### ICD-10-CM Diagnosis Codes

For claims with a date of service on or after October 1, 2015, the following ICD-10-CM codes may be used to identify patient medical conditions typically associated with Privigen use.

<table>
<thead>
<tr>
<th>Code</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>D80</td>
<td>Immunodeficiency with predominantly antibody defects</td>
</tr>
<tr>
<td>D80.0</td>
<td>Hereditary hypogammaglobulinemia</td>
</tr>
<tr>
<td>D80.01</td>
<td>Autosomal recessive agammaglobulinemia (Swiss type)</td>
</tr>
<tr>
<td>D80.02</td>
<td>X-linked agammaglobulinemia (Bruton) with growth hormone deficiency</td>
</tr>
<tr>
<td>D80.1</td>
<td>Nonfamilial hypogammaglobulinemia</td>
</tr>
<tr>
<td>D80.2</td>
<td>Agammaglobulinemia with immunoglobulin-bearing B-lymphocytes</td>
</tr>
<tr>
<td>D80.3</td>
<td>Common variable agammaglobulinemia (CVID/AGamma)</td>
</tr>
<tr>
<td>D80.4</td>
<td>Hypogammaglobulinemia NOS</td>
</tr>
<tr>
<td>D80.5</td>
<td>Selective deficiency of immunoglobulin A (IgA)</td>
</tr>
<tr>
<td>D80.6</td>
<td>Selective deficiency of immunoglobulin G (IgG) subclasses</td>
</tr>
<tr>
<td>D80.7</td>
<td>Selective deficiency of immunoglobulin M (IgM)</td>
</tr>
<tr>
<td>D80.8</td>
<td>Immunodeficiency with increased immunoglobulin M (IgM)</td>
</tr>
<tr>
<td>D80.9</td>
<td>Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia</td>
</tr>
<tr>
<td>D80.91</td>
<td>Transient hypogammaglobulinemia of infancy</td>
</tr>
<tr>
<td>D80.92</td>
<td>Other immunodeficiencies with predominantly antibody defects</td>
</tr>
<tr>
<td>D80.93</td>
<td>Kappa light chain deficiency</td>
</tr>
<tr>
<td>D80.94</td>
<td>Immunodeficiency with predominantly antibody defects, unspecified</td>
</tr>
<tr>
<td>D81</td>
<td>Combined immunodeficiencies</td>
</tr>
<tr>
<td>D81.0</td>
<td>Severe combined immunodeficiency (SCID) with reticular dysgenesis</td>
</tr>
<tr>
<td>D81.1</td>
<td>Severe combined immunodeficiency (SCID) with low T- and B-cell numbers</td>
</tr>
<tr>
<td>D81.2</td>
<td>Severe combined immunodeficiency (SCID) with low or normal B-cell numbers</td>
</tr>
<tr>
<td>D81.4</td>
<td>Nezelof's syndrome</td>
</tr>
<tr>
<td>D81.6</td>
<td>Major histocompatibility complex I deficiency</td>
</tr>
<tr>
<td>D81.7</td>
<td>Major histocompatibility complex II deficiency</td>
</tr>
<tr>
<td>D81.89</td>
<td>Other combined immunodeficiencies</td>
</tr>
<tr>
<td>D81.9</td>
<td>Combined immunodeficiency, unspecified</td>
</tr>
<tr>
<td>D82</td>
<td>Immunodeficiency associated with other major defects</td>
</tr>
<tr>
<td>D82.0</td>
<td>Immunodeficiency associated with other major defects (continued)</td>
</tr>
<tr>
<td>D82.0.0</td>
<td>Ataxia telangiectasia (Louis-Barr) (G11.3)</td>
</tr>
<tr>
<td>D82.01</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>D82.02</td>
<td>Immunodeficiency with thrombocytopenia and eczema</td>
</tr>
<tr>
<td>D82.1</td>
<td>Di George's syndrome</td>
</tr>
<tr>
<td>D82.2</td>
<td>Pharyngeal pouch syndrome</td>
</tr>
<tr>
<td>D82.3</td>
<td>Thymic alymphoplasia</td>
</tr>
<tr>
<td>D82.4</td>
<td>Thymic aplasia or hypoplasia with immunodeficiency</td>
</tr>
<tr>
<td>D82.8</td>
<td>Combined immunodeficiency with autoantibodies to B- or T-cells</td>
</tr>
<tr>
<td>D82.8</td>
<td>Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function</td>
</tr>
<tr>
<td>D82.9</td>
<td>Combined immunodeficiency with major defect, unspecified</td>
</tr>
</tbody>
</table>

