



Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology  
Division of Epidemiology

**ADDENDUM to MEMORANDUM 125590/0**

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Through: Adamma Mba-Jonas, MD  
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To: Pei Zhang, PhD  
Committee Chair

Subject: Pharmacovigilance Plan Review Addendum

Applicant: ADMA Biologics, Inc.

Proprietary Name: ASCENIV™

Established/Proper Name: Immune Globulin Intravenous (Human), 10% Liquid  
ASCENIV

BLA Submission: Class 2 Resubmission BLA 125590/0

Proposed Indication: Primary Humoral Immunodeficiency

Submission Date: October 1, 2018

Action Due Date: April 2, 2019

## 1. Objectives/Scope

This memorandum addendum is in response to a request from the Office of Tissues and Advanced Therapies (OTAT) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan submitted by ADMA Biologics, Inc., for ASCENIV™ BLA 125590.0, Immune Globulin Intravenous (Human) 10% Liquid. The sponsor is seeking approval for the indication of primary humoral immunodeficiency. The purpose of this review is to provide an addendum to the pharmacovigilance plan review previously submitted by Wambui Chege, MD dated 24 November 2015.

## 2. Background

Primary Immunodeficiency (PI) diseases are a family of congenital disorders of the immune system that lead to an increase in frequency of infections, notably, but not limited to, bacterial infections of the respiratory tract. It is estimated that 1:2,000 to 1:10,000 live births are affected by a Primary Immunodeficiency Disease (PIDD). Recurrent sinus and pulmonary infections, including recurrent otitis media, are hallmarks of PI. The most commonly identified organism is Streptococcus Pneumoniae, although Hemophilus Influenza, Staphylococcus and Pseudomonas species are also seen. Diarrhea, which affects up to 25% of patients, is often associated with Giardia Lambia infection. Rotavirus, Enterovirus, Campylobacter, Salmonella and Shigella may also be seen. Autoimmune manifestations may be seen in up to 25% of patients. PI syndromes are inherited disorders, often presenting in childhood. Intrauterine polyhydramnios, growth retardation, adverse reaction to vaccination, poor wound healing, delayed separation of the umbilical cord and delayed shedding of primary teeth are also noted.<sup>1</sup>

Replacement therapy with Immunoglobulin G (IgG) has been used to treat the condition since the early 1950s. IGIV is indicated to reduce susceptibility and frequency of infections in subjects with primary humoral immunodeficiency.<sup>2</sup>

## 3. Product Description

ASCENIV™ is an intravenous Immune Globulin (Human) 10% Liquid. Asceniv™ will be supplied as a liquid solution containing 10% IgG (100mg/mL) for intravenous (IV) infusion. The product will be available in a single vial size of 5g in 50mL solution. The current proposed indication is for the treatment of primary humoral immunodeficiency. The proposed trade name is ASCENIV™.

## 4. Regulatory History

On 31 July, 2015, ADMA Biologics, Inc. submitted an original Biologics License Application to the Food and Drug Administration (FDA) for RI-002, Immune Globulin Intravenous (Human), 10% Liquid with standardized (b) (4) [REDACTED]. On 29 July, 2016, a complete response was issued for numerous CMC issues.<sup>3</sup>

On 28 September, 2018, ADMA resubmitted the application addressing the deficiencies outlined in the complete response letter.

On 24 October, 2018, an information request was sent to ADMA requesting confirmation on whether Immune Globulin Intravenous had been approved or marketed in any country. ADMA responded with confirmation that Asceniv has not been approved or marketed in any country. As such, no post-marketing data are available.

On 2 November, 2018, an information request was sent to ADMA and a Type C Meeting was held on 6, March 2019. The original application was submitted stating that Asceniv™ contains standardized (b) (4) [REDACTED].

Negotiations between ADMA and FDA were centered on concerns about the inclusion of language about (b) (4) [REDACTED] without providing clinical efficacy data. ADMA agreed to remove any reference to (b) (4) [REDACTED] prior to commercial lot release.<sup>4</sup>

ADMA responded with revisions to the lot release protocol and label changes removing reference to (b) (4) [REDACTED].

