

Summary Basis for Regulatory Action

Date: 14 September 2017

From: L. Ross Pierce, M.D., Chair of the Review Committee

BLA STN#: 125201/728

Applicant Name: CSL Behring

Date of Submission: 14 November 2016

Goal Date: 14 September 2017

Proprietary Name/ Established Name: Privigen/ Immune Globulin Intravenous (Human), 10% Liquid

Indication: Privigen® is indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.

Recommended Action:

The Review Committee recommends approval of this efficacy supplement for the new indication for the treatment of adults with CIDP to improve neuromuscular disability and impairment.

Review Office(s) Signatory Authority(ies):

Tejashri Purohit-Sheth, M.D.

Director, Division of Clinical Evaluation and Pharmacology/Toxicology
OTAT/CBER/FDA

- ☐ 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.

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
Clinical Review(s) - Clinical (product office) - Postmarketing safety	L. Ross Pierce, M.D., OTAT/DCEPT 01 Sept 2017 Lei Xu, M.D., OTAT/DCEPT 17 May 2017

<i>epidemiological review (OBE/DE)</i> • <i>BIMO</i>	Shaokui Wei, M.D., M.P.H. OBE/DE 12 September 2017 Carla Jordan, BIMO 02 August 2017
Statistical Review(s) • <i>Clinical data</i> • <i>Non-clinical data</i>	Jiang (Jessica) Hu, Ph.D.. OBE/DB 06 Sept 2017
CMC Review(s) • <i>CMC (product office)</i> • <i>Facilities review (OCBQ/DMPQ)</i> • <i>Establishment Inspection Report (OCBQ/DMPQ)</i>	Pei Zhang, M.D. (CMC) 13 July 2017
Pharmacology/Toxicology Review(s) • <i>Toxicology (product office)</i> • <i>Developmental toxicology (product office)</i> • <i>Animal pharmacology</i>	Not applicable.
Clinical Pharmacology Review(s)	Iftekhar Mahmood, Ph.D., OTAT/DCEPT 28 July 2017
Labeling Review(s) • <i>APLB (OCBQ/APLB)</i>	Alpita Popat, OCBQ/APLB 01 August 2017
Other Review(s) • <i>additional reviews not captured in above categories</i> • <i>consult reviews</i>	Not applicable.
Advisory Committee Transcript	Not applicable.

1. Introduction

Privigen is a sterile, 10% protein liquid preparation of Immune Globulin Intravenous (Human) [IGIV, polyvalent human immunoglobulin G, (IgG)] for intravenous administration. Privigen was licensed in the United States in 2007. Privigen is approved in the United States, Canada, Switzerland, and the European Union (EU) for the treatment of primary humoral immunodeficiency (PHID) and chronic immune thrombocytopenic purpura (ITP). In addition, Privigen is approved in the EU, Switzerland and Canada for immunomodulation in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

The indication originally proposed by the applicant for Privigen under this supplement was for “the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment (b) (4)

The applicant subsequently revised the indication at FDA request to read: “the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.” This request was made because the applicant did not submit data to (b) (4) and the studies were conducted only in adults.

2. Background

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a neurological disorder of immune origin and is characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder is caused by damage to the myelin sheath of peripheral nerves. It can occur at any age and in both genders, but is more common among young adults, and in men more than women. The precise pathophysiology of CIDP remains uncertain although B and T cell mechanisms have been implicated.

The estimated prevalence of CIDP across all ages varies between 1.9 and 8.9 per 100,000 people. [Laughlin RS, et al. *Neurology*, 2009;73(1):39-45]. The prevalence of CIDP in children ages zero to <18 years is not well established. One study estimated a prevalence of 0.48 / 100,000 people (zero - 20 years of age) in Australia [McLeod JG et al. *Ann Neurol* 1999;46:910-3]. Another study estimated a prevalence of 0.23 / 100,000 children (zero - <15 years of age) in Japan [Iijima M et al. *J Neurol Neurosurg Psychiatry* 2008; 79:1040-3].