### Privigen Vial Sizes

Privigen Vial Sizes Ready-to-Use Privigen Vials

<table>
<thead>
<tr>
<th>Protein</th>
<th>Fill Size</th>
<th>NDC Number*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 g</td>
<td>50 mL</td>
<td>44206-0436-05</td>
</tr>
<tr>
<td>10 g</td>
<td>100 mL</td>
<td>44206-0437-10</td>
</tr>
<tr>
<td>20 g</td>
<td>200 mL</td>
<td>44206-0438-20</td>
</tr>
<tr>
<td>40 g</td>
<td>400 mL</td>
<td>44206-0439-40</td>
</tr>
</tbody>
</table>

*Privigen is covered by Medicare Part B for treatment in the patient’s home only for these diagnoses. Other diagnoses treated in the home may be covered by Medicare Part D. CPT codes are for informational purposes and are not an exhaustive list. The CPT®, HCPCS, and ICD-10-CM codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT coding). Because government and other third-party payer coding requirements change periodically, please verify current coding requirements directly with Privigen Vial Sizes Ready-to-Use Privigen Vials

Please see full Important Safety Information on back and enclosed full prescribing information for Privigen, including boxed warning.

Most insurers cover Privigen for the medically necessary treatment of primary immunodeficiency (PI) disease, chronic immune thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP). Medicaid coverage varies by state, and coverage by other payers varies by plan and by contract. Medicare coverage and billing requirements are dependent in part on where the patient is treated.
**Field 21**

Enter all appropriate ICD-10-CM diagnosis codes, starting on Field 21, Line A. This field allows the entry of 1 character indicator and 12 diagnosis codes at a maximum of 7 characters in length.

**Field 24D (CPT/HCPCS)**

- Enter HCPCS code J1459 for Privigen
- Include CPT codes for infusion: 96365, infusions first hour; 96366, infusion each additional hour

**Field 24G (Days or Units)**

Enter the total number of 500-mg billing units. For example, if 40 grams are dispensed, the number of billing units would equal 80.

**Field 24E (Diagnosis Pointer)**

Enter the line letter(s) from Field 21 that best describes the medical necessity for the service listed in Field 24D. For Medicare claims, only one line letter from Field 21 should be entered in Field 24E for each HCPCS code reported in Field 24D.

**Field 24D (Shaded Area)**

For Medicaid claims, and for Medicare claims that will cross over to Medicaid as the secondary payer, NDC information in a specific format is required in the shaded area above the line on which Privigen is reported in 24D. The various Medicaid plans and Medicare have different reporting formats for this information. In general, the billing entity will need to supply the NDC (in HIPAA-compliant 11-digit format) preceded by the Modifier N4 (eg, N499999999999). This is typically followed by the NDC unit of measure (F2 [international unit], GR [gram], ML [milliliter], or UN [unit]) and the numeric quantity of the NDC that was dispensed. Other payers may require similar information. Check with your payer for specific requirements related to reporting the information required in the shaded areas of Field 24.

**CMS-1500 Claim Example**

**Health Insurance Claim Form**

**A. Procedure/Service Description**

**B. Procedure/Service Description**

**C. Procedure/Service Description**

**D. Procedure/Service Description**

**E. Procedure/Service Description**

Please see full Important Safety Information on back and enclosed full prescribing information for Privigen, including boxed warning.
Important Safety Information

Privigen is indicated for the treatment of:

- Primary humoral immunodeficiency (PI)
- Chronic immune thrombocytopenic purpura (ITP) in patients age 15 years and older
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in adults

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

- Thrombosis may occur with immune globulin products, including Privigen. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinaemia, and in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. In patients at risk of developing acute renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Hyperproteinaemia, increased serum viscosity, or hyponatraemia can occur with Privigen. Infrequently, aseptic meningitis syndrome (AMS) may occur—especially with high doses or rapid infusion.

