Summary Basis for Regulatory Action

Date: July 30, 2015

From: Daniela J. Vanco, M.D., Clinical Reviewer

BLA/ STN#: 125329/112

Applicant Name: Bio Products Laboratory

Date of Submission: September 28, 2014

PDUFA Goal Date: July 30, 2015

Proprietary Name/ Established Name: Gammaplex/ Immune Globulin Intravenous (Human), 5% Liquid

Indication: For the treatment of primary humoral immunodeficiency (PI)

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

Paul D. Mintz, MD, Director
Division of Hematology Clinical Review, Office of Blood Research and Review

☐ **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.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Daniela J. Vanco, M.D.
Clinical Pharmacology Review	Iftekhar Mahmood, Ph. D.'s memo
Statistical Review	Jiang Hu. Ph.D.'s memo
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Bioresearch Monitoring Review	Bhanu Kannan's memo
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A
Other (list)	Package insert

1. Introduction

On September 29, 2014, Bio Products Laboratory (hereafter Bio Products) submitted an efficacy supplement application to Biologics License Application (sBLA) STN 125329/112 for Gammaplex®, Immune Globulin Intravenous (Human), 5% Liquid (hereafter Gammaplex), to include revisions to the package insert that reflect the pediatric population studied in the postmarketing study GAM04.

Gammaplex was licensed in the United States on September 17, 2009 for the indication treatment of primary humoral immunodeficiency (PI). At the time of approval, the pediatric study requirement for subjects 0 to <2 years of age were waived and the pediatric study for subjects >2 to 16 years of age was deferred.

The deferred pediatric postmarketing study under the Pediatric Research Equity Act (PREA), required under 505B(a) of the Federal Food, Drug, and Cosmetic Act, is the subject of this submission.

"A Phase 4, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Gammaplex® in Primary Immunodeficiency Diseases in Children and Adolescents" also included pharmacokinetic (PK) evaluation in both the children (>2 to <12 years of age) and adolescent (>12 to 16 years of age) age groups.

The clinical trial achieved its primary efficacy endpoint of a 1-sided 99% upper bound of less than one serious acute bacterial infection (SABI) per subject per year. The upper one sided 95% confidence limit for the proportion of Gammaplex 5% infusions with at least one temporally associated adverse event (AE) (regardless of causality) was 30.4%, which was less than the established historical control of 40%, thus also meeting the primary safety criterion. There were no deaths, thromboembolic, or hemolytic events in the clinical study. Gammaplex was shown to be safe and well-tolerated in the pediatric PI subjects. An impact of subjects' gender and race could not be established, due to the small sample size.

The revised final label is acceptable, and approval of the efficacy supplement is recommended.

2. Background

Gammaplex was licensed in the United States on September 17, 2009, indicated for replacement therapy in adults with primary humoral immunodeficiency (PI). On March 8, 2013, Gammaplex received licensure for the indication of treatment of adults with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts, for which Orphan Drug Designation was granted. Gammaplex is currently licensed in the United States, United Kingdom, Israel, Brazil, and Lebanon.

- September 17, 2009, at the time Gammaplex was licensed in the United States for the indication of treatment of PI, the postmarketing requirement (PMR) pediatric study for

the treatment of PI in pediatric subjects >2 to 16 years of age was deferred with the following timelines:

Protocol Submission: November 2009
Study Initiation: January 2010
Study Completion: September 2012
Final Report Submission: December 2012

- March 8, 2013, the ITP indication was approved (BLS 125329/55)

- April 9, 2013, Bio Products communicated to FDA that the ongoing GMX04 PMR study had been significantly delayed due to very slow recruitment, and the clinical study report would be delayed until December 2014. Deferral extension request was granted by FDA on July 9, 2013.

3. Chemistry Manufacturing and Controls (CMC)

Gammaplex 5% is an Immune Globulin Intravenous (Human), manufactured from source plasma from healthy U.S. donors. It is presented as a ready-prepared solution of human normal immunoglobulin G (IgG) at pH 4.9 for intravenous administration. The IgG is stabilized with sorbitol.

