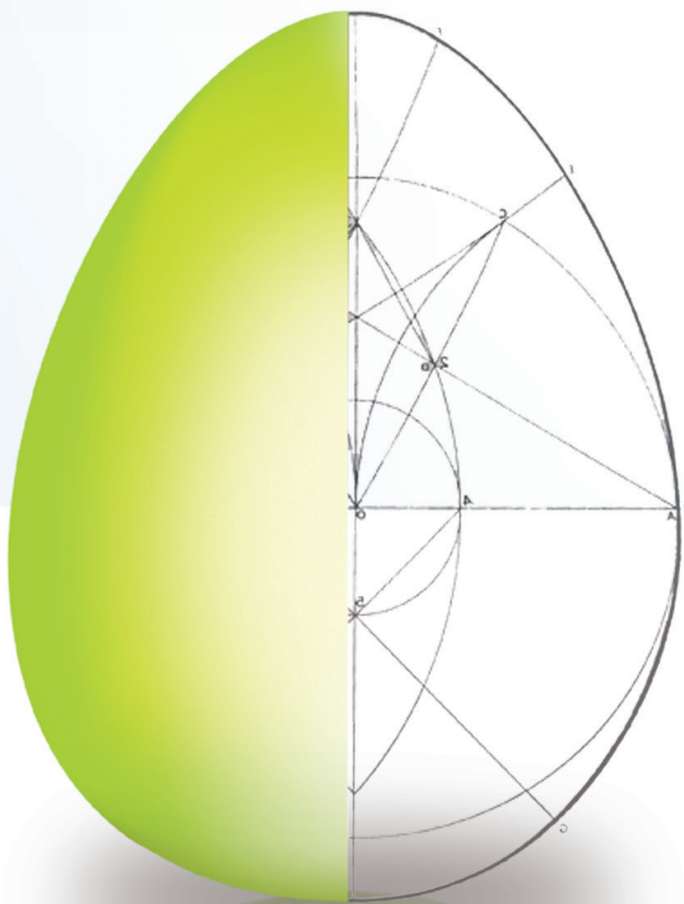


# Know your IVIg options for primary immunodeficiency



**Simple**

**Sophisticated**

**Safe**

10% Liquid Intravenous  
Immunoglobulin(IVIg) Therapy

Biotherapies for Life<sup>®</sup> **CSL Behring**

Please see full Important Safety Information for Privigen and Carimune NF on following pages and full prescribing information, including boxed warning, in pocket.

When the choice is IVIg therapy

## Discover why so many rely on **Privigen**

Simple	Sophisticated	Safe
<ul style="list-style-type: none"><li>• Convenient, ready-to-use 10% liquid IVIg</li><li>• Room-temperature storage for up to 36 months</li><li>• Available in 4 vial sizes</li></ul>	<ul style="list-style-type: none"><li>• First and only 10% IVIg stabilized with proline (contraindicated in patients with hyperprolinemia)</li><li>• Sugar free</li></ul>	<ul style="list-style-type: none"><li>• Proprietary 3-step inactivation/removal process*</li></ul> <p>*The risk of virus transmission cannot be completely eliminated</p>

For information on how to guarantee your Privigen supply through **The Privigen Promise** supply guarantee, go to [Privigen.com](http://Privigen.com).



### Important Safety Information for Privigen

Privigen is indicated as replacement therapy for 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 raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

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### WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including Privigen. 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 human immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen 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 full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA, who have had hypersensitivity reactions. Patients with IgA deficiency and antibodies to IgA are at greater risk of severe hypersensitivity and anaphylactic reactions.

In patients at risk for developing acute renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine; discontinue if renal function deteriorates. Ensure that patients with preexisting renal insufficiency or otherwise predisposed are not volume-depleted and administer Privigen at the minimum rate of infusion practicable.

Thrombosis might occur with Privigen, even in the absence of known risk factors. Patients could also experience hyperproteinemia, increased serum viscosity, or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur—more frequently with high doses (2 g/kg) and/or rapid infusion.

Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to treatment. Risk factors include non-O blood group, underlying inflammation, and high doses. Closely monitor patients for hemolysis and hemolytic anemia. Consider the relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload. Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

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

In clinical studies of patients being treated with Privigen for PI, the most common adverse reactions observed in >5% of subjects were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature.

In clinical studies of patients being treated with Privigen for chronic ITP, the most common adverse reactions seen in >5% of subjects were headache, elevated body temperature, positive DAT, anemia, nausea, epistaxis, vomiting, increases in conjugated and unconjugated bilirubin, decreased hematocrit, and increased blood lactate dehydrogenase. A serious adverse reaction was aseptic meningitis syndrome (AMS).

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing. Use in pregnant women only if clearly needed. In patients over 65 or in any patient at risk of developing renal insufficiency, do not exceed recommended dose and infuse Privigen at the minimum rate practicable.

Please see full prescribing information for Privigen, including boxed warning, in pocket.

Please see full Important Safety Information for Privigen on following page and full prescribing information, including boxed warning, in pocket.



Please see full Important Safety Information for Privigen above and full prescribing information, including boxed warning, in pocket.



## 36-Month Shelf Life, Room-Temperature Storage

### Privigen is a ready-to-use 10% liquid IgG preparation, requiring no reconstitution.

Privigen has been shown to maintain efficacy and stability at room temperature for up to 36 months.

Room-temperature stability eliminates the need for special refrigerated storage facilities, and, importantly, allows immediate infusion without the need to warm the solution to room temperature prior to administration.

### Available in four convenient vial sizes.

To accommodate the dose needed, Privigen offers 4 vial sizes, including the largest size of IVIg available:

5 g (50 mL)

10 g (100 mL)

20 g (200 mL)

40 g (400 mL)



### Important Safety Information for Privigen

#### WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

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See full prescribing information for complete boxed warning.

