Summary Basis for Regulatory Action

Date: 14 March 2018

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

***BLA* STN#: 125350/641**

Applicant Name: CSL Behring

Date of Submission: 18 May 2017

Goal Date: 18 March 2018

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

Indication: Hizentra® is indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.

Recommended Action:
The Review Committee recommends approval of this efficacy supplement for the new indication of Hizentra for the treatment of adult patients with CIDP as maintenance therapy to prevent relapse of 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

☐X 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 epidemiological review (OBE/DE)* • *BIMO*	L. Ross Pierce, M.D., OTAT/DCEPT 13 February 2018 and 13 March 2018 Ravi Goud, M.D., M.P.H. OBE/DE 13 March 2018 Anthony Hawkins, BIMO 18 December 2017
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Jiang (Jessica) Hu, Ph.D.. OBE/DB 6 March 2018
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Nancy Eller, M.H.S. (CMC) 12 March 2018
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Not applicable.
Clinical Pharmacology Review(s)	Iftekhar Mahmood, Ph.D., OTAT/DCEPT 26 February 2018
Labeling Review(s) • *APLB (OCBQ/APLB)*	Alpita Popat, OCBQ/APLB 10 January 2018
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	Not applicable.
Advisory Committee Transcript	Not applicable.

1. Introduction

Hizentra is a sterile, 20% protein liquid preparation of Immune Globulin Subcutaneous (Human) [IGSC, polyvalent human immunoglobulin G, (IgG)] for subcutaneous (SC) administration. Hizentra was licensed in the United States in 2010 with an indication for treatment of primary humoral immunodeficiency (PHID) in adults and pediatric patients two years of age and older. Hizentra is also approved in 48 other countries, including in the European Union (EU), Switzerland, Australia, New Zealand, and Japan for the treatment of PHID and also, in some cases, secondary immunodeficiency.

The indication originally proposed by the applicant for Hizentra under this supplement was for "the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment." The applicant subsequently revised the indication at FDA request to limit the indication to adult patients with chronic inflammatory

demyelinating polyneuropathy (CIDP) because the applicant did not submit data to establish efficacy for maintenance therapy in pediatric patients.

2. Background

CIDP is an immune-mediated neurological disorder 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, an IGIV product, was approved in 2008 for CIDP treatment of adults with CIDP to improve neuromuscular disability and impairment *and* for maintenance therapy to prevent relapse. The Gamunex-C approval for CIDP 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.

A second IGIV product, Privigen, was approved in 2017 for the treatment of adults with CIDP to improve neuromuscular disability and impairment, but the indication does not include maintenance therapy to prevent relapse. To support the approval of Privigen for CIDP, CSL Behring (hereafter CSLB) submitted data from two studies in its supplemental BLA: (1) PRIMA (Privigen Impact on Mobility and Autonomy) and (2) Pre-Randomization period data from the PATH (Polyneuropathy AND Treatment with

Hizentra [[Immune Globulin Subcutaneous (Human]). Although the PATH study was primarily designed to evaluate the safety and efficacy of Hizentra, the Pre-Randomization period of the study included a period of Privigen administration. The PRIMA study, which used the ICE study placebo group as an historical control, 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 study. The PRIMA study 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.

To support the current supplement for Hizentra for maintenance therapy in adults with CIDP, CSLB submitted the final study report for the PATH study, which was a randomized, double-blind, placebo-controlled, dose comparison study of Hizentra in subjects who were enrolled while being treated with IGIV, who had IGIV therapy discontinued in order to assess IGIV "dependency," and who, upon deterioration following withdrawal of IGIV, were restabilized using Privigen. These components of the Pre-Randomization phase occurred prior to randomizing subjects who had deteriorated following IGIV withdrawal and then improved on Privigen treatment into the 25-week randomized, double-blind subcutaneous (SC) treatment period.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

No changes to the manufacture of the product were proposed under this clinical efficacy supplement.

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 study. The study characterized the population pharmacokinetics (POPPK) of immunoglobulin G (IgG) after subcutaneous (SC) administration of Hizentra in subjects with chronic inflammatory demyelinating polyneuropathy (CIDP).

