

From: Do, Yu
To: ["James Maloney"](#)
Subject: URGENT Information Request (Response Due by Friday, March 22, 2019): Class 2 Resubmission, BL 125590/0, Immune Globulin Intravenous (Human), 10% Liquid, ADMA Biologics, Inc.
Date: Thursday, March 21, 2019 10:13:00 AM
Attachments: [image001.png](#)
[FDA Annotated ADMA PI March 20 2019 BL 125590 FINAL.docx](#)
Importance: High

Dear Mr. Maloney:

We are reviewing your resubmission of September 28, 2018, to BL 125590/0 for Immune Globulin Intravenous (Human), 10% Liquid. We have the following comment and request for additional information to continue our review:

Please revise the Prescribing Information according to the attached annotated version of the labeling and as follows. Please accept all those tracked changes with which you agree, but insert your own comments where further discussion is warranted. Please indicate clearly, point by point, whether you would accept each change or not. If not, please provide briefly your rationale or justification. Also, please be sure to submit in your response both clean and annotated versions of the revised labeling in Word and PDF files.

Our general comments/recommendations are stated below, while more specific changes are proposed within the text of the Prescribing Information.

Please note FDA will have additional comments, including update of the proper name to include a suffix, based on review of the revised labeling included in your response.

GENERAL

- The lower-case, stylized registered trademark of this product is not its proprietary name. The proprietary name, **ASCENIV**, should appear in upper-case letters, as it does in most SPL stylesheets. For consistency, please capitalize the proprietary name throughout the **FULL PRESCRIBING INFORMATION (FPI)**.
- The product proprietary and proper names, dosage form, and route of administration constitute the "product title" (see guidance for industry *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format*). The proprietary and proper names appear on one line (although it can continue to another line for lengthy names), and the dosage form and the route of administration usually appear on a second line in the two-column format of the **HIGHLIGHTS**. The data standard for the dosage form of this product is: injection, for intravenous use. However, *intravenous* is in the proper name. The solution strength is a modifier of the proper name, and there is precedent to its use in the product title for immune globulin solutions.

Thus, the product title for intravenous immune globulin products, such as ASCENIV, would be:

ASCENIV (immune globulin intravenous, human - xxxx), 10% solution

- Use bold headings only when required by the regulations. Underlining or italics can be used alternatively.
- When using an acronym, spell it out at the start of each labeling section. Each section must be able to stand on its own because sections can be commuted in different SPL stylesheets.
- Avoid vague terms such as ‘severe’ that do not have established definitions.
- To improve comprehension and readability, use active voice wherever possible.
- Please ensure that the SPL file (also from 2016) is updated with the approval of this product.

BOXED WARNING

The heading in the **BOXED WARNING** in the **HIGHLIGHTS** (WARNING: ACUTE RENAL DYSFUNCTION AND FAILURE) is not consistent with that found in the **FULL PRESCRIBING INFORMATION** (WARNING: THROMBOSIS, ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE). This warning is used in the intravenous immune globulin drug class. Please revise for consistency.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Revise the indications statement to the regulatory language, including the product class, as follows:

ASCENIV (immune globulin intravenous, human – xxxx) is a 10% immune globulin solution for intravenous injection indicated for the treatment of primary immunodeficiency.

DOSAGE AND ADMINISTRATION

Revise the route of administration statement to sentence case: **For intravenous use only.**

WARNINGS AND PRECAUTIONS

- **WARNINGS AND PRECAUTIONS** in the **HIGHLIGHTS** should summarize information in the FULL PRESCRIBING INFORMATION. These summaries should be shortened, if necessary, to keep the HIGHLIGHTS to its half-page limit (excluding BOXED WARNING).
- Verify that the **WARNINGS AND PRECAUTIONS** are listed in a manner consistent with the product class, and in the order of severity and public health significance. For example:
 - Hypersensitivity and anaphylactic reactions may occur. IgA deficient patients with

- antibodies against IgA are at greater risk of developing severe reactions. (4, 5.1)
 - Thrombosis may occur. Administer ASCENIV at minimum dose and infusion rate practicable. (5.2)
 - Monitor for renal function in patients at risk for renal failure. (5.3)
 - Aseptic Meningitis Syndrome (AMS) may occur within two days of treatment. (5.4)
 - Hemolysis can develop. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia. (5.5)
 - Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.6)
 - ASCENIV is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.7)
 - Passive transfer of antibodies may confound serologic testing. (5.8)*
- We note that passive transfer of antibodies (a class precaution) is missing from the current WARNINGS AND PRECAUTIONS section of ASCENIV. While this is in the ASCENIV DRUG INTERACTIONS section, it also appears in this section in other class labels. Please add it to this label.

