

Product Profiles

Feature	Privigen® (Immune Globulin Intravenous [Human], 10% Liquid)	Carimune NF® (Immune Globulin Intravenous [Human])
Form	10%, ready-to-use liquid	lyophilized
IgG Purity	≥98%	>96%
Median Half-life	36.6 days	3 weeks
Sucrose	sucrose-free	1.67 g sucrose/g
Sodium	trace (≤1 mmol/L)	<20 mg NaCl/g of protein
Osmolality	isotonic (320 mOsmol/kg)	depends on diluent type, concentration, and volume
IgA Content	≤25 mcg/mL	720 mcg/mL
Monomers	98%	92%
Dimers	<ul style="list-style-type: none"> • specification ≤12% • typical value: 4.4% at release, may increase to 8% during shelf-life 	N/A
Pathogen Safety	CSL Behring quality <ul style="list-style-type: none"> • fractionation and depth filtration • pH 4 incubation • nanofiltration (20 nm) 	CSL Behring quality <ul style="list-style-type: none"> • fractionation and depth filtration • pH 4 incubation • nanofiltration (50 nm)
Stabilizer	L-proline*	sucrose
pH	4.8	6.6
Storage	up to 25° C (77° F) for 24 months do not use after expiration date	≤30° C (86° F) do not use after expiration date
Indications	PI, ITP	PI, ITP
Dosage	200 to 800 mg/kg every 3-4 weeks	200 to 400 mg/kg every 3-4 weeks
Infusion Rate	<ul style="list-style-type: none"> • initial: 0.5 mg/kg/min (0.005 mL/kg/min) • minimum rate practicable in high risk patients 	<ul style="list-style-type: none"> • initial: 0.5-1.0 mL/min of 3% solution • after 15-30 min, increase to 1.5-2.5 mL/min • if first vial of 3% solution is well tolerated, may slowly increase rate or concentration at 15-30 min intervals
Maximum Labeled Infusion Rate in PI	gradually increase if tolerated — not to exceed 8 mg/kg/min (0.08 mL/kg/min)	gradually increase if tolerated — not to exceed 2 mg/kg/min (0.02 mL/kg/min) in patients at risk of renal insufficiency
Vial Sizes (NDC)	<ul style="list-style-type: none"> • 5 g (44206-436-05) • 10 g (44206-437-10) • 20 g (44206-438-20) 	<ul style="list-style-type: none"> • 3 g (44206-416-03) • 6 g (44206-417-06) • 12 g (44206-418-12)
Latex-free	product and packaging	product and packaging

*Proline is one of the 20 naturally occurring amino acids that form human proteins. It can be synthesized by the human body or obtained from dietary sources. CSL Behring chose proline as the stabilizer for Privigen® after extensive testing, analysis, and comparison to other amino acids, such as glycine.

See Important Safety Information for Privigen® and Carimune® NF, including Boxed Warnings, and accompanying full Prescribing Information.

Important Safety Information

Privigen® is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Privigen® is also indicated to rapidly raise platelet counts to prevent bleeding in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IVIg) products in predisposed patients. Administer IVIg products at the minimum infusion rate possible. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIg products containing sucrose. Privigen® does not contain sucrose. See full prescribing information for complete boxed warning.

Privigen® is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin, in patients with hyperprolinemia, and in patients with selective IgA deficiency. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have been reported with Privigen® and other IVIg treatments. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple cardiovascular risk factors, advanced age,

impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) has been reported infrequently with Privigen® and other IVIg treatments; AMS may occur more frequently with high doses and/or rapid infusion of IVIg. Hemolysis, hemolytic anemia, and pulmonary adverse events have also been reported. There have been reports of noncardiogenic pulmonary edema in patients administered IVIg. If transfusion-related acute lung injury is suspected, test product and patient for antineutrophil antibodies. Privigen® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies, the most common adverse reactions with Privigen® were headache, pain, nausea, pyrexia/hyperthermia, fatigue, and chills. Anemia was an additional common adverse reaction in patients being treated with Privigen® for chronic ITP. The most serious adverse reactions in chronic ITP patients were aseptic meningitis syndrome in one subject and hemolysis in eight subjects.

Important Safety Information

Privigen® is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

WARNING: Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IVIg) products in predisposed patients. Administer IVIg products at the minimum infusion rate possible. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIg products containing sucrose. Privigen® does not contain sucrose. See full prescribing information for complete boxed warning.

Privigen® is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin, in patients with hyperprolinemia, and in patients with selective IgA deficiency.

In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have been reported with Privigen® and other IVIg treatments. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple

cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) has been reported infrequently with Privigen® and other IVIg treatments; AMS may occur more frequently with high doses and/or rapid infusion of IVIg. Hemolysis, hemolytic anemia, and pulmonary adverse events have also been reported. There have been reports of noncardiogenic pulmonary edema in patients administered IVIg. If transfusion-related acute lung injury is suspected, test product and patient for antineutrophil antibodies.

Privigen® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies, the most common adverse reactions with Privigen® were headache, pain, nausea, pyrexia/hyperthermia, fatigue, and chills.

Important Safety Information

Carimune® NF is indicated for the maintenance treatment of patients with primary immunodeficiencies (PI), such as common variable immunodeficiency, X-linked agammaglobulinemia, and severe combined immunodeficiency, and for acute and chronic immune thrombocytopenic purpura (ITP).

WARNING: Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Severe renal adverse events with Immune Globulin Intravenous (Human) have included acute renal failure, acute tubular nephrosis, proximal tubular nephropathy, and osmotic nephrosis. Monitoring of renal function and urine output is advised in patients with a potential increased risk for developing acute renal failure. Increases in creatinine and blood urea nitrogen with progression to oliguria or anuria requiring dialysis have been observed.

As with all blood products containing IgA, Carimune® NF is contraindicated in patients with selective IgA deficiency who possess antibody to IgA. Carimune® NF may be contraindicated in patients with severe systemic reactions to IV or intramuscular administration of human immune globulin. Carimune® NF is derived from human plasma.

As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Privigen™ safely and effectively. See full prescribing information for Privigen™.

Immune Globulin Intravenous (Human), 10% Liquid Privigen™

Initial U.S. Approval: 2007

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

See full prescribing information for complete boxed warning.

- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.
- Administer IGIV products at the minimum infusion rate practicable.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Privigen™ does not contain sucrose.