The blood samples were collected from the 172 subjects who were randomized to placebo, or one of the two doses of Hizentra groups in the PATH study with 57 subjects assigned to receive 0.2 g/kg SC weekly Hizentra and 58 subjects assigned to receive 0.4 g/kg SC weekly Hizentra for a treatment period of 25 weeks. The blood samples were sparse and mainly drawn at peak and trough. The age and body weights of the subjects ranged from 22 to 83 years and 42-133 kg, respectively. The covariates included in this study were body weight, age, gender, baseline IgG, IgG pre-treatment, Japanese vs non-Japanese.

The pharmacokinetic (PK) of IgG was characterized by a 2-compartment model with first order absorption and elimination. Clearance (CL) and volume of distribution were 0.45 liters/day and 4.7 liters, respectively. Body weight had a significant effect on both CL and volume of distribution.

The POPPK model was used to simulate IgG concentration-time profiles in subjects with CIDP. The objectives of these simulations were to determine IgG exposure metrics (AUC, Cmax and Cmin) following different SC dosing regimens and different dosing intervals of Hizentra. The various dosing intervals were two-week dosing, twice weekly dosing (Monday and Thursday), and daily dosing. The results of the simulation study showed that the dosing interval of Hizentra administration can be flexible if the total weekly dose remains the same.

The applicant's POPPK analysis was considered deficient, mainly due to inadequate blood sampling. Due to inadequate sampling in the absorption phase, the absorption rate constant (Ka) could not be estimated and was therefore set to a previously estimated value. Due to these shortcomings, the estimated clearance and volume of distribution may not be reliable hence, the simulated PK parameters may also be unreliable.

FDA requested CSLB to remove the results of the potentially inaccurate POPPK model assessment from the draft package insert. CSLB complied with this request. FDA also requested that the provision for flexible dosing regimens (more frequent than weekly (up to daily) or every two weeks) that had not been studied be removed from the draft package insert because the extrapolations of efficacy (exposure-response model) and safety to these alternative dosage regimens had been based on the potentially inaccurate POPPK model.

6. Clinical/Statistical/Pharmacovigilance

a) Clinical Program

Clinical Review of Efficacy

On 18 May 2017, CSLB submitted this efficacy supplement to Biologics License Application (sBLA), STN 1252350/7641, supported by clinical data from the completed PATH study and later supplemented by interim safety data from the open-label PATH extension study. The PATH extension study was ongoing at the time of this BLA submission.

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 Hizentra Immune Globulin Subcutaneous (Human)) for the maintenance therapy of CIDP.

Efficacy was primarily assessed utilizing changes in the INCAT disability score to define CIDP relapse. The INCAT score 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 primary efficacy endpoint in the PATH Study was the proportion of subjects who relapsed (defined as having a ≥1 point deterioration in the INCAT disability score at a SC Treatment Period visit compared to baseline, excluding a change from zero to one solely due to upper limb score or an unchaged total INCAT score where the arm score decreased from 1 to 0 (not clinically meaningful improvement) and the leg score increased by 1 point (clinically meaningful worsening)), or who withdrew from the study for any other reason during the 25-week SC treatment period Post-Randomization phase. As previously noted, the adjusted INCAT disability score had previously been used as the primary efficacy endpoint in the Efficacy Period of the ICE Study and in the PRIMA study that had provided the primary evidence of effectiveness to support the approvals of Gamunex-C and Privigen, respectively, for treatment of CIDP to improve neuromuscular disability and impairment.

Secondary efficacy endpoints consisted of time to CIDP relapse or withdrawal for any othe cause, changes from baseline during the SC Treatment Period in mean adjusted INCAT score, mean maximum grip strength, mean Medical Research Council (MRC) sum score, and mean RASCH-build Overall Disability Scale (R-ODS). 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 R-ODS is a linearly weighted scale that specifically captures activity and social participation limitations in subjects with CIDP and other immune-mediated neuropathies. It is based on a variety of different activities of daily living representing a wide range of difficulties ranging from "reading a newspaper/book" to "running" (24 component items).

