Your Guide to Treatment With Privigen

For adults with chronic inflammatory demyelinating polyneuropathy (CIDP)

Improves functional ability
Featuring proline for Ig stability

Please see full Important Safety Information on pages 12–13 and full prescribing information for Privigen, including boxed warning, in pocket.
A proven IVIg treatment

Designed with you in mind

Important Safety Information

WARNINGS:

• Thrombosis (blood clotting) can occur with immune globulin products, including Privigen. Risk factors may include advanced age, prolonged immobilization, a history of blood clotting or hyperviscosity (thick blood), use of estrogens, installed vascular catheters, and cardiovascular risk factors.

• In predisposed patients, kidney malfunction and acute kidney failure, potentially fatal, can occur with the administration of human immune globulin intravenous (IGIV) products. Kidney problems occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.

• If you are at high risk of thrombosis or kidney problems, your doctor will prescribe and administer Privigen at the minimum dose and infusion rate practicable, and will monitor you for signs and symptoms of thrombosis and viscosity, as well as kidney function. Always drink sufficient fluids before administration.

Please see full Important Safety Information on pages 12–13 and full prescribing information for Privigen, including boxed warning, in pocket.
What is CIDP?

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disorder of the nervous system. Though your immune system generally keeps you healthy by fighting off germs, with CIDP, your immune system does not recognize parts of your nerves and attacks them.

Specifically, the immune system mistakenly attacks your nerves’ protective myelin. When the myelin is damaged or removed, messages transmitted to and from the brain are disrupted and may never make it to their final destination. Over time, this may cause gradual weakness and a loss of feeling in your arms and legs.

Other symptoms may include:
- Tingling or numbness beginning in the toes and fingers
- Weakness of the arms or legs
- Loss of reflexes
- Fatigue

If left untreated, CIDP can cause permanent damage to the nerves.

What is myelin?

Nerves are responsible for sending messages to and from the brain, like when you want to tell your hand to grasp an object or when your hand tells your brain the stove is hot. Healthy nerves are wrapped in a sheath called myelin, much like how electric wires are wrapped in rubber insulation. The insulation allows electric impulses to travel efficiently along the nerves.

Myelin Sheath

Damaged Nerve Connection
How is CIDP treated?

CIDP can be treated with corticosteroids, immunosuppressants, plasmapheresis (plasma exchange), or Ig therapies. Ig therapies, such as IVIg, are FDA approved specifically for the treatment of CIDP.

IVIg contains immunoglobulins—naturally occurring antibodies in your immune system—that have been obtained from healthy donors. These immunoglobulins are infused into your blood intravenously—through the veins—to help your immune system improve your physical function.

Important Safety Information

Treatment with Privigen might not be possible if your doctor determines you have hyperprolinemia (too much proline in the blood) or are IgA-deficient with antibodies to IgA and a history of hypersensitivity. Tell your doctor if you have previously had a severe allergic reaction (including anaphylaxis) to the administration of human immune globulin. Inform your physician if you notice early signs of hypersensitivity reactions to administration of Privigen, including hives, tightness of the chest, wheezing, or shock.

What is Privigen?

Privigen is a therapy that helps improve physical function for people with CIDP by supplying their immune system with extra antibodies.

- The primary antibody found in Privigen is known as immunoglobulin G (IgG)
  - An antibody is an essential part of the immune system that identifies and destroys disease-causing bacteria or viruses. IgG, found in Privigen, is the main type of antibody made by the immune system.

- Your doctor may refer to your Privigen treatment as “Ig,” “intravenous Ig,” or “IVIg”

The healthy antibodies Privigen provides help block the immune system from attacking the nerve myelin, though exactly how Privigen works is not completely understood.
What can I expect from Privigen?

Privigen was proven to work in 2 clinical trials for CIDP, studying a combined total of 235 people like you.

- Most people experienced an improvement in physical function with Privigen in these studies
  - This means that, with Privigen, it was easier for them to do things like buttoning their shirt, washing their hair, and walking (with or without support)
- Almost everyone whose physical function improved with Privigen experienced the improvement after 1–2 maintenance treatments,* and they maintained that improvement throughout treatment with Privigen in the trials

*At weeks 4 and 7.

Is Privigen safe?