Treatment of CIDP includes Immune Globulin Intravenous (Human) (IGIV), plasma exchange (PE), and corticosteroids.

In the United States, Gamunex-C is currently the only IGIV product approved (in 2008) for CIDP treatment to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse. The approval was based primarily on data from the ICE (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified CIDP Efficacy) study. The ICE study was a multicenter, randomized, double-blind, placebo-controlled study. The study included two separately randomized periods to assess whether Gamunex-C was more effective than placebo for the treatment of CIDP to improve neuromuscular disability and impairment (assessed in the 24-week Efficacy Period) and for maintenance therapy to prevent relapse (assessed in the 25-week Randomized Withdrawal Period). The ICE trial enrolled both IGIV-naïve and IGIV-pre-treated subjects. The latter were required to have discontinued IGIV treatment at least 3 months prior to study entry. According to the Gamunex-C package insert and FDA analysis described in the clinical review memo, 28 of 59 subjects (47.5%) responded to GAMUNEX-C compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; 95% CI 7%-43%; $p=0.006$). This translates to a number needed-to-treat (NNT) of four in order to obtain one responder due to the medication.

CSL Behring (hereafter CSLB) submitted data from two studies in support of this supplemental BLA, PRIMA (Privigen Impact on Mobility and Autonomy) and PATH (Polyneuropathy AND Treatment with Hizentra [[Immune Globulin Subcutaneous (Human)]]. The PRIMA study was conducted at foreign sites and was not conducted under an IND. As such, CSLB did not obtain input from the FDA in the design of the, which was the main study submitted to provide substantial evidence of efficacy. CSLB did obtain FDA input in the design of the PATH study, which was conducted under an IND and was considered a supportive study for efficacy and contributed the bulk of the safety data for Privigen in CIDP.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

No changes to the manufacture of the product were proposed under this clinical efficacy supplement. It was noted that the lots of Privigen used in the PRIMA and PATH clinical studies had not been manufactured using the recently approved step involving column immunoadsorption of isoagglutinins. Clinical data are not available regarding the effect, if any, on the incidence or severity of Privigen-associated hemolysis by the introduction of this manufacturing step which was undertaken in an attempt to improve product safety vis-à-vis hemolysis risk.

b) CBER Lot Release (only applicable for BLAs)

No changes regarding lot release status were applicable to this supplement.

c) Facilities review/inspection

No GMP facilities inspections were conducted in connection with this application.

d) Environmental Assessment

Not applicable. CSLB was granted a categorical exclusion of the requirement for environment assessment under 21 CFR 25.31 (c).

e) Product Comparability

Not applicable.

4. Nonclinical Pharmacology/Toxicology

Not applicable. No nonclinical pharmacology/toxicology information was included in this supplement.

5. Clinical Pharmacology

The clinical pharmacology program consisted of one population pharmacokinetic (POPPK) study. The following is the summary of the study.

A POPPK model for IgG was developed based on data from two studies of Privigen in patients with CIDP. The data for pharmacokinetic (PK) analysis were based on a total of 235 subjects (63% males) with a mean age of 57 years and a mean body weight of 82 kg.

The subjects provided either one blood sample (n = 207; trough) or two blood samples (n = 28; trough and peak). A two-compartment model with a first-order elimination described was used to describe the data. Body weight, age, and gender were examined

as covariates on clearance (CL) and volume of distribution of the central compartment (V_c). The final model included the impact of body weight on CL and V_c with an allometric exponent of 0.701 and 0.738, respectively. The model-generated values for CL and V_c of IgG in patients with CIDP were 0.42 liters/day and 5 liters, respectively.

Conclusions: A two compartment model with bodyweight as a covariate on CL and V_c described the PK of Privigen in patients with CIDP. However, the population PK analysis is flawed due to the use of an inappropriate sampling scheme (only trough and peak) and the reasons for this are provided below.