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 R-ODS (≥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). However, of the 208 subjects who deteriorated during the IGIV withdrawal period by any of the three stated deterioration criteria, only 151 subjects (62% of those who entered the IGIV Withdrawal Period) 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. 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 Privigen Restabilization treatment lasted up to 13 weeks.

Of these 207 subjects who received Privigen during the Privigen Restabilization Period , 36 were withdrawn from the Privigen Restabilization Period for the following reasons: failure to achieve CIDP symptom improvement and stability (22 subjects), withdrawal by subject (7 subjects), AEs (4 subjects), physician decision (2 subjects), and protocol violation (1 subject).

At the end of the Privigen Restabilization Period, a total of 172 subjects were randomized to placebo (2% albumin in 250 mMol/L L-proline and 8-30 mg/L polysorbate 80 weekly) (n = 57), 0.2 g/kg SC weekly Hizentra (n = 57), or 0.4 g/kg SC weekly Hizentra (n = 58) for a treatment peiod of 25 weeks. Within the three randomization groups, these subjects had mean ages of 56-57 years, were 53-74% male and 26-47% female, and were 88-93% Caucasians.

A total of 57 subjects received 0.2 g/kg Hizentra; of these, 21 subjects were withdrawn due to CIDP relapse (18 subjects), withdrawal by subject (2 subjects), and AE (1 subject). A total of 58 subjects received 0.4 g/kg Hizentra; of these, 19 subjects were withdrawn due to CIDP relapse (10 subjects), withdrawal by subject (8 subjects), and AE (1 subject). Of the 57 subjects who received placebo, 36 were withdrawn due to CIDP relapse (32 subjects), withdrawal by subject (3 subjects), and physician decision (1 subject).

For the primary endpoint analysis in the intent-to-treat (ITT) population (all subjects that were randomized), both doses of Hizentra showed statistically significant and clinically meaningful superiority over placebo. A lower percentage of subjects treated with Hizentra (32.8% for 0.4 g/kg Hizentra and 38.6% for 0.2 g/kg Hizentra) had CIDP relapse or were withdrawn for other reasons compared with subjects treated with placebo (63.2%). The absolute risk reduction was 24.6% for the 0.2 g/kg Hizentra group ($p = 0.007$) and 30.4% for the 0.4 g/kg Hizentra group ($p < 0.001$) compared with placebo. The 5.8% difference in relapse/withdrawal rates between the two active Hizentra arms was not statistically significant and was not considered to be clinically meaningful. The primary endpoint analysis of the per-protocol population supported the findings in the ITT population.

When only considering CIDP relapse based on the adjusted INCAT score ("relapse analysis," "sensitivity analysis A") and not including subjects who withdrew for any other reason as equivalent to relapsers, a statistically significant lower percentage of ITT population subjects treated with Hizentra(19.0% for 0.4 g/kg Hizentra and 33.3% for 0.2 g/kg Hizentra) had CIDP relapse compared with subjects treated with placebo (56.1%). The absolute risk reduction compared with placebo by this sensitivity analysis was 22.8% for the 0.2 g/kg Hizentra group and 37.2% for the 0.4 g/kg Hizentra group. The 14.3% absolute difference in relapse rates between the two active Hizentra treatment arms was not statistically significant and did not reach the 30% minimum difference pre-specified by the applicant as a clinically meaningful difference for the primary efficacy endpoint.

By the end of the 25-week SC Treatment Period, the mean adjusted INCAT score had partially reverted toward the reference value at the start of the Privigen Restabilization Period (end of the IGIV Withdrawal Period) in the Placebo group, whereas the improvements from that reference point value observed during the Privigen Restabilization Period were maintained throughout the SC Treatment Period for both Hizentra groups.

The point estimates for efficacy for the primary endpoint in the PATH study were greater for females compared to males, in part because there was a higher rate of relapse and dropout for other reasons in the subgroup of females randomized to placebo compared to males randomized to placebo. There was, however, overlap in the 95% confidence intervals between females and males, so the observation of a possible sex difference in efficacy should be interpreted with caution.

