



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE PLAN REVIEW FOR ORIGINAL BLA

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Subject: Review of Pharmacovigilance Plan

Applicant: Green Cross Biopharma Corporation

Product: Alyglo (Immune Globulin Intravenous (Human), 10% Liquid)

Application Number: BLA STN 125743\0\68

Proposed Indication: Alyglo is indicated for the treatment of primary humoral immunodeficiency in adults

Submission Date: July 14, 2021

Action Due Date: January 12, 2024

1 Objective

The sponsor, Green Cross Biopharma Corporation, submitted an original BLA 125743/0/68 seeking licensure for a novel immunoglobulin product, Alyglo (Immune Globulin Intravenous (Human), 10% Liquid), for the proposed treatment of primary humoral immunodeficiency in adults. This review assesses the adequacy of the pharmacovigilance plan based on the safety profile of Alyglo and identifies any potential safety concerns that may need to be addressed through additional pharmacovigilance activities, postmarketing studies, or Risk Evaluation and Mitigation Strategy (REMS), should this product be approved. A PVP for this product was previously comprehensively reviewed under STN 125743/0 (submitted December 15, 2021) for adults (b) (4). The PVP was found to be adequate, should the product be approved. Of note, lack of adequate data for (b) (4) led to the file receiving a complete response (CR) on February 25, 2022. The product was then resubmitted with (b) (4). This memo will focus on reviewing new safety data submitted by the sponsor since January 22, 2020 (the latest DLP associated with the original 125743/0 submission) and will address the adequacy of the PVP in light of the new data.

2 Product Information

2.1 Product description and indication

Alyglo is a 10% immune globulin liquid for intravenous injection. The sponsor proposes that the product be indicated for the treatment of primary humoral immunodeficiency (PI) in adults.

2.2 Proposed dosing regimen(s) and formulation(s)

Alyglo is a clear or slightly opalescent, colorless or pale-yellow solution infused using a separate infusion line. Prior to use, the infusion line may be flushed with Dextrose Injection, D5W (5% dextrose in water) or normal saline (0.9% Sodium Chloride for Injection). The product is manufactured in 50 mL, 100 mL, and 200 mL fill sizes.

The recommended dose of Alyglo for patients with PI is 300 to 900 mg/kg body weight administered every 21 or 28 days. If a patient misses a dose, the missed dose is administered as soon as possible and then the scheduled treatments are resumed to every 21 or 28 days, as applicable. The dosage is adjusted over time to achieve the desired serum IgG trough levels and clinical responses.

3 Pertinent Regulatory History

Pertinent Regulatory History

Dates	Details
2017 May 12	<ul style="list-style-type: none">Market authorization (international birth date) for GCC 10% IgIV was granted in the Republic of Korea (under the trade name IV-Globulin SN Inj. 10%) for the following indications: agammaglobulinemia/ hypogammaglobulinemia, combined therapy

	with antibiotics in severe bacterial or viral infections, idiopathic thrombocytopenic purpura, Guillain-Barre Syndrome, and Kawasaki disease
2021 Sep 08	<ul style="list-style-type: none"> Market authorization was granted in Philippines under the trade name Eugamma SN 10% inj.
2021 Nov 24	<ul style="list-style-type: none"> Market authorization was granted in Argentina under the trade name EUGAMMA SN 10% INJ.
2021 Dec 15	<ul style="list-style-type: none"> The BLA was resubmitted to FDA under STN 125743/0 for the treatment of primary humoral immunodeficiency in adults (b) (4)
2021 Dec 21	<ul style="list-style-type: none"> Market authorization was granted in Peru under the trade name Eugamma SN 10% Solution Injectable.
2021 Dec 22	<ul style="list-style-type: none"> Market authorization was granted in Paraguay under the trade name IMMUNOGLOBULINA HUMANA 10% GREEN CROSS.
2022 Feb 25	<ul style="list-style-type: none"> GCBP received complete response letter, citing concerns about lack of pharmacokinetic data for (b) (4) indication
2022 Nov 25	<ul style="list-style-type: none"> Market authorization was granted in Uruguay under the trade name Eugamma SN 10%
2023 Jul 14	<ul style="list-style-type: none"> Alyglo BLA resubmitted (STN 125743/0/68) with indication (b) (4)

