout, Hyperkalaemia, Hypoglycaemia, Vitamin D deficiency, Arthropathy, Myositis, Neck mass, Akathisia, Amnesia, Crying, Disturbance in attention, Memory impairment, Muscle contraction involuntary, Sciatica, Sensory disturbance, Abnormal behavior, Aggression, Agitation, Confusional state, Conversion disorder, Euphoric mood, Hallucination, Nervousness, Panic attack, Restlessness, Stress, Incontinence, Genital swelling, Menorrhagia, Menstruation irregular, Metrorrhagia, Pelvic pain, Vulvovaginal pruritus, Choking, Dysphonia, Hypopnoea, Increased upper airway secretion, Oropharyngeal blistering, Pharyngeal erythema, Sinus congestion, Sinus

8.2 Review of Relevant Cases:

8.2.1. Virus Infection: Case no. 2011027504:

- A 46-year-old male with a medical history of chronic bronchitis and sinusitis had received Hizentra SC 8 g weekly for CVID since July 2010.
- Seven hours after the infusion on 04-May-2011, he experienced extreme vomiting, nausea, abdominal cramping, and diarrhea and was hospitalized for virus infection (not further specified).
- The patient recovered on 08-May-2011.
- The case was assessed as “serious, unexpected”.
- Causality: Possible for infusion site reaction and malaise. Unlikely for viral infection.

8.2.2. Atrial Fibrillation: Case no. 2011027827:

- An 82-year-old male with diet controlled type II diabetes mellitus, received 10 g Hizentra SC for common variable immunodeficiency via 4 sites over 1-2 hours.
- 15 hours after the end of the infusion, the patient was awakened with a feeling of his “heart running away”. He was taken to an ER where he was treated for atrial fibrillation. He recovered and was discharged home.
- The case was assessed as “serious, unexpected, unlikely due to Hizentra.

8.2.3. Extremely High Blood Pressure: Case no. 2010026636:

- A 73-year old female with a history of pulmonary emboli, chronic sinusitis, many infections, and drug allergies (sulfa, clarithromycin, and levofloxacin).
- The patient had an episode of increased blood pressure (204/102) about 6 weeks after starting Hizentra for CVID.
- She had also experienced shortness of breath, weakness, fatigue and cough. At the time of the events, the patient concomitantly suffered from asthma and hypertension.
- The case was assessed as “serious, unexpected for ongoing hypertension and weakness.”
- Causality: Unlikely for increased blood pressure since the patient had pre-existing hypertension. Unlikely for shortness of breath, fatigue, weakness, and cough, because these symptoms were attributed to pre-existing conditions confirmed by a physician.

8.2.4 Sepsis (2 cases):

Case no. 2011028067:

- A 64-year-old male patient received 9 g Hizentra SC weekly for immunodeficiency. He was hospitalized with sepsis and pneumonia, and his clinical status was reported to have deteriorated.
- The case was assessed as “serious, unexpected and unrelated”.

Case no. 2011028445:

- A 22-year-old female received 3g Hizentra SC three times weekly for immunodeficiency.
- The patient was admitted to the hospital for tonsillectomy due to infections and chronic tonsillitis. The night before the scheduled surgery, the patient developed sepsis. The patient was transferred to the ICU and was provided IV antibiotics.
- The case was assessed as “serious, unexpected and unrelated”.

8.2.5. Dermatitis: Case no. 2011028505:

- A 69-year-old male with diabetes, lung cancer, emphysema, pneumonia, thrush and hyperlipidemia, CAD, chronic sinusitis, COPD, GERD, stent replacement (x3), allergies to diphenhydramine and codeine had 10g Hizentra SC weekly since June 2010.
- On 03-Mar-2011, the patient developed “broad and diffuse” reactions on abdomen and “widespread diffuse, itchy plaques”. The patient was hospitalized for pneumonia (17-Mar-2011 through 19-Mar-2011) and was treated with IV steroids and H1/H2 blockers. A punch biopsy of the left thigh provided a diagnosis of slight spongiotic dermatitis. The pathology report noted that

- The case was assessed as “serious and unexpected”.
- Causality: Unassessable due to lack of information on assessment of treating physician on differential diagnoses photo allergic drug reaction, allergic contact dermatitis, nummular dermatitis.

8.2.6. Psoriasis (Five cases):

Case no. 2011028112:

- A 9-year-old male patient has received 3g Hizentra SC weekly for PI since 23-Sep-2010.
- The patient had 7-8 patches on his head, including both eyes, and several spots on both arms. According to the dermatologist’s report from 30-Sep-2010, onset of all lesions was 2-3 months ago.
- The case was assessed as “non-serious, unexpected, unlikely related due to lack of temporal plausibility.

