Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Through:	Meghna Alimchandani, MD Associate Director for Medical Policy, OBE, CBER
From:	Shaokui Wei, MD, MPH Epidemiologist, Analytic Epidemiology Branch (AEB), DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Bio Products Laboratory (BPL) Limited
Product:	Gammaplex, Immune Globulin Intravenous [Human], 5% Liquid
STN:	125329/217
Indication:	Primary humoral immunodeficiency in adults and pediatric patients two years of age and older, and chronic immune thrombocytopenic purpura in adults
Meeting Date:	Pediatric Advisory Committee Meeting, September 2019

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review is the approval of efficacy supplement for Gammaplex 5% in the indication of "the treatment of primary immunodeficiency in adults and pediatric patients 2 years of age and older" on July 30, 2015.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

Gammaplex is an Immune Globulin Intravenous (IGIV) (Human), 5% or 10% liquid, manufactured from source plasma from healthy donors in the United States. The plasma is processed at Bio Products' facility in Elstree, Hertfordshire, UK. 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 or glycine for 5% or 10% liquid, respectively.

Gammaplex is indicated for the treatment of primary humoral immunodeficiency in adults and pediatric patients two years of age and older and chronic immune thrombocytopenic purpura in adults.

1.3 Regulatory History

- September 17, 2009: Initial approval for Gammaplex 5% in the treatment of primary humoral immunodeficiency
- March 8, 2013: Approval of efficacy supplement [STN 125329/55] for Gammaplex 5% to include a new indication for chronic immune thrombocytopenic purpura
- September 23, 2013: Approval Letter for Safety Labeling Changes [STN 125329/67]: "…under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA)…new safety information pertaining to the risk of thrombosis that we believe should be included in the labeling for the entire class of intravenous, subcutaneous, and intramuscular immune globulin (human) products." (Please see additional details in section 5.1.)

- July 30, 2015: Approval of efficacy supplement [STN 125329/112] for Gammaplex 5% for the indication of "the treatment of primary immunodeficiency in adults and pediatric patients 2 years of age and older" **(trigger for this PAC)**

- February 6, 2017: Approval of efficacy supplement [STN 125329/151] to include 10% formulation to treat Primary Humoral Immunodeficiency and Chronic Immune Thrombocytopenic Purpura

- April 6, 2018: Approval of efficacy supplement [STN 125329/176] to include the use of Gammaplex 10% in Primary Immunodeficiency in children 2 years of age and older.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Gammaplex for the period July 30, 2015 to March 31, 2019
- Manufacturer's Submissions
    - Gammaplex 5% Liquid, U.S. package insert, dated October 2018
    - Gammaplex 10% Liquid, U.S. package insert, dated April 2018
    - Letter regarding dose distribution data, received June 18, 2019
    - Pharmacovigilance Plan, 125329/220, Section 1.16, received June 19, 2019
- FDA Documents
    - Gammaplex 5% & 10% Approval Letter, dated April 6, 2018
    - Gammaplex 5% & 10% Approval Letter, dated February 6, 2017
    - Gammaplex 5% Approval Letter dated July 30, 2015
    - STN 125329/151, Division of Epidemiology Pharmacovigilance Review Memorandum dated July 8, 2016
    - STN 125329/55, Division of Epidemiology Pharmacovigilance Review Memorandum dated November 9, 2012
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There has been no label change related to safety concerns for Gammaplex in the PAC review period, July 30, 2015 (PAC trigger) through March 31, 2019 (data lock point for this review).

4 PRODUCT UTILIZATION DATA[1]

BPL provided distribution data for the U.S. and outside of the US for the period of August 1, 2015 to March 31, 2019.

US distribution of Gammaplex from August 1, 2015 to March 31, 2019 was (b) (4) grams. BPL captured age information on (b) (4) of the grams distributed in the US. The data showed that (b) (4) of the grams went to pediatric patients and (b) (4) went to adult patients. BPL applied these percentages to the total grams distributed during the time period requested, resulting in estimates of (b) (4) grams distributed to pediatric patients <18 years and (b) (4) grams to adults 18 years and older.