Hemolysis, either intravascular or due to enhanced red blood cell sequestration, may occur. Risk factors include non-O blood group and high doses. Closely monitor patients for hemolysis and hemolytic anemia.

During and shortly following Privigen infusion, elevations of systolic and diastolic blood pressure (including cases of hypertensive urgency) have been observed. These elevations resolved or significantly improved within hours with oral anti-hypertensive therapy or observation alone. Check patients for a history of hypertension and monitor blood pressure during this period.

Consider relative risks and benefits before prescribing high-dose regimen for chronic ITP and CIDP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload. Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).

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

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

In clinical studies of patients being treated for chronic ITP, the most common adverse reactions, seen in >5% of subjects, were laboratory findings consistent with hemolysis, headache, elevated body temperature, anemia, nausea, and vomiting. A serious adverse reaction was aseptic meningitis syndrome.

In clinical studies of patients being treated for CIDP, the most common reactions, observed in >5% of subjects, were headache, asthenia, hypertension, nausea, pain in extremity, hemolysis, influenza-like illness, leukopenia, and rash. Serious adverse reactions were hemolysis, exacerbation of CIDP, acute rash, increased diastolic blood pressure, hypersensitivity, pulmonary embolism, respiratory failure, and migraine.

Treatment with Privigen might interfere with a patient’s response to live virus vaccines and could lead to misinterpretation of serologic testing. In patients over 65 and those at risk of renal insufficiency, do not exceed recommended dose and infuse at the minimum rate practicable.

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

References:

Privigen is manufactured by CSL Behring AG and distributed by CSL Behring LLC. Privigen® is a registered trademark of CSL Behring AG. Biotherapies for Life® is a registered trademark of CSL Behring LLC. IgIQ™ is a service mark of CSL Behring LLC. CPT® is a registered trademark of the American Medical Association.

©2018 CSL Behring LLC  www.Privigen.com  PVG-0157-MAR18
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:

Indications (1.3) 09/2017

WARNINGS AND PRECAUTIONS (5.2, 5.6, 5.7, 5.9)                                                         09/2017

5.11 Interference with Laboratory Tests

5.9  Volume Overload

5.8  Transfusion-Related Acute Lung Injury (TRALI)

5.7   Hypertension

5.6   Hemolysis

5.3  Thrombosis

5.2  Thrombosis, Renal Dysfunction and Acute Renal Failure

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>
<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>
</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)

Full prescribing information: contents *

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

1 INDICATIONS AND USAGE

1.1 Primary Humoral Immunodeficiency

1.2 Chronic Immune Thrombocytopenic Purpura

1.3 Chronic Inflammatory Demyelinating Polyneuropathy

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Primary Humoral Immunodeficiency (PI)

2.2 Dosage for Chronic Immune Thrombocytopenic Purpura (ITP)

2.3 Dosage for Chronic Inflammatory Demyelinating Polyneuropathy

2.4 Preparation and Handling

2.5 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

5.2 Renal Dysfunction and Acute Renal Failure

5.3 Thrombosis

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

5.5 Aseptic Meningitis Syndrome (AMS)

5.6 Hemolysis

5.7 Hypertension

5.8 Tranfusion-Related Acute Lung Injury (TRALI)

5.9 Volume Overload

5.10 Transmissible Infectious Agents

5.11 Interference with Laboratory Tests

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

9 OVERDOSAGE

10 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

13 PHARMACOKINETICS

14 CLINICAL STUDIES

14.1 Treatment of Primary Humoral Immunodeficiency

14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

14.3 Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura

14.4 Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

See 17 for PATIENT COUNSELING INFORMATION.

Revised: September 2017

---

* Sections or subsections omitted from the full prescribing information are not listed.
Dose
Privigen®, Immune Globulin
CSL Behring

Table 1. Recommended Dosage and Administration for Privigen

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 indication 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>
<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>Primary Immunodeficiency</td>
<td>200-800 mg/100 kg/1000 ml 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>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 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>
<tr>
<td>Maintenance dose: 1 g/kg (10 mL/kg) administered in 1 to 2 infusions on consecutive days, every 3 weeks</td>
<td></td>
<td></td>
<td></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 (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload [see Warnings and Precautions (5.9)].