There were no new CMC data submitted in this efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

There were no new pharmacology/toxicology data submitted in this efficacy supplement.

5. Clinical Pharmacology

In this phase 4, multicenter, open-label, non-randomized study, there were 20 children aged 3 to 15 years, stratified to groups 2 to 5, 6 to 11, and 12 to 15 years of age. The demographics are shown below:

- 2-5 years 3 subjects (2 males, 1 female)
- 6-11 years 11 subjects (9 males, 2 females)
- 12-15 years 6 subjects (4 males, 2 females)

Subjects received 13 to 17 infusions (12 months of therapy on either a 21-day or 28-day treatment schedule) of Gammaplex at a dose of 300 to 800 mg/kg, and up to a maximum infusion rate of 0.08 mL/kg/min. Blood samples were taken on visit 11 (9th infusion) from subjects on the 21-day schedule, and on visits 9 or 10 (7th or 8th

infusion) from subjects on the 28-day schedule. In both studies, irrespective of the infusion schedules, blood samples were taken at the following intervals:

- Prior to infusion,
- End of the infusion
- At 1, 24 and 48 hours
- At 4, 7, 14, 21 and 28 days

PK parameters were estimated by non-compartmental analysis using both baseline adjusted, and baseline unadjusted total IgG concentrations. The results of the study are summarized in Table 1.

Table 1: Effect of age on absolute and baseline-adjusted PK parameters of IgG following intravenous infusion of doses of 304 to 813 mg/kg Gammaplex

PK Parameter	Baseline-Adjusted?	Age Category	Least Squares Geometric Mean	Ratio (Child Category/Adult) Estimate	90% CI	p-value
C_{max} (mg/dl)	No	2-5	1600	0.73	(0.62, 0.86)	0.002
		6-11	1800	0.82	(0.75, 0.90)	0.001
		12-15	1870	0.85	(0.76, 0.96)	0.034
		>16	2190			
	Yes	2-5	719	0.61	(0.47, 0.79)	0.002
		6-11	871	0.74	(0.63, 0.86)	0.001
		12-15	909	0.77	(0.64, 0.93)	0.024
		>16	1180			
C_{max}/Dose (kg.mg/dL/mg)	No	2-5	3.25	0.73	(0.62, 0.86)	0.002
		6-11	3.65	0.82	(0.75, 0.90)	0.001
		12-15	3.80	0.85	(0.76, 0.96)	0.034
		>16	4.44			
	Yes	2-5	1.46	0.61	(0.47, 0.79)	0.002
		6-11	1.76	0.74	(0.63, 0.86)	0.001
		12-15	1.84	0.77	(0.64, 0.93)	0.024
		>16	2.39			
$AUC_{0-\tau}$ (days.mg/dL)	No	2-5	28400	0.87	(0.75, 1.01)	0.125
		6-11	28600	0.88	(0.80, 0.96)#	0.018
		12-15	27600	0.85	(0.75, 0.95)	0.022
		>16	32500			
	Yes	2-5	5390	0.67	(0.50, 0.90)	0.025
		6-11	6140	0.76	(0.64, 0.91)	0.013
		12-15	6550	0.81	(0.65, 1.03)	0.142
		>16	8060			
CL (dL/days/kg)	No	2-5	0.0174	1.15	(0.99, 1.33)	0.125
		6-11	0.0173	1.14	(1.04, 1.24)#	0.018
		12-15	0.0180	1.18	(1.05, 1.33)	0.022
		>16	0.0152			
	Yes	2-5	0.0918	1.49	(1.12, 2.00)	0.025
		6-11	0.0806	1.31	(1.10, 1.56)	0.013
		12-15	0.0755	1.23	(0.97, 1.55)	0.142
		>16	0.0614			
V_{ss} (dL/kg)	No	2-5	1.13	1.72	(1.39, 2.13)	<.001
		6-11	0.903	1.38	(1.21, 1.57)	<.001
		12-15	0.940	1.43	(1.21, 1.70)	0.001
		>16	0.656			
	Yes	2-5	0.729	1.50	(1.02, 2.19)	0.081
		6-11	0.628	1.29	(1.03, 1.62)	0.069
		12-15	0.556	1.14	(0.84, 1.55)	0.466
		>16	0.487			
$t_{½}$ (days)	No	2-5	44.6	1.51	(1.26, 1.80)	<.001
		6-11	36.4	1.23	(1.10, 1.37)	0.002
		12-15	37.1	1.25	(1.08, 1.44)	0.012
		>16	29.6			
	Yes	2-5	5.32	0.92	(0.71, 1.20)	0.594
		6-11	5.20	0.90	(0.77, 1.05)	0.259
		12-15	5.20	0.90	(0.73, 1.11)	0.393
		>16	5.79			

