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

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.

Privilgen 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)

Intravenous Use Only

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

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).

**CONTRAINdications**

- History of anaphylactic or severe systemic reaction to human immune globulin (4)
- Hyperprolactinemia (Privigen contains the stabilizer L-proline) (4)
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (4)

**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 laboratory findings consistent with hemolysis (hemoglobin and hematocrit decrease without blood loss in conjunction with positive direct antiglobulin test (DAT) and elevated blood lactate dehydrogenase (LDH) and/or indirect bilirubin), headache, elevated body temperature, anemia, nausea, and vomiting. 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.

**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).
- Hyperproteinaemia, increased serum viscosity, and hypoaesthesia 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, especially in patients with pre-existing anemia and/or cardiovascular or pulmonary compromise. (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, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.9).

**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: May 2017

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**CSL Behring**

**FULL PRESCRIBING INFORMATION**

**Privigen®, Immune Globulin Intravenous (Human), 10% Liquid**

**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 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 predipsosed 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. 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)].

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**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**

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

**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 (eg, 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 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 (eg, 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 (≤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 predipsosed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Privigen does not contain sucrose.

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 (2.4)].

**5.3 Thrombosis**

Thrombosis may occur following treatment 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 central vascular catheters, hyperviscosity, and cardiovascular 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 (2.4), 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...
pseudohypoponatermia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.5

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.6 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 per cubic millimeter, predominately from the granulocytic 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.1,7 Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.10 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 (eg, ≥2 g/kg), given either as a single administration or divided over several days, and non-O blood group.11 Other individual patient factors, such as an underlying inflammatory process (eg, multiple sclerosis)11 or an underlying or preexisting immune deficiency, have been hypothesized to increase the risk of hemolysis following administration of IGIV,11 but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI.12

Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above and those with preexisting anemia and/or cardiovascular or pulmonary compromise. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 hours and again 7 to 10 days 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.13 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. TRALI may be managed using oxygen therapy with adequate ventilatory support. Use of inhaled nitric oxide is described but the value of this therapy is uncertain. 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.

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 (eg, viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent 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) [see Adverse Reactions (6.1)] are defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion. 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 reaction observed in >10% of clinical study subjects with Privigen was 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 premarketing 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 premarketing ITP study experienced hemolysis as documented from clinical laboratory data. No serious adverse reactions were observed in the postmarketing chronic ITP study. A total of 12 subjects (21%) in the postmarketing ITP study were adjudicated to have mild hemolysis as documented from clinical laboratory data [see Warnings and Precautions (5.6)]. The most common adverse reactions observed in >5% of subjects in both clinical studies of subjects with chronic ITP were laboratory findings consistent with hemolysis (hemoglobin and hematocrit decrease without blood loss in conjunction with positive direct antiglobulin test (DAT) and elevated lactate dehydrogenase (LDH) and/or indirect bilirubin), headache, elevated body temperature, anemia, nausea, and vomiting. 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; 64 (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 (4-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 antipiracetam, antihistamines, NSAIDs, or antiepileptic agents. During the study, 12 (20%) 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

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

* Excluding infusions

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 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 (B19).
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 Dosage and 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>
<thead>
<tr>
<th>AR*</th>
<th>Number (% of Subjects)</th>
<th>Number (Rate) of Infusions with AR</th>
<th>n=55</th>
<th>n=771</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18 (32.7)</td>
<td>76 (0.099)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (10.9)</td>
<td>10 (0.013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated body temperature</td>
<td>4 (7.3)</td>
<td>12 (0.016)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>4 (7.3)</td>
<td>7 (0.009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (5.5)</td>
<td>4 (0.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>3 (5.5)</td>
<td>7 (0.009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint swelling/effusion</td>
<td>3 (5.5)</td>
<td>7 (0.009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>3 (5.5)</td>
<td>6 (0.008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.5)</td>
<td>5 (0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (5.5)</td>
<td>5 (0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>3 (5.5)</td>
<td>5 (0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>3 (5.5)</td>
<td>4 (0.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (5.5)</td>
<td>3 (0.004)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
† Includes abdominal pain, abdominal pain upper, and abdominal pain lower.
* Excluding infections.

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 Privigen: 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 postmarketing clinical study, 57 subjects with chronic ITP and a platelet count of <30 x 10^9/L at screening were studied following treatment with Privigen. Twenty-one (21) subjects (37%) received 1 infusion of 1 g/kg on Day 1 and 36 subjects (63%) received 2 infusions each of 1 g/kg (Day 1 and Day 3). Comitant 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.

Concomitant medications affecting platelets or other treatments for chronic ITP were not

The following adverse reactions have been identified during postmarketing use of Privigen. The list does not include reactions already reported in clinical studies with Privigen [see Adverse Reactions (6.1)].

