

# Privigen Promise Enrollment Form



## Eligibility, Fulfillment & Term

*Eligibility:* The Privigen Promise is open to both current and first-time Privigen customers.

*Fulfillment:* CSL Behring guarantees availability of Privigen to enrolled customers in an amount equal to that purchased by the customer in the most recent 6 months. As such, the customer's guarantee grows with their purchase volume.

*Term:* This guarantee is effective through 12/31/2016.

The Privigen Promise is made in good faith by CSL Behring and

\_\_\_\_\_

Customer

\_\_\_\_\_

Street

\_\_\_\_\_

City

\_\_\_\_\_

State

\_\_\_\_\_

ZIP

Effective date is the date the form is signed by the customer representative.

### **CSL BEHRING LLC REPRESENTATIVE\***

Territory number: \_\_\_\_\_

Print name: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

### **CUSTOMER REPRESENTATIVE\***

Print name: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**Fax to: (610) 878-4929**

Office Use Only: ID \_\_\_\_\_

\*Form requires both signatures for enrollment into the program.

## **Important Safety Information**

**WARNING:** Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

See full Important Safety Information on back and accompanying full prescribing information for Privigen.

**privigen**<sup>®</sup>  
Immune Globulin Intravenous  
(Human), 10% Liquid  
IVIg therapy made simple

CSL Behring is committed to saving and improving lives of people with rare and serious diseases worldwide. Whether we are manufacturing, marketing, or researching and developing innovative biotherapies, we are first and foremost focused on fulfilling our customers' needs.

As a leader in the plasma protein biotherapeutics industry, CSL Behring is pleased to offer select customers up to a *five-year supply guarantee* of Privigen. Known as the Privigen Promise, this unique offer is intended to minimize customers' supply risk in times of IVIg shortage.

Please complete the form on the other side to enroll.



## Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

**WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.**

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Also monitor patients with risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.

Patients could experience increased serum viscosity, hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion). There have been reports of IVIg-related hemolysis, hemolytic anemia, and pulmonary adverse events, including transfusion-related acute lung injury (TRALI). Avoid high-dose regimen where fluid volume is of concern.

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

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

In clinical studies of patients being treated with Privigen for chronic ITP, the most serious adverse reactions were AMS (one subject) and hemolysis (eight subjects). Adverse reactions seen in >5% of subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, increases in conjugated and unconjugated bilirubin, hyperbilirubinemia, and increased blood lactate dehydrogenase.

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing.

**Please see accompanying full prescribing information for Privigen.**

Privigen is manufactured by CSL Behring AG and distributed by CSL Behring LLC.  
The Privigen Promise is a trademark of CSL Behring LLC.  
Privigen is a registered trademark of CSL Behring AG.



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www.CSLBehring-us.com www.Privigen.com PVG11-11-0017 12/2011



## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

### WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

See full prescribing information for complete boxed warning.

- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of human immune globulin intravenous (IGIV) products.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privilgen does not contain sucrose.
- For patients at risk of renal dysfunction or renal failure, administer Privilgen at the minimum infusion rate practicable.

### INDICATIONS AND USAGE

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

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

### DOSAGE AND ADMINISTRATION

#### Intravenous Use Only

Indication	Dose (2.2)	Initial Infusion Rate (2.3)	Maintenance Infusion Rate (if tolerated) (2.3)
PI	200-800 mg/kg (2-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

- Ensure that patients with pre-existing renal insufficiency are not volume depleted, and discontinue Privilgen if renal function deteriorates (2.3, 5.2).
- For patients at risk of renal dysfunction or thrombotic events, administer Privilgen at the minimum infusion rate practicable (2.3, 5.2, 5.4).

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

- History of anaphylactic or severe systemic reactions to human immune globulin (4)
- Hyperprolinemia (Privilgen 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 (5.3).
- Thrombotic events may occur. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity (5.4).
- Aseptic meningitis syndrome (AMS) may occur, especially with high doses or rapid infusion (5.5).
- Hemolysis can develop subsequent to Privilgen treatments due to enhanced red blood cell sequestration. Monitor patients for hemolysis and hemolytic anemia (5.6).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]) (5.7).
- Avoid use of the high-dose regimen (for chronic ITP) in patients with expanded fluid volume or where fluid volume is of concern (5.8).
- Privilgen is made from human blood and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.9).

### ADVERSE REACTIONS

- **PI** – The most common adverse reactions, observed in >5% of study subjects, were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature (6).
- **Chronic ITP** – The most common adverse reactions, observed in >5% of study subjects, were headache, pyrexia/hyperthermia, positive direct antiglobulin test (DAT), anemia, vomiting, nausea, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased. A serious adverse reaction was aseptic meningitis (6).