Source: Pharmacokinetic Report GMX01 and GMX04, [redacted] Ref. No. BPL109, Table 18, Pg 51 of 111.
90% CI contained within bioequivalence limits of (0.80, 1.25)

The baseline unadjusted IgG clearance values (based on per kg body weight) were comparable between children and adults (>16 years of age). On the other hand, the baseline adjusted IgG clearance values (based on per kg body weight) were 49%, 31%, and 23%; higher in children aged 2-5, 6-11, and 12-15 years, respectively, as compared with adults.

The baseline unadjusted IgG half-life was 51%, 23%, and 25%; higher in children aged 2-5, 6-11, and 12-15 years, respectively, as compared with adults. However, the baseline adjusted IgG half-life was comparable between children and adults (>16 years of age). Gender had no impact on the PK of Gammaplex.

Conclusions: In terms of clearance and half-life, the PK of IgG follows opposite directions when the baseline is either corrected or uncorrected. Based on an uncorrected baseline, the half-life in children 2-5 years of age is 51% longer than subjects >16 years of age, and approximately 25% longer in older children (6-15 years of age). However, baseline correction leads to comparable half-lives across all age groups. The clearance of Gammaplex based on uncorrected baseline values is comparable across all age groups; however, based on corrected baseline values, the clearance is higher (per kg body weight) in children 2-5 years, 6-11 years, and 12-15 years of age by 49%, 31%, and 23% respectively, as compared to adults (>16 years of age).

In addition to half-life and clearance, the baseline uncorrected and corrected dose adjusted C_{max} is 27% and 39% lower in children 2-5 years of age respectively, than in subjects >16 years of age. The baseline corrected AUC is 33% lower in children 2-5 years of age than in subjects >16 years of age, but based on an uncorrected baseline, the AUC is comparable across all age groups.

In conclusion, the PK of IgG is substantially different in children 2-5 years of age, as compared to adults, and may warrant an IgG dose adjustment in this age group. However, considering the small sample size (n =3), and the wide range of IgG dose (304-813 mg/kg) given to these children, dose adjustment considerations are limited by the small amount of data available. However, more frequent therapeutic monitoring is needed in the 2-5 years age group than in adults or older children.

6. Clinical/ Statistical

Clinical Program

"A Phase 4, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Gammaplex® in Primary Immunodeficiency Diseases in Children and Adolescents" included a pharmacokinetic evaluation in both the children (>2 to <12 years of age), and adolescent (>12 to 16 years of age) age groups. A total of 25 subjects enrolled in this multi-center study (nine centers) were administered the study drug by intravenous infusion, at a dose of 300-800 mg/kg per infusion (at the same dose of IGIV that was previously used to establish steady state) once every 21 or 28 days.