Although, in principle, it is possible to construct a POPPK model from such sparse samples (peak and trough); independent estimation of model parameters, such as inter-individual variability, residual error and % shrinkage, will lead to substantial errors in the estimated PK parameters. For example, the precision of inter-individual variability for CL was poor with relative standard error of 74% and the estimate of shrinkage was high (56%). Overall, the estimation of CL and V_c from the POPPK model may be inaccurate and cannot be used for dosing and exposure assessment. FDA therefore requested CSLB to remove the results of the flawed POPPK model assessment from the draft package insert. CSLB complied with this request.

6. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

Clinical Review of Efficacy

On 14 November 2016, CSLB submitted this efficacy supplement to Biologics License Application (sBLA), STN 125201/728, supported mainly by clinical data from the completed PRIMA study and supplemented by data from the completed Pre-randomization Phase of the PATH Study. The PATH study was ongoing at the time of this BLA submission.

The PRIMA study (protocol IgGPro10_3001) was a 25-week prospective, multicenter, open-label, historically-controlled, single-arm study to evaluate the efficacy and safety of Privigen in subjects with CIDP. The historical control was the placebo arm in Efficacy Period of the ICE Study [Hughes RA. Expert Rev Neurother 2009;9:789-795]. The study was conducted in 13 sites across five countries in the EU. The study enrolled 28 subjects with CIDP, ages 22 to 79 years (mean age 58.7 years), who either met the protocol definition of being IGIV-naïve ($n = 15$) or of having been previously treated with IGIV (IGIV-pretreated) ($n = 13$). The study enrolled 64% males and 36% females. Caucasians comprised 100% of the study population, which was similar to the results of a 2010 United States CIDP patient survey which found that whites/Caucasians comprised 94% of CIDP patients.

Subjects already receiving IGIV at the time of screening were required to discontinue IGIV and to show deterioration in the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score prior to receiving Privigen under the protocol. All subjects received a Privigen loading dose of 2 g/kg body weight (bw) divided over 2 to 5 days followed by seven Privigen maintenance doses of 1g/kg bw divided over 1 to 2 days every 3 weeks. The treatment lasted 25 weeks. The dosing regimen was based on current treatment guideline recommendations (European Federation of Neurological Societies and Peripheral Nerve Society). Similar dosing regimens had been used in the Efficacy Period of the ICE Study.

Efficacy was primarily assessed utilizing the INCAT score, which is a validated assessment that is widely-used and is based on a 10-point motor disability scale. A maximum of five points are derived from assessment of upper arm disability/function in terms of difficulty/ability to perform functions including doing all zippers and buttons when dressing, washing or brushing hair, using knife and fork together, and handling small coins. A maximum of five points are derived from assessment of leg disability affecting walking/mobility impairment. The higher the score, the worse is the disability. The Medical Research Council (MRC) was utilized as an additional supportive assessment of efficacy. The MRC sum score is an 80 point motor functional assessment score comprised of numerical contributions from the motor function of the arm, forearm, wrist, hip, leg, foot, and great toe on right and left sides. MRC sum scores can range from zero (complete paralysis) to 80 (normal strength).

The primary efficacy endpoint in the PRIMA Study was the responder rate based on the adjusted INCAT disability score. The same primary efficacy endpoint was used in the Efficacy Period of the ICE Study that provided the primary evidence of effectiveness to support the approval of Gamunex-C for treatment of CIDP to improve neuromuscular disability and impairment. Responders were those subjects who demonstrated a “clinically meaningful improvement” in the adjusted INCAT score (i.e., ≥ 1 point improvement [> 1 point decrease] except for a change from one to zero solely due to upper limb score) between baseline and Week 25 for those who completed the study, or between baseline and the last study visit before discontinuation for those who prematurely discontinued the study. The predefined aim of the PRIMA Study was to demonstrate superiority in the primary efficacy endpoint of Privigen against the historical control, the placebo arm in Efficacy Period of the ICE Study, with a lower limit of the 2-sided 95% Wilson-Score confidence interval (CI) of the responder rate above 35%. The responder rate in the placebo arm of Efficacy Period of the ICE study was 13/58 (22.4%%; 95% Wilson-Score CI: 13.6% to 34.7%). Other efficacy assessments included grip strength, which was also analyzed in the ICE study, and the Medical Research Council (MRC) sum score.