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

### DRUG INTERACTIONS

The passive transfer of antibodies may:

- Lead to misinterpretation of the results of serological testing (5.10, 7.2).
- Interfere with the response to live virus vaccines (7.1).

### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: February 2011

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

## WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

- Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.<sup>1</sup> Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (see *Warnings and Precautions* [5.2]). Privigen does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (see *Dosage and Administration* [2.3], *Warnings and Precautions* [5.2]).

## 1 INDICATIONS AND USAGE

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

### 1.1 Primary Humoral Immunodeficiency

Privigen is indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

### 1.2 Chronic Immune Thrombocytopenic Purpura

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Preparation and Handling

- Privigen is a clear or slightly opalescent, colorless to pale yellow solution. Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, turbid, or if it contains particulate matter.
- DO NOT SHAKE.
- Do not freeze. Do not use if Privigen has been frozen.
- Privigen should be at room temperature (up to 25°C [77°F]) at the time of administration.
- Do not use Privigen beyond the expiration date on the product label.
- The Privigen vial is for single-use only. Promptly use any vial that has been entered. Privigen contains no preservative. Discard partially used vials or unused product in accordance with local requirements.
- Infuse Privigen using a separate infusion line. Prior to use, the infusion line may be flushed with Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP.
- Do not mix Privigen with other IGIV products or other intravenous medications. However, Privigen may be diluted with Dextrose Injection, USP (D5W).
- An infusion pump may be used to control the rate of administration.
- If large doses of Privigen are to be administered, several vials may be pooled using aseptic technique. Begin infusion within 8 hours of pooling.

### 2.2 Dosage

#### Treatment of Primary Humoral Immunodeficiency

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.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

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.

The high-dose regimen (2 g/kg divided over 2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern (see *Warnings and Precautions* [5.8]).

### 2.3 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 thrombotic events, administer Privigen at the minimum infusion rate practicable, and discontinue Privigen administration if renal function deteriorates (see *Boxed Warning, Warnings and Precautions* [5.2, 5.4]). Table 1 provides the recommended infusion rates for Privigen.

**Table 1: Recommended Infusion Rates for Privigen**

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

The following patients may be at risk of developing inflammatory reactions on rapid infusion of Privigen (greater than 4 mg/kg/min [0.04 mL/kg/min]): 1) those who have never received Privigen or another IgG product or who have not received it within the past 8 weeks, and 2) those who are switching from another IgG product. These patients should be started at a slow rate of infusion (e.g., 0.5 mg/kg/min [0.005 mL/kg/min] or less) and gradually advanced to the maximum rate as tolerated.

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

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

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

### 5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IGIV products, including Privigen. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.<sup>1</sup> If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, 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, Dosage and Administration* [2.3]).

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

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.<sup>2</sup>

### 5.4 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.<sup>3-5</sup> Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (see *Dosage and Administration* [2.3]).

### 5.5 Aseptic Meningitis Syndrome (AMS)

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

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the 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.<sup>7-9</sup> Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.<sup>10</sup>

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (see *Adverse Reactions* [6]). These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after a Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

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

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen.<sup>11</sup> TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum.

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

### 5.8 Volume Overload

The high-dose regimen (1 g/kg/day for 2 days) used to treat patients with chronic ITP is not recommended for individuals with expanded fluid volumes or where fluid volume may be of concern (see *Dosage and Administration* [2.2]).

### 5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen.

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

### 5.10 Interference with Laboratory Tests

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

## 6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in >5% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

### 6.1 Clinical Trials Experience

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

#### Treatment of Primary Humoral Immunodeficiency

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

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

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

Temporally associated AEs are those occurring during an infusion or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2 lists the temporally associated AEs that occurred in >5% of subjects, *irrespective of causality*.

**Table 2: PI Pivotal Study – Adverse Events\* Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, Irrespective of Causality**

Adverse Event	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Event [n=1038]
Headache	35 (43.8)	82 (0.079)
Pain	20 (25.0)	44 (0.042)
Fatigue	13 (16.3)	27 (0.026)
Nausea	10 (12.5)	19 (0.018)
Chills	9 (11.3)	15 (0.014)
Vomiting	7 (8.8)	13 (0.013)
Pyrexia	6 (7.5)	10 (0.010)
Cough	5 (6.3)	5 (0.005)
Diarrhea	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

\* Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privigen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3 lists the adverse reactions (AEs at least possibly related to the infusion of Privigen) that occurred in >5% of subjects with PI, *irrespective of time of occurrence*.

**Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, Irrespective of Time of Occurrence**

Adverse Reaction	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Reaction [n=1038]
Headache	24 (30.0)	62 (0.060)
Pain, all types*	12 (15.0) <sup>†</sup>	26 (0.025)
Nausea	10 (12.5)	18 (0.017)
Fatigue	9 (11.3)	16 (0.015)
Chills	9 (11.3)	15 (0.014)
Vomiting	6 (7.5)	11 (0.011)

\* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain, pain in extremity, and pharyngolaryngeal pain.

<sup>†</sup> Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative DAT at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

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

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

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

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (see *Dosing and Administration* [2.3]). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporally associated with one or more AEs occurring during a Privigen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, *irrespective of causality*, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period. Table 4 lists the temporally associated AEs that occurred in >5% of subjects, *irrespective of causality*.

**Table 4: PI Extension Study – Adverse Events\* Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, Irrespective of Causality**

Adverse Event*	Number (%) of Subjects [n=55]	Number (Rate) of Infusions with Adverse Event [n=771]
Headache	18 (32.7)	56 (0.073)
Pain, all types <sup>†</sup>	14 (25.5) <sup>‡</sup>	31 (0.040)
Abdominal pain <sup>§</sup>	3 (5.5)	4 (0.005)
Chest pain	3 (5.5)	4 (0.005)
Pharyngolaryngeal pain	3 (5.5)	4 (0.005)
Nausea	6 (10.9)	10 (0.013)
Pyrexia	4 (7.3)	9 (0.012)
Chills	3 (5.5)	7 (0.009)
Influenza-like illness	3 (5.5)	4 (0.005)

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

\* Excluding infections.

<sup>†</sup> Includes abdominal pain, abdominal pain upper, arthralgia, back pain, chest pain, fibromyalgia, injection-site pain, myalgia, pain, pain in extremity, painful respiration, pharyngolaryngeal pain, and toothache.

<sup>‡</sup> Some subjects experienced more than one type of pain.

<sup>§</sup> Also includes abdominal pain, upper.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privigen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Table 5 lists the adverse reactions that occurred in >5% of subjects, *irrespective of time of occurrence*.

**Table 5: PI Extension Study – Adverse Reactions Occurring in >5% of Subjects, Irrespective of Time of Occurrence**

Adverse Reaction	Number (%) of Subjects [n=55]	Number (Rate) of Infusions With Adverse Reaction [n=771]
Headache	16 (29.1)	53 (0.069)
Pain, all types*	11 (20.0) <sup>†</sup>	26 (0.034)
Abdominal pain <sup>‡</sup>	4 (7.3)	6 (0.008)
Chest pain	3 (5.5)	4 (0.005)
Chills	3 (5.5)	7 (0.009)
Fatigue	3 (5.5)	5 (0.006)
Joint swelling/effusion	3 (5.5)	7 (0.009)
Pyrexia	3 (5.5)	10 (0.013)
Urticaria	3 (5.5)	4 (0.005)

\* Includes abdominal pain, abdominal pain lower, abdominal pain upper, arthralgia, back pain, chest pain, injection-site pain, musculoskeletal pain, myalgia, pain, and painful respiration.

<sup>†</sup> Some subjects experienced more than one type of pain.

<sup>‡</sup> Includes abdominal pain, lower and abdominal pain, upper.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of  $20 \times 10^9/L$  or less received a total of 2 g/kg dose of 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 (40.4%) were male and 34 (59.6%) were female.

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

Table 6 lists the temporally associated AEs that occurred in >5% of subjects with chronic ITP during a Privigen infusion or within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen, *irrespective of causality*.

**Table 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle\*, Irrespective of Causality**

Adverse Event	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Event [n=114]
Headache	37 (64.9)	41 (0.360)
Pyrexia/hyperthermia	21 (36.8)	22 (0.193)
Nausea	6 (10.5)	6 (0.053)
Epistaxis	6 (10.5)	6 (0.053)
Vomiting	6 (10.5)	6 (0.053)
Blood unconjugated bilirubin increased	6 (10.5)	6 (0.053)
Blood conjugated bilirubin increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	4 (7.0)	4 (0.035)
Hematocrit decreased	3 (5.3)	3 (0.026)

\* Two consecutive daily infusions.

Table 7 lists the adverse reactions that occurred in >5% of subjects, *irrespective of time of occurrence*.