Please see full Important Safety Information for Privigen on following page and full prescribing information, including boxed warning, in pocket.

  
privigen®  
Immune Globulin Intravenous  
(Human), 10% Liquid

# Review your IVIg options for primary immunodeficiency

Feature	Privigen® Immune Globulin Intravenous (Human), 10% Liquid CSL Behring AG	Carimune® NF Immune Globulin Intravenous (Human) CSL Behring AG	Bivigam® Immune Globulin Intravenous (Human), 10% Liquid Biotest Pharmaceuticals Corporation <sup>1</sup>	Gammaked™ Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified Kedrion Biopharma, Inc. <sup>2</sup>	Gamunex®-C Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified Grifols Therapeutics Inc. <sup>3</sup>	Gammagard® Liquid Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration Baxter Healthcare Corporation <sup>4</sup>	Gammagard® S/D Immune Globulin Intravenous (Human) Baxter Healthcare Corporation <sup>5</sup>	Flebogamma® 5% DIF Immune Globulin Intravenous (Human) Instituto Grifols, S.A. <sup>6</sup>	Flebogamma® 10% DIF Immune Globulin Intravenous (Human) Instituto Grifols, S.A. <sup>7</sup>	Octagam® Immune Globulin Intravenous (Human) 5% Liquid Preparation Octapharma USA Inc. <sup>8</sup>	Gammaplex® Immune Globulin Intravenous (Human), 5% Liquid Bio Products Laboratory Limited <sup>9</sup>
<b>Concentration/Dosage form</b>	Ready-to-use 10% liquid	<ul style="list-style-type: none"> <li>Lyophilized powder ranging from 3% to 12% concentration</li> <li>Reconstitution required prior to administration</li> </ul>	Ready-to-use liquid	Ready-to-use 10% liquid	Ready-to-use 10% liquid	Ready-to-use 10% liquid	<ul style="list-style-type: none"> <li>Freeze-dried</li> <li>Reconstitution required prior to administration</li> </ul>	Ready-to-use 5% liquid	Ready-to-use 10% liquid	Ready-to-use 5% liquid	Ready-to-use 5% liquid
<b>Vial sizes, grams (mL)</b>	5 g (50 mL), 10 g (100 mL), 20 g (200 mL), 40 g (400 mL)	3 g, 6 g, 12 g white lyophilized powder for reconstitution	5 g (50 mL), 10 g (100 mL)	1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL)	1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL), 40 g (400 mL)	1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL), 30 g (300 mL)	2.5 g, 5 g, 10 g freeze-dried preparation for reconstitution	0.5 g (10 mL), 2.5 g (50 mL), 5 g (100 mL), 10 g (200 mL), 20 g (400 mL)	5 g (50 mL), 10 g (100 mL), 20 g (200 mL)	1 g (20 mL), 2.5 g (50 mL), 5 g (100 mL), 10 g (200 mL), 25 g (500 mL)	2.5 g (50 mL), 5 g (100 mL), 10 g (200 mL), 20 g (400 mL)
<b>Storage requirement</b>	36 months at room-temperature storage up to 25°C (77°F)	24 months at ≤30°C (86°F)	Store at 2°–8°C (36°–46°F) until expiration date on vial packaging; do not freeze or heat	<ul style="list-style-type: none"> <li>36 months at refrigerated temperature 2°–8°C (36°–46°F). Do not freeze</li> <li>Up to 6 months at temperatures not to exceed 25°C (77°F) anytime during the 36-month shelf life</li> <li>Must be discarded after 6 months</li> </ul>	<ul style="list-style-type: none"> <li>36 months at refrigerated temperature 2°–8°C (36°–46°F). Do not freeze</li> <li>Up to 6 months at temperatures not to exceed 25°C (77°F) anytime during the 36-month shelf life</li> </ul>	<ul style="list-style-type: none"> <li>Store Gammagard Liquid in the refrigerator or at room temperature</li> <li>Refrigeration: 2°–8°C (36°–46°F) for up to 36 months. Do not freeze</li> <li>Room temperature: Up to 25°C (77°F) for up to 24 months</li> </ul>	24 months unconstituted; temperature not to exceed 25°C (77°F). Do not freeze.	24 months from date of manufacture at room temperature 2°–25°C (36°–77°F). Do not freeze.	Up to 24 months from date of manufacture at room temperature 2°–25°C (36°–77°F). Do not freeze.	24 months from date of manufacture at 2°–25°C (36°–77°F). Do not freeze.	24 months at 2°–25°C (36°–77°F) until expiration date. Protect from light; do not freeze.
<b>Sucrose/Sugars</b>	None	1.67 g sucrose per gram of protein	None	None	None	None	20 mg/mL glucose in a 5% solution	Contains D-sorbitol	Contains D-sorbitol	100 mg/mL maltose	5 g D-sorbitol in 100 mL of buffer solution
<b>IgA content</b>	≥25 mcg/mL	Trace amounts	Trace amounts of IgA (≤200 mcg/mL)	Trace amounts of IgA (average 46 mcg/mL)	Trace amounts of IgA (average 46 mcg/mL)	37 mcg/mL	<1 mcg/mL	<50 mcg/mL	<100 mcg/mL	≤200 mcg/mL	<10 mcg/mL
<b>Stabilizer</b>	Proline <sup>1</sup> : ~250 mmol/L (range 210–290)	Sucrose	Glycine and polysorbate 80	Glycine	Glycine	Glycine	Glycine, glucose, and polysorbate 80	D-sorbitol	D-sorbitol	Maltose	Sorbitol, glycine, and polysorbate 80
<b>IgG purity</b>	≥98%	≥96%	≥96%	≥98%	≥98%	≥98%	≥90%	≥97%	≥97%	≥96%	>95%
<b>Median half-life</b>	36.6 days	21 days	30 days	35 days	35 days	35 days	21 to 25 days in healthy individuals; 18 to 38 days in immunodeficient patients	<ul style="list-style-type: none"> <li>30 days (mean) for patients on 3-week dosing schedule</li> <li>32 days (mean) for patients on 4-week dosing schedule</li> </ul>	<ul style="list-style-type: none"> <li>34 days (mean) for patients on 3-week dosing schedule</li> <li>37 days (mean) for patients on 4-week dosing schedule</li> </ul>	36 days	<ul style="list-style-type: none"> <li>42±26 days for 21-day dosing interval</li> <li>41±14 days for 28-day dosing interval</li> </ul>
<b>Sodium</b>	Trace amounts	<20 mg NaCl/g of protein	0.100–0.140 M (0.100–0.140 mol/L) sodium chloride	0.9% sodium chloride for injection	0.9% sodium chloride for injection	No sodium added	~8.5 mg/mL sodium chloride	Trace amounts	Trace amounts	≤30 mmol/L	0.2 g sodium acetate and 0.3 g sodium chloride in 100 mL of buffer solution
