ASCENIV™
IMMUNE GLOBULIN INTRAVENOUS (HUMAN) – slra 10% LIQUID

ASCENIV GUIDE TO BILLING AND REIMBURSEMENT

Please see Important Safety Information on pages 15-16 and refer to the accompanying full Prescribing Information, including Boxed WARNING, for ASCENIV.

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Please see Important Safety Information on pages 15-16 and accompanying full Prescribing Information, including Boxed WARNING.

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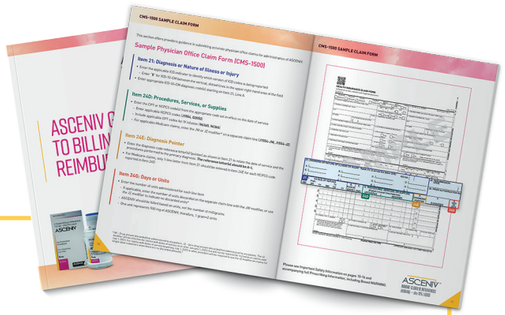

Introduction

ADMA Biologics has developed this Guide to Billing and Reimbursement to help assist healthcare providers in understanding third-party payment for ASCENIV, and to **provide you with general coding information and claims submission details for ASCENIV**. ADMA is committed to providing billing and coding information for the following FDA-approved indication:

ASCENIV (immune globulin intravenous, human-slra) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age).

PLEASE NOTE: The information contained in this guide is provided for informational purposes only. Providers are encouraged to contact their payers for specific information. Coding rules and guidelines are subject to payer discretion and should always be verified by the paying entity. Healthcare providers make the ultimate determination as to when to use a specific product, based on clinical appropriateness for a particular patient. This guide is not intended to provide specific guidance on how to utilize, code, bill, or charge for any product or service. Third-party payment for medical products and services is affected by numerous factors and ADMA Biologics cannot guarantee success in obtaining insurance payments.

This section describes the types of codes that are likely to be most relevant to claims for ASCENIV. ASCENIV is a solution for infusion to be administered intravenously (IV) in an infusion center, physician's office, or at home by a trained healthcare provider.

International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes[1]

ICD-10-CM diagnosis codes are used for identifying and documenting a patient's specific diagnosis. These codes are used by all healthcare providers and are recognized by all insurers. Local coverage determinations and articles should be consulted for additional covered indications.

D69	Purpura and other hemorrhagic conditions
D69.3	Immune thrombocytopenia purpura *Hemorrhagic (thrombocytopenic) purpura* *Idiopathic thrombocytopenic purpura* *Tidal platelet dysgenesis*
D80	**Immunodeficiency with predominantly antibody defects**
D80.0*	Hereditary hypogammaglobulinemia *Autosomal recessive agammaglobulinemia (Swiss type)* *X-linked agammaglobulinemia [Bruton] (with growth hormone deficiency)*
D80.1	Nonfamilial hypogammaglobulinemia *Agammaglobulinemia with immunoglobulin-bearing B-lymphocytes* *Common variable agammaglobulinemia [CVAgamma]* *Hypogammaglobulinemia NOS*
D80.2*	Selective deficiency of immunoglobulin A [IgA]
D80.3*	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4*	Selective deficiency of immunoglobulin M [IgM]
D80.5*	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6*	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7*	Transient hypogammaglobulinemia of infancy
D80.8	Other immunodeficiencies with predominantly antibody defects *Kappa light chain deficiency*
D80.9	Immunodeficiency with predominantly antibody defects, unspecified

Table continues on the next page.

*Please Note: Medicare Part B-approved diagnosis codes for treatment with ASCENIV in the home. All other diagnoses may qualify for coverage under Medicare Part D plans.[2]

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ICD-10-CM Diagnosis Codes[1] (continued)

D81	Combined immunodeficiencies
D81.0*	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1*	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2*	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.4	Nezelof's syndrome
D81.5*	Purine nucleoside phosphorylase [PNP] deficiency
D81.6*	Major histocompatibility complex class I deficiency *Bare lymphocyte syndrome*
D81.7*	Major histocompatibility complex class II deficiency
D81.82*	Activated Phosphoinositide 3-kinase Delta Syndrome [APDS]
D81.89*	Other combined immunodeficiencies
D81.9*	Combined immunodeficiencies, unspecified *Severe combined immunodeficiency disorder [SCID] NOS*
D82	**Immunodeficiency associated with major other defects**
D82.0*	Wiskott-Aldrich syndrome *Immunodeficiency with thrombocytopenia and eczema*
D82.1*	Di George's syndrome *Pharyngeal pouch syndrome* *Thymic alymphoplasia* *Thymic aplasia or hypoplasia with immunodeficiency*
D82.2	Immunodeficiency with short-limbed stature
D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus *X-linked lymphoproliferative disease*
D82.4*	Hyperimmunoglobulin E [IgE] syndrome
D82.8	Immunodeficiency associated with other specified major defects
D82.9	Immunodeficiency associated with major defect, unspecified

Table continues on the next page.

*Please Note: Medicare Part B-approved diagnosis codes for treatment with ASCENIV in the home. All other diagnoses may qualify for coverage under Medicare Part D plans.[2]

BILLING AND REIMBURSEMENT FOR ASCENIV

ICD-10-CM Diagnosis Codes[1] (continued)

D83	Common variable immunodeficiency
D83.0*	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1*	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2*	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8*	Other common variable immunodeficiencies
D83.9*	Common variable immunodeficiency, unspecified
D84	**Other immunodeficiencies**
D84.9	Immunodeficiency, unspecified *Immunocompromised NOS* *Immunodeficient NOS* *Immunosuppressed NOS*
G11	**Hereditary ataxia**
G11.3*	Cerebellar ataxia with defective DNA repair *Ataxia telangiectasia [Louis-Bar]*
G61	**Inflammatory polyneuropathy**
G61.81	Chronic inflammatory demyelinating polyneuritis

*Please Note: Medicare Part B-approved diagnosis codes for treatment with ASCENIV in the home. All other diagnoses may qualify for coverage under Medicare Part D plans.[2]

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Healthcare Common Procedure Coding System (HCPCS) Code[3]

HCPCS codes are used for billing drugs and services to Medicare, Medicaid, and Commercial payers. The HCPCS description for ASCENIV specifies that each billing unit is the equivalent of 500 mg. Therefore, each gram of ASCENIV represents 2 billable units. **For example**, if 30 grams of ASCENIV are administered, 60 units should be billed on the claim form.

The HCPCS J1554 code for ASCENIV is listed by CMS and Medicare Part B Administration Contractors in their National Drug Code (NDC) files.