**Table 7: Chronic ITP Study – Adverse Reactions Occurring in >5% of Subjects, Irrespective of Time of Occurrence**

Adverse Reaction	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Reaction [n=114]
Headache	37 (64.9)	52 (0.456)
Pyrexia/hyperthermia	19 (33.3)	21 (0.184)
Positive DAT	6 (10.5)	7 (0.061)
Anemia	6 (10.5)	6 (0.053)
Vomiting	5 (8.8)	6 (0.053)
Nausea	5 (8.8)	7 (0.061)
Bilirubin conjugated, increased	5 (8.8)	5 (0.044)
Bilirubin unconjugated, increased	5 (8.8)	5 (0.044)
Hyperbilirubinemia	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)

Of the 149 non-serious AEs related to Privigen, 103 were mild, 37 were moderate, and 9 were severe.

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

One subject withdrew from the study due to gingival bleeding that was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention; 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 (21.4%) developed a positive DAT during the 29-day study period.

## 6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.<sup>12</sup>

- **Infusion Reactions:** Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- **Renal:** Acute renal dysfunction/failure, osmotic nephropathy
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive DAT (Coombs' test)
- **Musculoskeletal:** Back pain
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain
- **General/Body as a Whole:** Pyrexia, rigors

## 7 DRUG INTERACTIONS

### 7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella (see *Patient Counseling Information [17]*).<sup>13</sup>

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

### 7.2 Serological Testing

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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

### 8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

## 8.4 Pediatric Use

### Treatment of Primary Humoral Immunodeficiency

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

## 8.5 Geriatric Use

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

Use caution when administering Privigen to patients age 65 and over who are judged to be at increased risk of developing acute renal insufficiency and thrombotic events (see *Boxed Warning, Warnings and Precautions [5.2, 5.4]*). Do not exceed recommended doses, and administer Privigen at the minimum 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 ( $\leq 12\%$ ), small amounts of fragments and polymers, and albumin. Privigen contains  $\leq 25$  mcg/mL IgA. The IgG subclass distribution (approximate mean values) is IgG<sub>1</sub>, 67.8%; IgG<sub>2</sub>, 28.7%; IgG<sub>3</sub>, 2.3%; and IgG<sub>4</sub>, 1.2%. Privigen has an osmolality of approximately 320 mOsmol/kg (range: 240 to 440) and a pH of 4.8 (range: 4.6 to 5.0).

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

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

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 HCV and HIV-1 and found to be nonreactive (negative). For HBV, an investigational NAT procedure is used and the plasma units found to be negative; however, the significance of a negative result has not been established. 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  $10^4$  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 8 shows the virus clearance during the manufacturing process for Privigen, expressed as the mean  $\log_{10}$  reduction factor (LRF).

**Table 8: Virus Inactivation/Removal in Privigen\***

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
<b>Virus property</b>						
Genome	RNA	DNA	RNA	RNA	RNA	DNA
Envelope	Yes	Yes	Yes	Yes	No	No
Size (nm)	80-100	120-200	50-70	50-70	25-30	18-24
<b>Manufacturing step</b>	<b>Mean LRF</b>					
pH 4 incubation	$\geq 5.4$	$\geq 5.9$	4.6	$\geq 7.8$	nt	nt
Depth filtration	$\geq 5.3$	$\geq 6.3$	2.1	3.0	4.2	2.3
Virus filtration	$\geq 5.3$	$\geq 5.5$	$\geq 5.1$	$\geq 5.9$	$\geq 5.4$	$\geq 5.5$
<b>Overall reduction (<math>\log_{10}</math> units)</b>	<b><math>\geq 16.0</math></b>	<b><math>\geq 17.7</math></b>	<b><math>\geq 11.8</math></b>	<b><math>\geq 16.7</math></b>	<b><math>\geq 9.6</math></b>	<b><math>\geq 7.8</math></b>

HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MVM, minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF,  $\log_{10}$  reduction factor; nt, not tested.

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

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a

model for CJD and its variant vCJD.<sup>16</sup> Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanoic acid fractionation ( $\geq 6.4 \log_{10}$ ), depth filtration (2.6  $\log_{10}$ ), and virus filtration ( $\geq 5.8 \log_{10}$ ). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Treatment of Primary Humoral Immunodeficiency

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

#### Treatment of Chronic Immune Thrombocytopenic Purpura

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

### 12.3 Pharmacokinetics

#### Treatment of Primary Humoral Immunodeficiency

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

Table 9 summarizes the pharmacokinetic parameters of Privigen, based on serum concentrations of total IgG.