4 Materials Reviewed

Materials reviewed in support of this assessment include:

Document	STN	Date Received/ Completed
DPV review of 125743/0	Not Applicable	2022 Feb 08
GC5107B-P3 Study Report Addendum 2	125743/0/68	2023 Jul 14
GC5107B-P3 Study Report Addendum 2 Tables, Figures, and Listings	125743/0/68	2023 Jul 14
Clinical Overview (resubmission)	125743/0/68	2023 Jul 14
GC5107B-P3 SAP	125743/0/68	2023 Jul 14
Summary of Clinical Safety (resubmission)	125743/0/68	2023 Jul 14
Draft package labeling text (resubmission)	125743/0/68	2023 Jul 14
Pharmacovigilance Plan version 2.0	125743/0/68	2023 Jul 14
Information request response to updated safety information since last submission	125743/0/69	2023 Jul 31
PBRER covering 12-May-2021 to 11-May-2022	125743/0/75	2023 Oct 18
PBRER covering 12-May-2022 to 11-May-2023	125743/0/75	2023 Oct 18
Information request response re updates in reference safety information	125743/0/76	2023 Nov 01
Information request response re AEs from Korean postmarket study	125743/0/77	2023 Nov 03

5 Review of Interval Safety Data

At the time of the original submission, data for 1 completed trial was submitted and reviewed. Please refer to the DPV memo for STN 125743/0 for a comprehensive review of the safety data from Phase III study GC5107B_P3. This memo reviews new safety data from any additional safety data that has become available since the original submission received a Complete Response on February 25, 2022.

5.1 Review of STN 125743/0/68 Sponsor-Submitted Clinical Trial Interval Safety Data

The sponsor submitted two documents describing relevant safety data from ongoing studies – the Clinical Overview and Summary of Clinical Safety. The Sponsor confirmed via IR that there have been no adverse events reported for any subjects in Study GC5107B_P3 or any other ongoing studies with Alyglo since the data lock point of the initial submission, January 22, 2020. (b) (4)

5.2 Summary of Prior Marketed Experience

Following an IR request for updated postmarket data since January 22, 2020, the Sponsor submitted 2 periodic safety reports covering May 12, 2021 to May 11, 2023. During this reporting period, per the sponsor, there were no publications relevant to the safety of the product.

Though IVIG SN 10% is currently approved in five countries (refer to Section 3), it is only marketed in the Republic of Korea as of the periodic safety report's DLP (11 May 2023). Study IVIG-SN 10% PMS (postmarket study) was requested by Korea. Per the Sponsor, the PMS was initiated as "a mandatory pharmacovigilance activity routinely requested by Korea regulatory authority for new drugs." Of note, the periodic safety report did not include its study protocol or final study report. The study yielded safety information for 615 subjects who were being treated for the following conditions:

- 1) Agammaglobulinemia/Hypogammaglobulinemia
- 2) Combined therapy with antibiotics in severe bacterial or viral infections
- 3) Idiopathic Thrombocytopenic Purpura (in the case where other medicinal products are not effective or patients show apparent hemorrhage and patients need temporary control of hemostasis such as surgical treatments or childbirth etc.)
- 4) Guillain-Barre Syndrome (acute idiopathic polyneuritis)
- 5) Kawasaki disease (to prevent the disease of coronary artery complication).

On October 30, 2023, an IR was sent to the Sponsor requesting specific safety data for subjects in the study relevant to this BLA's indication of adults with primary immunodeficiency. The Sponsor responded on November 3, 2023. Eighteen adult subjects had the BLA's indication of primary immunodeficiency. Of these, 11 (61.1%)

subjects sustained a total of 28 AEs during the study. The most common AEs experienced by PI subjects were neutropenia (n=5, 27.8%), pyrexia (n=4, 22.2%), and constipation (n=3, 16.7%). 5 subjects experienced 5 SAEs: febrile neutropenia (n=2, 11.1%), drug eruption (n=1, 5.6%), atypical pneumonia (n=1, 5.6%), and large intestine infection (n=1, 5.6%). Pyrexia was the only AE considered by the Sponsor as possibly related to Alyglo. However, there was a notable non-serious case of asthenia which was temporally associated (occurred the same day) with infusion; this case was considered unrelated by the investigator.