INDICATIONS AND USAGE

Privigen™ is an Immune Globulin Intravenous (Human), 10% Liquid indicated for treatment of:

- Primary immunodeficiency (PI) (1.1)
- Chronic immune thrombocytopenic purpura (ITP) (1.2)

DOSAGE AND ADMINISTRATION

- **PI** – 200 to 800 mg/kg intravenously (IV) every 3 to 4 weeks. Recommended infusion rate: initially, 0.5 mg/kg/min (0.005 mL/kg/min); if well tolerated, may be gradually increased to 8 mg/kg/min (0.08 mL/kg/min) (2.2).
- **Chronic ITP** – 1 g/kg IV daily for 2 consecutive days, for a total of 2 g/kg. Recommended infusion rate: initially, 0.5 mg/kg/min (0.005 mL/kg/min); if well tolerated, may be gradually increased to 4 mg/kg/min (0.04 mL/kg/min) (2.3).
- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Privigen™ if renal function deteriorates (5.1).
- For patients at risk of renal dysfunction or thrombotic events, administer Privigen™ at the minimum infusion rate practicable (5.1, 5.5).

DOSAGE FORMS AND STRENGTHS

5 g in 50 mL solution, 10 g in 100 mL solution, 20 g in 200 mL solution (3)

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin (4)
- Hyperprolinemia (Privigen™ contains the stabilizer L-proline) (4)
- Individuals with selective IgA deficiency can develop antibodies to IgA and are at greater risk of developing severe hypersensitivity and anaphylactic reactions (4)

WARNINGS AND PRECAUTIONS

- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure (5.1).
- Aseptic meningitis syndrome has been reported with Privigen™ and other IGIV treatments, especially with high doses or rapid infusion (5.2).
- Hemolysis has been reported with Privigen™ and other IGIV treatments. Monitor patients for hemolysis and hemolytic anemia (5.3).
- Monitor patients for pulmonary adverse reactions; if transfusion-related acute lung injury is suspected, test the product and patient for antineutrophil antibodies (5.4).
- Thrombotic events have been reported with Privigen™ and other IGIV treatments. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity (5.5).
- Products made from human plasma can contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.6).

ADVERSE REACTIONS

- **PI** – Most common adverse reactions are headache, pain, nausea, fatigue, and chills (6.1).
- **Chronic ITP** – Most common adverse reactions are headache, pyrexia/hyperthermia, and anemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring at 1-800-504-5434 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

IgG administration can transiently impair efficacy of live virus vaccines (7.1).

USE IN SPECIFIC POPULATIONS

In patients over age 65 at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Privigen™ at a rate less than 2 mg/kg/min (0.02 mL/kg/min) (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Issued: July 2007

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

CSL Behring

FULL PRESCRIBING INFORMATION

Immune Globulin Intravenous (Human), 10% Liquid Privigen™

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.¹ Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. In such patients, IGIV products should be administered at the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Privigen™ does not contain sucrose. (See *Dosage and Administration [2.4]* and *Warnings and Precautions [5.1]* for important information intended to reduce the risk of acute renal failure.)

1 INDICATIONS AND USAGE

1.1 Treatment of Primary Immunodeficiency

Privigen™ is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

1.2 Treatment of Chronic Immune Thrombocytopenic Purpura

Privigen™ is indicated for the treatment of patients with chronic immune thrombocytopenic purpura (ITP) to rapidly raise platelet counts to prevent bleeding.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Handling

Privigen™ is a clear or slightly opalescent, colorless to pale yellow solution. Privigen™ should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or contains particulates. Any solution that has been frozen must not be used. DO NOT SHAKE.

Do not mix Privigen™ with other IGIV products or other intravenous medications. If necessary, Privigen™ can be diluted with Dextrose Injection, USP (D5W). If large doses of Privigen™ are to be administered, several vials may be pooled using aseptic technique.

The Privigen™ vial is for single use only. Once the vial has been entered under aseptic conditions, its contents should be used promptly. Because the solution contains no preservative, Privigen™ should be infused as soon as possible. Any unused product or waste material should be disposed of in accordance with local requirements.

2.2 Treatment of Primary Immunodeficiency

The usual dose of Privigen™ for patients with PI is 200 to 800 mg/kg, administered every 3 to 4 weeks. An optimum target serum immunoglobulin G (IgG) trough level has not been established in randomized, controlled clinical studies. Doses should be adjusted to achieve the desired serum trough levels and clinical responses.

The recommended initial infusion rate is 0.5 mg/kg/min (0.005 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk of renal dysfunction or thrombotic events, Privigen™ should be administered at the minimum infusion rate practicable (see *Warnings and Precautions [5.1, 5.5]*).

2.3 Treatment of Chronic Immune Thrombocytopenic Purpura

The usual dose of Privigen™ for patients with chronic ITP is 1 g/kg administered daily for 2 consecutive days, resulting in a total dosage of 2 g/kg.

The recommended initial infusion rate is 0.5 mg/kg/min (0.005 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 4 mg/kg/min (0.04 mL/kg/min). For patients judged to be at risk of renal dysfunction or thrombotic events, Privigen™ should be administered at the minimum infusion rate practicable (see *Warnings and Precautions [5.1, 5.5]*).

2.4 Administration

Privigen™ is for intravenous (IV) administration and should be given by a separate infusion line. An infusion pump may be used to control the rate of administration. The Privigen™ infusion line can be flushed with Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP.

The following patients may be at risk of developing inflammatory reactions on rapid infusion of Privigen™ (greater than 4 mg/kg/min [0.04 mL/kg/min]): 1) those who have not received Privigen™ or another IgG product; 2) those who are switching from another IgG product; and 3) those who have not received IgG in more than 8 weeks. These patients should be started at a slow rate of infusion (e.g., 0.5 mg/kg/min [0.005 mL/kg/min] or less) and gradually advanced to the maximum rate as tolerated.

Ensure that patients with pre-existing renal insufficiency and those predisposed to acute renal failure are not volume depleted before administering Privigen™ (see *Boxed Warning, Warnings and Precautions [5.1]*).

The patient's vital signs should be observed and monitored carefully throughout the infusion. If side effects occur, the infusion should be slowed or stopped until the symptoms subside. The infusion may then be resumed at a lower rate that is comfortable for the patient.

3 DOSAGE FORMS AND STRENGTHS

- 5 g in 50 mL solution
- 10 g in 100 mL solution
- 20 g in 200 mL solution

4 CONTRAINDICATIONS

Privigen™ is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.

Because it contains the stabilizer L-proline, Privigen™ is contraindicated in patients with hyperprolinemia.

Privigen™ is contraindicated in individuals with selective IgA deficiency because they can develop antibodies to IgA and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Privigen™ contains trace amounts of IgA (see *Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Acute Renal Dysfunction and Acute Renal Failure

Patients should not be volume depleted prior to the initiation of the infusion of Privigen™. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, should be assessed before the initial infusion of Privigen™ and at appropriate intervals thereafter. For patients judged to be at risk of developing renal dysfunction, Privigen™ should be administered at the minimum rate of infusion practicable (see *Dosage and Administration [2.2, 2.3]*). If renal function deteriorates, consider discontinuing Privigen™. (See *Patient Counseling Information [17.1]*).

5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with Privigen™ and other IGIV treatments. The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.² (See *Patient Counseling Information [17.2]*).