**Table 9: PI Pivotal Study - Pharmacokinetic Parameters of Privigen in Subjects**

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

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

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

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

The IgG subclass levels observed in the pharmacokinetic study were consistent with a physiologic distribution pattern (mean trough values): IgG<sub>1</sub>, 564.91 mg/dL; IgG<sub>2</sub>, 394.15 mg/dL; IgG<sub>3</sub>, 30.16 mg/dL; IgG<sub>4</sub>, 10.88 mg/dL.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

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

## 14 CLINICAL STUDIES

### 14.1 Treatment of Primary Humoral Immunodeficiency

A prospective, open-label, single-arm, multicenter study (pivotal study) assessed the efficacy, safety, and pharmacokinetics of Privigen in adult and pediatric subjects with PI, who were treated for 12 months at a 3-week or 4-week dosing interval. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female; 77.5% were Caucasian, 15% were Hispanic, and 7.5% were African-American. All subjects had been 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 during this study was 8 mg/kg/min with 715 (69%) of the infusions administered at a rate of 7 mg/kg/min or greater. The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (aSBI), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject per year. Secondary analyses were based on the annual rate of other infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization. During the 12-month study period, the aSBI rate was 0.08 (with an upper 1-sided 99% confidence interval of 0.203), which met the predefined success rate of less than one aSBI per subject per year. Six subjects experienced an aSBI, including three cases of pneumonia and one case each of septic arthritis, osteomyelitis, and visceral abscess. All six subjects completed the study.

The rate of other infections was 3.55 infections per subject per year. The infections that occurred most frequently were sinusitis (31.3%), nasopharyngitis (22.5%), upper respiratory tract infection (18.8%), bronchitis (13.8%), and rhinitis (13.8%). Among the 255 infections, 16 (6.3%) occurring in 10 subjects were considered severe. Table 10 summarizes the efficacy results for all 80 subjects.

**Table 10: PI Pivotal Study – Summary of Efficacy Results in Subjects**

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

\* Defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.  
<sup>†</sup> Upper 1-sided 99% confidence interval: 0.203.

## 14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and tolerability of Privigen in 57 subjects with chronic ITP and a platelet count of  $20 \times 10^9/L$  or less. Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female; all were Caucasian.

Subjects received a 2 g/kg dosage of Privigen administered as 1 g/kg (10 mL/kg) intravenous infusion daily for 2 consecutive days, and were observed for 29 days. Fifty-three (93%) subjects received Privigen at the maximum infusion rate allowed (4 mg/kg/min [0.04 mL/kg/min]).

The primary analysis was based on the response rate defined as the percentage of subjects with an increase in platelet counts to at least  $50 \times 10^9/L$  within 7 days after the first infusion (responders). Secondary analyses were based on the increase in platelet counts and the time to reach a platelet count of at least  $50 \times 10^9/L$  at any point within the study period, the duration of that response, and the regression (decrease in the severity) of hemorrhage in subjects who had bleeding at baseline. Platelet counts were measured on Days 1, 2, 4, 6, 8, 15, 22, and 29. Additional measurements on Days 57 and 85 occurred in subjects with a platelet count of at least  $50 \times 10^9/L$  at the previous visit.

Of the 57 subjects in the efficacy analysis, 46 (80.7%) responded to Privigen with a rise in platelet counts to at least  $50 \times 10^9/L$  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 highest median increase in platelet counts was seen 7 days after the first infusion ( $123 \times 10^9/L$ ). The median maximum platelet count achieved was  $154 \times 10^9/L$ . The median time to reach a platelet response of more than  $50 \times 10^9/L$  was 2.5 days after the first infusion. Twenty-five (43%) of the 57 subjects reached this response by Day 2 prior to the second infusion and 43 (75%) subjects reached this response by Day 6.

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

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

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

When stored at room temperature (up to 25°C [77°F]), Privigen is stable for up to 36 months, as indicated by the expiration date printed on the outer carton and vial label.

Keep Privigen in its original carton to protect it from light.

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. 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
- Shortness of breath, changes in mental status, chest pain, and other manifestations of thrombotic events
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting, which may suggest aseptic meningitis syndrome
- Fatigue, increased heart rate, yellowing of skin or eyes, and dark-colored urine, which may suggest hemolysis
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever, which may suggest TRALI (a condition typically occurring within 1 to 6 hours following transfusion)

Inform patients that Privigen is made from human blood and may contain infectious agents that can cause disease (e.g., viruses and, theoretically the CJD agent). Explain that the risk that Privigen may transmit an infectious agent has been reduced by screening the plasma donors, by testing donated plasma for certain virus infections, and by inactivating or removing certain viruses during manufacturing, and counsel patients to report any symptoms that concern them.

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

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