Summary Basis for Regulatory Action

Date: March 29, 2018

From: Tara Waterman, M.D., J.D., Chair of the Review Committee

STN#: 125329/176

Applicant Name: Bio Products Laboratory

Date of Submission: June 5, 2017

Goal Date: April 6, 2018

Proprietary Name/ Established Name: Gammaplex 10%

Indication: Primary humoral immunodeficiency (PI) in pediatric patients 2 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

Review Office(s) Signatory Authority(ies): Tejashri Purohit-Sheth, Director, Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Tissues and Advanced Therapies

☐ **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.**

Office of Compliance and Biologics Quality Signatory Authority:

☐ **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*	Tara Waterman, M.D., J.D.
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Shuya Lu, PhD
Clinical Pharmacology Review(s)	Xiaofei Wang, Ph.D.
Labeling Review(s) • *APLB (OCBQ/APLB)*	Alpita Popat, PharmD, MBA

1. Introduction

This efficacy supplement was submitted by Bio Products Laboratory (BPL) to expand the indication of Gammaplex 10% to the pediatric population. Gammaplex 10% is Immune Globulin Intravenous (Human), 10% Liquid. In 2009, Gammaplex 5%, Immune Globulin Intravenous (Human), 5% Liquid, was approved for the treatment of primary humoral immunodeficiency in adults. Subsequently, BPL was granted approval for this product (5% Liquid) in the pediatric population for the same indication. This approval was based on demonstration of clinical efficacy, assessed by the yearly rate of infections.

Due to the time required for an infusion of Gammaplex 5%, BPL formulated Gammaplex 10%, which has twice the concentration of IgG as Gammaplex 5%, and change the excipient from sorbitol to glycine.

To support licensure of Gammaplex 10%, BPL conducted GMX07 clinical study, a phase III, multicenter, open-label, randomized, two-period, crossover bioequivalence study to evaluate the pharmacokinetics, safety, and tolerability of Gammaplex 10% and Gammaplex 5% as a treatment for primary immunodeficiency (PI). This study enrolled both adult and pediatric subjects, but bioequivalence of Gammaplex 10% to Gammaplex 5% was demonstrated only in the adult study population, using the above crossover trial design. In pediatric subjects, pharmacokinetic (PK) properties of Gammaplex 10% were compared to those of adults in the GMX07 clinical study. In the pediatric population, the main objectives were assessment of the comparability of PK outcomes (Cmax, AUC0-τ, trough IgG level) in pediatric subjects compared with adult subjects and assessment of safety and tolerability.

2. Background

While the exact mechanism of action of IGIV is not completely elucidated, IGIV has been an accepted therapy for PI for over a decade. In 2014, the lower-concentration product, BPL's Gammaplex 5%, was licensed for the treatment of PI in pediatric patients. In 2017, Gammaplex 10% was licensed for the treatment of PI in adult patients.

Primary immunodeficiency (PI) is a spectrum of more than 130 distinct disorders caused by intrinsic defects in humoral and cellular immune function that can cause aberrations in immune globulins (IG), rendering subjects more susceptible to infections. Pathologies include, but are not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. PI is considered a rare disease and about 1 in 500 people are born in the United States with PI.

Approval of an IGIV blood product for this indication is usually based on demonstration of clinical effectiveness, measured by the number of infections per year. Subsequently, efficacy supplements (e.g., supporting a new formulation or extension to a different population) are based on demonstration of pharmacokinetic (PK) equivalence as well as safety. The present study included a formal bioequivalence study comparing the 5% with the 10% formulations in adults. The pediatric portion of the study compared the PK characteristics of the 10% formulation in children with data derived from adults in this study (GMX07) without formal bioequivalence testing. However, the results for the major PK parameters were similar between the two populations.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

No CMC data were submitted in in this efficacy supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical pharmacology/toxicology information was submitted in this efficacy supplement.

5. CLINICAL PHARMACOLOGY

This was a phase 3, multicenter, open-label, randomized, two-period, crossover bioequivalence study to evaluate the pharmacokinetics, safety, and tolerability of Gammaplex® 10% and Gammaplex® 5% in primary immunodeficiency diseases (PI). There were two cohorts in the study: adult subjects and pediatric subjects. Results of the adult cohort were submitted on April 08, 2016, and the application was approved on February 06, 2017. In this supplement, the applicant submitted results of the pediatric cohort, seeking approval of Gammaplex® 10% in the pediatric population.

