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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Meghna Alimchandani, MD Deputy Director, Division of Pharmacovigilance (DPV), OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	ADMA Biologics, Inc.
Product:	Asceniv (Immune Globulin Intravenous, Human-slra, 10% Liquid)
STN:	125590/94
Indication:	Treatment of primary humoral immunodeficiency for adults and adolescents (12 to 17 years of age)
Meeting Date:	Pediatric Advisory Committee Meeting, September 2022

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 April 1, 2019, approval of Asceniv for the treatment of primary humoral immunodeficiency for adults and adolescents (12 to 17 years of age).

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

Asceniv (Immune Globulin Intravenous, Human-slra, 10% Liquid) is a 10% immune globulin solution for intravenous administration.

Asceniv is a purified, sterile, ready-to-use preparation of concentrated human immunoglobulin G (IgG) antibodies that is supplied in a single-use vial. The dosage form consists of a liquid solution containing 10% IgG (100 mg/mL) for intravenous infusion (5g in 50 mL solution).

1.3 Regulatory History

Asceniv was granted initial FDA approval for original Biologics License Approval (BLA 125590/0) on April 1, 2019.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Asceniv during April 1, 2019 to April 30, 2022
- Manufacturer's Submissions
    - Asceniv, U.S. package insert (USPI)
    - Applicant response to information request regarding dose distribution data
    - Pharmacovigilance plan (submitted in 2015)
    - Periodic safety reports
- FDA Documents
    - BLA 125590/0 Asceniv Approval Letter, dated April 1, 2019
    - BLA 125590/0 Pharmacovigilance Plan Review dated 2015
    - BLA 125590/0 Pharmacovigilance Plan Review Addendum dated 2019
- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA[1]

The sponsor provided U.S. distribution data as follows in Annual Reports:

- April 1, 2019, to March 31, 2020: (b) (4) vials
- April 1, 2020, to March 31, 2021: (b) (4) vials
- April 1, 2021, to March 31, 2022: (b) (4) vials
- Total number of vials April 2019 – March 2022: (b) (4) vials

The sponsor is not able to provide an estimation of patient exposure in the adult versus pediatric age group.

Asceniv has one dosage form of 5g in a 50 mL vial. Therefore, cumulative U.S. distribution of (b) (4) vials (using the U.S. distribution data above) corresponds to (b) (4) of product. Using a typical dose of 0.3g/Kg (for a 70 Kg adult treated for primary humoral immunodeficiency), a rough estimate of doses would be (b) (4) doses. (Since dose is based upon weight, indication, and clinical response, the above figure is only a general estimate. 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, and the dosage administered.)

Asceniv is only licensed for distribution in the United States.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan (PVP)

The manufacturer's current Pharmacovigilance Plan (PVP) (received in 2015) lists the important potential risks, and missing information displayed in Table 1. There were no important identified risks for this product.

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

Table 1: Asceniv safety concerns

Important Identified Risks
• None
Important Potential Risks
• Thrombotic events • Hypersensitivity • Acute renal dysfunction and acute renal failure • Hyperproteinemia, increased serum viscosity, and hyponatremia • Aseptic Meningitis Syndrome • Hemolysis • Transfusion-Related Acute Lung Injury (TRALI) • Transmissible Infectious Agents • Monitoring Lab Tests performed to assess potential risks • Interference with Lab Tests due to passive transfer of antibodies
Missing Information
• Limited experience in Pediatric <15yo and Elderly >65yo subjects • Limited experience with ethnic minorities • Pregnant or lactating women • Patients with Renal or Hepatic Insufficiency • Off-label use for conditions other than Primary Immunodeficiency (PI)

PVP is the Risk Management Plan (RMP) submitted in 2015

The potential risks for Asceniv listed in the above table are common to the immune globulin product class and are described in the USPI. Asceniv has a boxed warning for thrombosis. The USPI includes warnings for thrombosis, hypersensitivity, acute renal dysfunction and acute renal failure; hyperproteinemia, increased serum viscosity, and hyponatremia; aseptic meningitis syndrome, hemolysis; TRALI; transmissible infectious agents and interference with laboratory tests and provides instructions regarding monitoring laboratory tests.

Thrombotic events: Prior to this PAC trigger, in 2013, a boxed warning[2] for thrombosis was added to the label of all non-specific immune globulin products, as required by FDA. 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."[3] The risk of thrombosis was identified prior to the approval for

[2] 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

[3] 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

Asceniv, and it is considered applicable to all immune globulin products and labeled for this entire product class.