Case no. 2011028114:

- A 24-year-old male with a history of skin flakiness, received 6g Hizentra SC weekly for PI since Oct-2010.
- On 14-Feb-2011, psoriasis involving his face and scalp was diagnosed by a dermatologist. Patient reported prior to starting Hizentra he had some flakiness in his skin.
- The case was assessed as “non-serious, unexpected, unlikely related due to lack of temporal plausibility.

Case no. 2011028115:

- A 12-year-old male patient with a medical history of psoriasis has received 10g Hizentra SC weekly for PI since Jan-2011.
- Patient continues to experience psoriasis consisting of red, scaly lesions to calves, scalp, and eye lids. Patient was previously on Vivaglobin in 2007 and developed psoriasis, which was diagnosed by a dermatologist in 2009.
- The case was assessed as “non-serious, unexpected, unlikely related due to lack of temporal plausibility.

Case no. 2011028209:

- A male patient, with a medical history of CVID and psoriasis, which was in remission. The patient has recently experienced a psoriasis flare that coincides with his transition to Hizentra. The flare has been reported to be difficult to control without steroids.
- The case was assessed as “non-serious, unexpected, unassessable due to lack of information.

Case no. 2011028379:

- A 38-year-old male patient with a history of CVID and psoriasis started 12g Hizentra SC weekly for CVID on 04-Jun-2010.
- On 06-Apr-2011, the patient developed rash, rib pain, a patch of skin that looked like psoriasis, and infusion site knots.
- The case was assessed as “non-serious, unexpected, unlikely related”.

Comment:

- All of the five cases may not be related to the infusions because all of the patients had a history of psoriasis before Hizentra treatment. However, it is unknown if the treatment worsened the clinical course of psoriasis.

8.2.7. Thromboembolic Events (Four cases):

Case no. 2010026900:

- A 69 year-old female patient was switched from Vivaglobin to Hizentra 8g (40 mL) SC weekly for CVID. On 28-Oct-2010, the patient received Hizentra and she suffered a stroke on 29-Oct-2010 and was hospitalized.
- Concomitant therapy included Lasix 40 mg QOD (since 15-Oct-2010), simvastatin 40 mg daily, and sotalol 120 mg BID.
- The case was assessed as “serious, expected, unlikely related to Hizentra”.
- The physician thinks the patient's stroke was not related to Hizentra. According to the concomitant drugs, the patient appears to have several cardiovascular (arteriosclerotic) risk factors, which are much more likely to be the cause of stroke.

Comment:

- With the 24 hour time frame of the occurrence of the thromboembolic event, the event is possibly related to Hizentra, although the patient has other risk factors.

Case no. 2011027640:

- A 36-year-old female patient experienced nausea, vomiting, skin reactions and fever after Hizentra SC. Three months later a possible thromboembolic event with hospitalization was reported.
- The case was assessed as “serious, expected, unassessable causality because of lack of information”.

Comment:

- The event is possibly not related to Hizentra due to the 3 months time frame of the occurrence of the thromboembolic event.

Case no. 2011027928:

- A 61-year-old female with a history of multiple episodes of sinusitis and throat infection, anemia, hypertension, asthma, arthritis, dibromyalgia, fissures, irritable bowel syndrome (IBS), and cardiac issues in 1990's and concomitant medication celecoxib was receiving Hizentra 12 g weekly SC for hypogammaglobulinemia.
- She was hospitalized for bilateral DVT. She was treated and recovered.
- The case was assessed as “serious, expected, unlikely related due to concomitant medication with a risk for thromboembolic events.”

Comment:

- The event is possibly related to Hizentra, although the patient has other risk factors.

Case no. 2011028433:

- A 55-year-old female received 2g Hizentra SC daily for CVID (last dose 13-Apr-2011). On 03-May-2011, the patient was hospitalized for DVT.
- The case was assessed as “serious, expected, unlikely related due to 25 concomitant medications with a risk for thromboembolic events and the two week interval between the treatment and the event.”

Comment:

- The event is possibly related to Hizentra, although the patient has other risk factors.