The atypical pneumonia case was the only case with a fatal outcome. The pneumonia infection was ongoing prior to administration of Alyglo, but worsened after administration. Of note, this case was confounded by age (74) and concomitant conditions (chronic myeloid leukemia, chronic obstructive pulmonary disease, gamma-glutamyl transferase increased, hypertension, hypocalcemia, hypokalemia, internal hemorrhoid, and pulmonary tuberculosis).

Based on the results of the Korean study, changes were made to the reference safety information in light of AEs experienced by non-PI subjects. These included addition of 3 new PTs (herpes zoster infection, hypophosphatemia, dizziness) not reflected in the PI provided for this submission. On October 26, 2023 an IR was sent to the Sponsor for the narratives for cases and a response was received on November 3, 2023. All three cases were considered by the Sponsor possibly related to Alyglo due to temporal association. However, of note, all patients received the product for ITP, which is not the submitted indication for this BLA.

Reviewer Comment:

AEs experienced by subjects in the study relevant to this BLA’s indication were expected or related to AEs already in the proposed labeling. This reviewer concurs with the Sponsor’s assessment of causality for all AEs in patients with PI, except the non-serious AE of asthenia which was temporally associated (occurred the same day); as this AE has been previously associated with IVIGs, the reviewer considers this case possibly related.

6 Review of Sponsor’s Pharmacovigilance Plan

The sponsor submitted an updated PVP as part of STN 125743/0/68 (dated July 14, 2023). This version was compared to the PVP submitted and reviewed in STN 125743/0 (dated December 15, 2021). The PVP, including identified risks, potential risks, missing information, and rationale for the proposed action, is summarized in table below.

Sponsor-Proposed Pharmacovigilance Plan

Type of Important Risk	Potential Safety Concern	Planned pharmacovigilance Activity
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Identified	Thromboembolism/thrombosis	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Black box warning and Section 5.2 on label
Identified	Hypersensitivity reaction to IGIV including anaphylaxis and IgA sensitivity	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.1 on label
Identified	Acute renal failure	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Black box warning and Section 5.3 on label
Identified	Hemolytic anemia	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.6 on label
Identified	Aseptic meningitis	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.5 on label
Identified	Interference with serological testing (Positive Coombs test)	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.10 on label
Identified	Impaired efficacy of live attenuated virus vaccines	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 7 on label
Identified	Pseudohyponatremia	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.4 on label
Identified	Hyperproteinemia	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.4 on label
Potential	Transmissible infective agents	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.8 on label
Potential	Transfusion-related acute lung injury (TRALI)	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.7 on label
Missing Information	Pregnant or breast-feeding women	<ul style="list-style-type: none"> • Routine pharmacovigilance activity

Risk mitigation will also include standard labeling in Section 6.2 of AEs commonly spontaneously reported for IVIGs, previously reviewed in STN 125743/0.

The sponsor's rationale for the original PVP was reviewed in detail under STN 125743/0, and comparison of the original and updated versions of the PVP revealed no changes relevant to the safety specifications or risk mitigation.

7 Integrated Risk Assessment

The PVP submitted in STN 125743/0 was previously reviewed and found to be adequate. Safety data accumulated in the interval between the issuance of the Complete Response and the time of this review was consistent with findings documented with the original submission and does not change the assessment of the overall safety profile of the product. No additional risk mitigation beyond routine pharmacovigilance is needed for the postmarket safety monitoring for Alyglo.

8 DPV Recommendations

- Should Alyglo be approved, OBPV/DPV agrees with the pharmacovigilance activities proposed by the applicant in the PVP along with adverse event reporting as required under 21 CFR 600.80 for postmarket safety monitoring for Alyglo.
- The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study.