As per the package insert, the recommended dose for primary humoral immunodeficiency is 0.3 – 0.8 g/kg every 3 to 4 weeks. For chronic immune thrombocytopenic purpura, the recommended dose is 1g/kg for 2 consecutive days. Using the distribution data above, a rough estimate of doses would be between (b) (4) and (b) (4) doses. (Since dose is based upon weight, indication, and clinical response, these figures are only general estimates. The lower figure is based on a dose of 1g/kg for a 70kg adult for treatment of chronic immune thrombocytopenic purpura. The higher figure is based upon the typical immunodeficiency dose of 0.3g/kg for a 70kg adult. The actual number of doses administered could be substantially lower or higher depending on the amount of product that was distributed but not yet administered, the amount of use in pediatric patients, the route used, and the dosage administered.)

Distribution of Gammaplex outside of the US for the same period was (b) (4) grams. BPL did not have any reliable information to project/estimate product distribution by age outside of the US.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan for Gammaplex 5% is included in the Risk Management Plan, Version 5.1, and dated August 31, 2014. Table 1 describes safety concerns and proposed pharmacovigilance activities for Gammaplex 5%.

[1] Distribution data is protected as confidential commercial information and may require redaction from this review.

Table 1: Gammaplex safety concerns and planned pharmacovigilance activities[2]

Safety Concerns – Class Effects	**Proposed pharmacovigilance activities**
Reactions such as headache, chills, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, moderate low back pain and cutaneous reaction	Routine pharmacovigilance
Hemolysis	
True hypersensitivity reactions, anaphylactic or anaphylactoid reactions	
Renal dysfunction/failure	
Thrombotic events such as myocardial infarction and stroke, pulmonary embolism and deep vein thrombosis	
Aseptic meningitis syndrome	
Transfer of infective agents such as viruses, emerging viruses, other unidentified infective agents or pathogens	
Impairment of the efficacy of live attenuated virus vaccines	
Volume overload	
Interference with serological testing	
Hyperproteinemia, increased serum viscosity and hyponatremia	
Transfusion-related acute lung injury (TRALI)	
Other Safety Concerns – Specific to Gammaplex	**Proposed pharmacovigilance activities**
Potential for reactions in patients with Hereditary Fructose Intolerance	Routine pharmacovigilance
Higher incidence of headache and possibly hypertension and vomiting at infusion rates of 0.08 mL/kg/minute	
No experience in patients with hepatic impairment	

(Adapted from RMP version 5.1, Table 55-56, P79-80)

Thrombotic events: Prior to this PAC trigger, in 2013, a boxed warning for thrombosis was added to the label of all non-specific immune globulin products, including Gammaplex, as required by FDA[3]. As per FDA safety communication, "*A retrospective analysis of data from a large health claims-related database, as well as continued postmarketing adverse event reports of thrombosis have strengthened the evidence for an association between the use of intravenous, subcutaneous, and intramuscular human immune globulin products and the risk of thrombosis. This information necessitates a boxed warning for the entire class of products*.[4]" The risk of thrombosis

[2] Gammaplex 5% Risk Management Plan (RMP), Version 5.1, dated August 31, 2014
[3] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. November 7, 2013. Available at: https://www.gmp-compliance.org/gmp-news/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products
[4]FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. June 11, 2013. Available at: https://primaryimmune.org/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

was not identified specifically for Gammaplex; and is considered applicable to all immune globulin products and labeled for this entire product class.

The remaining identified and potential risks for Gammaplex listed in the above table are common to the IGIV class and are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted reports, published literature, and data mining. There are no ongoing or planned additional pharmacovigilance activities, postmarketing safety study, or Risk Evaluation and Mitigation Strategy.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Gammaplex between July 30, 2015 (PAC trigger) and March 31, 2019 (data lock point for this review). FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of adverse event reports for Gammaplex during the review period are listed in Table 2. There were 189 U.S. and 9 foreign reports.