The identified and potential risks for Asceniv are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no ongoing or planned additional pharmacovigilance activities for Asceniv, such as postmarketing safety studies or Risk Evaluation and Mitigation Strategy (REMS).

5.2 Postmarketing studies

There are no safety-related postmarketing requirement or commitment (PMR/PMC) studies for Asceniv.

Study under the Pediatric Research Equity Act (PREA) are listed below:

- Deferred pediatric study under PREA for the treatment of primary immunodeficiency in pediatric patients ages 2 to 12 years.
  Final Protocol Submission: December 31, 2019
  Study Completion Date: December 31, 2022
  Final Report Submission: June 30, 2023
  Current study status: *Ongoing*

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Asceniv received between April 1, 2019 (PAC trigger) to April 30, 2022 (data lock point for this review period). 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 Asceniv during the review period are listed in Table 2. There were 9 reports, including 4 U.S. reports and 5 foreign

reports.

Table 2: FAERS reports for Asceniv (April 1, 2019 to April 30, 2022)

Age (years)	Serious non-fatal, US	Serious non-fatal, foreign	Deaths, US	Deaths, foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18	0	1	0	0	0	0	0	1
≥18	3	2	0	1	0	0	3	3
Unknown	0	1	0	0	1*	0	1	1
All	3	4	0	1	1	0	4	5

*Narrative indicates the non-serious U.S. report involved a 42-year-old woman.

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

6.2.1 Deaths

There was a single foreign adult death report. This death was reported in scientific literature[4] and involved a 56-year-old woman with recurrent thymoma, pure red cell aplasia and Good's Syndrome (thymoma with immunodeficiency) who received an unnamed immune globulin product and several concomitant medications. She experienced sepsis and pneumonia and was intubated because of severe hypoxia. It was reported that, "*she suffered from uncontrollable sepsis and died*."
Reviewer comment: Of note, though this report was submitted by the manufacturer and lists Asceniv as a suspect product, the report narrative does not identify the trade name of the immune globulin product.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 7 serious non-fatal reports, including 3 U.S. and 4 foreign reports.

The single pediatric report cited a foreign literature case report[5] describing a 17-year-old female diagnosed with possible common variable immunodeficiency (CVID) and receiving immunoglobulin replacement therapy who developed interstitial nephritis and lymphocytic colitis, two years after initiation of immunoglobulin therapy. The patient

[4] Nakagawa Y, Matsumoto K, Yamamoto M, Hirata H, Shiroyama T, Miyake K, Yamamoto Y, Kuge T, Yoneda M, Naito Y, Suga Y, Fukushima K, Koyama S, Iwahori K, Nagatomo I, Takeda Y, Kumanogoh A. A case of synchronous triple autoimmune disorders secondary to thymoma: Pure red cell aplasia, Good's syndrome, and thymoma-associated multi-organ autoimmunity. Respir Med Case Rep. 2022 Feb 23;36:101619. doi: 10.1016/j.rmcr.2022.101619. PMID: 35251929; PMCID: PMC8892002.
[5] Figueiredo AC, Nunes I, Ferreira E, Faria E. Rare case of interstitial nephritis in a young adult under IgG therapy. BMJ Case Rep. 2022 Feb 2;15(2):e246651. doi: 10.1136/bcr-2021-246651. PMID: 35110283; PMCID: PMC8811552.

received multiple concomitant medications. The patient was switched from intravenous immunoglobulin to subcutaneous immunoglobulin which was followed by a slow recovery of her kidney function.
Reviewer comment: Renal dysfunction is a labeled event for this product class. Of note, though this report was submitted by the manufacturer and lists Asceniv as a suspect product, the narrative and the literature article do not specify the trade name of the immune globulin product.

Additionally, one of the U.S. reports involved a 23-year-old woman who experienced headache, fever, photophobia and neck stiffness.
Reviewer comment: Aseptic Meningitis Syndrome (AMS) is labeled under Warnings and Precautions section of the USPI.