Code	Description
J1554	Injection, immune globulin (ASCENIV), 500 mg
Additional information required by most payers on claim forms:	• Branded/generic name • Strength • Dosage administered • Route of administration • National Drug Code (NDC)
Some payers may also request:	• Package insert/Prescribing information • Drug purchase invoice • Documentation to support medical necessity (eg, Letter/Statement of Medical Necessity)

ASCENIV National Drug Codes (NDCs)

An NDC is a universal, unique, 3-segment number identifying drugs by manufacturer, dosage, and package size. NDCs are used for billing drugs and biologicals.

Billing NDC	Inner package NDC	Concentration
69800-0250-01	**69800-0250-02**	5 g/50 mL

Current Procedural Terminology (CPT®)* Codes[4]

CPT codes describe the medical, surgical, diagnostic, and therapeutic services and procedures.

Code	Description
96365	IV infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	IV infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (list separately in addition to code for primary procedure)

BILLING AND REIMBURSEMENT FOR ASCENIV

Codes for Home Specialty Pharmacies and Home Infusion Providers

Home Infusion Therapy[3]

HCPCS per diem S-codes are used by commercial payers and Medicaid to report drugs, services, and supplies. These codes are not payable by Medicare.

Code	Description
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

Permanent IVIG In-Home Coverage—Effective January 1, 2024[3,5]

Congress enacted the Consolidated Appropriations Act of 2023, which made the previous IVIG Demonstration for IVIG in-home coverage now a permanent benefit, with no need for patients or eligible suppliers to enroll in the Demonstration. Effective January 1, 2024, the Act provides for a permanent, bundled payment for items and services related to administration of IVIG in the home of a patient with a diagnosis of Primary Immune Deficiency Disease (PIDD). Payment covers cost of nursing services and supplies, including an infusion set and tubing, for the provision of IVIG administration in the home by a durable medical equipment supplier, per visit.

To qualify, providers must complete the claims procedurally and indicate both the drug J code for ASCENIV ["J1554 (Injection, immune globulin (ASCENIV), 500 mg)"] and the bundle code Q2052 ("Q2052 - Services, supplies, and accessories used in the home under Medicare Intravenous immune globulin (IVIG) demonstration"). Q2052 does not have to be included on same claim as the allowable J code. Providers should report visit length in 15-minute increments (15 minutes=1 unit) when billing for IVIG (Q2052). Claims may be denied if one of the allowable drug J codes is not on the same claim.

Code	Description
Q2052	Services, supplies and accessories used in the home under the Medicare IVIG demonstration

Codes are subject to change.

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CMS-1500 SAMPLE CLAIM FORM

This section offers providers guidance in submitting accurate physician office claims for administration of ASCENIV.

Sample Physician Office Claim Form (CMS-1500)

Item 21: Diagnosis or Nature of Illness or Injury

- Enter the applicable ICD indicator to identify which version of ICD codes is being reported
  - Enter "**0**" for ICD-10-CM between the vertical, dotted lines in the upper right-hand area of the field
- Enter appropriate ICD-10-CM diagnosis code(s) starting on Item 21, Line A

Item 24D: Procedures, Services, or Supplies

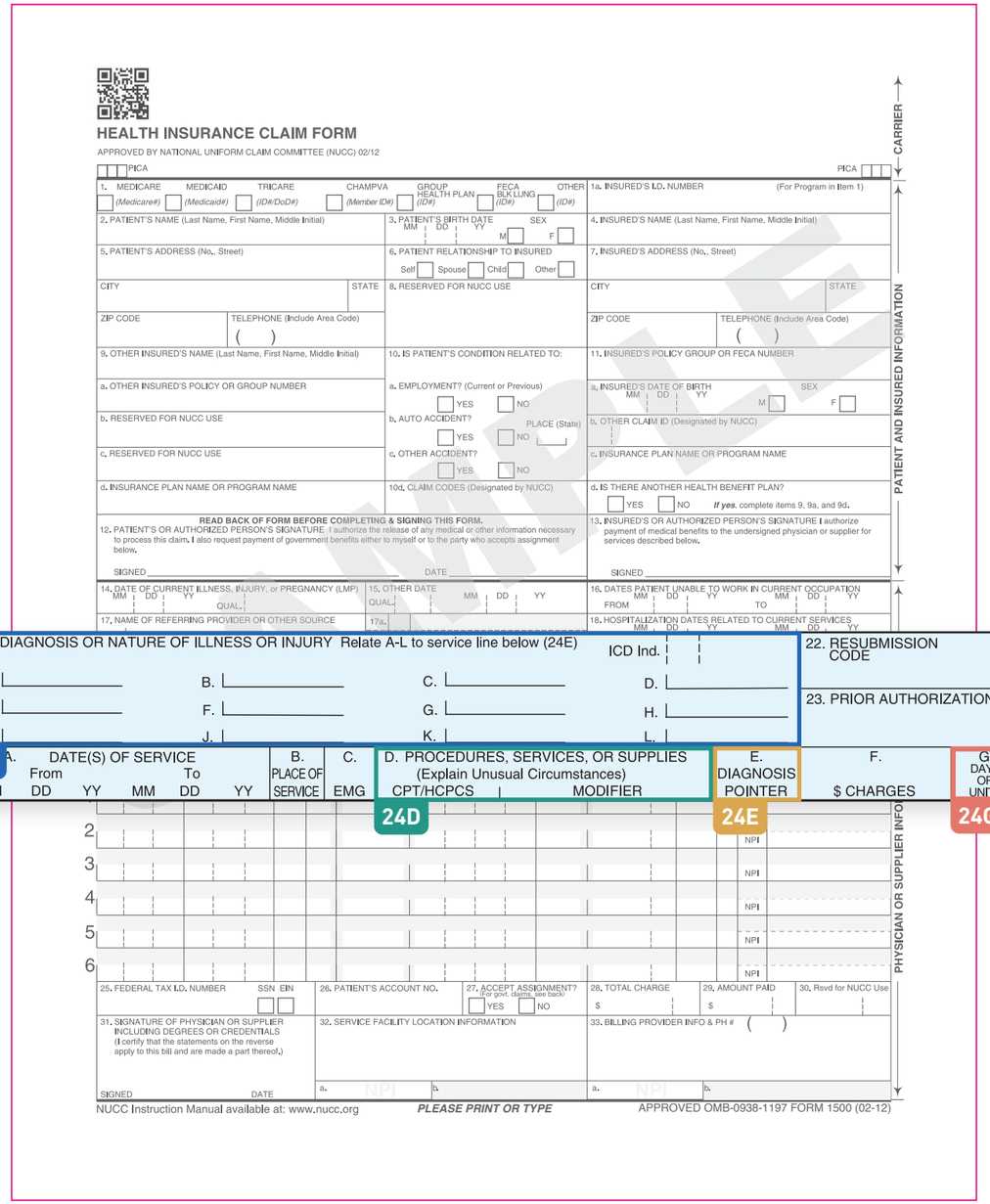
- Enter the CPT or HCPCS code(s) from the appropriate code set in effect on the date of service
  - Enter applicable HCPCS codes (**J1554**, **Q2052**)
  - Include applicable CPT codes for IV infusion (**96365**, **96366**)
  - For applicable Medicare claims, enter the JW or JZ modifier* on a separate claim line (**J1554-JW, J1554-JZ**)