Study subjects were on a stable IGIV regimen before entering the study. During the study, subjects received the same dose and treatment schedule (21-day or 28-day) as their prior IGIV treatment. A total of 15 pediatric subjects had received at least 1 infusion of Gammaplex 10%. Thirteen subjects who had complete PK profiles at assumed steady state were included in the PK analysis. Each subject received a minimum of 5 infusions of Gammaplex 10% with the dose ranging from 355 to 745 mg/kg.

The demographics (age in years and sex) are shown below:
2 – 5 years 2 subjects (1 male, 1 female; both on 28-day regimen)
6 – 11 years 6 subjects (3 males, 3 females; 4 on 21-day regimen and 2 on 28-day regimen)
12 – 15 years 5 subjects (3 males, 2 females; 3 on 21-day regimen and 2 on 28-day regimen)

Blood samples for PK analysis of IgG were collected at Visit 5 at following time points: 30 minutes pre-infusion, 10 minutes before end of infusion, and at 1, 3, 6, 24, 48 hours, and 4, 7, 14, 21 and 28 (for 28-day treatment schedule) days after end of infusion. Blood samples for measurement of trough levels of total IgG were collected before the start of each infusion and at the follow-up visit.

Pharmacokinetic parameters were estimated for each subject by non-compartmental analysis (NCA) using absolute (baseline unadjusted) and baseline adjusted serum total IgG concentrations. All trough concentrations were analyzed unadjusted.

At steady state, baseline adjusted Cmax and AUC0-τ (area under the concentration versus time curve within a dosing interval (21-day or 28-day)) were comparable between pediatric and adult subjects. The results are summarized in Table 1.

Table 1 Pharmacokinetic Parameters of GAMMAPLEX 10% in Pediatric Subjects (corrected for baseline concentration)

a. **2-5 years(n=2)**

Description	Cmax (mg/dL)	Tmax (h)	AUC0-τ (day*mg/dL)	Cmin (Trough)	CL (dL/day/kg)	$t_{1/2}$ (h)	Vss (dL/kg)
Geometric Mean	1120	-	7621	55	0.0716	167	0.690
Geometric CV (%)	33.5	-	69.8	2.6	19.4	8.9	7.5
Arithmetic Mean	1150	-	8390	55	0.0723	168	0.690
Arithmetic SD	368	-	4964	1.4	0.0138	15	0.052
Median	1150	3.24	8390	55	0.0723	168	0.690
Minimum	889	2.83	4880	54	0.0625	157	0.653
Maximum	1410	3.65	11900	56	0.0820	178	0.726
Lower 95% CI (GeoMean)	60	-	26	44	0.0128	75	0.351
Upper 95% CI (GeoMean)	20975	-	2195037	69	0.4019	371	1.350

b. 6-11 years (n=6)

Description	Cmax (mg/dL)	Tmax (h)	AUC0-τ (day*mg/dL)	Cmin (Trough)	CL (dL/day/kg)	$t_{1/2}$ (h)	Vss (dL/kg)
Geometric Mean	907	-	6161	42	0.0845	111	0.571
Geometric CV (%)	37.9	-	71.1	92.8	39.8	37.2	28.8
Arithmetic Mean	955	-	7140	53	0.0906	117	0.590
Arithmetic SD	314	-	3805	33	0.0419	40	0.164
Median	973	2.76	5980	56	0.0785	123	0.572
Minimum	501	1.98	2050	14	0.0591	68	0.392
Maximum	1290	5.13	11900	87	0.1730	179	0.810
Lower 95% CI (GeoMean)	617	-	3148	18	0.0566	76	0.425
Upper 95% CI (GeoMean)	1332	-	12059	96	0.1264	162	0.7674

c. 12-16 years (n=5)