<b>Osmolality</b>	~320 mOsmol/kg (range 240–440)	<ul style="list-style-type: none"> <li>In sterile water—3%: 192 mOsm/kg; 6%: 384 mOsm/kg; 9%: 576 mOsm/kg; 12%: 768 mOsm/kg</li> <li>In 5% dextrose—3%: 444 mOsm/kg; 6%: 636 mOsm/kg; 9%: 828 mOsm/kg; 12%: 1020 mOsm/kg</li> <li>In 0.9% saline—3%: 498 mOsm/kg; 6%: 690 mOsm/kg; 9%: 882 mOsm/kg; 12%: 1074 mOsm/kg</li> </ul>	No mention in labeling	258 mOsmol/kg	258 mOsmol/kg	240–300 mOsmol/kg	Not addressed in labeling	240–370 mOsm/L	240–370 mOsm/kg	310–380 mOsmol/kg	≥/≈ 240 mOsmol/kg (typically 42–500 mOsmol/kg)
<b>Latex content</b>	Packing components are not made with natural rubber latex	None	None	None	None	None	Not made with natural rubber latex	None	Not addressed in labeling	None	Packaging latex free
<b>Boxed Warnings</b>	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies	Boxed warning on administration in patients at risk of thrombosis, renal dysfunction, or renal failure applies
<b>Diluent</b>	May be diluted with dextrose injection	Sodium chloride, dextrose, or sterile water	Do not dilute	If dilution is required, may be diluted with 5% dextrose in water	If dilution is required, may be diluted with 5% dextrose in water	If dilution is desired, may be diluted with 5% dextrose in water	Sterile water for injection	None	None	None	None
<b>Dimers</b>	Specification ≤12%	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not <90% monomers and dimers	Not available
<b>Pathogen safety<sup>b</sup></b>	<ul style="list-style-type: none"> <li>Low pH 4 incubation</li> <li>Depth filtration—a virus partitioning process</li> <li>Nanofiltration (to ~20 nm)</li> <li>Validated Transmittable Spongiform Encephalopathy reduction steps</li> </ul>	<ul style="list-style-type: none"> <li>Fractionation and depth filtration</li> <li>pH 4/pepsin treatment</li> <li>Nanofiltration</li> <li>Validated Transmittable Spongiform Encephalopathy reduction steps</li> </ul>	<ul style="list-style-type: none"> <li>Precipitation and removal of fraction III/Depth filtration</li> <li>Solvent/detergent treatment</li> <li>35 nm virus filtration</li> </ul>	<ul style="list-style-type: none"> <li>Caprylate precipitation/Depth filtration</li> <li>Caprylate incubation</li> <li>Depth filtration</li> <li>Column chromatography</li> <li>Low pH incubation</li> </ul>	<ul style="list-style-type: none"> <li>Caprylate precipitation/Depth filtration</li> <li>Caprylate incubation</li> <li>Depth filtration</li> <li>Column chromatography</li> <li>Low pH incubation</li> </ul>	<ul style="list-style-type: none"> <li>Solvent/Detergent (S/D) treatment</li> <li>35 nm nanofiltration</li> <li>Low pH incubation at elevated temperature</li> </ul>	<ul style="list-style-type: none"> <li>Processing of cryo-poor plasma to Fraction I+II+III precipitate</li> <li>S/D treatment</li> </ul>	<ul style="list-style-type: none"> <li>Pasteurization</li> <li>S/D treatment</li> <li>Nanofiltration using 20 nm Planova filters</li> <li>Fraction I precipitation</li> <li>Fraction II+III precipitation</li> <li>4% PEG precipitation</li> <li>Acid pH treatment</li> </ul>	<ul style="list-style-type: none"> <li>Pasteurization</li> <li>S/D treatment</li> <li>Nanofiltration using 20 nm Planova filters</li> <li>Fraction I precipitation</li> <li>Fraction II+III precipitation</li> <li>4% PEG precipitation</li> <li>Acid pH treatment</li> </ul>	<ul style="list-style-type: none"> <li>Cold ethanol fractionation</li> <li>S/D treatment</li> <li>pH 4 treatment</li> </ul>	<ul style="list-style-type: none"> <li>S/D treatment</li> <li>Virus filtration</li> <li>pH incubation</li> </ul>
<b>Initial infusion rate</b>	<ul style="list-style-type: none"> <li>0.5 mg/kg/min (0.005 mL/kg/min)</li> <li>Minimum rate practicable in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>Initial: 0.5 mg/kg/min</li> <li>After 30 min, increase to 1 mg/kg/min as tolerated</li> <li>Minimum rate practicable in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>0.5 mg/kg/min (0.005 mL/kg/min)</li> <li>Minimum rate practicable in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>0.01 mL/kg/min (starting rate for patients with PID)</li> <li>Minimum rate practicable in high-risk patients</li> </ul>	0.01 mL/kg/min (starting rate for patients with PID)	0.5 mL/kg/h (0.8 mg/kg/min) for 30 minutes	0.5 mL/kg/h (5%)	0.01 mL/kg/min	0.01 mL/kg/min	<ul style="list-style-type: none"> <li>0.5 mg/kg/min (0.005 mL/kg/min)</li> <li>Minimum rate practicable in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>0.01 mL/kg/min</li> <li>Minimum rate practicable in high-risk patients</li> </ul>
<b>Maximum infusion rate for PID</b>	<ul style="list-style-type: none"> <li>Gradually increase to 8 mg/kg/min (0.08 mL/kg/min) as tolerated</li> <li>Administer at the minimum rate of infusion for those with renal dysfunction/impairment and other high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase as tolerated—not to exceed 3 mg/kg/min; 2 mg/kg/min for high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>Increase every 20 minutes (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to 0.08 mL/kg/min as tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to 0.08 mL/kg/min as tolerated</li> </ul>	<ul style="list-style-type: none"> <li>IV administration: <ul style="list-style-type: none"> <li>Increase every 30 minutes (if tolerated) up to 5 mL/kg/h</li> </ul> </li> <li>Subcutaneous administration: <ul style="list-style-type: none"> <li>40 kg BW and greater: 30 mL/site at 20–30 mL/h/site</li> <li>Under 40 kg BW: 20 mL/site at 15–20 mL/h/site</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to 4 mL/kg/h (5%) as tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to 0.10 mL/kg/min as tolerated</li> <li>Administer at the minimum rate of infusion for those with renal dysfunction/impairment and other high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to 0.08 mL/kg/min as tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to &lt;0.07 mL/kg/min as tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Gradually increase to 0.08 mL/kg/min as tolerated</li> </ul>