<sup>1</sup> Primary immunodeficiency diseases: a practical guide for clinicians. Turvey SE. Postgrad Med J. 2009

<sup>2</sup> The use of intravenous immune globulin in immunodeficiency diseases. Buckley RH. N Engl J Med. 1991

<sup>3</sup> Complete response RI002 29 Jul 2016 (b) (4) [REDACTED]

<sup>4</sup> 1.11.1. Quality Information Amendment [RI-002, ADMA Biologics] Response to Information request Nov 2, 2018

## 5. Materials Reviewed

The submitted Risk Management plan has previously been reviewed<sup>5</sup>. ADMA did not submit a new pharmacovigilance plan or new clinical study data. The adequacy of the previously submitted pharmacovigilance plan was discussed in the memo dated 24 November 2015, submitted by Wambui Chege, MD. Please refer to previously submitted PVP memo (Wambui Chege, MD) and clinical review memo (Charles Maplethorpe MD PhD).

## 6. Clinical Studies

The clinical data submitted by the sponsor in support of the licensure for Asceniv™ consist of a single clinical trial, ADMA-003, an open label, multicenter study to evaluate the pharmacokinetics, efficacy and safety of Asceniv™ in subjects with PI. The sponsor did not submit any additional clinical studies. Please refer to previous PVP review memo and clinical review memo.

## 7. Post-marketing data

Asceniv™ has not been approved or marketed anywhere. As such, no post-marketing data are available for review. This was confirmed by ADMA Biologics, Inc. A FAERS query was performed for independent confirmation and no data were identified.

Asceniv™ bears some manufacturing similarities to a previously licensed IgIV product named Bivigam, which was approved on 19Dec2012. Bivigam and Asceniv™ both have the excipient Polysorbate 80, which has been associated with hypotension in animal models. Given these similarities, it was reasonable to assess available postmarket data with respect to this AE; this data includes spontaneous reporting in FAERS, PSURs, Empirica data mining, and a postmarket commitment (PMC) study designed at the time of approval to characterize this risk. Review of postmarketing data for Bivigam since approval are reassuring regarding hypotension. Only one case of hypotension was noted on FAERS query. Review of past PSURs does not suggest a safety signal for hypotension, and data mining does not demonstrate disproportionate reporting of hypotension in patients who have received Bivigam. The PMC study is currently suspended due to product shortages; enrollment to date is insufficient for any evaluation.

## 8. Recommendations

ADMA did not submit a new pharmacovigilance plan. The sponsor's previously submitted PVP addressed some of the known safety concerns for the class of IgIV products, such as hemolysis and thrombosis, as well as potential safety concerns specific to Asceniv™, such as off-label use and use in underrepresented populations.<sup>6</sup> ADMA has addressed the risk of thrombosis and renal insufficiency in a boxed warning, and in sections 5.1 and 5.3 of the label. This is a class warning. DE agrees with the boxed warning.

Should the product be approved, potential safety issues may be monitored with routine pharmacovigilance. The available data do not indicate that a required post-marketing study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS) are warranted at this time.

In the previous PVP review, OBE/DE noted potential safety concerns which could result from the amount of the excipient PS80 in the final formulation of Asceniv™, the most important of which is hypotension. In the first-cycle review, ADMA agreed to a PMC (ADMA-005) to evaluate these safety concerns; however, in the interval between that review and the current review, evaluation of available relevant safety data for Bivigam® has been reassuring. Taken together with the lack of evidence of clinically significant hypotension in the Asceniv safety database, DE's opinion is that a PMC is not needed.

Finally, as part of routine pharmacovigilance, FDA regulations require Periodic Adverse Experience Reports (PAERs) to contain a narrative summary and analysis of the information in the report and an analysis of the 15-day alert reports submitted during the reporting interval (21CFR 600.80(c)(2)). As part of this reporting, DE will require ADMA to also include a summary and assessment of any adverse event reports for hypotension in the narrative summary in submitted PAERs.

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<sup>5</sup> 1.16.1 Risk Management [RI-002, ADMA Biologics, Inc.]eCTD 125590/0

<sup>6</sup> Chege RI002 PVP Review (b) (4)