The clinical studies also showed that Privigen is safe and effective in the treatment of CIDP.

- 97% of the side effects people had with Privigen were mild or moderate in intensity for both trials
  - 10 of the 235 people who participated in the studies had serious side effects

The most common† side effects of Privigen are headache, muscle weakness, hypertension, nausea, and arm or leg pain.

- Some people can have an allergic reaction to IVIg treatments such as Privigen; let your doctor know if you have had a previous reaction to IgG or have been told you have an IgA deficiency
- A vaccination for measles, mumps, and rubella might not work while on therapy with Privigen; before receiving any vaccination, tell the person administering the vaccine that you are being treated with Privigen
- The risk of transmission of infectious agents, including viruses, cannot be completely eliminated

Call your doctor if you experience any side effects, or if you have any other questions or concerns.

†Occurring in more than 10% of people in the clinical trials.

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What makes Privigen special?

Privigen is the first and only IVIg therapy stabilized with proline. Privigen was specifically designed with proline to improve convenience and preservation of the Ig.

Privigen is made from human plasma (part of the blood). The process used to make Privigen involves several steps, including a 3-step virus inactivation/removal process.

**1**
**2**
**3**

Virus Inactivation
pH 4 incubation

Virus Reduction
Depth filtration

Virus Removal
Virus filtration

What is proline?

Proline is a naturally occurring amino acid. It can be made by the body and is found in certain foods in a normal, healthy diet. The use of proline allows Privigen to be stored at room temperature, making it ready to use off the shelf.*

How is Privigen given?

Privigen comes in a small glass bottle and is given through a small needle into a vein. It is administered by a nurse or doctor every 3 weeks—whether you’re at a hospital, clinic, physician’s office, or in your home.

* Treatment with Privigen might not be possible if your doctor determines that you have hyperprolinemia (too much proline in the blood).

Important Safety Information

Immediately report to your physician the following symptoms, which could be signs of serious adverse reactions to Privigen:

- A decrease in urine output, sudden weight gain, fluid retention, and/or shortness of breath following infusion (possible symptoms of kidney problems)
- Pain and/or swelling or discoloration of an arm or leg, shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, and numbness or weakness on one side of the body (possible symptoms of a blood clot)
- Headache; a stiff neck; excessive drowsiness or fatigue; fever; sensitivity to light or painful eye movements; nausea; increased heart rate; yellowing of the skin or eyes, and/or dark-colored urine (possible symptoms of other conditions that may require treatment)

Important Safety Information (cont.)

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

Before receiving any vaccine, tell the immunizing physician if you have had recent therapy with Privigen, as the effectiveness of the vaccine could be compromised.

In clinical trials of Privigen, headache was the most common side effect seen in all conditions treated (PI, ITP, and CIDP). Other common side effects that can be seen with treatment include fatigue, nausea, fever, and high blood pressure. These are not the only side effects possible; see the full prescribing information for a complete list of adverse reactions possible with treatment for each condition. Alert your physician to any side effect that bothers you or does not go away.

Please see full Important Safety Information on pages 12–13 and full prescribing information for Privigen, including boxed warning, in pocket.
Important Safety Information

Privigen is approved to:

- Treat types of primary immunodeficiency (PI).
- Raise platelet counts in patients over 15 with chronic immune thrombocytopenic purpura (ITP).
- Treat chronic inflammatory demyelinating polyneuropathy (CIDP) in adults. Talk with your doctor about the length of your therapy.

WARNINGS:

- Thrombosis (blood clotting) can occur with immune globulin products, including Privigen. Risk factors may include advanced age, prolonged immobilization, a history of blood clotting or hyperviscosity (thick blood), use of estrogens, installed vascular catheters, and cardiovascular risk factors.
- In predisposed patients, kidney malfunction and acute kidney failure, potentially fatal, can occur with the administration of human immune globulin intravenous (IGIV) products. Kidney problems occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.
- If you are at high risk of thrombosis or kidney problems, your doctor will prescribe and administer Privigen at the minimum dose and infusion rate practicable, and will monitor you for signs and symptoms of thrombosis and viscosity, as well as kidney function. Always drink sufficient fluids before administration.

See your doctor for a full explanation and the full prescribing information for complete boxed warning.