<sup>1</sup>Proline is 1 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 and analysis. Privigen is contraindicated in patients with hyperprolinemia.

<sup>2</sup>The risk of transmission of infectious agents cannot be completely eliminated.





For more information, contact IglQ at  
**1-877-355-IGIQ (4447) Monday-Friday, 8 AM to 8 PM ET.**

#### Important Safety Information for Carimune NF

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

#### **WARNING: THROMBOSIS, RENAL DYSFUNCTION or ACUTE RENAL FAILURE**

- **Thrombosis may occur with immune globulin products, including Carimune NF. 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 might occur in absence of known risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death can occur in predisposed patients with immune globulin intravenous (IGIV) products, including Carimune NF. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age over 65, volume depletion, sepsis, paraproteinemia, and those receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Carimune NF contains sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Carimune NF 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 full prescribing information for full boxed warning.

Carimune NF is contraindicated in patients who have had anaphylactic or severe systemic reactions to the administration of human immune globulin. Individuals with selective IgA deficiency who possess antibody to IgA should only receive Carimune NF with utmost caution due to risk of severe, immediate hypersensitivity reactions, including anaphylaxis.

Increases in creatinine and blood urea nitrogen with progression to oliguria or anuria requiring dialysis have been observed as soon as one to two days following IGIV infusion. Severe renal adverse events have included acute renal failure, acute tubular nephrosis, proximal tubular nephropathy, and osmotic nephrosis.

Patients receiving Carimune NF should be monitored for clinical signs and symptoms of hemolysis, as well pulmonary adverse reactions, including TRALI. An aseptic meningitis syndrome (AMS) has been reported to occur infrequently with IVIG—more frequently in association with high dose (2 g/kg) treatment.

Inflammatory adverse reactions have been observed; they may become apparent within 30 minutes to an hour after beginning infusion. Slow or temporarily stop infusion if patient experiences facial flushing, tightness in chest, chills, fever, nausea, dizziness or other unusual response; stop infusion immediately if anaphylaxis or severe reaction occurs. Headache, usually mild, is the most common adverse reaction; mild hemolysis, arthralgia, myalgia, and transient skin reactions have also been reported.

Carimune NF is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Carimune NF should be given to a pregnant woman only if clearly needed.

**Please see full prescribing information for Carimune, including boxed warning on thrombosis and renal dysfunction/failure, in pocket.**

**References:** 1. Bivigam [package insert]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; 2013. 2. Gammaked [package insert]. Fort Lee, NJ: Kedrion Biopharma, Inc.; 2013. 3. Gamunex-C [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; 2014. 4. Gammagard Liquid [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; 2014. 5. Gammagard S/D [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; 2014. 6. Flebogamma 5% DIF [package insert]. Barcelona, Spain: Instituto Grifols, S.A.; 2014. 7. Flebogamma 10% DIF [package insert]. Barcelona, Spain: Instituto Grifols, S.A.; 2013. 8. Octagam [package insert]. Hoboken, NJ: Octapharma USA Inc.; 2013. 9. Gammaplex [package insert]. Hertfordshire, UK: Bio Products Laboratory Limited; 2014.

Biotherapies for Life® **CSL Behring**

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## 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 .

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid  
Initial U.S. Approval: 2007

### WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including Privigen. 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 immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Privigen does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen 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.**

### RECENT MAJOR CHANGES

Boxed Warning	09/2013, 11/2013
Dosage and Administration (2)	09/2013
Warnings and Precautions (5.2, 5.3)	09/2013, 11/2013

### INDICATIONS AND USAGE

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

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

### DOSAGE AND ADMINISTRATION

#### Intravenous Use Only

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (as tolerated)
PI	200-800 mg/kg (2-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

- Ensure that patients with pre-existing renal insufficiency are not volume depleted, and discontinue Privigen if renal function deteriorates (2.4, 5.2).
- For patients at risk of renal dysfunction or thrombosis, administer Privigen at the minimum dose and infusion rate practicable (2.4, 5.2, 5.3).

### DOSAGE FORMS AND STRENGTHS

Privigen is a liquid solution containing 10% IgG (0.1 g/mL) (3).

### CONTRAINDICATIONS

- History of anaphylactic or severe systemic reaction to human immune globulin (4)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

#### 1 INDICATIONS AND USAGE

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- 1.2 Chronic Immune Thrombocytopenic Purpura

#### 2 DOSAGE AND ADMINISTRATION

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- 5.10 Interference with Laboratory Tests

- Hyperprolinemia (Privigen contains the stabilizer L-proline) (4)
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (4)

### WARNINGS AND PRECAUTIONS

- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions (5.1).
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure (5.2).
- Thrombosis may occur with immune globulin products, including Privigen (5.3).
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur (5.4).
- Aseptic meningitis syndrome (AMS) may occur, especially with high doses or rapid infusion (5.5).
- Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to Privigen treatments. Risk factors for hemolysis include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia (5.6).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]) (5.7).
- Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload (5.8).
- Privigen is made from human blood and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.9).

