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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]**

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dose (2.1)	XX/XXXX

----------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*

WARNING:THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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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)

Measles Exposure

If a patient has been exposed to measles, it may be prudent to administer an extra dose of IGIV as soon as possible and within 6 days of exposure. A dose of 400 mg/kg should provide a serum level> 240 mIU/mL of measles antibodies for at least two weeks.

If a patient is at risk of future measles exposure and receives a dose of less than 530 mg/kg every 3-4 weeks, the dose should be increased to at least 530 mg/kg. This should provide a serum level of 240 mIU/mL of measles antibodies for at least 22 days after infusion.

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 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 process as well as anion and cation exchange steps for added purification. 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, and 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 and undergoes rigorous testing. 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 immune assay (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. NAT is also performed on a sample of the manufacturing pool and must be negative and/or non-reactive for HIV RNA, HCV RNA, HBV DNA, and Hepatitis A Virus (HAV) RNA , and the limit for B19 virus DNA in a manufacturing pool is set not to exceed 10^4 IU/mL.

The manufacturing process of ASCENIV employs six 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, "Q-membrane filtration", "Solvent/detergent treatment" (TnBP / Triton X-100), "Anion exchange chromatography" and "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 non-enveloped viruses.

Precipitation and removal of fraction III and Q-membrane filtration removes non-enveloped viruses, solvent/detergent treatment represents a virus inactivation step for enveloped viruses, Anion exchange chromatography binds enveloped and non-enveloped viruses, and 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 the ASCENIV process are shown in Table 3, expressed as $\log_{10}$ reduction factors.

Table 3: Virus Removal/Inactivation (log10)

Step/Virus	HIV	BVDV	SinV	WNV	PRV	MEV	EMC	BPV	PPV	SV40
Virus Type	Enveloped	Enveloped	Enveloped	Enveloped	Enveloped	Non-enveloped	Non-enveloped	Non-enveloped	Non-enveloped	Non-enveloped
Virus Family	Retro	Flavi	Flavi	Flavi	Herpes	Picorna	Picorna	Parvo	Parvo	Polyoma
Precipitation and Removal of Fraction III and Depth Filtration	--		--	--	--	**5.29**	**≥ 5.70**	--	**≥ 5.78**	**2.00***
Q-Membrane Filtration[1]	--	--	--	--	-	--	--	--	**2.02**	-
Solvent-Detergent TNBP/Triton X- 100 Treatment	**≥3.92**	**≥ 5.32**	**> 7.11**	**> 4.96**	**≥4.88**	--		--	--	--
Anion Exchange Chromatography	**1.04**	--	--	--	-	--	-	--	**1.09**	-
Virus Nanofiltration	**≥4.72**	**≥4.67**	--	--	**≥4.15**		**≥6.24**	**6.18**	**4.66**	**> 5.02**
Low pH Treatment[2]	**2.43**	--	--	--	**3.20**[2]	--	--	--	--	--
Total Clearance	**≥9.68**	**≥9.99**	**> 7.11**	**> 4.96**	**≥12.23**	**5.29**	**≥ 5.70**[3]	**6.18**	**11.49**	**> 7.02**

** without depth filtration*

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. **EMC**, Encephalomyocarditis virus, model virus for hepatitis A virus

1 Q-membrane filtration step is associated with the affinity stream part of the production process.

2 Low pH treatment included in total clearance calculation based on separate mode of inactivation than VRF

3 EMC total clearance was calculated with the most conservative approach of using the lowest reduction value (>5.70) between the Fraction III precipitation/ filtration and nanofiltration steps

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 (NDC 69800-0250-1).

- Store at 2°-8°C (36°-46°F) for up to 36 months from date of manufacture. Do not freeze.
- Product may be stored up to 4 weeks at ≤ 25° C (77° F). 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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