Treatment with Privigen might not be possible if your doctor determines you have hyperprolinemia (too much proline in the blood) or are IgA-deficient with antibodies to IgA and a history of hypersensitivity. Tell your doctor if you have previously had a severe allergic reaction (including anaphylaxis) to the administration of human immune globulin. Inform your physician if you notice early signs of hypersensitivity reactions to administration of Privigen, including hives, tightness of the chest, wheezing, or shock.

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In clinical trials of Privigen, headache was the most common side effect seen in all conditions treated (PI, ITP, and CIDP). Other common side effects that can be seen with treatment include fatigue, nausea, fever, and high blood pressure. These are not the only side effects possible; see the full prescribing information for a complete list of adverse reactions possible with treatment for each condition. Alert your physician to any side effect that bothers you or does not go away.

Please see accompanying full prescribing information for Privigen.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
What assistance is available to me?

IgIQ is ready to help

Call 1-877-355-IGIQ (4447)
Monday–Friday, 8 AM to 8 PM ET

Financial Assistance—The Patient Assistance Program helps provide therapy to qualified people who are uninsured, underinsured, or unable to afford their prescription.

Patient Support—Trained nurses are available by phone to answer your questions and provide helpful resources as well as product information.

CSL Behring AssuranceSM—CSL Behring is the only company to offer a loyalty program for their Ig products: earn points for every month of continuous product use and redeem 3 points for a free 1-month supply of Privigen in the event of a lapse in coverage.

Referral Triage—IgIQ can also coordinate patient referral to specialty pharmacies.

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www.CSLBehring.com   www.Privigen.com
PVG-0174-JUN18

Please see full Important Safety Information on pages 12–13 and full prescribing information for Privigen, including boxed warning, in pocket.
Privigen maintenance therapy in CIDP has not been studied beyond 6 months. (1.3)• Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of:

1.1 Primary Humoral Immunodeficiency
1.2 Chronic Immune Thrombocytopenic Purpura
1.3 Chronic Inflammatory Demyelinating Polyneuropathy

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

1.1 Primary Humoral Immunodeficiency (PI) (1.1)
1.2 Chronic Immune Thrombocytopenic Purpura (ITP) in patients age 15 years and older (1.2)
1.3 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults (1.3)

Limitations of Use:
Privigen maintenance therapy in CIDP has not been studied beyond 6 months. (1.3)

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>
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<td>ITP</td>
<td>10 mg/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>
<tr>
<td>CIDP</td>
<td>Loading dose: 2 g/kg (20 mL/kg) in divided doses over 2 to 3 consecutive days</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></td>
<td>Maintenance dose: 1 g/kg (10 mL/kg) administered in 1 to 2 infusions on consecutive days, every 3 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>
</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)

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

Indicators (1.3)
Dose and Administration (2, 2.3)
Warnings and Precautions (5.2, 5.6, 5.7, 5.9)

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**RECENT MAJOR CHANGES**
09/2017

**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) in patients age 15 years and older (1.2)
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in adults (1.3)

Limitations of Use:
Privigen maintenance therapy in CIDP has not been studied beyond 6 months. (1.3)

**DOSE AND ADMINISTRATION**

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**CONTRAINDICATIONS**

- History of anaphylactic or severe systemic reaction to human immune globulin (4)
- Hypersplenism (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)
- 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 may occur. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia. (5.6)
- Elevations of systolic and diastolic blood pressure (including cases of hypertensive urgency) have been observed during or shortly following Privigen infusion. These blood pressure elevations were resolved or significantly improved within hours with either observation alone or changes in oral anti-hypertensive therapy. Check patients for a history of hypertension and monitor blood pressure during and following Privigen infusion. (5.7)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.8)
- Carefully consider the relative risks and benefits before prescribing the high dose regimen for chronic ITP and CIDP in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload. (5.9)
- Privigen is made from human blood and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.10)

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**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. (6.1)
- 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. (6.1)
- CIDP – The most common adverse reactions observed in >5% of study subjects were headache, asthma, hypertension, nausea, pain in extremity, hemolysis, influenza-like illness, leukopenia, and rash. Serious adverse reactions were hemolysis, exacerbation of CIDP, acute rash, blood pressure diastolic increased, hypersensitivity, pulmonary embolism, respiratory failure, and migraine. (6.1)

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.