### ADVERSE REACTIONS

- **PI** – The most common adverse reactions, observed in >5% of study subjects, were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature (6).
- **Chronic ITP** – The most common adverse reactions, observed in >5% of study subjects, were headache, elevated body temperature, positive direct antiglobulin test (DAT), anemia, nausea, epistaxis, vomiting, blood bilirubin unconjugated increased, blood bilirubin conjugated increased, blood total bilirubin increased, hematocrit decreased, and blood lactate dehydrogenase increased. A serious adverse reaction was aseptic meningitis (6).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

The passive transfer of antibodies may:

- Lead to misinterpretation of the results of serological testing (5.10).
- Interfere with the response to live virus vaccines (7.1).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Geriatric: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Privigen at the minimum rate practicable (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November 2013

## 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
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\* Sections or subsections omitted from the full prescribing information are not listed.

# Privigen<sup>®</sup>, Immune Globulin Intravenous (Human), 10% Liquid

## WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- Thrombosis may occur with immune globulin products<sup>1-3</sup>, including Privigen. 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 (5.3), Patient Counseling Information (17)*].
- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.<sup>4</sup> Privigen does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction or failure, administer Privigen 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 (2.3), Warnings and Precautions (5.2, 5.3)*].

## 1 INDICATIONS AND USAGE

Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of the following conditions.

### 1.1 Primary Humoral Immunodeficiency

Privigen is indicated as replacement therapy for primary humoral immunodeficiency (PI). This 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.

### 1.2 Chronic Immune Thrombocytopenic Purpura

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

## 2 DOSAGE AND ADMINISTRATION

**Table 1: Recommended Dosage and Administration for Privigen**

Indication	Dose	Initial infusion rate	Maintenance infusion rate (as tolerated)
Primary Immunodeficiency	200-800 mg/kg (2-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
Chronic Immune Thrombocytopenic Purpura	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

### 2.1 Dosage for Primary Humoral Immunodeficiency (PI)

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

The recommended dose of Privigen for patients with PI is 200 to 800 mg/kg (2 to 8 mL/kg), administered every 3 to 4 weeks. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

Adjust the dosage over time to achieve the desired serum IgG trough levels and clinical responses. No randomized, controlled trial data are available to determine an optimal trough level in patients receiving immune globulin therapy.

### 2.2 Dosage for Chronic Immune Thrombocytopenic Purpura (ITP)

The recommended dose of Privigen for patients with chronic ITP is 1 g/kg (10 mL/kg) administered daily for 2 consecutive days, resulting in a total dosage of 2 g/kg.

Carefully consider the relative risks and benefits before prescribing the high dose regimen (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload [see *Warnings and Precautions (5.8)*].

### 2.3 Preparation and Handling

- Privigen is a clear or slightly opalescent, colorless to pale yellow solution. Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, turbid, or if it contains particulate matter.
- DO NOT SHAKE.
- Do not freeze. Do not use if Privigen has been frozen.
- Privigen should be at room temperature (up to 25°C [77°F]) at the time of administration.
- Do not use Privigen beyond the expiration date on the product label.

- The Privigen vial is for single-use only. Promptly use any vial that has been entered. Privigen contains no preservative. Discard partially used vials or unused product in accordance with local requirements.
- Infuse Privigen using a separate infusion line. Prior to use, the infusion line may be flushed with Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP.
- Do not mix Privigen with other IGIV products or other intravenous medications. However, Privigen may be diluted with Dextrose Injection, USP (D5W).
- An infusion pump may be used to control the rate of administration.
- If large doses of Privigen are to be administered, several vials may be pooled using aseptic technique. Begin infusion within 8 hours of pooling.

## 2.4 Administration

### Privigen is for intravenous administration only.

Monitor the patient's 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 lower rate that 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 thrombosis, administer Privigen at the minimum dose and infusion rate practicable, and discontinue Privigen administration if renal function deteriorates [see *Boxed Warning, Warnings and Precautions (5.2, 5.3)*].

The following patients may be at risk of developing systemic reactions (mimicking symptoms of an inflammatory response or infection) on rapid infusion of Privigen (greater than 4 mg/kg/min [0.04 mL/kg/min]): 1) those who have never received Privigen or another IgG product or who have not received it within the past 8 weeks, and 2) those who are switching from another IgG product. 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 increase as tolerated.

## 3 DOSAGE FORMS AND STRENGTHS

Privigen is a liquid solution containing 10% IgG (0.1 g/mL) for intravenous infusion.

## 4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline [see *Description (11)*].
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity [see *Warnings and Precautions (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Severe hypersensitivity reactions may occur [see *Contraindications (4)*]. In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA ( $\leq 25$  mcg/mL) [see *Description (11)*]. Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

### 5.2 Renal Dysfunction and Acute Renal Failure

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.<sup>4</sup> Privigen does not contain sucrose. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.<sup>4</sup> If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are obese, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable [see *Boxed Warning, Administration (2.4)*].

### 5.3 Thrombosis

Thrombosis may occur following treatment with immune globulin products<sup>1-3</sup>, including Privigen. 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 those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer Privigen 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)*].

### 5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as 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 thromboembolic events.<sup>5</sup>

### 5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen [see *Adverse Reactions* (6)] and other human immune globulin products. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae.<sup>6</sup> AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: 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 granulocytosis series, and with 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.

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

### 5.6 Hemolysis

Privigen 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 test (DAT) (Coombs' test) result and hemolysis.<sup>7-9</sup> Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.<sup>10</sup> Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen.

The following risk factors may be associated with the development of hemolysis: high doses (e.g.,  $\geq 2$  g/kg), given either as a single administration or divided over several days, and non-O blood group.<sup>11</sup> Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV,<sup>12</sup> but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI.<sup>9</sup>

Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform additional 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 on-going hemolysis.