CSLB's assessment of thromboembolic events (TE):

- With the four TE cases in relation to the number of 295,000 ESD, the rate is 1 TE/73,750 ESD or 4 TE /5670 EPY (1 TE case/1417 EPY). This translates into an annual reporting rate of 70 TE /100,000 EPY. Estimate patient year (EPY) was calculated under the assumption of weekly use in PI patients: $295,000 \text{ ESD} / 52 = 5,670 \text{ EPY}$
- Published annual incidence rates in the general population (per 100,000 person-years) are: DVT: 80-180; PE: 100-120; myocardial infarction: 200; and stroke: (any type): 80-150. From these figures a gross cumulative annual incidence for TE is estimated to be about 460-650 per 100,000 person-years.
- Thus, TE reported is lower than the cumulative annual incidence rate for TEE in the general population.

8.3 Conclusion and Comments on the Postmarketing Safety Report

- The submitted safety report showed that ARs included swollen face or tongue, pharyngeal edema, thromboembolic events.
- According to FDA’s labeling guidance, the decision to include ARs in section 6.2 “Postmarketing Experience” is based on seriousness of event, frequency of reporting, or strength of causal connection to the drug.
- The paragraph on Hizentra postmarketing experience in the Postmarketing Experience section has been revised as follows:

CSLB’s Originally Submitted Paragraph:

Hizentra

The following adverse reactions have been reported during postmarketing use of Hizentra for treatment of PI: injection-site reactions (including swelling, induration, erythema, pain, pruritus, warmth, hematoma, and rash), headache, fatigue, nausea, pain, pruritus, rash, diarrhea, chills, vomiting, abdominal discomfort (including abdominal distension and abdominal pain), dyspnea, chest discomfort (including chest pain), pyrexia, urticaria, dizziness, migraine, hypertension/blood pressure increase, and malaise.”

Revised Paragraph:

Hizentra

The following adverse reactions have been identified during postmarketing use of Hizentra. This list does not include reactions already reported in clinical studies with Hizentra (see Adverse Reactions [6.1]).

- *Infusion reactions: Allergic-anaphylactic reactions (including swollen face or tongue and pharyngeal edema), pyrexia, chills, dizziness, hypertension/changes in blood pressure, malaise*
- *Cardiovascular: Thromboembolic events, chest discomfort (including chest pain)*
- *Respiratory: Dyspnea*

9. Labeling Review and Recommendations:

9.1: Original Submission

The original submission on December 8, 2010 and amendment submission on March 31, 2011 included a 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 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) to CSLB. The major changes are:

a. Efficacy: Section 14.2 “European Study”:

From:

“14.2 European Study

A prospective, open-label, multicenter, single-arm, clinical study conducted in Europe evaluated the efficacy, tolerability, and safety of Hizentra in 51 adult and pediatric subjects with PI. Immediately prior to the study, 31 subjects had been receiving monthly treatment with IGIV, and 20 subjects had been receiving weekly treatment with another IGSC. Subjects received the weekly equivalent of their previous IGIV or IGSC dose. The study consisted of a 3-month wash-in/wash-out period followed by a 7-month efficacy period. The efficacy analysis included 46 subjects.

The weekly median doses of Hizentra ranged from 59 to 243 mg/kg body weight during the efficacy period. The mean dose was 120.1 mg/kg, which was 104% of the previous weekly equivalent IGIV or weekly IGSC dose. The mean IgG trough levels increased by 8.1%, from 749 mg/dL prior to the study to 810 mg/dL, during the efficacy period.

None of the subjects had an SBI during the efficacy period, resulting in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.”

To:

“14.2 European Study

In a prospective, open-label, multicenter, single-arm, clinical study conducted in Europe, 51 adult and pediatric subjects with PI switched from monthly IGIV (31 subjects) or weekly IGSC (20 subjects) to weekly treatment with Hizentra®. 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.

None of the subjects had an SBI during the efficacy period, resulting in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.”

Rational:

The PK evaluation in study ZLB06_001CR is 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. CSLB has been advised that the PK information to be provided in labeling for this study should be limited.

b. Safety: Section 6.1 “Adverse Reaction”

- CSLB submitted a Table 5 to summarize the most frequent AEs (experienced by at least 4 subjects), *irrespective of causality* during the European study. The Table truncated the adverse event data by “excluding infections.”
- FDA revised the Table to include the AEs (such as pyrexia) the occurrences of which could not be presumably as being associated with infections.

9.2 CSLB’s Submission of Revised Labeling on July 20, 2011

- On July 20, 2011, CSLB submitted the revised package insert 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 is to support

- FDA provided additional comments on the labeling including the revised postmarketing experience section and the changes of the AR Tables 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.

10. Risk-Benefit Considerations and Recommendations

10.1 Risk/ Benefit Assessment

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

10.2 Recommendations on Postmarketing Actions

There are no Postmarketing actions.