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**DRUG INTERACTIONS**

The passive transfer of antibodies may:
- Lead to misinterpretation of the results of serological testing. (5.11)
- Interfere with the response to live virus vaccines. (7.1)

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**USE IN SPECIFIC POPULATIONS**

- 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: September 2017
Privigen®
Intravenous Globulin (Human), 10% Liquid

1 INDICATIONS AND USAGE
Privigen is an Intravenous Globulin (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 age 15 years and older with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

1.3 Chronic Inflammatory Demyelinating Polyneuropathy
Privigen is indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.

Limitation of Use:
Privigen maintenance therapy in CIDP has not been studied for periods longer than 6 months. After responding during an initial treatment period, not all patients require indefinite maintenance therapy with Privigen in order to remain free of CIDP symptoms. Individualize the duration of any treatment beyond 6 months based upon the patient’s response and demonstrated need for continued therapy.

2 DOSAGE AND ADMINISTRATION

Table 1. Recommended Dosage and Administration for Privigen

<table>
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<td>Increase to 8 mg/kg/min (0.08 mL/kg/min)</td>
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<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>
<tr>
<td>Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>loading dose: 2 g/kg (20 mL/kg) in divided doses over 2 to 5 consecutive days</td>
<td>0.5 mg/kg/min (0.005 mL/kg/min)</td>
<td>Increased to 8 mg/kg/min (0.08 mL/kg/min)</td>
</tr>
</tbody>
</table>

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 hyperprolactinemia 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, cosinophilic nephropathy, 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. Acute renal failure may also occur as a result of Privigen-induced hemolysis. 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. 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 products10,11, 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, hypercoagulability, 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 hypercoagulability, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammapathies. 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 (2.3), 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.1

5.5 Aseptic Meningitis Syndrome (AMS)
AMS may occur infrequently following treatment with Privigen [see Adverse Reactions (6.3)] and other human immune globulin products. Discontinuation of Treatment has resulted in remission of AMS within several days without sequelae. 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, photophobia, painful eye movements, nausea, vomiting, Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, 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.12 Delayed hemolysis can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.13 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., ≥2 g/kg), given either as a single administration or divided over several days, and non-O blood group.14 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 IGIVs. The role of iron is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP, CDP, and PI.15 Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above and those with pre-existing 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 Hypertension
Elevations of systolic blood pressure to >180 mm Hg and/or of diastolic blood pressure to >120 mm Hg (hypertensive urgency) have been observed during and/or shortly following infusion of Privigen. These blood pressure elevations were usually of short duration and inversed within hours with either observation alone or changes in oral anti-hypertensive therapy [see Adverse Reactions (6.1)]. Such elevations were reported more often among patients with a history of hypertension. Check patients for a history of hypertension and current antihypertensive medication use. Monitor blood pressure prior to, during, and following Privigen infusion.

5.8 Transfusion-Related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen. 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.

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

5.10 Transmissible Infectious Agents
Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., 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.

5.11 Interference with Laboratory Tests
Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS
The following important adverse reactions are reported with IGIV: hypersensitivity, renal dysfunction and acute renal failure, thrombosis, hyperproteinemia, increased serum viscosity, hyponatremia, aseptic meningitis syndrome, hemolysis, hypertension, transfusion related acute lung injury, volume overload, and transmissible infectious agents [see Warnings and Precautions (5.5)]. These adverse reactions are defined elsewhere in the prescribing information. 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 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 reaction observed in the premartckling 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 premartckling 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 blood lactate dehydrogenase (LDH) and/or indirect billirubin, headache, elevated body temperature, anemia, nausea, and vomiting.

Chronic Inflammatory Demyelinating Polyneuropathy
The most serious adverse reaction observed in clinical study subjects receiving Privigen for CIDP was hemolysis. The most common adverse reactions observed in >5% of subjects in both clinical studies of subjects with CIDP were headache, asthenia, hypertension, nausea, pain in extremity, hemolysis, influenza like illness, leukopenia, and rash.

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, 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 mg/kg (3-week schedule) or 441 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 antihistamines. 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 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 Infusions with AR [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>

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

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

Three subjects experienced ARs: 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 premarketing clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/l or less received a total of 2 g/kg dose of Privigen 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%) were male and 34 (60%) were female.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 3 summarizes the most frequent ARs that occurred in >5% of subjects with chronic ITP.