### 5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen.<sup>13</sup> 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 and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum.

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

### 5.8 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

### 5.9 Transmissible Infectious Agents

Because Privigen 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). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen.

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

### 5.10 Interference with Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

## 6 ADVERSE REACTIONS

Adverse reactions (ARs), as presented below and in Clinical Trials Experience (6.1), are defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion or treatment cycle (for ITP).

### Primary Humoral Immunodeficiency

The most serious adverse reaction observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject [see *Warnings and Precautions* (5.1)]. The most common adverse reactions observed in  $>5\%$  of clinical study subjects with PI were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness.

### Chronic Immune Thrombocytopenic Purpura

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects [see *Warnings and Precautions* (5.5, 5.6)]. A total of 8 subjects (14%) in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in  $>5\%$  of clinical study subjects with chronic ITP were headache, elevated body temperature, positive DAT, anemia, nausea, epistaxis, vomiting, blood bilirubin unconjugated increased, blood bilirubin conjugated increased, blood total bilirubin increased, hematocrit decreased, and blood lactate dehydrogenase increased.

## 6.1 Clinical Trials Experience

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

### Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen every 3 or 4 weeks for up to 12 months [see *Clinical Studies* (14.1)]. All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule.

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related ARs 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.

Table 2 summarizes the most frequent ARs (defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion) that occurred in  $>5\%$  of subjects.

**Table 2: PI Pivotal Study – ARs\* Occurring in  $>5\%$  of Subjects**

AR	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with AR [n=1038]
Headache	36 (45.0)	100 (0.096)
Fatigue	13 (16.3)	29 (0.028)
Nausea	11 (13.8)	23 (0.022)
Chills	9 (11.3)	15 (0.014)
Vomiting	9 (11.3)	15 (0.014)
Back pain	8 (10.0)	15 (0.014)
Pain	7 (8.8)	14 (0.013)
Elevated body temperature	7 (8.8)	12 (0.012)
Diarrhea	6 (7.5)	6 (0.006)
Cough	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

\* Excluding infections.

Of the 192 ARs reported (including 5 serious, severe ARs described below) 91 were mild (awareness of sign, symptom or event, but easily tolerated), 81 were moderate (discomfort enough to cause interference with usual activity and may have warranted intervention), 19 were severe (incapacitating with inability to do usual activities or significantly affected clinical status, and warranted intervention), and 1 was of unknown severity.

The five serious ARs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to ARs (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative 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).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min [see *Administration* (2.4)]. The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding



tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

Table 3 summarizes the ARs that occurred in >5% of subjects.

**Table 3: PI Extension Study – ARs\* Occurring in >5% of Subjects**

AR*	Number (%) of Subjects [n=55]	Number (Rate) of Infusions with AR [n=771]
Headache	18 (32.7)	76 (0.099)
Nausea	6 (10.9)	10 (0.013)
Elevated body temperature	4 (7.3)	12 (0.016)
Abdominal pain†	4 (7.3)	7 (0.009)
Chest pain	3 (5.5)	4 (0.005)
Chills	3 (5.5)	7 (0.009)
Joint swelling/effusion	3 (5.5)	7 (0.009)
Pain	3 (5.5)	6 (0.008)
Fatigue	3 (5.5)	5 (0.006)
Influenza-like illness	3 (5.5)	5 (0.006)
Pharyngolaryngeal pain	3 (5.5)	4 (0.005)
Urticaria	3 (5.5)	4 (0.005)
Dizziness	3 (5.5)	3 (0.004)

Note: The AR rates in this study cannot be compared directly to the rates in other IGIV studies, including the original pivotal study described earlier in this section, because (1) the extension study used an enriched population and (2) the selective use of higher infusion rates at the investigators' discretion in a subset of subjects may have introduced bias.

\* Excluding infections.

† Includes abdominal pain, abdominal pain upper, and abdominal pain lower.

Of the 125 reported ARs, 76 were mild (does not interfere with routine activities), 40 were moderate (interferes somewhat with routine activities), and 9 were severe (impossible to perform routine activities).

Three subjects experienced ARs that were considered to be at least possibly related to Priviligen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of  $20 \times 10^9/L$  or less received a total of 2 g/kg dose of Priviligen administered as 1 g/kg infusions daily for 2 consecutive days [see *Clinical Studies (14.2)*]. Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

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 4 summarizes the most frequent ARs (adverse events at least possibly related or events occurring during or within 72 hours after the end of a treatment cycle [two consecutive infusions]) that occurred in >5% of subjects with chronic ITP.

**Table 4: Chronic ITP Study – ARs Occurring in >5% of Subjects**

AR	Number (%) of Subjects [n=57]	Number (Rate) of Infusions with AR [n=114]
Headache	37 (64.9)	52 (0.456)
Elevated body temperature	21 (36.8)	23 (0.202)
Positive DAT	7 (12.3)	8 (0.070)
Anemia	6 (10.5)	6 (0.053)
Nausea	6 (10.5)	8 (0.070)
Epistaxis	6 (10.5)	8 (0.070)
Vomiting	6 (10.5)	7 (0.061)
Blood bilirubin unconjugated increased	6 (10.5)	6 (0.053)
Blood bilirubin conjugated increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)

Of the 149 non-serious ARs, 103 were mild (awareness of sign, symptom or event, but easily tolerated), 37 were moderate (discomfort enough to cause interference with usual activity and may have warranted intervention), and 9 were severe (incapacitating with inability

to do usual activities or significantly affected clinical status, and warranted intervention).

One subject experienced a serious AR (aseptic meningitis).

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 Priviligen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

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 Priviligen 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

Because adverse reactions are reported voluntarily post-approval 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.

### Priviligen

The following adverse reactions have been identified during postmarketing use of Priviligen.

This list does not include reactions already reported in clinical studies with Priviligen [see *Adverse Reactions (6.1)*].