5.3 Hemolysis

IGIV products can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.³⁻⁵ Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (extravascular hemolysis) or intravascular RBC destruction (intravascular hemolysis).⁶ Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen™ in the ITP study. These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (see *Patient Counseling Information [17.3]*). If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be performed. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, adequate cross-matching should be performed to avoid exacerbating on-going hemolysis.

5.4 Transfusion-related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema in patients administered IGIV.⁷ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours following transfusion. IGIV recipients should be monitored for pulmonary adverse reactions (see *Patient Counseling Information [17.4]*). Patients with

TRALI may be managed using oxygen therapy with adequate ventilatory support. If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and the patient's serum.

5.5 Thrombotic Events

Thrombotic events have been reported with Privigen™ and other IGIV treatments.⁸⁻¹⁰ Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies in all patients for whom IGIV administration is being considered.

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk of hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

5.6 Transmissible Infectious Agents

Privigen™ is made from human plasma. Products made from human plasma may contain infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing through pH 4 incubation, depth filtration, and virus filtration (see *Description* [1.1]).

Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434. (See *Patient Counseling Information* [17.5].)

5.7 Interference With Laboratory Tests

After infusion of IgG, 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.

5.8 Interference With Live Virus Vaccines

Immunoglobulin administration may transiently impair the efficacy of live virus vaccines such as measles, mumps, and rubella. The immunizing physician should be informed so that appropriate measures may be taken (see *Drug Interactions* [7.1], *Patient Counseling Information* [17.6]).

6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen™ for PI was hypersensitivity in one subject. The most serious adverse reactions observed in subjects receiving Privigen™ for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. (See *Warnings and Precautions* [5.2, 5.3].)

The most common adverse reactions observed in subjects with PI were headache, pain, nausea, fatigue, and chills. The most common adverse reactions observed in subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia. In general, reported adverse reactions to Privigen™ in subjects with either PI or chronic ITP were similar in kind and frequency to those observed with other IGIV products.

6.1 Clinical Studies Experience

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

Treatment of Primary Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI received median doses of Privigen™ ranging from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg) for up to 12 months (see *Clinical Studies* [14.1]).

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen™ infusions with temporally associated AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint.¹¹ The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion).

Table 1 lists the temporally associated AEs that occurred in more than 5% of subjects within 72 hours after the end of a Privigen™ infusion, *irrespective of causality*.

Table 1: Temporally Associated Adverse Events* (TAAEs) in >5% of Subjects With PI Within 72 Hours After the End of a Privigen™ Infusion, Irrespective of Causality

TAAE	No. Subjects Reporting TAAE (% of Subjects [n=80])	No. TAAEs Reported (as % Rate of Infusions [n=1038])	No. Infusions With TAAE (% of Infusions [n=1038])
Headache	35 (43.8)	90 (8.7)	82 (7.9)
Pain	20 (25.0)	51 (4.9)	44 (4.2)
Fatigue	13 (16.3)	29 (2.8)	27 (2.6)
Nausea	10 (12.5)	22 (2.1)	19 (1.8)
Chills	9 (11.3)	15 (1.4)	15 (1.4)
Vomiting	7 (8.8)	13 (1.3)	13 (1.3)
Pyrexia	6 (7.5)	11 (1.1)	10 (1.0)
Cough	5 (6.3)	5 (0.5)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)	5 (0.5)

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen™ (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen™, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects). Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that occurred in one subject and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen™ (chills and headache in one subject; vomiting in the other). Seventy-seven of the 80 subjects enrolled in this study had a negative direct antiglobulin test (DAT) at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP received a 2 g/kg dose of Privigen™ administered daily as two 1 g/kg intravenous infusions for 2 consecutive days (see *Clinical Studies* [14.2]).

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen™, *irrespective of causality*.

Table 2: Temporally Associated Adverse Events (TAAEs) in >5% Subjects With Chronic ITP Within 72 hours After the End of a Treatment Cycle* With Privigen™, Irrespective of Causality

TAAE	No. Subjects Reporting TAAE (% of Subjects [n=57])	No. TAAEs Reported (as % Rate of Infusions [n=114])	No. Infusions With TAAE (% of Infusions [n=114])
Headache	37 (64.9)	48 (42.1)	41 (36.0)
Pyrexia/hyperthermia	21 (36.8)	23 (20.2)	22 (19.3)
Nausea	6 (10.5)	8 (7.0)	6 (5.3)
Epistaxis	6 (10.5)	8 (7.0)	6 (5.3)
Vomiting	6 (10.5)	7 (6.1)	6 (5.3)
Blood unconjugated bilirubin increased	6 (10.5)	6 (5.3)	6 (5.3)
Blood conjugated bilirubin increased	5 (8.8)	5 (4.4)	5 (4.4)
Blood total bilirubin increased	4 (7.0)	4 (3.5)	4 (3.5)
Hematocrit decreased	3 (5.3)	3 (2.6)	3 (2.6)

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen™ (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen™, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be “at least possibly” related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen™.

One subject withdrew from the study due to gingival bleeding, which was not related to Privigen™.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen™. Two of the eight subjects were clinically anemic but did not require clinical intervention.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen™ infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility. The following adverse reactions have been identified and reported during the postapproval use of IGIV products.¹²

- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, tremor
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
- **General/Body as a Whole:** Pyrexia, rigors
- **Musculoskeletal:** Back pain
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain

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. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, and rubella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response.¹³ The immunizing physician should be informed of recent therapy with Privigen™ so that appropriate measures may be taken (see *Patient Counseling Information* [17.6]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Privigen™. It is not known whether Privigen™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Privigen™ should be given to pregnant women only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.^{14,15}

8.3 Nursing Mothers

Privigen™ has not been evaluated in nursing mothers.

8.4 Pediatric Use

Treatment of Primary Immunodeficiency

Privigen™ was evaluated in 19 children and 12 adolescents with PI. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen™ has not been

established in pediatric subjects with PI who are under the age of 3.

Treatment of Chronic Immune Thrombocytopenic Purpura

The safety and effectiveness of Privigen™ has not been established in pediatric subjects with chronic ITP who are under the age of 15.

8.5 Geriatric Use

Privigen™ should be used with caution in patients over 65 years of age who are judged to be at increased risk of developing renal insufficiency (see *Boxed Warning, Warnings and Precautions* [5.1]). Recommended doses should not be exceeded, and the infusion rate selected should be the minimum practicable. Privigen™ should be infused at a rate less than 2 mg/kg/min (0.02 mL/kg/min). Clinical studies of Privigen™ did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Privigen™ is a ready-to-use, sterile, 10% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous administration. Privigen™ is prepared from large pools of human plasma by a combination of cold ethanol fractionation, octanoic acid fractionation, and anion exchange chromatography. The IgG proteins are not subjected to heating or to chemical or enzymatic modification. The Fc and Fab functions of the IgG molecule are retained. Fab functions tested include antigen binding capacities, and Fc functions tested include complement activation and Fc-receptor-mediated leukocyte activation (determined with complexed IgG). Privigen™ does not activate the complement system or prekallikrein in an unspecific manner. Privigen™ has a purity of at least 98% IgG, consisting primarily of monomers. The balance consists of IgG dimers (≤12%), small amounts of fragments and polymers, and albumin. Privigen™ contains ≤25 mcg/mL IgA. The IgG subclass distribution (approximate mean values) is IgG₁, 67.8%; IgG₂, 28.7%; IgG₃, 2.3%; and IgG₄, 1.2%. Privigen™ has an osmolality of approximately 320 mOsmol/kg (range: 240 to 440) and a pH of 4.8 (range: 4.6 to 5.0).