Table 2: FAERS reports for Gammaplex* (July 30, 2015 through March 31, 2019)

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious Foreign	Total, US	Total, Foreign
<18 years	5**	0	1	0	5	0	11	0
≥18 years	72	5	2	0	69	1	143	6
Unknown	11	0	0	1	24	2	35	3
All ages	88	5	3	1***	98	3	189	9

Note: Serious non-fatal adverse events include otherwise medically important conditions (OMIC), life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability.
*Note that reports may be for 5% or 10% formulation of Gammaplex.
** One report appears to have been misclassified as a pediatric report; there are inaccuracies in data (the patient is reported as 0.48 years and weighing "88.9kg" and PTs and narrative describe an adult).
*** Appears to have been mistakenly submitted as an adult death report; upon further review this is an adult serious non-fatal foreign report involving exposure during pregnancy, and occurrence of intrauterine fetal death (see section 6.2.2 of memo).

6.2.1 Deaths

There were 3 death reports, including 1 pediatric recipient, received during the review period. All fatal reports were individually reviewed.

Pediatric death report: The FAERS received 1 death report involving a 15-year-old female who was being treated with Gammaplex (dose and batch number unknown) for an unknown indication and passed away on an unknown date. The cause of death and autopsy report was not provided. As per the manufacturer, "due to the scarcity of information and as the event leading to death is unknown; the report is classified as not assessable."

Adult death reports: The FAERS received 2 death reports in adult Gammaplex recipients during the reporting period. These 2 reports are summarized in Table 3.

Table 3: Adult death reports received in FAERS during the reporting period

Case #	Clinical summary
1	A 54-year-old female received Gammaplex 5% for an unknown indication. The patient's medical history included a diagnosis of systemic connective tissue disease (unspecified), diabetes, high cholesterol, immobilization, obesity, immune mediated necrotizing myopathy, avascular necrosis of hip, Graves disease, and post-menopausal symptoms. The patient was treated with Gammaplex 5% at a dose of 60 grams every day for 4 days every 4 weeks. The patient received 3 courses of treatment and died from a pulmonary embolism 4 days after the last dose of Gammaplex. Details of the patient's death were unknown. The sponsor commented that the combination of several risk factors together with a large dose of Gammaplex 5% probably contributed to the fatal pulmonary embolus. The case was regarded as possibly related to Gammaplex 5% but confounded by several risk factors.
2	A 54-year-old female with immune mediated necrotizing myopathy treated with IVIG developed pulmonary embolism and died on an unknown date. This case report is a likely duplicate to Case #1.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 94 serious non-fatal reports; 4 of which involved pediatric patients. There was one foreign report (source: literature case report) involving a pregnant woman (age unknown) with a history of significant red cell antibody titers in early pregnancy, who was administered IVIG (brand name unknown) for Hemolytic Disease of the Fetus and Newborn (HDFN). The pregnancy outcome was intrauterine fetal death, and additional clinical details were not provided. The sponsor assessment was that the cause of intrauterine fetal death was related to HDFN, e.g., hydrops fetalis.

The 4 serious non-fatal reports in pediatric patients are summarized in Table 4.

Table 4: Summary of serious non-fatal reports in pediatric patients (n=4)

Case#	Age	Sex	Indication	Preferred Term	Interval	Outcome	Reviewer comments
1	1.75 years	Male	unknown	Bacterial infection	1 day after nfusion	Unknown	Causality unassessable due to lack of
2	25 days	Female	Immunoglobulin G decreased	Infusion related reaction, pruritus, throat irritation	during nfusion	Recovered	Labeled events
3	8 years	Female	Sydenham's chorea	Cough, dyspnea, off label use	during nfusion	Recovered	Labeled events

4	17 years	Female	Myasthenia gravis	Headache, photophobia, Pyrexia, off label	1 day after nfusion	Recovered	Labeled events

The events reported in these 4 serious non-fatal reports in pediatric patients are commonly observed in adult patients and labeled in the package insert of Gammaplex; there are no new safety concerns.

The most frequently reported MedDRA preferred terms (PTs), occurring with a frequency >3 reports, for serious non-fatal AEs among all ages are summarized in Table 5. (Note that a report may have one or more PTs.)