In the 25-week PRIMA Study, Privigen administered in accordance with the above dosing regimen was associated with an adjusted INCAT score-based responder rate of 17/28 (60.7%; 95% CI: 42.4% to 76.4%). The lower limit of the 95% CI was higher than the pre-specified responder rate threshold of 35%. The primary efficacy

endpoint was met in the PRIMA study using the pre-specified analysis methodology described in the protocol and statistical analysis plan (SAP). Of note, post-hoc robustness analyses that attempted to more closely emulate the ICE trial analysis methodology, which required an early response be sustained throughout the remainder of the treatment period, produced somewhat lower responder rates ranging from 39.3% to 53.6%. For example, the overall percentage of subjects who responded by week 10 and maintained the response through week 25 and lacked confounding changes in glucocorticoid/immunosuppressant dosage was 53.6% (95% CI: 35.8% to 70.5%). The primary endpoint result was supported by consistent improvements in both secondary efficacy endpoints (maximum grip strength and MRC sum score) from baseline to completion.

As in the ICE study, the percentage of responders to Privigen in the full analysis set of the PRIMA study was considerably lower among IGIV-naïve subjects (47%, 7 of 15 subjects) than among IGIV-pretreated subjects (77%, 10 of 13 subjects). While the current study was not powered for subgroup analyses, it is noted that the lower bound of the 95% CI for the percentage of responders among IGIV-naïve subjects was 24.8%, which is well below the a priori 35% study success threshold for the overall study population. Given the results and the historical nature of this comparison, it is concluded that the evidence that Privigen is effective in improving adjusted INCAT score in IGIV-naïve patients with CIDP is uncertain.

CSLB provided the results from the PATH study, which was ongoing at the time of this BLA supplement submission, and has since been completed. The PATH study was a randomized, multicenter, double-blind, placebo-controlled, parallel-group Phase 3 clinical study designed to investigate the efficacy, safety and tolerability of two different doses of subcutaneous immunoglobulin (Hizentra, Immune Globulin Subcutaneous (Human)) for the maintenance therapy of CIDP. Although designed to evaluate the safety and efficacy of Hizentra, the PATH study included a Privigen Restabilization Period, which was completed at the time of this sBLA submission, and provided supportive data for this sBLA.

The PATH study was conducted in 16 countries, including 14 centers in the United States. The study consisted of two study phases, an open-label, single-arm Pre-randomization phase and a parallel-group, double-blind, randomized, placebo-controlled post-randomization phase. The Pre-randomization Phase consisted of an IGIV Withdrawal Period and a Privigen Restabilization Period. A total of 245 IGIV-pretreated subjects with CIDP entered the IGIV Withdrawal Period. Based on worsening of the adjusted INCAT score (≥ 1 point worsening (except solely due to a change in the upper extremity score component from one to zero), the Rasch-built Overall Disability Scale (R-ODS, a 20-component scale that assesses the ability to perform a wide variety of different tasks, such as making a sandwich, moving a chair, turning a key in a lock, catching an object, travelling by public transport, dancing, etc.) (≥ 4 point worsening), or mean grip strength (≥ 8 kPa worsening), 208 out of 245 (85%) subjects deteriorated and entered the Privigen Restabilization Period while 37 were withdrawn due to failure to demonstrate CIDP deterioration (n=28), withdrawal by subject (n=8), or protocol violation (n=1). It should be noted that of

the 208 subjects who deteriorated during the IGIV withdrawal period by any of the three stated deterioration criteria, only 151 subjects had deteriorated by one or more points in adjusted INCAT score. Of the 208 subjects who deteriorated, 207 subjects received Privigen in the Restabilization Period. These subjects had a mean age of 56.5 years, were 63% male and 37% female, and were 90% Caucasian. The dosing regimen included a Privigen loading dose of 2 g/kg bw divided over 2 to 5 days followed by three or four (if needed) Privigen maintenance doses of 1g/kg bw divided over 1 to 2 days every 3 weeks. The treatment lasted up to 13 weeks.