Privigen™ contains approximately 250 mmol/L (range: 210 to 290) of L-proline (a nonessential amino acid) as a stabilizer and trace amounts of sodium. Privigen™ contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative. All plasma units used in the manufacture of Privigen™ are tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to HCV and HIV-1/2 as well as FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be nonreactive (negative). For HBV, an investigational NAT procedure is used and the plasma units found to be negative; however, the significance of a negative result has not been established.

The manufacturing process for Privigen™ includes three steps to reduce the risk of virus transmission. Two of these are dedicated virus clearance steps: pH 4 incubation to inactivate enveloped viruses and virus filtration to remove, by size exclusion, both enveloped and non-enveloped viruses as small as approximately 20 nanometers. In addition, a depth filtration step contributes to the virus reduction capacity.

These steps have been independently validated in a series of *in vitro* experiments for their capacity to inactivate and/or remove both enveloped and non-enveloped viruses. Table 3 shows the virus clearance during the manufacturing process for Privigen™, expressed as the mean log₁₀ reduction factor (LRF).

Table 3: Virus Inactivation/Removal in Privigen™

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
Virus property						
Genome	RNA	DNA	RNA	RNA	RNA	DNA
Envelope	Yes	Yes	Yes	Yes	No	No
Size (nm)	80-100	120-200	50-70	50-70	25-30	18-24
Manufacturing step	Mean LRF					
pH 4 incubation	≥5.4	≥5.9	4.6	≥7.8	nt	nt
Depth filtration	≥5.3	≥6.3	2.1	3.0	4.2	2.3
Virus filtration	≥5.3	nd	≥2.7	≥5.9	≥3.7	≥5.5
Overall reduction (log₁₀ units)	≥16.0	≥12.2	≥9.4	≥16.7	≥7.9	≥7.8

HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MVM, minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF, log₁₀ reduction factor; nd, not determined; nt, not tested.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of TSE, considered a model for CJD and its variant vCJD.¹⁶ Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanoic acid fractionation (≥6.4 log₁₀), depth filtration (2.6 log₁₀), and virus filtration (≥5.8 log₁₀). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treatment of Primary Immunodeficiency

Privigen™ contains a broad spectrum of antibody specificities. Appropriate doses of Privigen™ should restore abnormally low IgG levels to the normal range.

Treatment of Chronic Immune Thrombocytopenic Purpura

The mechanism of action of immunoglobulins in the treatment of chronic ITP is not fully understood. One possible mechanism may be the inhibition of the elimination of autoantibody-reacted platelets from the blood circulation by IgG-induced Fc-receptor blockade of phagocytes.¹⁷ Another proposed mechanism is the down-regulation of platelet autoantibody-producing B cells by anti-idiotypic antibodies in IGIV.¹⁸

12.3 Pharmacokinetics

Treatment of Primary Immunodeficiency

In the clinical study assessing the efficacy and safety of Privigen™ in 80 subjects with PI (see *Clinical Studies [14.1]*), serum concentrations of total IgG and IgG subclasses were measured in 25 subjects (ages 13 to 69) following the 7th infusion for the 3 subjects on the 3-week dosing interval and following the 5th infusion for the 22 subjects on the 4-week dosing interval. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively.

Table 4 summarizes the pharmacokinetic parameters of Privigen™, measured as serum concentrations of total IgG.

Table 4: Pharmacokinetic Parameters of Privigen™ in Subjects with PI

Parameter	3-Week Dosing Interval (n=3)		4-Week Dosing Interval (n=22)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
C _{max} (peak, mg/dL)	2,550 (400)	2,340 (2,290-3,010)	2,260 (530)	2,340 (1,040-3,460)
C _{min} (trough, mg/dL)	1,230 (230)	1,200 (1,020-1,470)	1,000 (200)	1,000 (580-1,360)
t _{1/2} (days)	27.6 (5.9)	27.8 (21.6-33.4)	45.4 (18.5)	37.3 (20.6-96.6)
AUC _{0-t} (day × mg/dL)*	32,820 (6,260)	29,860 (28,580-40,010)	36,390 (5,950)	36,670 (19,680-44,340)
Clearance (mL/day/kg)*	1.3 (0.1)	1.3 (1.1-1.4)	1.3 (0.3)	1.3 (0.9-2.1)

C_{max}, maximum serum concentration; C_{min}, trough (minimum level) serum concentration; t_{1/2}, elimination half-life; AUC_{0-t}, area under the curve from 0 hour to last sampling time.

* Calculated by log-linear trapezoidal rule.

The median half-life of Privigen™ was 36.6 days for the 25 subjects in the pharmacokinetic subgroup.

Although no systematic study was conducted to evaluate the effect of gender and age on the pharmacokinetics of Privigen™, based on the small sample size (11 males and 14 females) it appears that clearance of Privigen™ is comparable between males (1.27 ± 0.35 mL/day/kg) and females (1.34 ± 0.22 mL/day/kg). In six subjects between 13 and 15 years of age, the clearance of Privigen™ (1.35 ± 0.44 mL/day/kg) is comparable to that observed in 19 adult subjects 19 years of age or older (1.29 ± 0.22 mL/day/kg).

The IgG subclass levels observed in the pharmacokinetic study were consistent with a physiologic distribution pattern (mean trough values): IgG₁, 564.91 mg/dL; IgG₂, 394.15 mg/dL; IgG₃, 30.16 mg/dL; IgG₄, 10.88 mg/dL.

Treatment of Chronic Immune Thrombocytopenic Purpura Pharmacokinetic studies with Privigen™ were not performed in subjects with chronic ITP.

14 CLINICAL STUDIES

14.1 Treatment of Primary Immunodeficiency

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and pharmacokinetics of Privigen™ in adult and pediatric subjects with PI, who were treated for 12 months at a 3-week or 4-week dosing interval. Subjects ranged in age from 3 to 69; 57.5% were male and 42.5% were female; 77.5% were Caucasian, 15% were Hispanic, and 7.5% were African-American. All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study.