- **Infusion reactions:** Changes in blood pressure, dyspnea, tachycardia, flushing
- **Hematologic:** Hemoglobinuria/hematocrit decrease, anemia
- **Integumentary:** Erythema multiforme, bullous dermatitis

Additional information in 7.4 was added in the following adverse reactions have been identified during postmarketing use of Privigen. The list does not include reactions already reported in clinical studies with Privigen. This list does not include reactions already reported in clinical studies with Privigen [see Adverse Reactions (6.1)].

- **Infusion reactions:** Changes in blood pressure, dyspnea, tachycardia, flushing
- **Hematologic:** Hemoglobinuria/hematocrit decrease, anemia
- **Integumentary:** Erythema multiforme, bullous dermatitis
- **Neurological:** Photophobia

### 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.

**Privigen**

The following adverse reactions have been identified during postmarketing use of Privigen. This list does not include reactions already reported in clinical studies with Privigen [see Adverse Reactions (6.1)].

- **Infusion reactions:** Changes in blood pressure, dyspnea, tachycardia, flushing
- **Hematologic:** Hemoglobinuria/hematocrit decrease, anemia
- **Integumentary:** Erythema multiforme, bullous dermatitis
- **Neurological:** Photophobia

### 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 (17.1)].

Inform the immunizing physician of recent therapy with Privigen 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 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.
8.3 Nursing Mothers
Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use
Treatment of Primary Humoral Immunodeficiency
Privigen 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 Privigen have not been established in pediatric patients with PI who are under the age of 15.

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

Use caution when administering Privigen 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 Privigen 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
Privigen is a ready-to-use, sterile, 10% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous administration. 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 mg/mL IgG. 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 mOsm/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. Sodium contains no carbohydrate stabilizers (eg, sucrose, maltose) and no preservative.

Privigen is prepared from large pools of human plasma by a combination of cold ethanol fractionation, octanic 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 unspecified manner.

To specifically reduce blood group A and B antibodies (isoagglutinins A and B) the manufacturing process for Privigen includes an immunoadsorption chromatography step. All plasma units used in the manufacture of Privigen 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 10^5 IU of B19V DNA per mL.

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 5 shows the virus clearance during the manufacturing process for Privigen, expressed as the mean log_{10} reduction factor (LRF).

model for CID and its variant vCID.\textsuperscript{14} Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanionic acid fractionation (≥14 log_{10}), depth filtration (2.6 log_{10}), and virus filtration (≥5.8 log_{10}). These studies provide reasonable assurance that low levels of vCID/CID agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Treatment of Primary Humoral Immunodeficiency
Privigen 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.

12.3 Pharmacokinetics
Treatment of Primary Humoral Immunodeficiency
In the clinical study (pivotal 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. The dose of Privigen 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 Privigen, based on serum concentrations of total IgG.

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

![Table 6: PI Pivotal Study - Pharmacokinetic Parameters of Privigen in Subjects](image)

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 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 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, 10.16 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 Humoral Immunodeficiency
A prospective, open-label, single-arm, multicenter study (pivotal 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; 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

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The provided content seems to be a large text block regarding the description, pharmacokinetics, and clinical studies related to Privigen, a replacement therapy for primary humoral immunodeficiency. It includes detailed sections on the manufacturing process, virus clearance, pharmacokinetic parameters, and clinical trial outcomes, among other details. The text is rich in scientific and medical terminology, typical of a pharmaceutical product's information sheet. The content is structured to provide comprehensive information on the product’s characteristics, clinical use, and safety aspects. It is important for medical professionals and researchers to understand the detailed procedures and findings to ensure proper use and interpretation of the product within the clinical setting.
on regular IGV 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 (range: 1 to 82) over the 6-month 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 (89%) 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 (aSBIs), defined as pneumonia, bacteremia/septicaemia, sepsis/myelitis/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. For 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

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results from Case Report Forms</strong></td>
<td></td>
</tr>
<tr>
<td>Total Number of Subject Days</td>
<td>26,198</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Annual rate of confirmed aSBIs*</td>
<td>0.08 aSBIs/subject year</td>
</tr>
<tr>
<td>Annual rate of other infections</td>
<td>3.55 infections/subject year</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td></td>
</tr>
<tr>
<td>Number of subjects (%)</td>
<td>64 (80%)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>87.4 days/subject year</td>
</tr>
<tr>
<td><strong>Results from Subject Diaries</strong></td>
<td></td>
</tr>
<tr>
<td>Total Number of Diary Days</td>
<td>24,059</td>
</tr>
<tr>
<td>Out of work/school/day care or unable to perform normal activities due to illness</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>570 (2.07%)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>8.65 days/subject year</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>166 (0.69%)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>2.52 days/subject year</td>
</tr>
</tbody>
</table>

---

**14.4 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 10⁹/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 maintained a response up to Day 29 and two (4%) up to Day 85. The median duration of platelet response in these subjects was 9.7 months (range: 1.5 to 12 months). The median duration of platelet response was analyzed for the 48 subjects who achieved a response rate of 50%.

### Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura

A prospective, open-label, single-arm, multicenter study assessed efficacy and safety parameters in 57 IGV-treated subjects with chronic ITP with a platelet count of <30 x 10⁹/L. At screening, fifty-three subjects had a history of chronic ITP with a duration of greater than 6 months and 48 subjects achieved a confirmed platelet response. A subsequent elevation followed by falls in platelet counts, had a duration of ITP less than 6 months. The study examined the incidence of subjects who met laboratory and clinical criteria for hemolysis and was intended to identify antibodies most frequently bound to erythrocytes in subjects who experienced clinically significant intravascular hemolysis. Subjects ranged in age from 18 to 65; 20 (35.1%) were male and 37 (64.9%) were female; all were Caucasian. Twenty-one (21) subjects (37%) received 1 infusion of 1 g/kg on Day 1 and 36 subjects (63%) received 2 infusions of 1 g/kg (Day 1 and Day 3). The second infusion was administered based on the subject’s platelet response to the Day 1 dose (<5 x 10⁹/L) and investigator’s discretion.

The efficacy endpoint platelet response (increase in platelet count at least once to at least 50 x 10⁹/L within 6 days after the first infusion) was achieved in 42 subjects (74%; 95% confidence interval [CI] 64% to 83%). Fifteen subjects with a suspicion of hemolysis based on laboratory data were referred for independent expert adjudication during the study. The adjudication committee selected from 3 options for their determination: no hemolysis, hemolysis, or clinically significant intravascular hemolysis. The set of antibodies most frequently bound to erythrocytes in subjects with clinically significant intravascular hemolysis could not be analyzed, because no subject experienced clinically significant intravascular hemolysis. No irregular antibodies were detected in any subject; therefore, no association between such antibodies and hemolytic laboratory changes could be established. Hemolytic laboratory changes were most often observed in non-O blood group (especially the A blood group) subjects and those receiving 2 infusions. These laboratory parameters improved or normalized by the end of the study in the majority of subjects. Seven subjects (12% of the study population) with a normal hemoglobin at baseline had an abnormal hemoglobin at Day 29 (end of study) with a hemoglobin range from 11.2 to 13.6 g/dL.

Post-hoc analyses were performed using a set of defined criteria for hemolysis. The hemolysis group (18 subjects, 32%) met the criteria for greater than 1 g/dl drop in hemoglobin within a 21-day interval since the last IGV administration not explained by blood loss or repeated phlebotomy, were treatment-emergent DAT positive, and met at least one other minor criterion (eg, fall in serum haptoglobin level to below the lower limit of normal, rise in lactate dehydrogenase level above the upper limit of normal, rise in total bilirubin to above the upper limit of normal, or rise in plasma-free hemoglobin above the upper limit of normal). Fourteen of 15 previously adjudicated presumptive hemolysis cases during the study were included in this post-hoc hemolysis group.

### REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

• Privigen is supplied in a single-use, tamper-evident vial containing the labeled amount of functionally active IgG. The Privigen packaging components are not made with natural rubber latex.

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

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>44206-436-05</td>
<td>Vial containing 5 grams of protein (NDC 44206-436-90)</td>
</tr>
<tr>
<td>100 mL</td>
<td>44206-437-10</td>
<td>Vial containing 10 grams of protein (NDC 44206-437-91)</td>
</tr>
<tr>
<td>200 mL</td>
<td>44206-438-20</td>
<td>Vial containing 20 grams of protein (NDC 44206-438-92)</td>
</tr>
<tr>
<td>400 mL</td>
<td>44206-439-40</td>
<td>Vial containing 40 grams of protein (NDC 44206-439-93)</td>
</tr>
</tbody>
</table>

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.

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 [see Warnings and Precautions (5.1)].

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 [see Warnings and Precautions (5.2)].
• 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 [see Warnings and Precautions (5.3)].
• Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting, which may suggest aseptic meningitis syndrome [see Warnings and Precautions (5.5)].
• Fatigue, increased heart rate, yellowing of skin or eyes, and dark-colored urine, which may suggest hemolysis [see Warnings and Precautions (5.6)].
• 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) [see Warnings and Precautions (5.7)].

Inform patients that Privigen is made from human blood and may contain infectious agents that can cause disease (eg, viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent 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 [see Warnings and Precautions (5.9)].

Inform patients that administration of IgG may interfere with the response to live virus vaccines (eg, measles, mumps, rubella, and varicella), and instruct them to notify their immunizing physician of recent therapy with Privigen [see Warnings and Precautions (5.10)].

Manufactured by:
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Bern, Switzerland

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

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