

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

See full prescribing information for complete boxed warning.

- Use of Immune Globulin Intravenous (Human) (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death in predisposed patients. Privigen does not contain sucrose.
- For patients at risk of renal dysfunction or renal failure, administer Privigen at the minimum infusion rate practicable.

RECENT MAJOR CHANGES

Warnings and Precautions, Hyperproteinemia (5.3)

06/2009

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

Intravenous Use Only

Indication	Dose (2.2)	Initial Infusion Rate (2.3)	Maintenance Infusion Rate (if tolerated) (2.3)
PI	200-800 mg/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 for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- History of anaphylactic or severe systemic reactions to human immunoglobulin (4)
- Hyperprolinemia (Privigen contains the stabilizer L-proline) (4)
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (4)

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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 in patients receiving IGIV therapy (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 may occur, especially with high doses or rapid infusion (5.5).
- Hemolysis can develop subsequent to Privigen 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).
- Privigen is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.9).
- Passive transfer of antibodies may confound serologic testing (5.11).

ADVERSE REACTIONS

- **PI** – The most common adverse reactions are headache, pain, nausea, fatigue, and chills (6).
- **Chronic ITP** – The most common adverse reactions are headache, pyrexia/hyperthermia, and anemia (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.

DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines (7).

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 Privigen at the minimum rate practicable (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November 2009

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Privigen[®], 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.¹ 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 immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital 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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy or 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) if necessary.
- 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 usual dose of Privigen for patients with PI is 200 to 800 mg/kg (2 to 8 mL/kg), administered every 3 to 4 weeks. Adjust the dosage over time to achieve the desired serum trough levels and clinical responses. 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.

Treatment of Chronic Immune Thrombocytopenic Purpura

The usual 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	Initial infusion rate	Maintenance infusion rate (if tolerated)
PI	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
ITP	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 not received Privigen or another IgG product; 2) those who are switching from another IgG product; and 3) those who have not received IgG in more than 8 weeks. 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 had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Because it contains the stabilizer L-proline, Privigen is contraindicated in patients with hyperprolinemia.
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

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]**). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction (see **Contraindications [4]**).

5.2 Renal Failure

Ensure that patients are not volume depleted before administering Privigen. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction, administer Privigen at the minimum infusion rate practicable (see **Boxed Warning, Dosage and Administration [2.3]**).

5.3 Hyperproteinemia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Privigen and other IGIV product treatments. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because 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 thrombotic events.²

5.4 Thrombotic Events

Thrombotic events may occur following treatment with Privigen and other IGIV products.³⁻⁵ 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.

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]**). Weigh the potential risks and benefits of IGIV against those of alternative therapies in all patients for whom Privigen therapy is being considered.

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with Privigen (see *Adverse Reactions [6, 6.1]*) and other IGIV product treatments. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.⁶ AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (see *Patient Counseling Information [17]*). 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. 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 reaction and, rarely, hemolysis.⁷⁻⁹ Hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration and/or intravascular RBC destruction.¹⁰

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (see *Adverse Reactions [6, 6.1]*). 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 (see *Patient Counseling Information [17]*). If these are present after 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 in patients following IGIV treatment.¹¹ 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 (see *Patient Counseling Information [17]*). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil 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

Privigen is made from human plasma. Based on effective donor screening and product manufacturing processes (see *Description [11]*), Privigen carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Privigen. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare professional to CSL Behring Pharmacovigilance at 1-866-915-6958. Before prescribing Privigen, the physician should discuss the risks and benefits of its use with the patient (see *Patient Counseling Information [17]*).

5.10 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.
- 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.
- If signs and/or symptoms of hemolysis are present after an infusion of Privigen, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.11 Interference With Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >10% of clinical study subjects with PI were headache, pain, nausea, fatigue, and chills.

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 (see *Warnings and Precautions [5.5, 5.6]*). The most common adverse reactions observed in >10% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia.

6.1 Clinical Trials Experience

Because different clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in practice.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI (with a diagnosis of XLA or COVID) received Privigen intravenously 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; 57.5% were male and 42.5% were female.