The efficacy analysis included 80 subjects, 16 on the 3-week dosing interval and 64 on the 4-week dosing interval. Doses ranged from 200 mg/kg to 888 mg/kg. The median dose for the 3-week interval was 428.3 mg/kg; the median dose for the 4-week interval was 440.6 mg/kg. Subjects received a total of 1038 infusions of Privigen™, 272 in the 3-week dosing interval and 766 in the 4-week dosing interval. The maximum infusion rate allowed during this study was 8 mg/kg/min with 69% (715) of the infusions administered at a rate of 7 mg/kg/min or greater.

The primary endpoint was the annual rate of acute serious bacterial infections (aSBIs), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject per year. Secondary endpoints included

days out of work/school/day care or days unable to perform normal activities due to illness, days of hospitalization, and use of antibiotics.

During the 12-month study period, the aSBI rate was 0.08 (with an upper 1-sided 99% confidence interval of 0.203), which met the predefined success rate of less than one aSBI per subject per year. Six subjects experienced an aSBI, including three cases of pneumonia and one case each of septic arthritis, osteomyelitis, and visceral abscess. All six subjects completed the study.

The rate of other infections was 3.55 infections per subject per year. The infections that occurred most frequently were sinusitis (31.3%), nasopharyngitis (22.5%), upper respiratory tract infection (18.8%), bronchitis (13.8%), and rhinitis (13.8%). The majority of these infections were mild or moderate; among the 255 infections, 16 (6.3%) occurring in 10 subjects were considered severe.

Table 5 summarizes the efficacy results for all 80 subjects.

Table 5: Summary of Efficacy Results in Subjects With PI

Number of Subjects	80
Results from Case Report Forms	
Total Number of Subject Days	26,198
Infections	
Annual rate of confirmed aSBIs*	0.08 aSBIs/subject year [†]
Annual rate of other infections	3.55 infections/subject year
Antibiotic use	
Number of subjects (%)	64 (80%)
Annual rate	87.4 days/subject year
Results from Subject Diaries	
Total Number of Diary Days	24,059
Out of work/school/ day care or unable to perform normal activities due to illness	
Number of days (%)	570 (2.37%)
Annual rate	8.65 days/subject year
Hospitalization	
Number of days (%)	166 (0.69%)
Annual rate	2.52 days/subject year

* Defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.

[†] Upper 1-sided 99% confidence interval: 0.203.

14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and tolerability of Privigen™ in 57 subjects with chronic ITP and a platelet count of 20 × 10⁹/L or less. Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male; all were Caucasian.

Subjects received a 2 g/kg dose of Privigen™ administered daily as two 1 g/kg intravenous infusions for 2 consecutive days and were observed for 29 days. Fifty-three (93%) subjects received Privigen™ at the maximum infusion rate allowed (4 mg/kg/min [0.04 mL/kg/min]).

The primary endpoint was the response rate defined as the percentage of subjects with an increase in platelet counts to at least 50 × 10⁹/L within 7 days after the first infusion (responders). Secondary endpoints included the increase in platelet counts and the time to reach a platelet count of at least 50 × 10⁹/L at any point within the study period, the duration of that response, and the regression (decrease in the severity) of hemorrhage in subjects who had bleeding at baseline. Platelet counts were measured on Days 1, 2, 4, 6, 8, 15, 22, and 29. Additional measurements on Days 57 and 85 occurred in subjects with a platelet count of at least 50 × 10⁹/L at the previous visit.

Of the 57 subjects in the efficacy analysis, 46 (80.7%) responded to Privigen™ with a rise in platelet counts to at least 50 × 10⁹/L within 7 days after the first infusion. The lower bound of the 95% confidence interval for the response rate (69.2%) is above the predefined response rate of 50%.

The highest median increase in platelet counts was seen 7 days after the first infusion (123 × 10⁹/L). The median maximum platelet count achieved was 154 × 10⁹/L. The median time to reach a platelet response of more than 50 × 10⁹/L was 2.5 days after the first infusion. Twenty-five (43%) of the 57 subjects reached this response by Day 2 prior to the second infusion and 43 (75%) subjects reached this response by Day 6.

The duration of platelet response was analyzed for the 48 subjects who achieved a response any time after the first infusion. The median duration of platelet response in these subjects was 15.4 days (range: 1 to >82 days). Thirty-six (75%) of the 48 subjects maintained the response for at least 8.8 days and 12 (25%) of them for at least 21.9 days. Five (9%) subjects maintained a response up to Day 29 and two (4%) up to Day 85.

A decrease in the severity of hemorrhage from baseline was observed in the following bleeding locations: skin (31 of 36 subjects), oral cavity (11 of 11 subjects), and genitourinary tract (7 of 9 subjects). This decrease was not sustained in all subjects up to the end of the 29-day study period.

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16 HOW SUPPLIED/STORAGE AND HANDLING

Privigen™ is supplied in a single-use, tamper-evident vial containing the labeled amount of functionally active IgG. The components used in the packaging for Privigen™ are latex-free.

The following dosage forms are available:

NDC Number	Fill Size (mL)	Grams
44206-436-05	50	5
44206-437-10	100	10
44206-438-20	200	20

Each vial has an integral suspension band and a label with two peel-off strips showing the product name, lot number, and expiration date.

When stored at room temperature (up to 25°C [77°F]), Privigen™ is stable for up to 24 months, as indicated by the expiration date printed on the outer carton and vial label. Do not freeze. Keep Privigen™ in its original carton to protect it from light.

17 PATIENT COUNSELING INFORMATION

17.1 Renal Dysfunction

Instruct patients to immediately report symptoms of 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 [5.1]*). **17.2 Aseptic Meningitis Syndrome (AMS)** Instruct patients to immediately report signs and symptoms of AMS. These symptoms include severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (see *Warnings and Precautions [5.2]*).

17.3 Hemolysis

Instruct patients to immediately report signs and symptoms of hemolysis. These symptoms include fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine (see *Warnings and Precautions [5.3]*).

17.4 Transfusion-Related Acute Lung Injury (TRALI)

Instruct patients to immediately report signs and symptoms of TRALI, which is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. TRALI typically occurs within 1 to 6 hours following transfusion (see *Warnings and Precautions [5.4]*).

17.5 Transmissible Infectious Agents

Inform patients that Privigen™ is made from human plasma (part of the blood) and may contain infectious agents that can cause disease (e.g., viruses, and, theoretically, the CJD agent). Explain that the risk that Privigen™ may transmit an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by inactivating and/or removing certain viruses during manufacturing (see *Warnings and Precautions [5.6]*).

17.6 Live Virus Vaccines

Inform patients that administration of IgG may transiently impair the effectiveness of live virus vaccines (e.g., measles, mumps, and rubella) and to notify their immunizing physician of recent therapy with Privigen™ (see *Drug Interactions [7.1]*).