- *Infusion reactions*: Changes in blood pressure, dyspnea, tachycardia, flushing
- *Hematologic*: hemoglobinuria/hematuria/chromaturia, renal failure
- *Neurological*: photophobia
- *Integumentary*: pruritus, rash

### General

In addition, the following adverse reactions have been identified and reported during the post-approval use of immune globulin products.<sup>14</sup>

- *Infusion Reactions*: Tachycardia, malaise, flushing, rigors
- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, 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
- *Gastrointestinal*: Hepatic dysfunction

## 7 DRUG INTERACTIONS

### 7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella [see *Patient Counseling Information (17)*].<sup>15</sup>

Inform the immunizing physician of recent therapy with Priviligen so that appropriate measures can be taken.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Priviligen. It is not known whether Priviligen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Priviligen should be given to pregnant women only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.<sup>16,17</sup>

### 8.3 Nursing Mothers

Use of Priviligen in nursing mothers has not been evaluated.

### 8.4 Pediatric Use

#### Treatment of Primary Humoral Immunodeficiency

Priviligen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI (pivotal study). There were no apparent differences in the safety and efficacy profiles as compared to those in adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Priviligen have not been established in pediatric patients with PI who are under the age of 3.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

The safety and effectiveness of Priviligen have not been established in pediatric patients with chronic ITP who are under the age of 15.

### 8.5 Geriatric Use

Clinical studies of Priviligen did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Use caution when administering Priviligen to patients age 65 and over who are judged to be at increased risk of developing acute renal insufficiency and thrombosis [see *Boxed Warning, Warnings and Precautions (5.2, 5.3)*]. Do not exceed recommended doses, and administer Priviligen at the minimum dose and infusion rate practicable.

## 10 OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with impaired renal function.

## 11 DESCRIPTION

Priviligen is a ready-to-use, sterile, 10% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous administration. Priviligen has a purity of at least 98% IgG, consisting primarily of monomers. The balance consists of IgG dimers ( $\leq 12\%$ ),

small amounts of fragments and polymers, and albumin. Privilgen contains  $\leq 25$  mcg/mL IgA. The IgG subclass distribution (approximate mean values) is IgG<sub>1</sub>, 67.8%; IgG<sub>2</sub>, 28.7%; IgG<sub>3</sub>, 2.3%; and IgG<sub>4</sub>, 1.2%. Privilgen has an osmolality of approximately 320 mOsmol/kg (range: 240 to 440) and a pH of 4.8 (range: 4.6 to 5.0).

Privilgen contains approximately 250 mmol/L (range: 210 to 290) of L-proline (a nonessential amino acid) as a stabilizer and trace amounts of sodium. Privilgen contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative.

Privilgen 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). Privilgen does not activate the complement system or prekallikrein in an unspecific manner.

All plasma units used in the manufacture of Privilgen have been tested and approved for manufacture 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 HBV, HCV and HIV-1 and found to be nonreactive (negative). In addition, the plasma has been tested for B19 virus (B19V) DNA by NAT. Only plasma that passed virus screening is used for production, and the limit for B19V in the fractionation pool is set not to exceed 10<sup>4</sup> IU of B19V DNA per mL.

The manufacturing process for Privilgen 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 5 shows the virus clearance during the manufacturing process for Privilgen, expressed as the mean log<sub>10</sub> reduction factor (LRF).

**Table 5: Virus Inactivation/Removal in Privilgen\***

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
<b>Virus property</b>						
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
<b>Manufacturing step</b>		<b>Mean LRF</b>				
pH 4 incubation	$\geq 5.4$	$\geq 5.9$	4.6	$\geq 7.8$	nt	nt
Depth filtration	$\geq 5.3$	$\geq 6.3$	2.1	3.0	4.2	2.3
Virus filtration	$\geq 5.3$	$\geq 5.5$	$\geq 5.1$	$\geq 5.9$	$\geq 5.4$	$\geq 5.5$
<b>Overall reduction (log<sub>10</sub> units)</b>	<b><math>\geq 16.0</math></b>	<b><math>\geq 17.7</math></b>	<b><math>\geq 11.8</math></b>	<b><math>\geq 16.7</math></b>	<b><math>\geq 9.6</math></b>	<b><math>\geq 7.8</math></b>

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, log<sub>10</sub> reduction factor; nt, not tested.

\* The virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. The estimated LRF obtained was  $\geq 5.3$ .

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for CJD and its variant vCJD.<sup>18</sup> Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanoic acid fractionation ( $\geq 6.4$  log<sub>10</sub>), depth filtration (2.6 log<sub>10</sub>), and virus filtration ( $\geq 5.8$  log<sub>10</sub>). 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 Humoral Immunodeficiency

Privilgen is a replacement therapy for primary humoral immunodeficiency, and supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacterial, viral, parasitic and mycoplasma agents and their toxins. The mechanism of action in PI has not been fully elucidated.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

The mechanism of action of high doses of immunoglobulins in the treatment of chronic ITP has not been fully elucidated.

### 12.3 Pharmacokinetics

#### Treatment of Primary Humoral Immunodeficiency

In the clinical study (pivotal study) assessing the efficacy and safety of Privilgen 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 7<sup>th</sup> infusion for the 3 subjects on the 3-week dosing interval and following the 5<sup>th</sup> infusion for the 22 subjects on the 4-week dosing interval. The dose of Privilgen used in these subjects ranged from 200.0 mg/kg to 714.3 mg/kg. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively.

Table 6 summarizes the pharmacokinetic parameters of Privilgen, based on serum concentrations of total IgG.