The study subjects were treated for 12 months at 21-day (14 subjects) or 28-day (11subjects) dosing intervals. Three subjects were between the ages of 2 to 5 years, 12 subjects between the ages of 6 to 11 years, and 10 subjects were between the ages of 12 to 16 years. The median age of subjects was 11.0 years, and ranged from 3 to 16 years. Subjects were predominantly male (19 subjects, 76.0%). All of the subjects were Caucasian. Doses ranged from 300 mg/kg to 800 mg/kg. The mean dose (range) for the 21-day interval was 545 mg/kg (429 - 689 mg/kg); the mean dose (range) for the 28-day interval was 521 mg/kg (316- 800 mg/kg). Subjects received a total of 368 infusions of Gammaplex. The maximum infusion rate allowed during the clinical study was 0.08 mL/kg/min (4 mg/kg/min).

The objectives of the study were to determine the safety and efficacy of Gammaplex. Efficacy was based on the annual rate of SBIs, defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis, per subject per year. The primary safety and tolerability endpoint was measured by the number and percentage of AEs.

There were no deaths, thromboembolic, or hemolytic events in the clinical study.
Two subjects (8%) had a total of two Serious Adverse Events (SAEs) requiring hospitalization, with onset between the first infusion date, and 30 days after the last infusion. One subject experienced an SAE of lobar pneumonia of moderate intensity, and a second subject experienced an SAE of lobar pneumonia of severe intensity. Neither of the SAEs was considered related to study drug.

The clinical study achieved its primary efficacy endpoint of a 1-sided 99% upper bound of less than one SBI per subject per year (0.36 per subject-year). The upper one-sided 95% confidence limit for the proportion of Gammaplex infusions with at least one temporally associated AE (regardless of causality) was 30.4%, which was less than the established historical control of 40%, thus meeting the primary safety criterion.

The Division of Inspections and Surveillance conducted Biomedical Monitoring (BIMO) inspections of two clinical sites, accounting for approximately 56% of the total subjects enrolled in the study. The data audit portion of the inspections focused on the verification of the safety and efficacy data, submitted by Bio Products in the sBLA, for 100% of the enrollees at the site. The BIMO inspections of two clinical investigators did not reveal substantive problems that would impact data integrity.

Gammaplex was shown to be safe and well-tolerated in the pediatric PI subjects. An impact of subjects' gender and/or race could not be established, due to the small sample size.

Pediatrics
The pediatric assessment in this submission, and the associated labeling changes were presented to the Pediatric Review Committee (PeRC) on May 27, 2015. The PeRC agreed that the PMR has been fulfilled by the current efficacy supplement, and found the pediatric population adequately addressed in the proposed language of the package insert.

7. Safety

There were no deaths, thromboembolic, or hemolytic events in the clinical study.
Two subjects (8%) had a total of two SAEs requiring hospitalization, between the first infusion date, and 30 days after the last infusion. One subject experienced an SAE of lobar pneumonia of moderate intensity, and a second subject experienced an SAE of lobar pneumonia of severe intensity. Neither of the SAEs was considered related to study drug.

Out of the 368 total number of infusions administered in the in GMX04 study, 97 (26.4%) were temporally associated (occurring within 72 hours of the end of infusion) with at least one AE, irrespective of causality. The upper one sided 95% confidence limit for the proportion of Gammaplex infusions with at least one temporally associated AE (regardless of causality) was 30.4%, which was less than the established historical control of 40%, thus achieving the primary safety endpoint.

8. Advisory Committee Meeting

There were no issues for the Blood Products Advisory Committee to address.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Labeling

The final labeling was negotiated and agreed upon.

11. Recommendations and Risk/ Benefit Assessment

There are currently no concerns regarding the risk/benefit ratio. Thromboembolic events have been described after the administration of immune globulin class of products. Measures to mitigate the risk of thromboembolic events following use of Gammaplex are highlighted in the label as a boxed warning.

The clinical study showed that the product is reasonably safe and effective in the pediatric population, without clinically significant differences from the adult population. As for all age groups, dosing for pediatric subjects is also based on body weight, and the labeling clearly instructs dosing to be titrated to subject's clinical response. No pediatric-specific dose requirements are necessary to achieve the desired serum IgG levels.

This submission fulfills the PMR. No further postmarketing clinical studies are needed at this time.