Item 24E: Diagnosis Pointer

- Enter the diagnosis code reference letter(s) (pointer) as shown in Item 21 to relate the date of service and the procedures performed to the primary diagnosis. **The reference letter(s) should be A–L**
- For Medicare claims, only 1-line letter from Item 21 should be entered in Item 24E for each HCPCS code reported in Item 24D

Item 24G: Days or Units

- Enter the number of units administered for each line item
  - If applicable, enter the number of units discarded on the separate claim line with the JW modifier, or use the JZ modifier to indicate no discarded units*
  - ASCENIV should be billed based on units, not the number of milligrams
  - One unit represents 500 mg of ASCENIV, therefore, 1 gram=2 units



*JW – Drug amount discarded/not administered to any patient. JZ – Zero drug amount discarded/not administered to any patient. The JZ modifier will be effective for claims with dates of service on or after January 1, 2023, but will not be required for inclusion on claims until July 1, 2023. For claims with dates of service beginning July 1, 2023 or after, providers will be required to use the JZ modifier on claims for single-dose containers when there are no discarded amounts.[6]

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Submitting claims when the billed amount exceeds $99,999.99

One general rule pertaining to an 837P (Part B (DME) electronic claim) transaction is the maximum number of characters submitted in any dollar amount field is **seven characters**. Claims containing a dollar amount more than $99,999.99 will be rejected.[7]

The Health Care Claim: Professional (837P)* can be found on the CEDI - Technical Specifications website and contains information regarding the X12 837 Professional claim format including Medicare specific information and requirements. This is intended to be used in addition to the other X12 837P reference documents. This document clarifies and specifies data content when exchanging transactions electronically with Medicare.

PLEASE NOTE: The information contained in this guide is provided for informational purposes only. Every Medicare Administrative Contractor (MAC) is different and outlines how they require claims to be processed. Providers are encouraged to contact their local (MAC) for additional information on how to properly file claims that are over the $99,999.99.

Example

Claims for services that exceed this amount will have to be submitted on separate claims as follows:

Claim 1

- Submit the service with an acceptable dollar amount (< 9999999.) See example below, splitting total. **(Do not use dollar signs, decimals, dashes, commas for dollar amounts.)**
- In the narrative field, identify this as, "Claim 1 of 2; Dollar amount exceeds charge line amount."

Claim 2

- Enter the charge as the remaining dollar amount from the total split.
- In the narrative field, identify this as, "Claim 2 of 2; Remaining dollar amount from Claim 1 amount exceeds charge line amount."

You must note in the narrative the reason why the claim is split this way. It will deny as a duplicate without the narrative.

Narrative must be added in loop 2400 (line note), segment NTE02 (NTE01=ADD) of the ANSI X12N, version 5010A1 professional electronic claim format or on Item 19 of the paper claim form in the narrative field

Also, when splitting the charge of the service, be sure the **dollar amounts are slightly different**, as this will prevent the system from assuming the two claims are an exact duplicate.

- **Example**: If the charge for a service is $100,000.00, submit the charge on Claim 1 as 5200000; on Claim 2 submit the charge as 4800000. Ensure the narrative is added as above. (Do not use dollar signs, decimals, dashes, commas for dollar amounts.)

*Centers for Medicare & Medicaid Services (CMS) Standard Companion Guide Health Care Claim Professional (837P).

Simplify access to ASCENIV for your patients

When you have decided ASCENIV is appropriate for your patient, ADvantage Ig may help your patients with understanding their coverage and potential for financial support

Comprehensive Support for Your Practice

- Answers to general questions
- Materials fulfillment
- Requests for information

ADMA ADvantage Ig™ PATIENT SUPPORT PROGRAM

Financial Assistance for Your Patients

- Educates your patients about their insurance benefits
- Helps patients navigate their assistance options so they can pay the lowest amount possible
- Provides patients with assistance in locating alternative funding and other payment options such as nonprofit patient assistance foundations

Prescription Triage

- Triages IVIG prescriptions to appropriate site of care when needed
- Notifies requester of referral
- Coordinates delivery with patient, payer, and provider
- Follows up with specialty pharmacy to ensure processing

Coverage and Reimbursement Support

- Insurance benefits verification, determination of patient coverage, cost-share responsibility, prior authorization (PA) & predetermination requirement
- Assistance with PA requests, including sample letter of medical necessity and payer-specific PA form
- Assistance with coding and claims support, including appeals process overviews and facilitation

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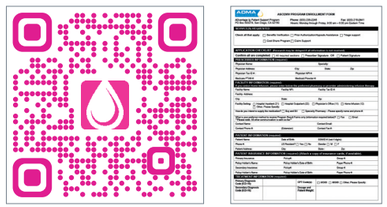
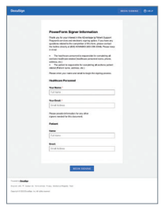
Enroll your patients in ADMA ADvantage Ig™ for support

Scan QR code below for PDF Option



Scan QR code below for DocuSign Option



For Benefits Verification and guidance on Prior Authorization, Medical Exception, and Appeals, please contact us:

1-833-ADMA-BIO (1-833-236-2246) • Monday-Friday • 9 AM to 6 PM ET

Requests received by 2 PM ET are typically completed the same day.