Description	Cmax (mg/dL)	Tmax (h)	AUC0-τ (day*mg/dL)	Cmin (Trough)	CL (dL/day/kg)	$t_{1/2}$ (h)	Vss (dL/kg)
Geometric Mean	978	-	6655	129	0.0787	144	0.712
Geometric CV (%)	35.1	-	31.9	56.7	19.5	16.0	26.5
Arithmetic Mean	1021	-	6896	141	0.0800	146	0.732
Arithmetic SD	317	-	1889	57	0.0162	24	0.196
Median	976	2.33	7700	171	0.0788	142	0.664
Minimum	577	1.67	4080	54	0.0645	118	0.513
Maximum	1430	4.47	8550	194	0.1060	181	1.030
Lower 95% CI (GeoMean)	641	-	4523	67	0.0619	118	0.515
Upper 95% CI (GeoMean)	1492	-	9792	248	0.1001	176	0.983

Serum total IgG trough levels were measured. All except one pediatric subject had total IgG trough concentrations above 600 mg/dL at baseline and during the study. Six-hundred mg/mL of total IgG is thought to be the threshold clinically significant level of IgG concentration, which provides protection against serious infections. The pediatric subject had developed a change in metabolism of IGIV before switching to Gammaplex 10% and showed total IgG trough levels below 600 mg/dL at baseline and during the study.

Conclusions:

1. At steady state, both absolute and baseline adjusted Cmax and AUC0-τ were comparable between pediatric and adult subjects.

2. All except one pediatric subject had total IgG trough concentrations above 600 mg/dL at baseline and during the study. That pediatric subject had developed a change in metabolism of IGIV before switching to Gammaplex 10% and showed total IgG trough levels below 600 mg/dL at baseline and during the study.

Table 2 Pharmacokinetic Parameters of GAMMAPLEX 10% compared with GAMMAPLEX 5% in Adults, and GAMMAPLEX 10% in Pediatric Subjects (corrected for baseline concentration)

Indication/ Parameter (unit)	**ADULTS GAMMAPLEX 10% / 28-day Dosing Interval (n=16)** Mean§ (CV%)	**ADULTS GAMMAPLEX 10% / 21-day Dosing Interval (n=14)** Mean§ (CV%)	**ADULTS GAMMAPLEX 5% / 28-day Dosing Interval (n=16)** Mean§ (CV%)	**ADULTS GAMMAPLEX 5% / 21-day Dosing Interval (n=14)** Mean§ (CV%)	**PEDIATRICS GAMMAPLEX 10% / 2-5 years (n=2)** Mean§ (CV%)	**PEDIATRICS GAMMAPLEX 10% / 6-11 years (n=6)** Mean§ (CV%)	**PEDIATRICS GAMMAPLEX 10% / 12-15 years (n=5)** Mean§ (CV%)
C_{max} (mg/dL)	1090 (20.5)	1150 (27.6)	1020 (23.6)	1090 (21.6)	1120 (33.5)	907 (37.9)	977 (34.9)
T_{max} (hr)[a]	2.87 (1.6-31)	2.70 (1.8-7.8)	3.73 (2.1-9.0)	3.68 (2.2-5.7)	3.24 (2.8-3.7)	2.76 (2.0-5.1)	2.33 (1.7-4.5)
AUC¶ (days*mg/dL)	7830 (30.2)	6980 (33.0)	7230 (35.3)	6380 (32.8)	7620 (70.0)	6160 (71.1)	6650 (31.9)
Half-Life (hr)	123 (32.3)	118 (39.3)	132 (45.8)	119 (48.7)	167 (9.14)	111 (37.3)	144 (16.0)
Clearance (dL/day/kg)	0.0635 (24.0)	0.0674 (21.9)	0.0684 (37.6)	0.0743 (38.6)	0.0716 (19.3)	0.0845 (39.7)	0.0787 (19.3)
Volume of Distribution (dL/kg)	0.498 (27.4)	0.528 (50.3)	0.569 (38.4)	0.536 (32.6)	0.688 (7.45)	0.571 (28.8)	0.711 (26.4)

¶ $AUC_{0\text{-}tau}$ = area under the concentration versus time curve within a dosing interval, tau = dosing interval