The safety analysis included all 80 subjects, 16 on the 3-week schedule and 64 on the 4-week schedule. The median doses of Privigen administered intravenously ranged from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg). A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule. Of the 1038 infusions, 435 were administered to females and 603 to males.

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 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%). This is below the target of 40% for this safety endpoint. 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 more than 5% of subjects during a Privigen infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

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

Adverse Event	Subjects (%) [n=80]	Infusions (%) [n=1038]
Headache	35 (43.8)	82 (7.9)
Pain	20 (25.0)	44 (4.2)
Fatigue	13 (16.3)	27 (2.6)
Nausea	10 (12.5)	19 (1.8)
Chills	9 (11.3)	15 (1.4)
Vomiting	7 (8.8)	13 (1.3)
Pyrexia	6 (7.5)	10 (1.0)
Cough	5 (6.3)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects).

Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that 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 direct antiglobulin test (DAT) at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

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

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 x 10⁹/L or less received a total of 2 g/kg dose of Privigen

administered as 1 g/kg intravenous infusions daily for 2 consecutive days (see *Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male.

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 3 lists the temporally associated AEs that occurred in more than 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 3: Adverse Events Occurring in >5% Subjects With Chronic ITP During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle*, *Irrespective of Causality*

Adverse Event	Subjects (%) [n=57]	Infusions (%) [n=114]
Headache	37 (64.9)	41 (36.0)
Pyrexia/hyperthermia	21 (36.8)	22 (19.3)
Nausea	6 (10.5)	6 (5.3)
Epistaxis	6 (10.5)	6 (5.3)
Vomiting	6 (10.5)	6 (5.3)
Blood unconjugated bilirubin increased	6 (10.5)	6 (5.3)
Blood conjugated bilirubin increased	5 (8.8)	5 (4.4)
Blood total bilirubin increased	4 (7.0)	4 (3.5)
Hematocrit decreased	3 (5.3)	3 (2.6)

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be “at least possibly” related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).

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, which 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.

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 postmarketing reporting of adverse events is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

Privigen Postmarketing Experience

Adverse reactions reported during worldwide postmarketing use of Privigen do not differ from what has been observed in clinical studies with Privigen and from what is known for IGIV products.

General

The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility.

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

- **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 direct antiglobulin (Coombs') test

- **Musculoskeletal:** Back pain
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain
- **General/Body as a Whole:** Pyrexia, rigors

7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, and rubella.¹³ The immunizing physician should be informed of recent therapy with Privigen so that appropriate measures may be taken (see *Patient Counseling Information [17]*).

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.^{14,15}

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. 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

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 renal insufficiency (see *Boxed Warning, Warnings and Precautions [5.2]*). 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 (≤12%), small amounts of fragments and polymers, and albumin. Privigen contains ≤25 mcg/mL IgA. The IgG subclass distribution (approximate mean values) is IgG₁, 67.8%; IgG₂, 28.7%; IgG₃, 2.3%; and IgG₄, 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 10⁴ 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 4 shows the virus clearance during the manufacturing process for Privigen, expressed as the mean log₁₀ reduction factor (LRF).

Table 4: Virus Inactivation/Removal in Privigen

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
Virus property						
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
Manufacturing step						
	Mean LRF					
pH 4 incubation	≥5.4	≥5.9	4.6	≥7.8	nt	nt
Depth filtration	≥5.3	≥6.3	2.1	3.0	4.2	2.3
Virus filtration	≥5.3	≥5.5	≥5.1	≥5.9	≥5.4	≥5.5
Overall reduction (log₁₀ units)	≥16.0	≥17.7	≥11.8	≥16.7	≥9.6	≥7.8

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, log₁₀ reduction factor; nt, not tested. In addition, viral clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. The estimated Log Reduction Factor obtained was ≥5.3.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of TSE, considered a model for CJD and its variant vCJD.¹⁶ Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanoic acid fractionation (≥6.4 log₁₀), depth filtration (2.6 log₁₀), and virus filtration (≥5.8 log₁₀). 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 assessing the efficacy and safety of Privigen in 80 subjects with PI (see *Clinical Studies* [14.1]), serum concentrations of total IgG and IgG subclasses were measured in 25 subjects (ages 13 to 69) following the 7th infusion for the 3 subjects on the 3-week dosing interval and following the 5th infusion for the 22 subjects on the 4-week dosing interval. The dose of Privigen used in these subjects ranged from 200.0 mg/kg to 714.3 mg/kg. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively.