The primary objective of the Pre-randomization Phase of the PATH study final protocol (version 5.0 dated 8 December 2015) was to assess the efficacy of Privigen. However, in version 1.0 of the protocol dated 22 September 2011, the PATH study did not list a primary objective of the Pre-randomization Phase to assess Privigen efficacy or any study endpoints related to Privigen efficacy or safety. FDA thus regards the submitted efficacy analyses of the PATH study to be post-hoc. Responders, according to the final protocol, were those subjects who demonstrated a “clinically meaningful improvement” in the adjusted INCAT score (≥ 1 point improvement [≥ 1 point decrease] as in the PRIMA study) between Reference Visit and any time during the Privigen Restabilization Period.

The lack of a standardized point in time during the Privigen Restabilization period for assessing change in adjusted INCAT score from the Reference Visit makes it more difficult to interpret the results in comparison to historical data, such as the ICE study that required an adjusted INCAT response by week 6 that was required to be maintained at each visit through week 24. For this reason, and because of the difference in the duration of Privigen treatment in the two studies (13 weeks versus 24 weeks), as well as the post-hoc nature of efficacy assessments of Privigen in the PATH study, the assessment of efficacy of Privigen during the Pre-Randomization period (and as rescue therapy post-randomization) in the PATH study is considered only supportive.

Among the subset of 151 subjects in the PATH study who had deteriorated by one or more points in adjusted INCAT score following IGIV withdrawal during the pre-randomization washout phase, 137 subjects (90.7%) responded during the Privigen “restabilization” period with an improvement of one or more points in adjusted INCAT score. This responder rate was considerably greater than that observed at week 25 in the overall PRIMA study population (60.7%), and was also well above the upper bound of the 95% CI for the responder rate in the PRIMA study. The apparent difference in responder rates seems likely to be due to the enrichment nature of the PATH study design: all subjects were required to be on IGIV therapy for CIDP at the time of enrollment. Another possible contributor to the difference in outcomes with Privigen IGIV treatment between the two studies was the fact that in PATH (unlike in PRIMA), a subject could be scored as a responder if, *at any time* during the 13-week Privigen restabilization phase, the requisite improvement in adjusted INCAT score had been observed. Because all PATH study subjects were previously treated with IGIV, it may be more appropriate to compare the responder rate during the pre-randomization period of the PATH study to the responder rate among the IGIV-

pretreated subjects in the PRIMA study. The latter responder rate in the PRIMA study was 76.9% (10/13 subjects) with an upper bound of the 95% CI of 91.8%. The latter CI for the responder rate in the PRIMA study IGIV-pretreated subgroup just overlaps with the point estimate for responder rate during the Privigen “restabilization” pre-randomization period of the PATH study. By this analysis, Privigen response among IGIV-pretreated subjects appears to be consistent across the two CSLB-sponsored studies, notwithstanding methodological differences.

Notwithstanding the limitations of using a historical control in a disease in which some patients are expected to demonstrate spontaneous improvement, it was concluded that substantial evidence of efficacy had been demonstrated by the submitted data from the PRIMA and PATH studies. In addition to being statistically superior to the historical control, the responder rates in adjusted INCAT score with Privigen treatment in the PRIMA and PATH studies compare favorably to those observed with licensed Gamunex-C in the ICE study. Further support for a conclusion of efficacy was provided by secondary outcome measures, particularly by grip strength in both dominant and non-dominant hands.

Biostatistical Review

CSLB investigated Privigen’s efficacy and safety for treatment of CIDP in the completed PRIMA study, with 28 subjects (13 IGIV-pretreated and 15 IGIV-naïve). The primary efficacy endpoint is a responder rate, defined as the proportion of subjects who had a decrease of at least 1 point in the adjusted INCAT disability score (except for a change of 1 to 0 solely due to upper limb score). The lower limit of the two-sided 95% confidence interval (CI) for the responder rate was 42.4%, higher than the pre-specified threshold of 35%. Therefore the PRIMA study was determined successful for the primary efficacy endpoint.