C_{max} = maximum observed concentration

T_{max} = time at which C_{max} was apparent

[a] Median and range are presented for t_{max}

§ Geometric mean

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

BPL submitted one study, GMX07, in support of its application. Study GMX07 was designed to administer 5 doses of Gammaplex 10% at a dose of 300 to 800 mg/kg via IV infusion either once every 21 days or once every 28 days in adult and pediatric subjects. The adult portion of the study was an open-label, randomized, two-period, crossover (five infusions of Gammaplex 10% and five infusions of Gammaplex 5%) bioequivalence study. The pediatric portion of the study was a non-randomized, open-label, single-arm study. For the pediatric cohort, the main objectives were assessment of safety and tolerability as well as the PK profile of Gammaplex 10% IGIV. Since bioequivalence between Gammaplex 10% and Gammaplex 5% had previously been established using the adult cohort of study GMX07, and related products (10% IGIV formulations from different manufacturers) are licensed for the treatment of PI, FDA did not require that the Applicant demonstrate efficacy of Gammaplex 10%, or bioequivalence to a licensed IGIV product to support expansion of the labeled indication to include treatment of pediatric subjects with PI. Rather, the FDA would consider a demonstration of comparability between the PK profile of Gammaplex 10% in pediatric subjects and adults to be sufficiently predictive of the effects of Gammaplex 10% to support a pediatric indication for treatment of PI. Study GMX07 enrolled 33 adult subjects (age range 17 to 55 years) and 15 pediatric subjects (age range: 3 to 15 years; n = 8 male subjects, n=7 female subjects). There were six subjects in the 12-15 year age group, seven subjects in the 6-11 year age range, and two subjects in the 3-5 year age range. The unit doses for pediatric subjects were all within a range of 300 to 800 mg/kg, administered either once every 21 days (n = 7 subjects), or once every 28 days (n = 8 subjects). Complete PK data were evaluable in 13 pediatric subjects. Gammaplex 10% was well-tolerated in pediatric subjects in study GMX07. A total of 82 infusions of the product were administered to 15 pediatric subjects. In all but one subject, the trough levels were above 600mg/dL

There were no statistical issues in the submission. No formal efficacy analysis was performed, but the analysis of the PK and safety data support the extension of the indication to the pediatric population.

b) Pediatrics

July 9, 2014, the PeRC concluded that a marketing application for this product with a new concentration does not trigger PREA.

c) Other Special Populations

7. SAFETY

The primary safety endpoint for study GMX07 was met by demonstrating that for the pediatric cohort the upper 1-sided 95% confidence interval (CI) for the proportion of infusions with at least one temporally-associated adverse event (AE) for Gammaplex 10% was lower (30.8%) than the accepted level (FDA Guidance, "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency") of 40%, which was based on historical data. No subjects died and no SUSARs (suspected unexpected serious adverse reactions) were reported to have occurred in pediatric subjects in study GMX07. The most common adverse reactions that were reported in the 15 pediatric subjects were headache (4/15 subjects; 27%) and chest pain/musculoskeletal chest pain (2/15 subjects; 13%). No episodes of hemolysis or thromboembolism were reported.

8. ADVISORY COMMITTEE MEETING

This efficacy supplement was not presented to the advisory committee because this product is not a first of its kind product and there were no areas of scientific or technical uncertainty raised by the supplement.

9. OTHER RELEVANT REGULATORY ISSUES

The review committee did not identify any other regulatory issues.

10. LABELING

The APLB Reviewer found the FULL PRESCRIBING INFORMATION for GAMMAPLEX® [Immune Globulin Subcutaneous (Human) 10%, Liquid] to be acceptable from a promotional and comprehension perspective. The review committee required revisions to the PI. All issues were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Approve the efficacy supplement.

b) Risk/ Benefit Assessment

Based on the demonstrated PK (Cmax, AUC0-τ, trough IgG level) and safety outcomes in the pediatric cohort of study GMX07, combined with well-established effectiveness (reduction in the incidence of serious bacterial infections) for other class products (IGIVs) when administered as

treatment for PI, the review team's assessment is that the benefit-risk for use of Gammaplex 10% for treatment of PI in pediatric patients 2 years of age and above is favorable.

c) Recommendation for Postmarketing Activities

No specific postmarketing activities are recommended. The pharmacovigilance plan already in place for Gammaplex 10% is sufficient.