It was concluded that substantial evidence of effectiveness had been demonstrated by the submitted data from the adequate and well-controlled PATH study. The primary endpoint demonstrated statistically significant and clinically meaninffful superiority to placebo for both the 0.2 g/kg and 0.4 g/kg Hizentra groups. Further support for a conclusion of efficacy was provided by all secondary efficacy outcome measures. The point estimate difference in the primary efficacy endpoint between the the 0.2 g/kg and 0.4 g/kg Hizentra groups was modest and did not achieve statistical significance. Secondary efficacy outcome measures were generally very

similar for the the 0.2 g/kg and 0.4 g/kg Hizentra groups . Taking all primary and secondary efficacy measures into account, the nominal differences in efficacy parameters observed between the 0.2 g/kg SC weekly and 0.4 g/kg SC weekly Hizentra groups were not considered clinically meaningful.

Biostatistical Review

CSLB investigated Hizentra's efficacy and safety for treatment of CIDP in the completed PATH study, with 172 subjects randomized 1:1:1 to placebo, 0.2 g/kg SC weekly Hizentra, or 0.4 g/kg SC weekly Hizentra treatment groups. The primary efficacy endpoint is defined as the proportion of subjects who had a deterioration (increase) of at least 1 point in the adjusted INCAT disability score (except for a change of 0 to 1 solely due to upper limb score or an unchaged total INCAT score where the arm score decreased from 1 to 0 (not clinically meaningful improvement) and the leg score increased by 1 point (clinically meaningful worsening)). Therefore the PATH study was determined successful for the primary efficacy endpoint.

The applicant also submitted data from the PATH extension study. In the PATH extension study, Hizentra was evaluated for the maintenance of CIDP over 48 weeks.

Safety analyses for both the PATH and PATH extension studies revealed no new safety issues.

Conclusion: Overall, statistical analysis results from the PATH and PATH extension studies support the new indication, i.e., for the treatment of CIDP in adult subjects as maintenance therapy to prevent relapse of neuromuscular disability and impairment.

Pharmacovigilance Review

The pharmacovigilance plan (PVP) is mostly unchanged from the time of the original product approval, except for the specific mention of ulceration-like infusion site reaction (UL-ISR) in the local reaction section, and the removal of aspects previously identified as missing information: "potential off-label use in therapeutic areas which have become medical practice for IVIg products," and "safety-profile of Hizentra in the pediatric population."

The data presented in this supplemental BLA are consistent with the known safety profile for this product, with the exception of injection site necrosis.While local reactions (e.g., swelling, redness, heat, pain, and itching at the injection site) are labeled, necrosis is not in the currently approved Hizentra package insert. Review of FDA Adverse Event Reporting System (FAERS) reports of injection site necrosis found that a majority of these reports did not identify an alternate etiologic factor. Based on this FDA review, the applicant agreed to add "injection site necrosis" to the product package insert (PI) in section 6.2, Postmarketing Experience.

The applicant agreed to include "injection site necrosis" in its evaluation of local reactions as an identified risk.

CBER agrees with the removal of pediatric safety data and off-label use safety data as missing information, as pediatric safety data was analyzed as part of the 2011 pediatric indication approval process, and safety data for off-label use is not normally considered missing information.

BioResearch Monitoring (BIMO) Inspections

CBER Bioresearch Monitoring (BIMO) issued four inspection assignments for four U.S. sites that participated in the PATH study in support of this BLA supplement. The inspections did not identify data integrity issues that affected the overall conclusions regarding the safety and efficacy of Hizentra for the proposed CIDP indication. Two inspections were classified "No Action Indicated" and two were classified "Voluntary Action Indicated."

b) Pediatrics

The application is not subject to the Pediatric Research and Equity Act (PREA) with respect to the new indication because Hizentra has orphan drug designation for CIDP. The clinical development program for Hizentra for CIDP has not included any pediatric subjects or studies.

c) Other Special Populations

The point estimates for efficacy for the primary endpoint was somewhat greater for subjects over age 65 years compared to younger subjects, but there was considerable overlap in the 95% confidence intervals.

7. Safety

The clinical studies safety database in CIDP was considered adequate.