The applicant also submitted data from the Pre-randomization Phase of the PATH study, as secondary supportive results. In the PATH study, Privigen was evaluated for the treatment and maintenance of CIDP during the Pre-randomization Phase. The efficacy analysis of the Pre-randomization Phase from the PATH study was also confirmed. The lower limit of the two-sided 95% CI for the proportion of subjects who experienced a decrease of at least 1 point in adjusted INCAT disability score in PATH was 66.5%, showing the clinically meaningful improvement was also achieved in Pre-randomization Phase of the PATH study.

Safety analyses for both the PRIMA study and pre-randomization phase of the PATH study revealed no new safety issues.

Conclusion: Overall, statistical analysis results from the PRIMA and PATH studies support the new indication, i.e., for the treatment of CIDP in adults to improve neuromuscular disability and impairment.

Pharmacovigilance Review

The pharmacovigilance reviewer noted that hypertension was a common adverse event in Privigen CIDP studies and was reported both in subjects with and without a history of hypertension. Five subjects in the clinical studies were noted to have transient hypertensive crisis/hypertensive urgency during and/or shortly following Privigen infusion, generally requiring [additional] antihypertensive medication. See the safety section of this document for further information.

A review of postmarketing reports of hypertension in patients treated with Privigen and various commercial IGIV products for various indications was consistent with the conclusion that hypertension is a class effect with IGIV products.

BioResearch Monitoring (BIMO) Inspections

CBER Bioresearch Monitoring (BIMO) issued three inspection assignments for three sites that participated in the PRIMA study in support of this Biologics Licensing Application (BLA) supplement. The inspections did not identify any data integrity issues, and all inspections were classified “No Action Indicated.”

b) Pediatrics

The application is subject to the Pediatric Research and Equity Act (PREA) because a new indication is being sought. CSLB requested full waiver of pediatric studies. FDA disagreed and asked for a partial waiver for pediatric patients aged less than two years and partial deferral of studies in subjects aged 2 to less than 17 years, as a PREA-related postmarketing requirement (PMR). CSLB submitted, at FDA request, a PREA PMR study outline for studying CIDP in pediatric subjects ages 2 years to <17 years. The PREA PMR study outline was subsequently revised to incorporate a randomized dose-duration-controlled design based on input from FDA. In addition, CSLB submitted, at FDA request, a partial pediatric waiver request for ages zero to < 2 years, a pediatric study deferral request for ages 2 years to <17 years, and a Pediatric Study Plan (PSP).

The FDA Pediatric Review Committee (PeRC) agreed with 1) the partial pediatric waiver request for ages zero to < 2 years as necessary studies are impossible or highly impracticable as there are no validated appropriate neurological assessment tools available for this age group and because of the rarity of the condition in this age range) and 2) the pediatric study deferral for ages 2 years to <17 years as this product is ready for approval for use in adults and the pediatric study has not been completed.

c) Other Special Populations

There were no clear differences in efficacy or safety overall among subgroups younger than age 65 years versus 65 years and older. However, there was a trend for all measured efficacy parameters to have higher responder rates/larger mean responses in the younger age category.

7. Safety

The clinical studies safety database in CIDP was considered adequate.

Notable safety findings from clinical studies (PRIMA and PATH) of Privigen in CIDP included thrombotic events, hemolysis, and hypertension. These adverse reactions are already known to be associated with the class of IGIV products.

No deaths occurred during the 28-subject, 25-week PRIMA study. Two subjects discontinued prematurely due to adverse events (AEs) (during the induction period). These subjects discontinued because of serious adverse events (SAEs) of hemolysis. One subject had the infusion rate of Privigen adjusted because of an AE of hypertension considered probably related to the product. Four subjects (14%) had SAEs, all of which resolved. Of these, two (both hemolysis) were assessed by the investigator and FDA reviewer as at least possibly related to Privigen administration. AEs that were considered at least possibly related to Privigen administration by the investigator/CSLB and FDA were headache, dysaesthesia, migraine, asthenia, influenza-like illness, fatigue, chills, pyrexia, hypertension, blood pressure increased, peripheral vascular disorder, nausea, hemolysis, leukopenia, vertigo, muscular weakness, rash, and urticaria. Only one case of urticaria considered related to Privigen administration was observed. The most frequently observed adverse reactions (defined as AEs considered by the investigator/CSLB (and FDA) as at least possibly related to Privigen administration, as well as AEs occurring during or within 72 hours of Privigen infusion) occurring in 5% or more of subjects were headache, asthenia, hypertension, nausea, extremity pain, hemolysis, influenza-like illness, leukopenia, and rash.