Summary of eligibility requirements

- Patient must be a US resident
- Must have private commercial insurance
- IVIG treatment must be covered by insurance
- The ADvantage Ig Patient Support Program provides deductible, copay or coinsurance and administration support only for IVIG products from ADMA Biologics
- Program covers up to a fixed amount of out-of-pocket costs per calendar year for eligible patients, after the patient has paid the first $75 of their required deductible, copay or coinsurance and administration amount. The program will pay the amount covered by the payer's allowed amount as indicated on the explanation of benefits (EOB)
- The Program does not cover office/facility copays not directly associated with IGIV treatment or any other costs excluded by the Program guidelines not specifically mentioned here, which are subject to change

Terms and Conditions

This offer is valid only in the United States. Patient must be prescribed an IVIG product manufactured by ADMA Biologics, Inc. and prescribed by a licensed practitioner. Eligible patients must have private commercial insurance that covers medication costs for these products, and acceptance of this offer must be consistent with the terms of that insurer's drug benefit. Patients who pay cash or who are enrolled in or participate in any type of government insurance or reimbursement programs, including but not limited to Medicare, Medicare Advantage, Medicare Part D, Medicaid, Medigap, TRICARE, Veterans Affairs (VA), the Department of Defense (DoD) or other federally funded or state funded healthcare programs, are not eligible. Patients who move from commercial to federally funded or state-funded insurance will no longer be eligible for the program. Proof required for receiving payment for out-of-pocket drug costs must be a valid Explanation of Benefits (EOB) or specialty pharmacy invoice, which must be submitted within 120 days after each treatment. As a condition precedent of the cost share support provided under this program, e.g., copay or coinsurance amounts paid to administering providers, participating patients and administering providers are obligated to inform insurance companies and third-party payers of any benefits they receive and the value of this program, as required by contract or otherwise. Patient/Guardian may not seek reimbursement for value received from the Cost Share Program from any third-party payers, including flexible spending accounts or healthcare savings accounts.

Void where prohibited by law, taxed, or restricted. Additional terms and conditions may apply. ADMA Biologics, Inc. may determine eligibility, monitor participation, and modify or discontinue any aspect of this program at any time.

Indication

ASCENIV™ (immune globulin intravenous, human – slra) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age). PI includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).

Important Safety Information for ASCENIV

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin (IGIV) products, including ASCENIV. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of IGIV products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. ASCENIV does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer ASCENIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

Contraindications

ASCENIV is contraindicated in:

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

Warnings and Precautions

Severe hypersensitivity reactions may occur with IGIV products, including ASCENIV. In case of hypersensitivity, discontinue ASCENIV infusion immediately and institute appropriate treatment. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.

Thrombosis may occur following treatment with immunoglobulin products and in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity and ensure adequate hydration before administration. For patients at risk of thrombosis, administer ASCENIV at the minimum dose and infusion rate practicable. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering ASCENIV. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of ASCENIV and at appropriate intervals thereafter. Discontinue ASCENIV if renal function deteriorates. In at-risk patients, administer ASCENIV at the minimum infusion rate practicable.

Hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia may occur in patients receiving IGIV treatment, including ASCENIV. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia. Treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.

Please see additional Important Safety Information on back cover and accompanying full Prescribing Information, including Boxed WARNING.

Important Safety Information for ASCENIV (cont'd)

Warnings and Precautions (cont'd)

Aseptic meningitis syndrome (AMS) may occur with IGIV treatments, including ASCENIV. AMS usually begins within several hours to 2 days following IGIV treatment. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. Conduct a thorough neurological examination on patients exhibiting signs and symptoms of AMS, including cerebrospinal fluid (CSF) studies, to rule out other causes of meningitis.

IGIV products, including ASCENIV, may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis. Monitor patients for clinical signs and symptoms of hemolysis, including appropriate confirmatory laboratory testing.

Noncardiogenic pulmonary edema may occur with IV administered IG. Monitor patients for pulmonary adverse reactions. If suspected, perform appropriate tests for presence of anti-neutrophil in both product and patient serum. May be managed using oxygen therapy with adequate ventilatory support.

Because ASCENIV is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections suspected by a physician to possibly have been transmitted by this product should be reported to ADMA Biologics at **(1-800-458-4244).**

After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

Adverse Reactions

The most common adverse reactions to ASCENIV (≥5% of study subjects) were headache, sinusitis, diarrhea, gastroenteritis viral, nasopharyngitis, upper respiratory tract infection, bronchitis, and nausea.

You are encouraged to report side effects of prescription drugs to ADMA Biologics at 1-800-458-4244 or the FDA. Visit www.fda.gov/MedWatch or call 1-800-FDA-1088.

References: 1. National Center for Health Statistics. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM): 2024 Codes Tables and Index. Accessed September 18, 2023. https://www.cdc.gov/nchs/icd/Comprehensive-Listing-of-ICD-10-CM-Files.htm **2.** Centers for Medicare and Medicaid Services. Billing and coding: immune globulin intravenous (IVIg). Accessed September 15, 2023. Article - Billing and Coding: Immune Globulin Intravenous (IVIg) (A57187) (cms.gov) **3.** Centers for Medicare and Medicaid Services. MLN Fact Sheet. Intravenous Immune Globulin Demonstration. MLN3191598 November 2023. Accessed February 19, 2024. MLN3191598-intravenous-immune-globulin-demonstration (Demonstration Ends on December 31, 2023) (cms.gov) **4.** Centers for Medicare and Medicaid Services. CHAPTER XI MEDICINE EVALUATION AND MANAGEMENT SERVICES CPT CODES 90000 - 99999 FOR NATIONAL CORRECT CODING INITIATIVE POLICY MANUAL FOR MEDICARE SERVICES. Accessed September 19, 2023. https://www.cms.gov/files/document/chapter11cptcodes90000-99999final11.pdf **5.** Centers for Medicare and Medicaid Services. CMS Manual System, Pub 100-02 Medicare Benefit Policy. November 8, 2023. Accessed February 19, 2024. r12352bp.pdf (cms.gov) **6.** Centers for Medicare and Medicaid Services. Billing and Coding: JW and JZ Modifier Billing Guidelines. Accessed September 18, 2023. Article - Billing and Coding: JW and JZ Modifier Billing Guidelines (A55932) (cms.gov) **7.** Noridian Healthcare Solutions Medicare Administrative Contractor (MAC): Accessed September 18, 2023. Submitting Claims When the Billed Amount Exceeds $99,999.99 - JD DME - Noridian (noridianmedicare.com)

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ASCENIV™
IMMUNE GLOBULIN INTRAVENOUS (HUMAN) – slra 10% LIQUID

ADMA BIOLOGICS

10910-22-IGG-11172023_R00

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ASCENIV™ safely and effectively. See full prescribing information for ASCENIV.

ASCENIV (immune globulin intravenous, human – slra)
10% Liquid
Initial U.S. Approval: 2019

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin intravenous (IGIV) products, including ASCENIV. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of IGIV products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. ASCENIV does not contain sucrose. [5.3]**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer ASCENIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. [2.1, 2.3, 5.3]**

----------INDICATIONS AND USAGE----------
ASCENIV (immune globulin intravenous, human – slra) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age). [1]

----------DOSAGE AND ADMINISTRATION----------

For intravenous use only.

Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
300-800 mg/kg every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min) for the first 15 minutes	Increase gradually every 15 minutes (if tolerated) up to 8 mg/kg/min (0.08 mL/kg/min)

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue ASCENIV if renal function deteriorates. [5.3]
- For patients at risk of renal dysfunction or thrombotic events, administer ASCENIV at the minimum infusion rate practicable. [5.2, 5.3]

----------DOSAGE FORMS AND STRENGTHS----------
ASCENIV is a liquid solution containing 10% IgG (100 mg/mL) for intravenous infusion; (5g in 50 mL solution). [3]

----------CONTRAINDICATIONS----------
- History of anaphylactic or severe systemic reactions to human immunoglobulin. [4]
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. [4, 5.1]

----------WARNINGS AND PRECAUTIONS----------
- IgA-deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have medications such as epinephrine available to treat any acute severe hypersensitivity reactions. [4, 5.1]
- Thrombotic events have occurred in patients receiving IGIV treatments. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for patients at risk of hyperviscosity. [5.2, 5.4]
- In patients at risk of developing acute renal failure. monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output. [5.3, 5.9]
- Hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia can occur in patients receiving IGIV treatment. [5.4]
- Aseptic meningitis syndrome (AMS) has been reported with IGIV treatments, especially with high doses or rapid infusion. [5.5]
- Hemolytic anemia can develop subsequent to IGIV treatment. Monitor patients for hemolysis and hemolytic anemia. [5.6]
- Monitor patients for pulmonary adverse reactions (Transfusion-related acute lung injury [TRALI]). If transfusion-related acute lung injury is suspected, test the product and patient for antineutrophil antibodies. [5.7]
- Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. [5.8]

----------ADVERSE REACTIONS----------
The most common adverse reactions to ASCENIV (≥5% of study subjects) were headache, sinusitis, diarrhea, gastroenteritis viral, nasopharyngitis, upper respiratory tract infection, bronchitis, and nausea. [6]

To report SUSPECTED ADVERSE REACTIONS, contact ADMA Biologics at (1-800-458-4244) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, rubella, and varicella. [7]
- Passive transfer of antibodies may confound the results of serological testing. [5.10]

----------USE IN SPECIFIC POPULATIONS----------
Geriatric Use: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse ASCENIV at the minimum infusion rate practicable. [8.5]

See 17 for PATIENT COUNSELING INFORMATION

Issued: MM/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin (IGIV) products, including ASCENIV. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors (see *Warnings and Precautions [5.2], Patient Counseling Information [17]*).**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of IGIV products in predisposed patients..**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. ASCENIV does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer ASCENIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity (*see* *Dosage and Administration [2.1, 2.3], Warnings and Precautions [5.3]*).**

1 INDICATIONS AND USAGE

ASCENIV (immune globulin intravenous, human – slra) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age). PI includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).

2 DOSAGE AND ADMINISTRATION

2.1 Dose

The recommended dose of ASCENIV for replacement therapy in primary humoral immunodeficiency (PI) is 300 to 800 mg/kg body weight administered every 3 to 4 weeks. The dose may be adjusted over time to achieve the desired trough levels and clinical response.

ASCENIV dose adjustments may be required in patients who fail to maintain trough total IgG concentrations of at least 500 mg/dL with a target of 600 mg/dL. Starting with the second infusion, adjust the dose proportionally, targeting a trough of ≥ 600 mg/dL, based on the previous trough and the associated dose.

For intravenous use only.

Table 1

Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
300-800 mg/kg every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min) for the first 15 minutes	Increase gradually every 15 minutes (if tolerated) up to 8 mg/kg/min (0.08 mL/kg/min)

2.2 Preparation and Handling

- ASCENIV is a clear to opalescent, colorless to pale yellow solution. Inspect visually for particulate matter and discoloration prior to administration. Do not use if the liquid is cloudy or turbid, or if it contains visible particulate matter.
- Allow refrigerated product to come to room temperature before use and maintain ASCENIV at room temperature during administration.
- DO NOT MICROWAVE.
- DO NOT SHAKE.
- DO NOT MIX with other IGIV products or other intravenous medications.
- DO NOT DILUTE.
- ASCENIV contains no preservatives. Each vial is for single use only. Do not reuse or save for future use.
- If large doses are required, several vials may be pooled using aseptic technique into sterile infusion bags and infused.

2.3 Administration

Begin with an initial infusion rate of 0.5 mg/kg/min. If there are no adverse reactions, the infusion rate for subsequent infusions can be slowly increased to the maximum rate.

Monitor patient vital signs throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a slower rate which is comfortable for the patient.

Ensure that patients with pre-existing renal insufficiency are not volume-depleted. For patients judged to be at risk for renal dysfunction or thrombotic events, administer ASCENIV at the minimum infusion rate practicable, and consider discontinuation of administration if renal function deteriorates *(see Boxed Warning, Warnings and Precautions [5.2, 5.3]*).

3 DOSAGE FORMS AND STRENGTHS

ASCENIV is a liquid solution containing 10% IgG (100 mg/mL) for intravenous infusion.

4 CONTRAINDICATIONS

ASCENIV is contraindicated in:

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur with IGIV products, including ASCENIV. In case of hypersensitivity, discontinue ASCENIV infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for treatment of acute hypersensitivity reactions.

ASCENIV contains trace amounts of IgA (≤ 200 micrograms per milliliter) (*see Description [11]*). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. ASCENIV is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity reaction (*see Contraindications [4]*).

5.2 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including ASCENIV.[4,5,6] Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including patients with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer ASCENIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of

thrombosis and assess blood viscosity in patients at risk for hyperviscosity (see *Boxed Warning, Dosage and Administration [2], Patient Counseling Information [17]*).

5.3 Acute Renal Dysfunction and Acute Renal Failure
Acute renal dysfunction/failure, osmotic nephrosis, and death[1,2] may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering ASCENIV. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[2] Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of ASCENIV and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing ASCENIV *(see Patient Counseling Information [17]*). In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of >65 years), administer ASCENIV at the minimum infusion rate practicable (*see Dosage and Administration [2]*).