Notable safety findings from clinical studies (PATH and PATH extension studies) of Hizentra in CIDP included a higher incidence on a per-subject basis of local infusion site reactions in both Hizentra groups versus placebo, a higher incidence of such reactions in the 0.4 g/kg Hizentra group (29%) versus the 0.2 g/kg Hizentra group (19%) and a single causally-related serious adverse reaction ("Dermatitis Allergic") in the 0.2 g/kg Hizentra group, as well as the finding of a modest incidence of treatment-emergent hypertension in the two Hizentra groups only. Hypertension is already known to be associated with the class of IGIV products and is listed in the currently approved Hizentra package insert. No cases of thrombosis, aseptic meningitis syndrome, or

hemolysis (adverse reactions known to be associated with commercial IGIV products) were observed.

There were no deaths reported during the Hizentra/Placebo SC treatment period of the PATH study or in the 120-day safety update containing interim safety data for the PATH extension study. In the PATH study, three subjects had five serious adverse events (SAEs) in the 0.2 g/kg Hizentra group, two subjects had five SAEs in the 0.4 g/kg Hizentra group, and one patient had one SAE in the placebo group. Of these, only the one SAE referenced above ("Dermatitis Allergic") was considered causally related by the investigator/applicant and the FDA Clinical Reviewer.

During the SC Treatment Period, one subject in the 0.2 g/kg Hizentra group experienced one non-serious adverse event (AE) of Fatigue that led to subject discontinuation (causally related by investigator/applicant assessment, but unlikely related to Hizentraby FDA Clinical Reviewer). In the 0.4 g/kg Hizentra group, one subject experienced three SAEs leading to subject discontinuation (Anemia, Cholecystitis Acute, and Sepsis). None were assessed by the investigator/applicant or the FDA Clinical Reviewer as causally related and / or were temporally associated.

AEs, severe AEs, SAEs, and AEs leading to discontinuation of Hizentra / placebo, or subject withdrawal were all more frequent in the active Hizentra treatment groups than in the placebo group. No dose relationship was evident for AEs overall; however, as noted above, the percentage of subjects reporting local infusion site reactions was greater in the 0.4 g/kg Hizentra group than in the 0.2 g/kg Hizentra group.

The most frequently reported adverse reactions in the Hizentra groups were local reactions (swelling, redness, heat, pain, hematoma, and pruritis at the infusion site), headache, fatigue, back pain, pain in extremity, fall, and nasopharyngitis.

Review of postmarketing surveillance data for Hizentra use for any indication identified acute hypersensitivity reactions, chest discomfort, dyspnea, tremor, infusion site ulcer, and infusion site necrosis as additional risks.

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 generally similar to or no worse that of other immunoglobulin 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,
- Introduce a limitation of use in the Full Prescriber Information regarding maintenance therapy to be consistent with the recently approved Privigen package insert,
- Recommend a starting dose of 0.2 g//kg SC weekly, while indicating that the 0.4 g/kg SC weekly dose was also demonstrated to be safe and effective.
- Eliminate the results of a potentially inaccurate population pharmacokinetic analysis,
- Remove the provision for flexible dosing regimens (more frequent than weekly (up to daily) or every two weeks) that had not been studied and that had been based on extrapolations of efficacy (exposure-response model), and safety to these alternative dosage regimens that relied on results from the potentially inaccurate POPPK model.

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 as maintenance therapy to prevent relapse of 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 maintenance of documented IGIV-induced improvements in clinically meaningful assessments of neurologic function in the PATH study compare favorably to the known and observed risks of Hizentra, which include local infusion site reactions, hypersensitivity reactions, aseptic meningitis, headache, etc., and the remote theoretical risk of adventitious infectious agent transmission.

c) Recommendation for Postmarketing Activities

No clinical PMCs or PMRs are recommended.

The applicant has agreed to a CMC postmarketing commitment to develop an (b) (4) assay relevant to CIDP to assess the consistency of product lots for potency in this

regard. Specifically, “CSL Behring commits to develop and validate an assay related to (b) (4) as a lot release test. CSL Behring commits to submitting this as a Prior Approval Supplement by April 1, 2020.”