No deaths were reported during the pre-randomization phase of the PATH study. Four subjects (2%) had AEs leading to premature discontinuation from the study. All were considered related to Privigen administration. These were pulmonary embolism, respiratory failure, worsening renal failure, and headache. Eleven subjects (5%) each had one SAE. Of these, seven were considered causally related by the investigator/CSLB and FDA: pulmonary embolus, diastolic blood pressure increase, respiratory failure, migraine headache, rash, and chest pain plus lip and throat swelling. Two subjects had worsening of CIDP reported as SAEs that could be considered therapeutic failures. Hemolysis (seven events) was reported for seven (3.4%) subjects. One further subject had hemolytic anemia reported, so the overall incidence of hemolysis/hemolytic anemia was 3.9%. None of the hemolysis cases were considered serious, but all were considered causally related to Privigen. The most frequent (incidence > 1%) adverse reactions were headache, fatigue, hemolysis, hypertension, pyrexia, nausea, vomiting, and diarrhea.

Six AEs of hypertensive crisis/hypertensive urgency were reported across the two clinical studies (Five AEs with systolic BP $\geq$ 180 mm Hg and one AE with diastolic BP >120 mm Hg). Three subjects without a prior history of hypertension had treatment-emergent rises in blood pressure (BP) reported as AEs, of which one qualified as hypertensive crisis/hypertensive urgency by the above criteria. Based on the frequency

of hypertension reported as an AE in Privigen CIDP trials in comparison to the frequency of other AEs reported in these trials, at FDA's request, CSLB added hypertension to the WARNINGS AND PRECAUTIONS section of the package insert (in addition to the ADVERSE REACTIONS sections). FDA regards hypertension as a class effect for IGIV products.

8. Advisory Committee Meeting

No advisory committee meeting was held in connection with this supplement because (a) this biologic is not the first in its class, (b) the safety profile is similar to that of other drugs approved for this indication, (c) evaluation of the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class, (d) the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease, and (e) outside expertise was not necessary; there were no controversial issues that would have benefited from advisory committee discussion.

9. Other Relevant Regulatory Issues

None.

10. Labeling

The draft package insert was revised at FDA request to:

- Limit the new indication to adult patients with CIDP
- Eliminate the portion of the indication relating to maintenance therapy
- Introduce a limitation of use regarding maintenance therapy
- Add information to WARNINGS AND PRECAUTIONS regarding hypertension as an adverse reaction
- Eliminate the results of a flawed population pharmacokinetic analysis
- Add the results of a post-hoc robustness analysis of the primary endpoint of the PRIMA study that more closely emulated the analysis methodology used in the ICE study (historical control for the PRIMA study).

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends approval of this efficacy supplement for the new indication for the treatment of adults with CIDP to improve neuromuscular disability and impairment.

No review committee members dissented with this recommendation.

b) Risk/ Benefit Assessment

Given the serious nature of CIDP, the observed benefits in terms of improvements in clinically meaningful assessments of neurologic function in PRIMA and PATH studies compare favorably in a quantitative (frequency-based) sense to the known and observed risks of Privigen, which include hemolysis, substantial increases in blood pressure, and thrombotic events.

c) Recommendation for Postmarketing Activities

A PREA PMR is recommended to conduct a randomized trial investigating safety and efficacy of Privigen in pediatric subjects with CIDP ages 2 years to < 17 years. CSLB has agreed to conduct such a study and has submitted a PREA PMR pediatric study protocol outline, which has been resubmitted following FDA-requested revisions. No PMCs are recommended.