**Table 6: PI Pivotal Study - Pharmacokinetic Parameters of Privilgen in Subjects**

Parameter	3-Week Dosing Interval (n=3)		4-Week Dosing Interval (n=22)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
C <sub>max</sub> (peak, mg/dL)	2,550 (400)	2,340 (2,290-3,010)	2,260 (530)	2,340 (1,040-3,460)
C <sub>min</sub> (trough, mg/dL)	1,230 (230)	1,200 (1,020-1,470)	1,000 (200)	1,000 (580-1,360)
t <sub>1/2</sub> (days)	27.6 (5.9)	27.8 (21.6-33.4)	45.4 (18.5)	37.3 (20.6-96.6)
AUC <sub>0-t</sub> (day × mg/dL)*	32,820 (6,260)	29,860 (28,580-40,010)	36,390 (5,950)	36,670 (19,680-44,340)
AUC <sub>0-∞</sub> (day × mg/dL)*	79,315 (20,170)	78,748 (59,435-99,762)	104,627 (33,581)	98,521 (64,803-178,600)
Clearance (mL/day/kg)*	1.3 (0.1)	1.3 (1.1-1.4)	1.3 (0.3)	1.3 (0.9-2.1)
Mean residence time (days)*	38.6 (8.1)	39.5 (30.1-46.2)	65.2 (24.7)	59.0 (33.2-129.6)
Volume of distribution at steady state (mL/kg)*	50 (13)	44 (40-65)	84 (35)	87 (40-207)

C<sub>max</sub>, maximum serum concentration; C<sub>min</sub>, trough (minimum level) serum concentration; t<sub>1/2</sub>, elimination half-life; AUC<sub>0-t</sub>, area under the curve from 0 hour to last sampling time; AUC<sub>0-∞</sub>, area under the curve from 0 hour to infinite time.

\* Calculated by log-linear trapezoidal rule.

The median half-life of Privilgen 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 Privilgen, based on the small sample size (11 males and 14 females) it appears that clearance of Privilgen is comparable in 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 Privilgen (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): IgG<sub>1</sub>, 564.91 mg/dL; IgG<sub>2</sub>, 394.15 mg/dL; IgG<sub>3</sub>, 30.16 mg/dL; IgG<sub>4</sub>, 10.88 mg/dL.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

Pharmacokinetic studies with Privilgen were not performed in subjects with chronic ITP.

## 14 CLINICAL STUDIES

### 14.1 Treatment of Primary Humoral Immunodeficiency

A prospective, open-label, single-arm, multicenter study (pivotal study) assessed the efficacy, safety, and pharmacokinetics of Privilgen 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; 46 (57.5%) were male and 34 (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 (20%) on the 3-week dosing interval and 64 (80%) on the 4-week dosing interval. Doses ranged from 200 mg/kg to 888 mg/kg per infusion. The median dose for the 3-week interval was 428.3 mg/kg per infusion; the median dose for the 4-week interval was 440.6 mg/kg per infusion. Subjects received a total of 1038 infusions of Privilgen, 272 for the 3-week dosing regimen and 766 for the 4-week dosing regimen. The maximum infusion rate allowed during this study was 8 mg/kg/min with 715 (69%) of the infusions administered at a rate of 7 mg/kg/min or greater. The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (aSBI), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject per year. Secondary analyses were based on the annual rate of other infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization. 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%). Among the 255 infections, 16 (6.3%) occurring in 10 subjects were considered severe.

Table 7 summarizes the efficacy results for all 80 subjects.

**Table 7: PI Pivotal Study – Summary of Efficacy Results in Subjects**

Number of Subjects	80
<b>Results from Case Report Forms</b>	
Total Number of Subject Days	26,198
Infections	
Annual rate of confirmed aSBIs*	0.08 aSBIs/subject year <sup>†</sup>
Annual rate of other infections	3.55 infections/subject year
Antibiotic use	
Number of subjects (%)	64 (80%)
Annual rate	87.4 days/subject year
<b>Results from Subject Diaries</b>	
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.  
<sup>†</sup> 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 x 10<sup>9</sup>/L or less. Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female; all were Caucasian.

Subjects received a 2 g/kg dosage of Privigen administered as 1 g/kg (10 mL/kg) intravenous infusion daily 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 analysis was based on the response rate defined as the percentage of subjects with an increase in platelet counts to at least 50 x 10<sup>9</sup>/L within 7 days after the first infusion (responders). Secondary analyses were based on the increase in platelet counts and the time to reach a platelet count of at least 50 x 10<sup>9</sup>/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 x 10<sup>9</sup>/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 x 10<sup>9</sup>/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 x 10<sup>9</sup>/L). The median maximum platelet count achieved was 154 x 10<sup>9</sup>/L. The median time to reach a platelet response of more than 50 x 10<sup>9</sup>/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

##### 16.1 How Supplied

- Privigen is supplied in a single-use, tamper-evident vial containing the labeled amount of functionally active IgG.

Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
50 mL	44206-436-05	Vial containing 5 grams of protein (NDC 44206-436-90)
100 mL	44206-437-10	Vial containing 10 grams of protein (NDC 44206-437-91)
200 mL	44206-438-20	Vial containing 20 grams of protein (NDC 44206-438-92)
400 mL	44206-439-40	Vial containing 40 grams of protein (NDC 44206-439-93)

##### 16.2 Storage and Handling

- Keep Privigen in its original carton to protect it from light.
- 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 36 months, as indicated by the expiration date printed on the outer carton and vial label.
- Do not freeze.
- The Privigen packaging components are not made with natural rubber latex.

#### 17 PATIENT COUNSELING INFORMATION

Inform patients of the early signs of hypersensitivity reactions to Privigen (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis), and advise them to notify their physician if they experience any of these symptoms.

Inform patients to immediately report the following signs and symptoms to their physician:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath, which may suggest kidney problems
- Instruct patients to immediately report symptoms of thrombosis. These symptoms may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting, which may suggest aseptic meningitis syndrome
- Fatigue, increased heart rate, yellowing of skin or eyes, and dark-colored urine, which may suggest hemolysis
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever, which may suggest TRALI (a condition typically occurring within 1 to 6 hours following transfusion)

Inform patients that Privigen is made from human 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 donated plasma for certain virus infections, and by inactivating or removing certain viruses during manufacturing, and counsel patients to report any symptoms that concern them.

Inform patients that administration of IgG may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella), and instruct them to notify their immunizing physician of recent therapy with Privigen.

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