Manufactured by:

CSL Behring AG
Bern, Switzerland
US License No. 1766

Distributed by:

CSL Behring LLC
Kankakee, IL 60901 USA

Immune Globulin Intravenous (Human)

Carimune® NF

Nanofiltered, Lyophilized Preparation

CSL Behring

Ⓡ only

DESCRIPTION

Immune Globulin Intravenous (Human) (IGIV), Carimune® NF, nanofiltered, is a sterile, highly purified polyvalent antibody product containing in concentrated form all the IgG antibodies which regularly occur in the donor population (1). This immunoglobulin preparation is produced by cold alcohol fractionation from the plasma of US donors. Part of the fractionation may be performed by another US-licensed manufacturer. Carimune® NF is made suitable for intravenous use by treatment at acid pH in the presence of trace amounts of pepsin (2, 3). The manufacturing process by which Carimune® NF is prepared from plasma consists of fractionation and purification steps that comprise filtrations in the presence of filter aids. Four of these steps were validated for virus elimination of both enveloped and non-enveloped viruses. Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents (4). To complement the existing virus elimination/inactivation mechanism in the Carimune® NF manufacturing process, nanofiltration (removing viruses via size-exclusion) was introduced as an additional virus removal step into the manufacturing process (5, 6). Nanofiltration is performed prior to the viral inactivation step (pH 4 in presence of pepsin) in order to reduce the potential viral load before inactivation is performed. Treatment with pepsin at pH 4 rapidly inactivates enveloped viruses (7).

The Carimune® NF manufacturing process provides a significant viral reduction in *in vivo* studies. These studies results are summarized in Table 1, demonstrate virus clearance during Carimune® NF manufacturing using model viruses for lipid enveloped and non-enveloped viruses. The LRFs (log₁₀ reduction factors) from nanofiltration, and viral elimination and inactivation steps were:

Table 1
Viral Elimination and Inactivation

Virus	HIV	BVDV	PRV	SFV	SV	BEV
Genome	RNA	RNA	DNA	RNA	RNA	RNA
Envelope	Yes	Yes	Yes	Yes	Yes	No
Size (nm)	80–100	40–60	120–200	50–70	50–70	28–30
Fractionation & Depth filtration	15.5	nt	16.0	9.3	12.4	14.1
pH 4 / pepsin	≥ 6.1	≥ 4.4	≥ 5.3	≥ 6.8	nt	nt
Nanofiltration	≥ 4.9	≥ 4.5	≥ 4.4	nt	≥ 7.5	≥ 5.1
Overall reduction	≥ 26	≥ 9	≥ 25	≥ 16	≥ 19	≥ 19

HIV: Human immunodeficiency virus, model for HIV 1 and HIV 2
 BVDV: Bovine viral diarrhoea virus, model for HCV (Hepatitis C virus)
 PRV: Pseudorabies virus, model for large, enveloped DNA viruses (e.g., herpes virus)
 SFV: Semliki Forest virus, model for HCV
 SV: Sindbis virus, model for HCV
 BEV: Bovine enterovirus, model for HAV (Hepatitis A virus)
 nt: not tested

PRV and the two model viruses for HCV, BVDV and SFV, were inactivated within 1/10, and HIV within 1/2 of the incubation time (pH 4/pepsin treatment) used during production of Carimune® NF.

Several of the individual production steps in the Carimune® NF manufacturing process have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include precipitation (3.5 logs), depth filtrations (7.3 logs), and nanofiltration (4.4 logs). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

The preparation contains at least 96% of IgG and after reconstitution with a neutral unbuffered diluent has a pH of 6.6 ± 0.2. Most of the immunoglobulins are monomeric (7 S) IgG; the remainder consists of dimeric IgG and a small amount of polymeric IgG, traces of IgA and IgM and immunoglobulin fragments (8). The distribution of the IgG subclasses corresponds to that of normal serum (9–12). Final container lyophilized units are prepared so as to contain 1, 3, 6, or 12 g protein with 1.67 g sucrose and less than 20 mg NaCl per gram of protein. The lyophilized preparation contains no preservative and may be reconstituted with sterile water, 5% dextrose or 0.9% saline to a solution with protein concentrations ranging from 3% to 12% (see Table 3). The patient's fluid, electrolyte, caloric requirements and renal function should be considered in selecting an appropriate diluent and concentration.

Table 2
Calculated Carimune® NF Osmolality (mOsm/kg)

Diluent	Concentration			
	3%	6%	9%	12%
0.9% NaCl	498	690	882	1074
5% Dextrose	444	636	828	1020
Sterile Water	192	384	576	768

CLINICAL PHARMACOLOGY

Carimune® NF contains a broad spectrum of antibody specificities against bacterial, viral, parasitic, and mycoplasma antigens, that are capable of both opsonization and neutralization of microbes and toxins. The 3 week half-life of Carimune® NF corresponds to that of Immune Globulin (Human) for intramuscular use, although individual variations in half-life have been observed (13, 14).

Appropriate doses of Carimune® NF restore abnormally low immunoglobulin G levels to the normal range. One hundred percent of the infused dose of IGIV-products is available in the recipient's circulation immediately after infusion. After approximately 6 days, equilibrium is reached between the intra- and extravascular compartments, with immunoglobulin G being distributed approximately 50% intravascular and 50% extravascular. In comparison, after the intramuscular injection of immune globulin, the IgG requires 2–5 days to reach its maximum concentration in the intravascular compartment. This concentration corresponds to about 40% of the injected dose (14).

While Carimune® NF has been shown to be effective in some cases of Immune Thrombocytopenic Purpura (ITP) (see INDICATIONS AND USAGE), the mechanism of action in ITP has not been fully elucidated. Toxicity from overdose has not been observed on regimens of 0.4 g/kg body weight each day for 5 days (15–17). Sucrose is added to Carimune® NF for reasons of stability and solubility. Since sucrose is excreted unchanged in the urine when given intravenously, Carimune® NF may be given to diabetics without compensatory changes in insulin dosage regimen. Please see WARNINGS section.

INDICATIONS AND USAGE

Immunodeficiency

Carimune® NF is indicated for the maintenance treatment of patients with primary immunodeficiencies (PID), e.g., common variable immunodeficiency, X-linked agammaglobulinemia, severe combined immunodeficiency (16, 18–20). Carimune® NF is preferable to intramuscular Immune Globulin (Human) preparations in treating patients who require an immediate and large increase in the intravascular immunoglobulin level (14), in patients with limited muscle mass, and in patients with bleeding tendencies for whom intramuscular injections are contraindicated. The infusions must be repeated at regular intervals. Please see DOSAGE AND ADMINISTRATION section.

Immune Thrombocytopenic Purpura (ITP)

Acute

A controlled study was performed in children in which Immune Globulin Intravenous (Human), Carimune, was compared with steroids for the treatment of acute (defined as less than 6 months duration) ITP. In this study sequential platelet levels of 30,000, 100,000, and 150,000/μL were all achieved faster with Carimune than with steroids and without any of the side effects associated with steroids (15, 21). However, it should be noted that many cases of acute ITP in childhood resolve spontaneously within weeks to months. Carimune has been used with good results in the treatment of acute ITP in adult patients (22–24). In a study involving 10 adults with ITP of less than 16 weeks duration, Carimune therapy raised the platelet count to the normal range after a 5 day course. This effect lasted a mean of over 173 days, ranging from 30 to 372 days (25).