### Table 3. PI Extension Study – ARs* Occurring in >5% of Subjects

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

* Includes abdominal pain upper, abdominal pain lower.

Of the 149 non-serious ARs, 103 were mild (awareness of sign, symptom or event, but easily tolerated), 81 were moderate (discomfort or discomfort with routine activities), and may have warranted intervention), and 9 were severe (impossible to perform routine activities).

### Treatment of Chronic ITP Premarketing Clinical Study – ARs* Occurring in >5% of Subjects

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

* Includes abdominal pain upper, abdominal pain lower.

Of the 149 non-serious ARs, 103 were mild (awareness of sign, symptom or event, but easily tolerated), 81 were moderate (discomfort or discomfort with routine activities), and may have warranted intervention), and 9 were severe (impossible to perform routine activities).

### Conclusions

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.
Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21%) developed a positive DAT during the 29-day study period.

**Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura**

In a prospective, open-label, single-arm, multicenter postmarketing clinical study whose primary objective was to evaluate mechanisms of hemolysis, 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). Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Subjects received premedication with acetaminophen and/or an antihistamine [see Clinical Studies (14.3)].

The most frequent ARs (adverse events at least possibly related or events occurring during or within 72 hours after the end of treatment) that occurred in ≥5% of subjects with chronic ITP were headache (16 subjects [28%]) and pyrexia (3 subjects [5%]). No subject experienced a serious adverse reaction.

Of the 23 non-serious ARs, 22 were mild (does not interfere with routine activities), 1 was moderate (interferes somewhat with routine activities), and none were severe (impossible to perform routine activities).

All 57 subjects had a negative DAT at baseline. Twenty-two (38%) developed a positive DAT by Day 4, 19 of these subjects were from blood group A. Fifteen subjects were adjudicated by an independent expert committee, for presumptive/possible hemolysis, all of whom received 2 g/kg IgIV during the study [see Clinical Studies (14.3)]. Twelve subjects (21%) were judged to have mild hemolysis. In these 12 subjects there was a median hemoglobin drop from baseline at Day 9 (nadir) of -3.0 g/dL (range -0.9 to -5.8 g/dL) with Day 9 hemoglobin values ranging from 9.9 to 13.2 g/dL, and a median drop from baseline in hemoglobin of -1.2 g/dL (range -0.1 to -2.7 g/dL) at Day 29 (end of study) with hemoglobin values ranging from 11.8 to 15.8 g/dL. Ten subjects were blood group A and 2 subjects were blood group B. These hemoglobin drops were transient and were followed by recovery or partial recovery by Day 29. One subject experienced mild dyspnea between Day 9 and Day 16. One subject experienced mild dizziness on Day 4. No subject was judged as having experienced clinically significant intravascular hemolysis. Three of the 15 adjudicated subjects were judged not to have experienced hemolysis.

**Risk Summary**

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with Privigen. It is not known whether Privigen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation to the fetus. The safety of Privigen in pregnancy has not been established. Women of childbearing potential should be informed of the potential for adverse effects on the breastfed infant from Privigen or from the underlying maternal condition.

**8. USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

<table>
<thead>
<tr>
<th>AR</th>
<th>Number (%) of Subjects</th>
<th>Number (Rate) of Infusions with AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8 (28.6%)</td>
<td>19 (0.073)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (14.3%)</td>
<td>4 (0.015)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (14.3%)</td>
<td>6 (0.023)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (10.7%)</td>
<td>3 (0.012)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (10.7%)</td>
<td>3 (0.012)</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>2 (7.1%)</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>2 (7.1%)</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Luekopenia</td>
<td>2 (7.1%)</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (7.1%)</td>
<td>2 (0.008)</td>
</tr>
</tbody>
</table>

* ARs were defined as adverse events at least possibly related or events occurring during or within 72 hours after IV infusion.

Two hemolysis serious adverse reactions occurred after the start of the Privigen induction dose in subjects with non-O blood groups (A and AB). The reactions resolved after discontinuation without the need for transfusion.