The remaining 5 reports were all literature case reports submitted by the manufacturer:

- 26-year-old woman received intravenous immune globulin for the treatment of myasthenia gravis and experienced pulmonary embolism and deep vein thrombosis.[6]
- 55-year-old-woman with COVID-19 developed systemic capillary leak syndrome (SCLS) and respiratory failure and received multiple medications including intravenous immune globulin[7]
- The remaining three case reports described different types of skin lesions after intravenous immune globulin infusion.[8, 9, 10]

Reviewer comment: Thrombosis is a known risk and labeled for this product class (Boxed Warning, Warnings and Precautions). Note that these literature cases were foreign reports involving unspecified brands of immune globulin; Asceniv is not approved for use outside of the U.S. There were no Preferred Terms (PTs) occurring in >1 serious report and no new safety concerns were identified.

[6] Abdulrazaq A, Smith R, Digala LP, Govindarajan R. Minimal Manifestations With Eculizumab Therapy in a Patient With Refractory Generalized Seropositive Myasthenia Gravis. J Clin Neuromuscul Dis. 2022 Mar 1;23(3):170-173. doi: 10.1097/CND.0000000000000388. PMID: 35188923.
[7] Beber A, Dellai F, Abdel Jaber M, Peterlana D, Brunori G, Maino A. Systemic Capillary Leak Syndrome triggered by SARS-CoV2 infection: Case Report and Systematic Review. Scand J Rheumatol. 2022 Jan;51(1):67-69. doi: 10.1080/03009742.2021.1917145. Epub 2021 Jun 25. PMID: 34169783.
[8] Johnson N, Rush P, Holliday A. Recurrent episodes of palpable migratory arciform erythema associated with IVIg infusions. Dermatol Online J. 2021 Apr 15;27(4):13030/qt7xg2k983. PMID: 33999580.
[9] Koizumi R, Fukumoto T, Jimbo H, Nishigori C. Intravenous immunoglobulin-induced severe vesicular eczematous eruption successfully treated with narrow band-ultraviolet B therapy. Photodermatol Photoimmunol Photomed. 2021 Sep;37(5):371-373. doi: 10.1111/phpp.12666. Epub 2021 Feb 19. PMID: 33559335.
[10] Doyle C, Eustace K. Pompholyx as a side effect of intravenous immunoglobulin (IVIg). BMJ Case Rep. 2022 Mar 30;15(3):e248772. doi: 10.1136/bcr-2022-248772. PMID: 35354565; PMCID: PMC8968538.

6.2.3 Non-serious Reports

During the reporting period, there was a single U.S. non-serious report involving a 42-year-old woman who had to delay her Asceniv infusion appointments because of illness related to cough, fever, loss of appetite.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Asceniv 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 as of May 15, 2022. 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 did not identify any PTs with a disproportional reporting alert.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Asceniv covering the surveillance period were reviewed. The adverse events reported were consistent with those seen in the FAERS. The sponsor presented additional literature case reports, including foreign publications, which do not identify the trade name of the immune globulin product. 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 June 29, 2022, for peer-reviewed literature, with the search term "Asceniv" (no other limits), retrieved 2 articles (summarized below). No new safety concerns were identified.

Table 5: Summary of safety conclusion in published literature

Article	Authors' safety conclusion
Wasserman RL, Garcia D, Greener BN, Kestenberg K, Pinkert A, Mond J, Grossman A. Manufacturing process optimization of ADMA Biologics' intravenous immunoglobulin products, BIVIGAM® and ASCENIV™. Immunotherapy. 2019 Nov;11(16):1423-1433. doi: 10.2217/imt-2019-0157. Epub 2019 Oct 9. PMID: 31596642.	Authors describe small-scale manufacturing processes for two immune globulin products, Bivigam and Asceniv. Authors conclude that these manufacturing processes have improved purity resulting in products with lot-to-lot consistency.

Article	Authors' safety conclusion
Bates BN, Olah ME. A New Intravenous Immune Globulin: Novel or Not? Ann Pharmacother. 2021 Jan;55(1):117-122. doi: 10.1177/1060028020934722. Epub 2020 Jun 21. PMID: 32567360.	Presents a review of immune globulin use for treatment of primary immune deficiency diseases (PIDD). Immune globulin-slra (ASCENIV) includes donor plasma with respiratory syncytial virus (RSV) antibody titers. The authors concluded that adverse events with the above product occurred at rates similar to or less than other available immune globulin products.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Asceniv does not indicate any new safety concerns. The PAC review was initiated due to the April 1, 2019 approval of Asceniv for the treatment of primary humoral immunodeficiency for adults and adolescents (12 to 17 years of age). There were very few reports overall during this review period and no pediatric death reports. 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 Asceniv.