2.3 Dosage for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Privigen may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to five consecutive days. Privigen may be administered as a maintenance infusion of 1 g/kg (10 mL/kg) administered in a single infusion given in one day or divided into two doses given on two consecutive days, every 3 weeks. Maintenance therapy beyond 6 months has not been studied.

The recommended initial infusion rate is 0.5 mg/kg/min (0.005 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for thrombosis, renal dysfunction, or volume overload, administer Privigen at the minimum infusion rate practiceable [see Warnings and Precautions (5.2, 5.3)].

2.4 Preparation and Handling
Privigen is a clear or slightly opalescent, colorless to pale yellow solution. Inspect parental drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, turbid, or if it contains particulate matter.

- DO NOT SHAKE.
- Do not freeze. Do not use if Privigen has been frozen.
- Privigen should be at room temperature (up to 25°C [77°F]) at the time of administration.
- Do not use Privigen beyond the expiration date on the product label.
- The Privigen vial is for single-use only. Promptly use any vial that has been entered. Privigen contains no preservative. Discard partially used vials or unused product in accordance with local requirements.
- Infuse Privigen using a separate infusion line. Prior to use, the infusion line may be flushed with Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP.
- Do not mix Privigen with other IgG 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.

2.5 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.

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 (1.1)). 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, nephrotic syndrome, 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 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. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, 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 (2.2), Patient Counseling Information (17)).

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia
Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.

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. 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, loss of photophobia, painful eye movements, nausea, vomiting, somnolence. Cerebrospinal fluid (CSF) studies are frequently normal, 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. Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported. 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. Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV, but the role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP, CDP, and PI.

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 infusions of Privigen. These blood pressure elevations were resolved or significantly improved within hours with either observation alone or changes in oral anti-hypertensive therapy (see Adverse Reactions (6.1)). Such elevations were reported more often in 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 transmitting 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 (5.6)).

Secondary 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 (5.6)). The most common adverse reaction observed in ≥5% of subjects with PI were headache, fatigue, nausea, and vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, phosphorylasegnal pain, urticaria, and dizziness.

Chronic Immune Thrombocytopenic Purpura
The most serious adverse reaction observed in the 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 blood lactate dehydrogenase (LDH) and/or indirect bilirubin), 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
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>

Note: AR rates in this study cannot be compared directly to the rates in other IVIG 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.

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 (33.7)</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>

* ARs are defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion. Infections are excluded from this table.

Of the 125 reported ARs (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) were all related to Privigen. 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.

Table 4 summarizes the most frequent ARs that occurred in >5% of subjects with chronic ITP.

Table 4. 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>

* ARs were defined as adverse events at least possibly related or events occurring during or within 72 hours after the end of a treatment cycle (two consecutive infusions).

Of the 149 non-serious ARs, 103 were mild (awareness of sign, symptom or event, but easily tolerated), 20 were moderate (discomfort enough to cause interference with usual activity and may have warranted intervention), and 9 were severe (incapacitating with inability to do usual activities or significantly affected clinical status, and warranted intervention). One subject experienced a serious AR (aseptic meningitis).

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

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

In this study, there was a decrease in hemoglobin after the first 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 were blood group O (20% 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; 1 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.

Table 5. CIDP Clinical Study – ARs* Occurring in >5% of Subjects

<table>
<thead>
<tr>
<th>AR</th>
<th>Number (%) of Subjects [n=28]</th>
<th>Number (Rate) of Infusions with AR [n=259]</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>Leukopenia</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 transfusion.

Four subjects, three of whom had a history of hypertension, had reversible increases in systolic blood pressure to ≥180 mm Hg during or within 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 71 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).

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.

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

8.1 Pregnancy

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with Privigen. It is not known whether Privigen can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Immune globulin may 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.

8.2 Lactation

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Privigen and any potential adverse effects on the breastfed infant from Privigen or from the underlying maternal condition.