Table 5: Top preferred terms (PTs) for serious non-fatal reports in all ages

Preferred Term (PT)	Number of reports	Label status
Headache	18	Labeled (6.1), (6.2)
Meningitis aseptic	11	Labeled (5.5), (6.2)
Chills	9	Labeled (6.1), (6.2)
Infusion related reaction	9	Labeled (6.2: Infusion reactions)
Rash	9	Labeled (6.1), (6.2)
Dyspnea	8	Labeled (6.1), (6.2)
Off label use	7	Not applicable (N/A)
Thrombosis	7	Labeled (5.2), (6.2)
Nausea	6	Labeled (6.1), (6.2)
Pyrexia	6	Labeled (6.1), (6.2)
Vomiting	6	Labeled (6.1), (6.2)
Asthenia	5	Labeled (6.1)
Back pain	4	Labeled (6.2)
Blood pressure increased	4	Labeled (6.1), (6.2)
Chest discomfort	4	Labeled (6.1), (6.2)
Fatigue	4	Labeled (6.1), (6.2)
Influenza like illness	4	Unlabeled
Pruritus	4	Labeled (6.1), (6.2)
Skin exfoliation	4	Unlabeled, but related to labeled event “other skin reactions” (6.2)

Label section: 5 Warnings and Precautions, 5.2 Thrombotic Events, 5.5 Aseptic Meningitis Syndrome (AMS); 6 Adverse Reactions, 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience

Most reported PTs listed above are labeled events. The unlabeled PT for “influenza-like illness” is a non-specific event. Off-label use has been reported and is common practice with immunoglobulin products.

6.2.3 Non-serious Reports

During the reporting period, there were 101 non-serious reports; 5 of which involved pediatric patients. These 5 non-serious reports in pediatric patients are summarized in Table 6.

Table 6: Summary of non-serious reports in pediatric patients (n=5)

Case#	Age (Yrs.)	Sex	Indication	Preferred Term	Interval	Outcome	Reviewer comments
1	10	Female	not reported	Bacterial nfection	after nfusion	Unknown	Underlying disease
2	12	Male	Myasthenia gravis	disorientation, off label use	during nfusion	Recovered	Related to labeled event, confusion (section 6.1)
3	6	Male	Henoch-Schonlein purpura	Off label use, therapeutic response unexpected	after nfusion	Unknown	Off label use
4	8	Female	Sydenham's chorea	Cough, dyspnea, dry throat, nfusion related reaction	during nfusion	Recovered	Labeled events
5	15	Male	Common variable immune deficiency	Chest pain	during nfusion	Recovered (without intervention)	Labeled events

The top PTs occurring with a frequency >3 reports, for non-serious AEs in all ages are shown in Table 7.

Table 7: Top PTs for non-serious reports in all ages

Preferred Term (PT)	Number of reports	Label status
Off label use	25	N/A
Headache	20	Labeled (6.1), (6.2)
Nausea	13	Labeled (6.1), (6.2)
Rash	11	Labeled (6.1), (6.2)
Rash pruritic	11	Labeled (6.1), (6.2)
Back pain	7	Labeled (6.2)
Myalgia	7	Labeled (6.1), (6.2)

Preferred Term (PT)	Number of reports	Label status
Chills	6	Labeled (6.1), (6.2)
Vomiting	6	Labeled (6.1), (6.2)
Pruritus	6	Labeled (6.1), (6.2)
Infusion related reaction	5	Labeled (6.2: Infusion reactions)
Fatigue	5	Labeled (6.1), (6.2)
Influenza like illness	5	Unlabeled
Rash maculo-papular	5	Labeled (6.1 & 6.2: Rash)
Malaise	4	Labeled (6.1), (6.2)
Rash generalized	4	Labeled (6.1 &6.2: Rash)
Chest pain	4	Labeled (6.1), (6.2)
Migraine	4	Labeled (6.2)
Blister	4	Unlabeled, but related to labeled event "other skin reactions" (6.2)
Pain in extremity	4	Labeled (6.1: Pain)

Label section: 5 Warnings and Precautions, 5.2 Thrombotic Events, 5.5 Aseptic Meningitis Syndrome; 6 Adverse Reactions, 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience

PTs in non-serious reports in adult patients and pediatric patients are either labeled events, non-specific events (influenza like illness), or confounded by indication/ underlying disease. There are no new safety concerns.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Gammaplex were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis [May 19, 2019]. Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified the preferred terms (PTs) summarized in Table 8, with a disproportional reporting alert.