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia
Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV treatment, including ASCENIV. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.[3]

5.5 Aseptic Meningitis Syndrome (AMS)
AMS may occur with IGIV treatments, including ASCENIV. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[7,8,9]

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (*see Patient Counseling Information [17]*). Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

5.6 Hemolysis
IGIV products, including ASCENIV, may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis.[10,11,12] Delayed hemolytic anemia can develop subsequent to IGIV treatment due to enhanced RBC sequestration,[13] and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Monitor patients for clinical signs and symptoms of hemolysis (*see Patient Counseling Information [17]*). If these are present after ASCENIV infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating ongoing hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema may occur in patients following IGIV treatment,[14] including ASCENIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum (*see Patient Counseling Information [17]*).

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Transmissible Infectious Agents
Because ASCENIV is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to ADMA Biologics at **(1-800-458-4244)**. Before prescribing ASCENIV, the physician should discuss the risks and benefits of its use with the patient (*see Patient Counseling Information [17]*).

5.9 Monitoring Laboratory Tests
- Periodic monitoring of renal function and urine output is particularly important in patients at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of ASCENIV and at appropriate intervals thereafter.
- Because of the potentially increased risk of thrombosis with IGIV treatment, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of ASCENIV, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.10 Interference with Laboratory Tests
After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

The most common adverse reactions to ASCENIV (reported in ≥5% of clinical study subjects) were headache, sinusitis, diarrhea, gastroenteritis viral, nasopharyngitis, upper respiratory tract infection, bronchitis, and nausea.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.

In a multicenter, open-label, non-randomized clinical trial, 59 subjects with PI, on regular IGIV replacement therapy, received doses of ASCENIV ranging from 284 to 1008 mg/kg (mean dose 505 mg/kg) every 3 weeks or 4 weeks for up to 12 months (mean 346 days; range 36 to 385 days) (*see Clinical Studies [14]*). The use of pre-medication was discouraged; however, if after two infusions of ASCENIV subjects required pre-medication (antipyretic, antihistamine, or antiemetic agent) for recurrent reactions, they could continue those medications for the duration of the trial. Of the 793 infusions administered during this trial, only 7 (11.9%) subjects received premedication prior to 7 (0.9%) infusions.

Fifty-eight subjects (98%) had an adverse reaction during the study. The proportion of subjects who had at least one adverse reaction was similar for both the 3- and 4-week cycles. The most common adverse reactions observed in this clinical trial were headache (22 subjects, 37%), sinusitis (16 subjects, 27%), diarrhea (14 subjects, 23%), gastroenteritis viral (13 subjects, 22%), nasopharyngitis (13 subjects, 22%), upper respiratory tract infection (13 subjects, 22%), bronchitis (12 subjects, 20%), nausea (12 subjects, 20%), and acute sinusitis (11 subjects, 19%).

Adverse reactions (ARs) occurring during or within 72 hours after the end of an infusion are presented in Table 2. In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of ASCENIV infusions with one or more temporally associated adverse reactions was 16.4%. The total number of adverse reactions was 158 (a rate of 0.20 ARs per infusion).

Table 2: Adverse Reactions (ARs) (within 72 hours after the end of an ASCENIV infusion) in ≥ 5% of Subjects

Preferred Term (MedDRA v16.0)	Number (%) of Subjects (N=59)	Number (%) of Infusions (N=793)
Headache	14 (24)	21 (2.6)
Sinusitis	6 (10)	7 (0.9)
Nausea	5 (9)	5 (0.6)
Acute sinusitis	4 (7)	4 (0.5)
Fatigue	4 (7)	9 (1.1)
Muscle spasms	4 (7)	4 (0.5)
Bronchitis	3 (5)	3 (0.4)
Diarrhea	3 (5)	3 (0.4)
Nose Bleed	3 (5)	4 (0.5)
Muscle Pain	3 (5)	5 (0.6)
Oropharyngeal pain	3 (5)	3 (0.4)
Pain in extremity	3 (5)	3 (0.4)
Itching	3 (5)	3 (0.4)

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. The following adverse reactions have been identified and reported during the post-approval use of IGIV products:

- Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), cyanosis, dyspnea, bronchospasm.
- Cardiovascular: Cardiac arrest, vascular collapse, hypotension.
- Neurological: Coma, loss of consciousness, seizures, tremor.
- Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis.
- Hematologic: Pancytopenia, leukopenia,.
- General/Body as a Whole: Pyrexia, rigors.
- Gastrointestinal: Hepatic dysfunction, abdominal pain.

7 DRUG INTERACTIONS

Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response.[15,16] The immunizing physician should be informed of recent therapy with ASCENIV so that appropriate measures may be taken (see *Patient Counseling Information [17]*).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with ASCENIV. It is not known whether ASCENIV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively. ASCENIV should be given to pregnant women only if clearly needed.[17,18]

8.2 Lactation

Risk Summary

No human data are available to indicate the presence or absence drug-associated risk. The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for ASCENIV and any potential adverse effects on the breast-fed infant from ASCENIV or from the underlying maternal condition.

8.4 Pediatric Use

ASCENIV was evaluated in 11 pediatric subjects (6 children less than 12 years and 5 adolescents age 12 – 16 years) with primary humoral immunodeficiency (PI). The pharmacokinetic (PK), safety, and effectiveness profile of ASCENIV in adolescent subjects appeared to be comparable to that demonstrated in adult subjects. There are insufficient PK, safety, and effectiveness data from pediatric subjects younger than 12 years. Safety and effectiveness has not been studied in pediatric patients with PI who are under the age of 3 years (*see Clinical Studies [14]*).

8.5 Geriatric Use

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.

10 OVERDOSAGE

With intravenous administration, overdose may lead to fluid overload and hyperviscosity. Patients at risk of complications of fluid overload and hyperviscosity include elderly patients and those with cardiac or renal impairment.

11 DESCRIPTION

ASCENIV is a purified, sterile, ready-to-use preparation of concentrated human immunoglobulin G (IgG) antibodies. The product is a clear to opalescent liquid, which is colorless to pale yellow. The distribution of IgG subclasses is similar to that of normal plasma. The active ingredient is human immunoglobulin purified from source human plasma and processed using a modified classical Cohn Method 6 / Oncley Method 9 fractionation procedure. ASCENIV contains 100 ± 10 mg/mL protein, of which not less than 96% is human immunoglobulin obtained from source human plasma. It is formulated in water for injection containing 0.100-0.140 M sodium chloride, 0.20-0.29 M glycine, 0.15–0.25% polysorbate 80, with pH 4.0–4.6. ASCENIV contains ≤ 200 µg/mL of IgA.