ADVERSE REACTIONS

The proposed labeling contains the following uninformative phrase, “adverse drug reaction,” (emphasis added):

The most common adverse reactions to ASCENIV (reported in = 5% of clinical study subjects were headache, *adverse drug reaction*, myalgia, and pruritus.

Adverse drug reaction is a high-level MedDRA *preferred term* (MedDRA version 16.0) that refers to a set of symptoms. The regulatory requirement for this section is to list the symptoms (see also the comment below for Table 2 in 6 ADVERSE REACTIONS). Please revise.

USE IN SPECIFIC POPULATIONS

- Delete the bullet regarding pregnancy. The absence of information is not reported in the HIGHLIGHTS for specific populations.
- Geriatric Use will not need bulleting if it is the only concept, as bullets are reserved for more than one item.

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure that the **FULL PRESCRIBING INFORMATION: CONTENTS** aligns with the sections and subsections of the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION (FPI)

1 INDICATIONS AND USAGE

Do not subsection this section. There only is one indication.

2 DOSAGE AND ADMINISTRATION

- Revise the route of administration statement to sentence case: **For intravenous use only.**
- This section has reduced readability and comprehension because of wordy paragraphs mixed with practice of medicine. Also, dose and administration concepts are tightly together in this product class. Therefore, consider revising the dose subsection with a table combining dose and administration (similar to HIGHLIGHTS). For example:

DOSE	RATE	MAINTENANCE
300 to 800 mg/kg body weight every 3 to 4 weeks based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min) for 30 minutes	Increase every 15 minutes (if tolerated) up to 5 mL/kg/hr (8 mg/kg/min) to achieve desired trough level

Consider placing the table first to enhance readability.

2.1 Dose

2.2 Preparation and Handling

- In the current subsection 2.1, the third bullet belongs in **16 HOW SUPPLIED/STORAGE AND HANDLING.**

4 CONTRAINDICATIONS

Starting both bullets of this parallel list with the phrase, “ASCENIV is contraindicated in,” distracts the reader from the contraindication, thus minimizing the readability of the actual risk. Parallel lists should start beneath such a phrase or the phrase may be omitted. For example:

ASCENIV is contraindicated in:

- patients who have had an anaphylactic or severe systemic reaction to prior administration of human immune globulin.
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

- Warnings and precautions in this section must be listed in decreasing order of severity and public health significance.
- Revise this section to the class warnings and precautions.

6 ADVERSE REACTIONS

- Place the most common adverse reactions, with a cutoff frequency, directly beneath this heading. This should include the same common adverse reactions that appear in the HIGHLIGHTS). However, there are others listed in this FPI statement. Please reconcile.
- *Adverse drug reaction* is a high-level MedDRA *preferred term* (MedDRA version 16.0) that refers to a set of symptoms. The regulatory requirement for this section is to list the symptoms.
- Use international English spellings; for example, replace diarrhoea with diarrhea.
- In Table 2, round percentages for a number of subject to the nearest whole number. There is not statistical significance, so support percentages expressed as decimals.
- Identify the serious adverse reactions suffered by two subjects. If “neither of these were related serious ARs,” then they are not adverse reactions by regulatory definition and should not be included in the Prescribing Information.
- Identify the serious adverse reactions that caused two subjects to withdraw from the study.
- The paragraph beginning with, “No cases of transmission of viral diseases, vCJD or CJD, have been associated with the use of ASCENIV....” is a promotional statement that minimizes the warning that this may occur with the use of the ASCENIV. Adverse reactions observed or not observed in a given clinical trial may not reflect what happens when the product is broadly used in clinical practice. Delete this paragraph.
- **6.2 Postmarketing Experience** focuses on domestic and foreign spontaneous reports that are not addressed anywhere else in the risk information of the FPI. Therefore, TRALI, hypoxemia, pulmonary edema, hemolysis, and positive direct antiglobulin (Coombs’) test should be deleted from this section.

7 USE IN SPECIFIC POPULATIONS

Revise this section to be consistent with the guidance for industry *Pregnancy, Lactation and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

8.1 Pregnancy

- Pregnancy category is no longer used because it is not informative. Similarly, the statement “ASCENIV should be given to a pregnant woman only if clearly needed,” is not informative.
- When a product is systemically absorbed, this section must have a Risk Summary that

includes information about the background risk of major birth defects and miscarriage in the

U.S. general population, regardless of product exposure (§ 201.57(c)(9)(i)(B)), in order to establish a basis for comparison. The most reliable, stable U.S. data on the prevalence of birth defects come from the Centers for Disease Control and Prevention (CDC) birth defects surveillance programs, and the rates for miscarriage are based on published data. If information on birth defects and miscarriage is available, it also must be included (§201.57(c)(9)(i)(B)).