Four subjects, three of whom had a history of hypertension, had reversible increases in systolic blood pressure by 80 mm Hg during or within 1 to 4 hours following Privigen infusion. One of these subjects who had a history of untreated hypertension had a reversible increase in diastolic blood pressure from 84 mm Hg pre-infusion to 135 mm Hg at 1 hour after the end of the infusion. All were resolved or significantly improved within 1 to 6 hours with either observation alone or changes in oral anti-hypertensive therapy.

A total of 21 ARs were reported: 46 were mild (does not interfere with routine activities), 23 were moderate (interferes somewhat with routine activities), and 2 were severe (impossible to perform routine activities) in intensity. In a second prospective, open-label Privigen pre-randomization phase of a multicenter, randomized, double-blind, placebo-controlled clinical study (Polyneuropathy and Treatment Study with Hizentra [PATH]), 207 IGIV-pretreated subjects with CIDP received a Privigen loading dose of 2 g/kg followed by up to 4 Privigen maintenance doses of 1 g/kg every three weeks for up to 13 weeks. Additionally, 60 of these subjects received Privigen rescue treatment by the same dosing regimen following CIDP relapse during the double-blind post-randomization phase [see Clinical Studies (14.4)]. Eight subjects experienced a serious adverse reaction (acute rach cutaneous, blood pressure diastolic increased, exacerbation of CIDP [2], hypesensitivity, pulmonary embolism, respiratory failure, and migraine). The serious adverse reactions of pulmonary embolism and respiratory failure occurred in subjects with preexisting risk factors. All serious adverse reactions resolved without sequelae.

Adverse reactions that occurred in ≥5% of subjects with CIDP were headache (33 subjects, 15.9% [rate per infusion 56/1894, 0.030]). A total of 225 ARs were reported: 160 were mild (transient, does not usually interfere with routine activities but minimal treatment or therapeutic intervention may be required), 59 were moderate (interferes somewhat with routine activities and usually associated with specific intervention but poses no significant or permanent risk of harm), and 6 were severe (interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention) in intensity.

### 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/hematuria/chronic, renal failure
- **Neurologic:** photophobia
- **Integumentary:** pruritus

### 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)]. Inform the immunizing physician of recent therapy with Privigen so that appropriate measures can be taken.

### 8. USE IN SPECIFIC POPULATIONS

#### 8.2 Lactation

Risk Summary

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

#### 8.4 Pediatric Use

**Treatment of Primary Humoral Immunodeficiency**

 Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI (prospective, open label, single arm, multicenter clinical 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 studied in clinical trials in pediatric patients with PI who are under the age of 15.

**Treatment of Chronic Immune Thrombocytopenic Purpura**

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

**Treatment of Chronic Inflammatory Demyelinating Polyneuropathy**

The safety and effectiveness of Privigen have not been established in pediatric patients with CIDP who are under the age of 18.

### 8.5 Geriatric Use

Clinical studies of Privigen in PID and ITP did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.
The safety and effectiveness of Privigen in CIDP subjects age 65 and over was similar to those under age 65. 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 mcg/mL IgA. The IgG subclass distribution (approximate mean values) is IgG1, 67.8%; IgG2, 28.7%; small amounts of fragments and polymers, and albumin. Privigen contains approximately 250 mmol/L (range: 210 to 290) of L-proline (a nonessential amino acid) as a stabilizer and trace amounts of sodium. Privigen contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative.

Privigen is prepared from large pools of human plasma by a combination of cold ethanol fractionation, octanoic acid fractionation, and anion exchange chromatography. The IgG proteins are not subjected to heating or to chemical or enzymatic modification. The Fc and Fab functions of the IgG molecule are retained. Fab functions tested include antibody binding capacities, and Fc functions tested include complement activation and Fc-receptor-mediated leukocyte activation (determined with complexed IgG). Privigen does not activate the complement system or prekallikrein in an unspecific manner.

To specifically reduce blood group A and B antibodies (iso-antigens A and B), the manufacturing process for Privigen includes an immunoaffinity 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 10^6 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 6 shows the virus clearance during the manufacturing process for Privigen, expressed as the mean log10 reduction factor (LRF).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Privigen supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action has not been fully elucidated, but may include immunomodulatory effects.