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 3.

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 Demineralizing 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 OVERDOSE

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 polyclonal 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 (overdose may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with impaired renal function).

11.1 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 CLINICAL PHARMACOLOGY

12.1 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- 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 (n=3)</th>
<th>4-Week Dosing Interval (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (peak, mg/dl)*</td>
<td>2,550 (400)</td>
<td>2,340 (2,290-3,010)</td>
</tr>
<tr>
<td>Cmin (trough, mg/dl)*</td>
<td>1,230 (230)</td>
<td>1,200 (1,020-1,470)</td>
</tr>
<tr>
<td>t1/2 (days)</td>
<td>27.6 (5.9)</td>
<td>27.8 (21.6-33.4)</td>
</tr>
<tr>
<td>AUC0-∞ (day × mg/dl)*</td>
<td>32,820 (6,260)</td>
<td>29,860 (28,580-40,010)</td>
</tr>
<tr>
<td>AUC0-∞ (day × mg/dl)*</td>
<td>79,315 (20,170)</td>
<td>78,748 (59,435-99,762)</td>
</tr>
<tr>
<td>Clearance (ml/day/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 (1.27 ± 0.35 ml/dkg) and females (1.31 ± 0.22 ml/dkg). In six subjects between 13 and 15 years of age, the clearance of Privigen (1.35 ± 0.44 ml/d/kg) is comparable to that observed in 19 adult subjects 19 years of age or older (1.29 ± 0.22 ml/d/kg). The IgG subclass levels observed in the pharmacokinetic study were consistent with a physiologic distribution pattern.

Treatment of Chronic Immune Thrombocytopenic Purpura

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

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

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 (1 g/kg) given over 1 or 2 days every 3 weeks, the mean IgG trough concentration was 17.5 ± 3.1 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 ± 3.2 g/L to 33.2 ± 6.9 g/L. At Week 7, before the second maintenance treatment (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 19.

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.
14 CLINICAL STUDIES

14.1 Treatment of Primary Humoral Immunodeficiency

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and pharmacokinetics of Privigen in adult and pediatric subjects with PI, who were treated for 12 months at a 3-week to 4-week dosing interval. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 42 (52.5%) were female; 77.5% were Caucasian, 15% were Hispanic, and 7.5% were African-American. All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study.

The efficacy analysis included 80 subjects, 16 (20%) on the 3-week dosing interval and 64 (80%) on the 4-week dosing interval. Doses ranged from 200 mg/kg to 888 mg/kg per infusion. The median dose for the 3-week interval was 428.3 mg/kg per infusion; the median dose for the 4-week interval was 440.6 mg/kg per infusion. Subjects received a total of 1038 infusions of Privigen, 272 for the 3-week dosing regimen and 766 for the 4-week dosing regimen. The maximum infusion rate allowed for the 3-week regimen was 7 mg/kg/min with 715 (69%) of the infusions administered at a rate of 7 mg/kg/min or greater.

The median duration of platelet response in these subjects was 428.3 mg/kg per infusion; the median dose for the 4-week interval was 440.6 mg/kg per infusion. Subjects received a total of 1038 infusions of Privigen, 272 for the 3-week dosing regimen and 766 for the 4-week dosing regimen. The maximum infusion rate allowed for the 3-week regimen was 7 mg/kg/min with 715 (69%) of the infusions administered at a rate of 7 mg/kg/min or greater.

The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (ASBI), defined as pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject per year. Secondary analyses were based on the annual rate of other infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization. During the 12-month study period, the ASBI rate was 0.08 (with an upper 1-sided 99% confidence interval of 0.203), which met the predefined success rate of less than one ASBI per subject per year. Six subjects experienced an ASBI, including three cases of pneumonia and one case each of septic arthritis, osteomyelitis, and visceral abscess. All six subjects completed the study.

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

14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

A prospective, open-label, single-arm, multicenter study assessed efficacy and safety parameters in 57 IGIV-treated subjects with chronic ITP with a platelet count of <30 x 10^9/L at screening. Fifty-three subjects had a history of chronic ITP with a duration of greater than 6 months and 4 subjects, all of whom had received prior treatment for ITP with 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 with 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 found 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 criterion for greater than 1 g/dL drop in hemoglobin within a 21-day interval since the last IGIV 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 indirect or 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.