8.2 Lactation

- Delete this sentence as it is not informative: *ASCENIV should be given to nursing mothers only if clearly needed.*
- This subsection also requires a Risk Summary. Clinical lactation data may come from published literature or lactation databases. If only animal lactation data are available, the Risk Summary must state only whether or not the drug and/or its active metabolite(s) were detected in animal milk and specify the animal species (§ 201.57(c)(9)(ii)(A)(2)(i)), with a cross- reference to the Data portion of **8.2 Lactation** (§201.57(c)(9)(ii)(A)), where the data are fully described (§ 201.57(c)(9)(ii)(C)). Due to species-specific differences in lactation physiology, animal lactation data typically do not reliably predict levels in human milk; however, animal lactation data can be helpful in predicting whether a drug and/or its active metabolite(s) will be present in human milk.

8.5 Geriatric Use

Revise this subsection to the required regulatory language for instances where there are little or no data on geriatric patients:

Clinical studies of ASCENIV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

11 DESCRIPTION

- The fact that the product is preservative-free, as well as the fact that the product container and packaging are not manufactured with natural rubber latex, often is included in this section, but the language describing latex content needs to follow the labeling recommendations in the FDA Guidance on Natural Rubber Latex.

12 CLINICAL PHARMACOLOGY

(See Draft guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*)

Revise required subsection titles and content for 12.1, 12.2, and 12.3 as follows:

12.1 Mechanism of Action (Required)

12.2 Pharmacodynamics (Required)

12.3 Pharmacokinetics (Required)

- Subsection 12.2 Pharmacodynamics was omitted; however, this subsection is required. This subsection describes biochemical or physiological pharmacologic effects of the product or active metabolites, with respect to clinical effect, adverse reactions, or toxicity.
- Avoid the terms such as “Phase 3” and “pivotal” in the previously described 12.2 Pharmacokinetics subsection. These terms are not easily defined, vague or promotional in tone. Instead, describe as a major effectiveness study.

13 NONCLINICAL TOXICOLOGY

Subsection 13.2 is not required when there are no data.

14 CLINICAL STUDIES

- Do not subsection this section when there is only one study.
- Further describe the study population in terms of ethnicity (See 21 CFR 201.57 (c)(15)).

16 HOW SUPPLIED/STORAGE AND HANDLING

- Extra section headings in an otherwise small section reduces readability. Bullets that focus attention to the same concept will increase readability in this section.
- Several sentences and phrases in this section are redundant. Please edit.
- Use active voice.
- Do not use the term “latex-free.”
- The subsection entitled “Incompatibilities” presents information that belongs in DOSAGE AND ADMINISTRATION rather than HOW SUPPLIED/STORAGE AND HANDLING.

17 PATIENT COUNSELING INFORMATION

This section is intended to be a checklist for the practitioner to discuss with the patient. Do not subsection this section, as it is cumbersome and reduces readability. Furthermore, subsections may be deleted in some SPL stylesheets. Consider revising this section as follows:

Instruct patients taking ASCENIV to immediately report symptoms of:

- *Thrombosis* which includes pain and/or swelling of an arm or legs/feet with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, acute chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body (see *Warning and Precaution [5.2]*).
- *Acute Renal Dysfunction and Acute Renal Failure* which includes decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath. Such symptoms may suggest kidney damage (see *Boxed Warning, Warnings and Precautions [5.3]*).
- *Aseptic Meningitis Syndrome (AMS)* which includes severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting (see *Warnings and Precautions [5.4]*).
- *Hemolysis* which includes fatigue, increased heart rate, yellowing of skin or eyes, dark- colored urine (see *Warnings and Precautions [5.5]*).
- *Transfusion-Related Acute Lung Injury (TRALI)* which includes trouble breathing, chest pain, blue lips or extremities, fever (see *Warnings and Precautions [5.6]*)

Inform patients that ASCENIV:

- Is made from human plasma and may contain infectious agents that can cause disease. While the risk that ASCENIV can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, patients should report any symptoms that concern them (see *Description [11] and Warnings and Precautions [5.7]*).
- Can interfere with their immune response to live viral vaccines (e.g., measles, mumps, rubella, and varicella), and instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations (see *Drug Interactions [7]*).

CONTAINER AND PACKAGE LABEL

- The Expiration Date and Lot Number are missing from the package label.

The review of this submission is ongoing, and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file (BL 125590/0) by Friday, March 22, 2019, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is April 2, 2019.

Please acknowledge receipt of this request and contact me at (240) 402-8343 or Yu.Do@fda.hhs.gov if you have any questions.

Sincerely,

Yu Do, M.S.
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