Each plasma donation used for the manufacture of ASCENIV is collected from FDA-licensed facilities. Plasma donations must test negative for hepatitis B virus (HBV) surface antigen (HBsAg), antibodies to human immunodeficiency virus (HIV) strains 1 and 2 (anti-HIV-1/2), and antibodies to the hepatitis C virus (anti-HCV) as determined by enzyme immunoassay (EIA). In addition, each plasma unit must test negative and/or non-reactive for HIV RNA, HCV RNA, HBV DNA, Hepatitis A Virus (HAV) RNA, and Parvovirus B19 (B19 virus) DNA as determined by Nucleic Acid Amplification Testing (NAT) of plasma minipools. NATs for HIV, HAV, HBV, HCV and B19 virus DNA are also performed on a sample of the manufacturing pool. The limit for B19 virus DNA in a manufacturing pool is set not to exceed 10^4 IU/mL and all other NAT results must be negative.

The manufacturing process of ASCENIV employs three steps to remove/inactivate adventitious viruses to minimize the risk of virus transmission. The steps are "Precipitation and removal of fraction III" during cold ethanol fractionation, classical "solvent/detergent treatment" and "35 nm virus filtration." In compliance with current guidelines, the steps have been separately validated in a series of in vitro experiments for their capacity to inactivate or remove both enveloped and nonenveloped viruses.

Precipitation and removal of fraction III removes both enveloped and non-enveloped viruses, solvent/detergent treatment represents a virus inactivation step for enveloped viruses, and 35 nm virus filtration removes both enveloped and non-enveloped viruses by size exclusion. In addition to the steps above, low pH during several steps of the production process contributes to virus inactivation. The results of virus validation studies for ASCENIV are shown in Table 3, expressed as $\log_{10}$ reduction factors.

Table 3: Virus Validation Data for ASCENIV

	Virus Reduction ($\log_{10}$)								
Virus Type Family	Enveloped Viruses					Non-enveloped Viruses			
	Retro	Flavi			Herpes	Parvo		Picorna	Polyoma
Step / Test Virus	HIV	BVDV	SinV	WNV	PRV	PPV	BPV	MEV	SV40
Precipitation and Removal of Fraction III and Depth Filtration	-	1.87*	-	-	-	4.00	-	5.29	2.00*
TnBP/Triton X-100 Treatment	> 4.43	> 5.04	> 7.11	> 4.96	> 4.01	-	-	-	-
35 nm Virus Filtration	> 5.19	> 4.88	-	-	> 4.64	< 1.0	6.18	< 1.0	> 5.02

Virus Type Family	Virus Reduction (log_{10})								
	Enveloped Viruses					Non-enveloped Viruses			
	Retro	Flavi			Herpes	Parvo		Picorna	Polyoma
Step / Test Virus	HIV	BVDV	SinV	WNV	PRV	PPV	BPV	MEV	SV40
Total Clearance	> 9.62	> 11.79	> 7.11	> 4.96	> 8.65	4.00	6.18	5.29	> 7.02

** without depth filtration*
-- not done
values below 1 log_{10} are considered insignificant and are not used for total clearance;
HIV, human immunodeficiency virus; **BVDV**, Bovine viral diarrhea virus, model virus for HCV; **SinV**, Sindbis virus, model virus for HCV; **WNV**, West Nile virus; **PRV**, Pseudorabies virus, model virus for herpes viruses and Hepatitis B virus; **MEV**, Murine encephalomyelitis virus, model virus for hepatitis A virus; **BPV**, Bovine parvovirus, model virus for human B19 virus; **PPV**, Porcine parvovirus, model virus for human B19 virus; **SV40,** Simian virus 40, model virus for highly resistant non-enveloped viruses.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
ASCENIV is a replacement therapy for patients with primary humoral immunodeficiency (PI) (e.g. agammaglobulinemia, hypogammaglobulinemia, CVID, SCID).

The broad spectrum of neutralizing IgG antibodies against bacterial and viral pathogens and their toxins helps to avoid recurrent serious opportunistic infections. IgG antibodies are opsonins that increase phagocytosis and elimination of pathogens from the circulation. The mechanism of action has not been fully elucidated in PI.

12.2 Pharmacodynamics
ASCENIV contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against various infectious agents, reflecting the IgG activity found in the donor population. ASCENIV which is prepared from pooled plasma from not less than 1,000 donors, has an IgG subclass distribution similar to that of native human plasma. Adequate doses of IGIV can restore an abnormally low IgG level to the normal range. Standard pharmacodynamics studies were not performed.

12.3 Pharmacokinetics
In a prospective, open-label, single-arm, multicenter clinical study, efficacy, safety and pharmacokinetics of ASCENIV were evaluated in 59 subjects with PI (See Clinical Studies [14]). Serum concentrations of total IgG were measured in 30 subjects (four subjects, ages 7 to 16 years and 26 subjects from 17 to 74 years) following the seventh infusion for subjects on a 4-week dosing interval and the ninth infusion for subjects on a 3-week dosing interval. The dose of ASCENIV used in these subjects ranged from 291 mg/kg to 760 mg/kg. After the infusion, blood samples were taken until Day 28 after infusion for the 4-week dosing interval and until Day 21 after infusion for the 3-week dosing interval. Table 4 summarizes the Total IgG Pharmacokinetic Parameters of ASCENIV, based on serum concentration of total IgG. The mean ± SD half-life of ASCENIV was 28.5 ± 4.4 days for subjects on a 3-week dosing interval and 39.7 ± 11.6 days for subjects on a 4-week dosing interval for the 30 subjects in the pharmacokinetic subgroup. Although no systematic study was conducted to evaluate the effect of sex on the pharmacokinetics of ASCENIV, based on the small sample size (11 males and 19 females) the pharmacokinetics of ASCENIV was comparable between males and females. In adolescents the pharmacokinetics of ASCENIV was comparable with adults. There were insufficient PK data in children younger than 12 years.