14.3 Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura

A prospective, open-label, single-arm, multicenter study assessed efficacy and safety parameters in 57 IGIV-treated subjects with chronic ITP with a platelet count of <30 x 10^9/L at screening. Fifty-three subjects had a history of chronic ITP with a duration of greater than 6 months and 4 subjects, all of whom had received prior treatment for ITP with 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 with 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 found 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 criterion for greater than 1 g/dL drop in hemoglobin within a 21-day interval since the last IGIV 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 indirect or 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.

14.4 Treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In a prospective, open-label, single-arm, multicenter clinical study (Privigen Impact on Mobility and Autonomy [PRIMA]), 28 subjects with CIDP (13 IGIV-pretreated and 15 IGIV-unpretreated) received a Privigen loading dose of 2 g/kg followed by Privigen maintenance doses of 1 g/kg for up to 21 weeks with a 3 week follow-up. Efficacy in the PRIMA study was based on the responder rate of Privigen in comparison to a historical control in the adjusted 10-point Inflammatory Neuropathy Cause and Treatment (INCAT) score.19 The responder rate was defined as the proportion of subjects who demonstrated clinically meaningful improvement (at least 1 point decrease on adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score) between baseline and Week 25, with a pre-specified threshold of 35% in the lower limit of the 2-sided 95% Wilson-Score confidence interval (CI). The overall percentage of responders in PRIMA was 61% (95% CI: 42.4% to 76.4%). Response rate of 47% (95% CI: 32.4% to 62.6%) was achieved in the IGIV pretreated and 77% in IGIV-pretreated subject subgroups. In a post-hoc analysis, the overall percentage of subjects in PRIMA who responded by week 10 and maintained the response through week 25 and lacked confounding changes in glucocorticoid/immunosuppressant dosage was 53.6% (95% CI: 35.8% to 70.5%).

In a second study (PATH) with the same Privigen dosing regimen, all 207 subjects were IGIV-pretreated and had relapsed following withdrawal of IGIV prior to being administered Privigen [see Dosage and Administration (2.3)]. The response rate was 73% (see Figure 1). Among the subset of 151 subjects in the PATH study who had deteriorated by one or more points in adjusted INCAT score following withdrawal of IGIV, 137 subjects...
(90.7%) responded during the Privigen “restabilization” period with an increase of one or more adjusted INCAT score points. The overall median time to first adjusted INCAT response in PRIMA was 7.5 weeks (18 weeks in IGIV-untreated and 3 weeks in IGIV-pretreated). The median time to first adjusted INCAT response in PATH (all IGIV-pretreated) was 3.7 weeks (95% CI: 3.4 to 5.9 weeks). Mean INCAT score in PRIMA showed a clinically meaningful improvement by 1.4 points (1.1 points for IGIV-untreated, and 1.8 points for IGIV-pretreated [1.2 points in PATH]).

Figure 1. Percentage of Responders (Adjusted INCAT Score)

Medical Research Council (MRC) sum score in PRIMA improved by a mean of 6.9 points (7.7 points for IGIV-untreated and 6.1 points for IGIV-pretreated). MRC sum score in PATH improved by a mean of 3.6 points. Grip strength of the dominant hand improved in PRIMA by a mean of 14.1 kPa (17.0 kPa for IGIV-untreated and 10.8 kPa for IGIV-pretreated subgroups). Grip strength of the dominant hand improved in PATH by a mean of 12.2 kPa. Similar results were observed for the non-dominant hand in both studies.

Grip strength of the dominant hand improved in PATH by a mean of 12.2 kPa. Similar results were observed for the non-dominant hand in both studies.

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 IgGs. 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 (5.8)].

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 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 (5.10)].

Inform patients that administration of IgG may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella), and instruct them to notify their immunizing physician of recent therapy with Privigen [see Warnings and Precautions (5.11)].

Manufactured by: CSL Behring AG Bern, Switzerland
US License No. 1766

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

(continued on next page)