Table 8: Data mining results

PT or SMQ[5] with EB05>2	Number of Reports	Label status
Meningitis aseptic	13	Labeled (5.5, 6.2)
Noninfectious meningitis (SMQ) [narrow]	15	Labeled (5.5, 6.2: aseptic meningitis)
Infusion related reaction	16	Labeled event (6.2: infusion reactions)
Rash pruritic	14	Labeled (6.1 and 6.2: Rash)
Chills	22	Labeled (6.1, 6.2)
Headache	45	Labeled (6.1, 6.2)
Rash maculo-papular	6	Labeled (6.1 and 6.2: Rash)
Rash	23	Labeled (6.1 and 6.2)
Migraine	10	Labeled (6.2)
Hypersensitivity (SMQ) [narrow]	71	Labeled (5.3, 6.2)
Rash generalized	7	Labeled (6.1 and 6.2: Rash)
Thrombosis	8	Labeled (5.2. 6.2)
Off label use	32	Not applicable
Influenza like illness	9	Unlabeled

Label section: 5 Warnings and Precautions, 5.2 Thrombotic Events, 5.3 Hypersensitivity; 5.5 Aseptic Meningitis Syndrome; 6 Adverse Reactions, 6.1 Clinical Trials Experience; 6.2 Postmarketing Experience

Most of these events appeared among the most frequently reported PTs and are discussed in Section 6.2.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Gammaplex covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in the FAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the U.S. National Library of Medicine's PubMed.gov database on May 20, 2019, for peer-reviewed literature, with the search term "Gammaplex" and published dates between July 30, 2015 and March 31, 2019 retrieved 3 articles. The articles were

[5] Standardized MedDRA Queries (SMQs) are validated and standard sets of MedDRA terms to be used to support signal detection and monitoring. (MedDRA website, accessed on July 9, 2019. https://www.meddra.org/how-to-use/tools/smqs)

reviewed, and the safety conclusions are summarized in Table 9. No new safety concerns for Gammaplex were identified in these articles.

Table 9: Summary of safety conclusion in literature published between July 30, 2015 and March 31, 2019

Article	Authors' safety conclusion
Melamed IR, et al. Efficacy and safety of Gammaplex5% in children and adolescents with primary immunodeficiency diseases. *Clin Exp Immunol*. 2016 May;184(2):228-36	This open-label multi-center study evaluated Gammaplex 5% in 25 children and adolescent patients (aged 3-16 years) with primary immunodeficiency disease. The study concluded that Gammaplex 5% is effective in preventing serious acute bacterial infections and is well tolerated in children and adolescents with primary immunodeficiency disease.
Wasserman RL, et al. Evaluation of the Safety, Tolerability, and Pharmacokinetics of Gammaplex 10% Versus Gammaplex 5% in Subjects with Primary Immunodeficiency. *J Clin Immunol*. 2017 Apr;37(3):301-310.	This phase 3, multicenter, open-label, randomized, two-period, crossover bioequivalence trial evaluated the safety, tolerability, and pharmacokinetics of Gammaplex 5% and Gammaplex 10% in 33 adults and 15 children with primary immunodeficiency disease. The study concluded that Gammaplex 10% formulation was safe and well tolerated in pediatric and adult subjects.
Guptill JT, et al. Two comparative assessments of intravenous immunoglobulin therapy switching patterns in the treatment of chronic inflammatory demyelinating polyneuropathy in the US. *Patient Prefer Adherence*. 2019 Apr; 30;13:649-655	This study evaluated switching patterns between IVIG products for chronic inflammatory demyelinating polyneuropathy patients in 2 separate retrospective databases. The study concluded that IVIG therapy is generally well tolerated.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Gammaplex does not indicate any new safety concerns. The PAC review was initiated due to approval of Gammaplex 5% for the treatment of primary immunodeficiency in adults and pediatric patients 2 years of age and older on July 30, 2015. There were very few adverse events reported in the pediatric age group (<18 years) during the review period. There was only one report of pediatric death with unassessable causality. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Gammaplex 5%.