Chronic

Children and adults with chronic (defined as greater than 6 months duration) ITP have also shown an increase (sometimes temporary) in platelet counts upon administration of Carimune (21, 25–29). Therefore, in situations that require a rapid rise in platelet count, for example prior to surgery or to control excessive bleeding, use of Carimune should be considered. In children with chronic ITP, Carimune therapy resulted in a mean rise in platelet count of 312,000/μL with a duration of increase ranging from 2 to 6 months (26, 29). Carimune therapy may be considered as a means to defer or avoid splenectomy (28–30). In adults, Carimune therapy has been shown to be effective in maintaining the platelet count in an acceptable range with or without periodic booster therapy. The mean rise in platelet count was 93,000/μL and the average duration of the increase was 20–24 days (25, 26). However, it should be noted that not all patients will respond. Even in those patients who do respond, this treatment should not be considered to be curative.

CONTRAINDICATIONS

As with all blood products containing IgA, Immune Globulin Intravenous (Human) (IGIV), Carimune® NF is contraindicated in patients with selective IgA deficiency, who possess antibody to IgA. It may also be contraindicated in patients who have had severe systemic reactions to the intravenous or intramuscular administration of human immune globulin.

WARNINGS

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death (31–36).

Patients predisposed to acute renal failure include patients with:

1. any degree of pre-existing renal insufficiency
2. diabetes mellitus
3. age greater than 65
4. volume depletion
5. sepsis
6. paraproteinemia
7. patients receiving known nephrotoxic drugs

In such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Carimune® NF is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and through the application of viral elimination/reduction steps such as alcohol fractionation in the presence of filter aids, nanofiltration and pH4/pepsin treatment (5–7; see Table 1). Despite these measures, such products may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

Patients with agammaglobulinemia or extreme hypogammaglobulinemia who have never before received immunoglobulin substitution treatment or whose time from last treatment is greater than 8 weeks, may be at risk of developing inflammatory reactions on rapid infusion (greater than 1 mL per minute) of Carimune® NF. These reactions are manifested by a rise in temperature, chills, nausea, and vomiting. The patient's vital signs should be monitored continuously. The patient should be carefully observed throughout the infusion, since these reactions on rare occasions may lead to shock. Epinephrine should be available for treatment of an acute anaphylactic reaction.

PRECAUTIONS

Please see DOSAGE AND ADMINISTRATION below, for important information on Carimune® NF compatibility with other medications or fluids. Patients should not be volume depleted prior to the initiation of the infusion of IGIV. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, should be assessed prior to the initial infusion of Carimune® NF and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing Carimune® NF at a rate less than 2 mg/kg/min.

Information for Patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

Laboratory Tests

IGIV recipients should be monitored for clinical signs and symptoms of hemolysis. IGIV recipients should be monitored for pulmonary adverse reactions. If Transfusion-Related Acute Lung Injury (TRALI) is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

Pregnancy Category C

Animal reproduction studies have not been conducted with Carimune® NF. It is also not known whether Carimune® NF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Carimune® NF should be given to a pregnant woman only if clearly needed (24). Intact immune globulins such as those contained in Carimune® NF cross the placenta from maternal circulation increasingly after 30 weeks gestation (37, 38). In cases of maternal ITP where Immune Globulin Intravenous (Human), Carimune was administered to the mother prior to delivery, the platelet response and clinical effect were similar in the mother and neonate (24, 38–47).

Pediatric Use

High dose administration of Carimune in pediatric patients with acute or chronic Immune Thrombocytopenic Purpura did not reveal any pediatric-specific hazard (15). Antibodies in Immune Globulin Intravenous (Human) may impair the efficacy of live attenuated viral vaccines such as measles, rubella, and mumps (48–50). Immunizing physicians should be informed of recent therapy with Immune Globulin Intravenous (Human) so that appropriate precautions may be taken.

Geriatric Use

Carimune® NF should be used with caution in patients over 65 years of age and judged to be at increased risk of developing renal insufficiency (see section DOSAGE AND ADMINISTRATION). In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable. The product should be infused at a rate less than 2 mg/kg/min.

Aseptic Meningitis Syndrome

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) (IGIV) treatment. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to

rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis

Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolytic agents and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis (51–53). Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (54) (see ADVERSE REACTIONS). IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (see PRECAUTIONS: Laboratory Tests).

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema Transfusion-Related Acute Lung Injury (TRALI) in patients administered IGIV (55). TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1–6 hrs after transfusion. Patients with TRALI may be managed by using oxygen therapy with adequate ventilatory support.

IVIG recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see PRECAUTIONS: Laboratory Tests).

Thrombotic Events

Thrombotic events have been reported in association with IGIV (56–63) (see ADVERSE REACTIONS). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see PRECAUTIONS: Laboratory Tests).

ADVERSE REACTIONS

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion. Progression to oliguria or anuria, requiring dialysis has been observed. Types of severe renal adverse events that have been seen following IGIV therapy include: acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis (31–36, 64, 71–73). Inflammatory adverse reactions have been described in agammaglobulinemic and hypogammaglobulinemic patients who have never received immunoglobulin substitution therapy before or in patients whose time from last treatment is greater than 8 weeks and whose initial infusion rate exceeds 1 mL per minute.

This occurs in approximately 10% of such cases. Such reactions may also be observed in some patients during chronic substitution therapy. These reactions, which generally become apparent only 30 minutes to 1 hour after the beginning of the infusion, are as follows: flushing of the face, feelings of tightness in the chest, chills, fever, dizziness, nausea, diaphoresis, and hypotension. In such cases the infusion should be temporarily stopped until the symptoms have subsided. Immediate anaphylactoid and hypersensitivity reactions due to previous sensitization of the recipient to certain antigens, most commonly IgA, may be observed in exceptional cases, described under CONTRAINDICATIONS (16, 17, 65). In patients with ITP, who receive higher doses (0.4 g/kg/day or greater), 2.9% of infusions may result in adverse reactions (21). Headache, generally mild, is the most common symptom noted, occurring during or following 2% of infusions. A few cases of usually mild hemolysis have been reported after infusion of intravenous immunoglobulin products (51–53). These were attributed to transferal of blood group (e.g., anti-D) antibodies.

Postmarketing

The following adverse reactions have been identified and reported during the post-approval use of IGIV products:

Respiratory

Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm

Cardiovascular

Cardiac arrest, thromboembolism, vascular collapse, hypotension

Neurological

Coma, loss of consciousness, seizures, tremor

Integumentary

Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis

Hematologic

Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test

General/Body as a Whole

Pyrexia, rigors

Musculoskeletal

Back pain

Gastrointestinal

Hepatic dysfunction, abdominal pain

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently (66).