Table 4: Total IgG Pharmacokinetic Parameter Estimates (PK Population) in Subjects

	3-week cycle (n = 10)		**4-week cycle (n = 20)**	
Statistic	**Mean (SD)**	**CV%**	**Mean (SD)**	**CV%**
C_{max} (mg/dL)	2,427 (452)	18.6	2,227 (584)	26.2
C_{min} (mg/dL)	1,152 (308)	26.7	954 (245)	25.7
T_{max} (h) [a]	2.93 (1.8, 4.5)	NA	2.78 (1.43, 99.1)	NA
AUC_{tau} (d*mg/dL)	32,128 (7,020)	21.9	35,905 (9,351)	26.0
$t_{½}$ (d)	28.47 (4.4)	15.4	39.70 (11.6)	29.1
CL (mL/d/kg)	1.68 (0.4)	25.4	1.47 (0.5)	33.6
V_{ss} (mL/kg)	76.79 (13.5)	17.5	89.57 (26.2)	29.2

AUC_{tau} = steady-state area under the plasma concentration versus time curve with tau = dosing interval; CL = total body clearance;
C_{max} = maximum concentration; C_{min} = minimum concentration; CV = coefficient of variation; n = number of subjects;
NA = not applicable; SD = standard deviation; T_{max} = time of maximum concentration; $t_{½}$ = terminal half-life;
V_{SS} = Volume of distribution steady-state; [a] median (range)

Table 5: Total IgG Pharmacokinetic Parameter Estimates (PK Population) in Subjects—Baseline Corrected

	3-week cycle			4-week cycle		
Statistic	**Mean (SD)**	**CV%**	**N**	**Mean (SD)**	**CV%**	**N**
C_{max} (mg/dL)	1223 (297)	24.2	10	1231 (453)	37	20
C_{min} (mg/dL)	19 (31)	166	10	46 (42)	178	20
T_{max} (h)	3.04 (0.8)	27	10	8 (22)	282	20
$AUC_{(0-t)}$ (d*mg/dL)	6604 (2913)	44	10	7936 (3482)	44	20
$t_{½}$ (d)	6 (2)	41	5	10 (8)	80	9
CL (mL/d/kg)	9 (4)	42	10	8 (5)	61	20
V_z (mL/kg)	82 (62)	75	5	82 (35)	43	9

$AUC_{(0-t)}$ = steady-state area under the plasma concentration versus time curve with 0-t = dosing interval; CL = total body clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; CV = coefficient of variation; N = number of subjects; SD = standard deviation; T_{max} = time of maximum concentration; $t_{½}$ = terminal half-life; V_Z = Apparent Volume of distribution during terminal phase;

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effects of ASCENIV or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

No animal studies were conducted to evaluate possible toxicity of ASCENIV.

ASCENIV contains Polysorbate 80; Intravenous administrations of Polysorbate 80 in multiple species have been linked with a decrease in blood pressure. In rats, single doses of Polysorbate 80 that were up to 25 times higher than the amount from 800 mg/kg ASCENIV resulted in an increase of liver enzymes and total bilirubin.

14 CLINICAL STUDIES

A prospective, open-label, single-arm, multicenter trial assessed the efficacy, safety, and pharmacokinetics of ASCENIV in adult and pediatric subjects with PI. Study subjects were receiving regular IGIV replacement therapy, with a stable dose between 300 and 800 mg/kg for at least 3 months prior to participation in this trial. Subjects received an ASCENIV infusion administered every 3 or 4 weeks (both the dose and schedule depending on their prior therapy) for 12 months.

A total of 59 subjects were enrolled into the trial, 28 men and 31 women with a mean age of 42 years; 93% were Caucasian, 5% were Hispanic and 2% African American. Forty-eight subjects were adults (81%) between 17 and 74 years of age. There were 11 pediatric subjects (*see Pediatric Use [8.4]*), and 11 subjects (18.6%) ≥65 years of age. The oldest subject was 74 years of age. The youngest subject was 3 years of age.

There were 19 subjects with a 3-week cycle and 40 subjects with a 4-week cycle. There were 45 subjects (76%) with common variable immunodeficiency (CVID) as their primary diagnosis, followed by X-linked Agammaglobulinemia (10%), Antibody Deficiencies and 'Other' (7% each). The modified intent-to-treat (mITT) population included 59 subjects and was used for efficacy analysis.

The study assessed the efficacy of ASCENIV in preventing serious bacterial infections (SBIs), defined as a rate of <1.0 cases of bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per person-year. Secondary efficacy parameters included time to first SBI and time to first infection of any kind/seriousness, days on antibiotics (excluding prophylaxis), days off school/work due to infections, all confirmed infections of any kind or seriousness, and hospitalizations due to infection.

During the 12-month study period, zero (0) serious acute bacterial infections occurred. Thus, the mean event rate of serious, acute, bacterial infections per year was 0.0 (with an upper 1-sided 99% confidence interval of <1.0 per subject year, which met the study's primary efficacy endpoint).

Thirty-nine percent (39%) of subjects had days off work, school or daycare due to an infection. Of the infections reported, 1 resulted in hospitalization as a post-op local wound infection from elective surgery (see Table 6). The incidence and severity of infections in adolescents were similar to those in adult subjects.

Table 6: Summary of Efficacy Results in Subjects with PI

Number of Subjects (mITT Population)	59
Total Number of person-years[a]	55.9
Infections	
Number of confirmed serious acute bacterial infections[b]	0
Rate of SBIs (SBIs/total person-years)	0.0
Rate of Infections (Infections/total person-years) [a]	3.4
Antibiotic use due to infection[c]	
Number of subjects (%)	37 (63%)
Days per subject per year	32.9
Days off school/daycare/work due to infection	
Number of persons with days off of school, daycare or work due to infections	23 (39%)
Total days	93
Days per subject per year	1.7
Unscheduled Medical Visits due to infection	
Number of persons with unscheduled medical visits due to infections (%)	24 (41%)
Total visits	54
Visits per subject per year	0.97
Hospitalization due to infection	
Number of subjects (%)	1 (1.7%)
Number of Days	5
Hospitalizations per subject per year	0.02

SBI = serious bacterial infections.
[a]Person-years: Person-time in years with 2 decimals = (the Final Clinical Visit Date - the Day 0 date+1) / 365.25, where the final clinical visit date is defined as the specimen collection date of the final clinical visit for urinalysis, or the specimen collection date for the clinical laboratory tests at the final clinical visit and Day 0 date is the start date of the first ASCENIV infusion.
[b] Defined as bacterial pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.
[c] The calculation of antibiotic use includes subjects who received antibiotics for therapeutic use.

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16 HOW SUPPLIED/STORAGE AND HANDLING

ASCENIV is supplied in a single-use, tamper-evident vial. The components used in the packaging for ASCENIV are not made with natural rubber latex. ASCENIV is supplied in 50 mL size containing 5 grams of protein.

- Store at 2°-8°C (36°-46°F) for up to 36 months from date of manufacture. Do not freeze.
- Within the first 24 months of shelf-life, product may be stored up to 4 weeks at ≤ 25° C (77° F). After 24 months, product may be stored at ≤ 25°C up to 2 weeks, until expiry. After storage at room temperature, product must be used or discarded.

17 PATIENT COUNSELING INFORMATION

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 [5.5]).
- *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 [5.7])

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]).

- Can interfere with their immune response to live viral vaccines (e.g., measles, mumps, rubella, and varicella). Instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations (see Drug Interactions [7]).

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