Table 5 summarizes the pharmacokinetic parameters of Privigen, based on serum concentrations of total IgG.

Table 5: Pharmacokinetic Parameters of Privigen in Subjects with PI

Parameter	3-Week Dosing Interval (n=3)		4-Week Dosing Interval (n=22)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
C _{max} (peak, mg/dL)	2,550 (400)	2,340 (2,290-3,010)	2,260 (530)	2,340 (1,040-3,460)
C _{min} (trough, mg/dL)	1,230 (230)	1,200 (1,020-1,470)	1,000 (200)	1,000 (580-1,360)
t _{1/2} (days)	27.6 (5.9)	27.8 (21.6-33.4)	45.4 (18.5)	37.3 (20.6-96.6)
AUC _{0-t} (day × mg/dL)*	32,820 (6,260)	29,860 (28,580-40,010)	36,390 (5,950)	36,670 (19,680-44,340)
AUC _{0-∞} (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_{max}, maximum serum concentration; C_{min}, trough (minimum level) serum concentration; t_{1/2}, elimination half-life; AUC_{0-t}, area under the curve from 0 hour to last sampling time.

AUC_{0-∞}, 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 between males (1.27 ± 0.35 mL/day/kg) and females (1.34 ± 0.22 mL/day/kg). In six subjects between 13 and 15 years of age, the clearance of Privigen (1.35 ± 0.44 mL/day/kg) is comparable to that observed in 19 adult subjects 19 years of age or older (1.29 ± 0.22 mL/day/kg).

The IgG subclass levels observed in the pharmacokinetic study were consistent with a physiologic distribution pattern (mean trough values): IgG₁, 564.91 mg/dL; IgG₂, 394.15 mg/dL; IgG₃, 30.16 mg/dL; IgG₄, 10.88 mg/dL.

Treatment of Chronic Immune Thrombocytopenic Purpura

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

14 CLINICAL STUDIES

14.1 Treatment of Primary Humoral Immunodeficiency

A prospective, open-label, single-arm, multicenter study 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; 57.5% were male and 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 on the 3-week dosing interval and 64 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 69% (715) of the infusions administered at a rate of 7 mg/kg/min or greater.

The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (aSBIs), defined as pneumonia, bacteremia/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%). The majority of these infections were mild or moderate. Among the 255 infections, 16 (6.3%) occurring in 10 subjects were considered severe.

Table 6 summarizes the efficacy results for all 80 subjects.

Table 6: Summary of Efficacy Results in Subjects With PI

Number of Subjects		80
Results from Case Report Forms		
Total Number of Subject Days		26,198
Infections		
Annual rate of confirmed aSBIs*	0.08 aSBIs/subject year [†]	
Annual rate of other infections	3.55 infections/subject year	
Antibiotic use		
Number of subjects (%)	64 (80%)	
Annual rate	87.4 days/subject year	
Results from Subject Diaries		
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.

[†] 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 × 10⁹/L or less. Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male; 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
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 to immediately report the following signs and symptoms to their healthcare professional:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (see *Warnings and Precautions* [5.2]).
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting (see *Warnings and Precautions* [5.5]).
- Increased heart rate, fatigue, yellowing of skin or eyes, dark-colored urine (see *Warnings and Precautions* [5.6]).
- Trouble breathing, chest pain, blue lips or extremities, fever (see *Warnings and Precautions* [5.7]).

Inform patients that Privigen is made from human plasma and may contain infectious agents that can cause disease. While the risk that Privigen can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, patients should report any symptoms that concern them (see *Warnings and Precautions* [5.9]).

Inform patients that Privigen can interfere with their immune response to live viral vaccines (e.g., measles, mumps, and rubella), and instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations (see *Drug Interactions* [7]).

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