DOSAGE AND ADMINISTRATION

It is generally advisable not to dilute plasma derivatives with other infusible drugs. Immune Globulin Intravenous (Human) (IGIV), Carimune® NF, should be given by a separate infusion line. No other medications or fluids should be mixed with Carimune® NF preparation.

Carimune® NF should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs). In these cases especially it is important to assure that patients are not volume depleted prior to Carimune® NF infusion. No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable. The product should be infused at a rate less than 2 mg/kg/min.

Adult and Child Substitution Therapy

The usual dose of Carimune® NF in immunodeficiency syndromes is 0.2 g/kg of body weight administered once a month by intravenous infusion. If the clinical response is inadequate, the dose may be increased to 0.3 g/kg of body weight or the infusion may be repeated more frequently than once a month (16, 18–20).

The first infusion of Carimune® NF in previously untreated agammaglobulinemic or hypogammaglobulinemic patients must be given as a 3% immunoglobulin solution (use the total volume of fluid provided, or see Table 3, to reconstitute the lyophilized product).

1. Start with a flow rate of 10–20 drops (0.5–1.0 mL) per minute.
2. After 15–30 minutes the rate of infusion may be further increased to 30–50 drops (1.5–2.5 mL) per minute.
3. After the first bottle of 3% solution is infused and the patient shows good tolerance, subsequent infusions may be administered at a higher rate or concentration. Such increases should be made gradually allowing 15–30 minutes before each increment.

The first infusion of Carimune® NF in previously untreated agammaglobulinemic and hypogammaglobulinemic patients may lead to systemic side effects. The nature of these effects has not been fully elucidated. Some of them may be due to the release of proinflammatory cytokines by activated macrophages in immunodeficient recipients (67, 68). Subsequent administration of Carimune® NF to immunodeficient patients as well as to normal individuals usually does not cause further untoward side effects.

Therapy of Idiopathic Thrombocytopenic Purpura (ITP)

Induction

0.4 g/kg of body weight on 2–5 consecutive days.

Acute ITP – Childhood

In acute ITP of childhood, if an initial platelet count response to the first two doses is adequate (30–50,000/ μ L), therapy may be discontinued after the second day of the 5 day course (21).

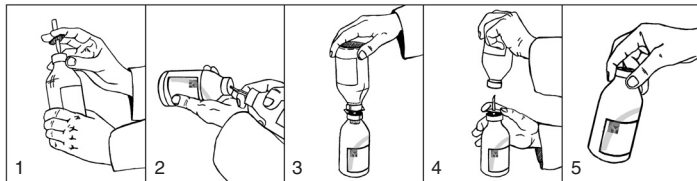
Maintenance – Chronic ITP

In adults and children, if after induction therapy the platelet count falls to less than 30,000/ μ L and/or the patient manifests clinically significant bleeding, 0.4 g/kg of body weight may be given as a single infusion. If an adequate response does not result, the dose can be increased to 0.8–1.0 g/kg of body weight given as a single infusion (22, 69, 70).

Reconstitution

(see also pictures below)

1. Remove the protective plastic caps from the lyophilisate and diluent bottles and disinfect both rubber stoppers with alcohol. Remove the protective cover from one end of the transfer set and insert the exposed needle through the rubber stopper into the bottle containing the diluent.
- 2 and 3. Remove the second protective cover from the other end of the transfer set. Grasp both bottles as shown in picture 2, quickly plunge the diluent bottle onto the lyophilisate bottle and bring the bottles into an upright position. Only if this is done quickly and the bottles are immediately brought into an upright position can the vacuum in the lyophilisate bottle be maintained, thus speeding up reconstitution and facilitating the transfer. Allow the diluent to flow into the lyophilisate bottle.
4. Once the appropriate amount of diluent is transferred (see Table 3), lift the diluent bottle off the spike to release the vacuum. This will reduce foaming and facilitate dissolution. Remove the spike.
5. Swirl vigorously but do not shake, otherwise a foam will form which is very slow to subside. The lyophilisate dissolves within a few minutes.



To reconstitute Immune Globulin Intravenous (Human) (IGIV), Carimune® NF from the individual vial package, or when using other diluents or higher concentrations, Table 3 indicates the volume of sterile diluent required. Observing aseptic technique, this volume should be drawn into a sterile hypodermic syringe and needle. The diluent is then injected into the corresponding Carimune® NF vial size.

Table 3
Required Diluent Volume*

Target Concentration	1 g Vial	3 g Vial	6 g Vial	12 g Vial
3%	33.0 cc	100 cc	200 cc	**
6%	16.5 cc	50 cc	100 cc	200 cc
9%	11.0 cc	33 cc	66 cc	132 cc
12%	8.3 cc	25 cc	50 cc	100 cc

* In patients judged to be at increased risk of developing renal insufficiency, the concentration and infusion rate of Carimune® NF should be the minimum practicable.

** Container not large enough to permit this concentration.

If large doses of Carimune® NF are to be administered, several reconstituted vials of identical concentration and diluent may be pooled in an empty sterile glass or plastic i.v. infusion container using aseptic technique.

Carimune® NF normally dissolves within a few minutes, though in exceptional cases it may take up to 20 minutes.

DO NOT SHAKE! Excessive shaking will cause foaming.

Any undissolved particles should respond to careful rotation of the bottle. Avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Filtering of Carimune® NF is acceptable but not required. Pore sizes of 15 microns or larger will be less likely to slow infusion, especially with higher Carimune® NF concentrations. Antibacterial filters (0.2 microns) may be used. When reconstitution of Carimune® NF occurs outside of sterile laminar air flow conditions, administration must begin promptly with partially used vials discarded. When reconstitution is carried out in a sterile laminar flow hood using aseptic technique, administration may begin within 24 hours provided the solution has been refrigerated during that time. Do not freeze Carimune® NF solution.

PROCEED WITH INFUSION ONLY IF SOLUTION IS CLEAR AND AT APPROXIMATELY ROOM TEMPERATURE! HOW SUPPLIED

Carimune® NF is available as a white lyophilized powder in 1, 3, 6 and 12 g size vials. The only diluents which may be used to reconstitute the product are sterile (0.9%) Sodium Chloride Injection USP, 5% Dextrose, or Sterile Water. Carimune® NF is available in individual vial packages.

1 g Individual vial package (NDC 44206-415-01)

3 g Individual vial package (NDC 44206-416-03)

6 g Individual vial package (NDC 44206-417-06)

12 g Individual vial package (NDC 44206-418-12)

Please see Table 2 for Calculated Carimune® NF Osmolality (mOsm/kg).

Storage and Dispense

Carimune® NF should be stored at room temperature not exceeding 30 °C (86 °F). The preparation should not be used after the expiration date printed on the label.

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