12.3 Pharmacokinetics

Treatment of Primary Humoral Immunodeficiency

In the clinical study assessing the efficacy and safety of Privigen in 80 subjects with PI [see Clinical Studies (14.1)], serum concentrations of total IgG and IgG subclasses were measured in 25 subjects (ages 13 to 69) following the 7th infusion for the 3 subjects on the 3-week dosing interval and following the 5th infusion for the 22 subjects on the 4-week dosing interval. The dose of Privigen used in these subjects ranged from 200 mg/kg to 714 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 7 summarizes the pharmacokinetic parameters of Privigen, based on serum concentrations of total IgG.

Table 7. PI Study – Pharmacokinetic Parameters of Privigen in Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-Week Dosing Interval</th>
<th>4-Week Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>C_{\text{max}} (peak, mg/dL)*</td>
<td>2,550 (400)</td>
<td>2,340 (2,290-3,010)</td>
</tr>
<tr>
<td>C_{\text{trough}} (trough, mg/dL)*</td>
<td>1,230 (230)</td>
<td>1,200 (1,020-1,470)</td>
</tr>
<tr>
<td>t_{1/2} (days)</td>
<td>27.6 (5.9)</td>
<td>27.8 (21.6-33.4)</td>
</tr>
<tr>
<td>AUC_{\text{tmax}} (day × mg/dL)*</td>
<td>32,820 (6,260)</td>
<td>29,860 (28,580-40,010)</td>
</tr>
<tr>
<td>AUC_{\text{trough}} (day × mg/dL)*</td>
<td>79,315 (20,170)</td>
<td>78,748 (59,435-99,762)</td>
</tr>
<tr>
<td>Clearance (ml/d/kg)*</td>
<td>1.3 (0.1)</td>
<td>1.3 (1.1-1.4)</td>
</tr>
<tr>
<td>Mean residence time (days)*</td>
<td>38.6 (8.1)</td>
<td>39.5 (30.1-46.2)</td>
</tr>
<tr>
<td>Volume of distribution at steady state (ml/kg)*</td>
<td>50 (13)</td>
<td>44 (40-65)</td>
</tr>
</tbody>
</table>

* Calculated by log-linear trapezoidal rule.

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 (1.77 ± 0.25 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 subclasses levels observed in the pharmacokinetic study were consistent with a physiologic distribution pattern.

Trough concentrations: In both the PRIMA and PATH studies, on Day 1, subjects received an induction dose (2 g/kg) given over 2 to 5 days, followed by maintenance doses of 1 g/kg every 3 weeks. In the PRIMA study, from Day 1 (reference) to Day 2, the mean serum IgG trough concentration increased from 12.6 ± 3.8 g/L to 24.4 ± 7.0 g/L. At Week 7, before the second maintenance treatment of (1 g/kg) given over 1 or 2 days every 3 weeks, the mean IgG trough concentration was 17.5 ± 3.2 g/L and remained stable from Week 7 to Week 19.

In the PATH study, from Day 1 (reference) to Day 5, the mean serum IgG trough concentration increased from 12.7 ± 3.3 g/L to 33.2 ± 6.9 g/L. At Week 7, before the second maintenance treatment of (1 g/kg) given over 1 or 2 days every 3 weeks, the mean IgG trough concentration was 17.7 ± 4.0 g/L and remained stable from Week 7 to Week 13.

Post-infusion concentrations: In the PRIMA study, from Day 1 to Day 2, the post-infusion serum IgG concentration increased from 28.6 ± 8.5 g/L to 40.0 ± 11.5 g/L. At Week 7 (after the second maintenance treatment), the post-infusion IgG concentration was 32.3 ± 8.0 g/L and remained stable from Week 7 to Week 19.
Tables include summary data and primary analysis based on response rate defined as percentage of subjects reaching a platelet count of at least 50 x 10^9/L at any point during the study period. The median maximum platelet count achieved was 154 x 10^9/L. 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 10^9/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 primary analysis was based on the response rate defined as the percentage of subjects with a rise in platelet counts to at least 50 x 10^9/L within 7 days after the first infusion. The lower bound of the 95% confidence interval for the response rate was 69.2%.

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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 IgGs. The Privigen packaging components are not made with natural rubber latex.

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

Table: Privigen Presentation Information

<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/enema, 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 hemolytic anemia [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 (5.8)].

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 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 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 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 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 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 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 agents that can cause disease (eg, viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent and, theoretically the CJD agent).

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