

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™.

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

Initial U.S. Approval: XXXX

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

See full prescribing information for complete boxed warning.

- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.
- Administer IGIV products at the minimum infusion rate practicable.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Privigen™ does not contain sucrose.

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

- **PI** – 200 to 800 mg/kg intravenously (IV) every 3 to 4 weeks. Recommended infusion rate: initially, 0.5 mg/kg/min (0.005 mL/kg/min); if well tolerated, may be gradually increased to 8 mg/kg/min (0.08 mL/kg/min) (2.2).
- **Chronic ITP** – 1 g/kg IV daily for 2 consecutive days, for a total of 2 g/kg. Recommended infusion rate: initially, 0.5 mg/kg/min (0.005 mL/kg/min); if well tolerated, may be gradually increased to 4 mg/kg/min (0.04 mL/kg/min) (2.3).
- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Privigen™ if renal function deteriorates (5.1).
- For patients at risk of renal dysfunction or thrombotic events, administer Privigen™ at the minimum infusion rate practicable (5.1, 5.5).

DOSAGE FORMS AND STRENGTHS

5 g in 50 mL solution, 10 g in 100 mL solution, 20 g in 200 mL solution (3)

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin (4)
- Hyperprolinemia (Privigen™ contains the stabilizer L-proline) (4)
- Individuals with selective IgA deficiency can develop antibodies to IgA and are at greater risk of developing severe hypersensitivity and anaphylactic reactions (4)

WARNINGS AND PRECAUTIONS

- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure (5.1).
- Aseptic meningitis syndrome has been reported with Privigen™ and other IGIV treatments, especially with high doses or rapid infusion (5.2).
- Hemolysis has been reported with Privigen™ and other IGIV treatments. Monitor patients for hemolysis and hemolytic anemia (5.3).
- Monitor patients for pulmonary adverse reactions; if transfusion-related acute lung injury is suspected, test the product and patient for antineutrophil antibodies (5.4).
- Thrombotic events have been reported with Privigen™ and other IGIV treatments. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity (5.5).
- Products made from human plasma can contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.6).

ADVERSE REACTIONS

- **PI** – Most common adverse reactions are headache, pain, nausea, fatigue, and chills (6.1).
- **Chronic ITP** – Most common adverse reactions are headache, pyrexia/hyperthermia, and anemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring at 1-800-504-5434 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

IgG administration can transiently impair efficacy of live virus vaccines (7.1).

USE IN SPECIFIC POPULATIONS

In patients over age 65 at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Privigen™ at a rate less than 2 mg/kg/min (0.02 mL/kg/min) (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION: CONTENTS***WARNING – ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE****1 INDICATIONS AND USAGE**

- 1.1 Treatment of Primary Immunodeficiency
- 1.2 Treatment of Chronic Immune Thrombocytopenic Purpura

2 DOSAGE AND ADMINISTRATION

- 2.1 Preparation and Handling
- 2.2 Treatment of Primary Immunodeficiency
- 2.3 Treatment of Chronic Immune Thrombocytopenic Purpura
- 2.4 Administration

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Acute Renal Dysfunction and Acute Renal Failure
- 5.2 Aseptic Meningitis Syndrome (AMS)
- 5.3 Hemolysis
- 5.4 Transfusion-related Acute Lung Injury (TRALI)
- 5.5 Thrombotic Events
- 5.6 Transmissible Infectious Agents
- 5.7 Interference With Laboratory Tests
- 5.8 Interference With Live Virus Vaccines

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Live Virus Vaccines

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

14 CLINICAL STUDIES

- 14.1 Treatment of Primary Immunodeficiency
- 14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

15 REFERENCES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

- 17.1 Renal Dysfunction
- 17.2 Aseptic Meningitis Syndrome (AMS)
- 17.3 Hemolysis
- 17.4 Transfusion-related Acute Lung Injury (TRALI)
- 17.5 Transmissible Infectious Agents
- 17.6 Live Virus Vaccines

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

Immune Globulin Intravenous (Human), 10% Liquid Privigen™

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.¹ Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. In such patients, IGIV products should be administered at the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Privigen™ does not contain sucrose. (See *Dosage and Administration [2.4]* and *Warnings and Precautions [5.1]* for important information intended to reduce the risk of acute renal failure.)

1 INDICATIONS AND USAGE

1.1 Treatment of Primary Immunodeficiency

Privigen™ is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

1.2 Treatment of Chronic Immune Thrombocytopenic Purpura

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

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Handling

Privigen™ is a clear or slightly opalescent, colorless to pale yellow solution. Privigen™ should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or contains particulates. Any solution that has been frozen must not be used. DO NOT SHAKE.

Do not mix Privigen™ with other IGIV products or other intravenous medications. If necessary, Privigen™ can be diluted with Dextrose Injection, USP (D5W). If large doses of Privigen™ are to be administered, several vials may be pooled using aseptic technique.

The Privigen™ vial is for single use only. Once the vial has been entered under aseptic conditions, its contents should be used promptly. Because the solution contains no preservative, Privigen™ should be infused as soon as possible. Any unused product or waste material should be disposed of in accordance with local requirements.

2.2 Treatment of Primary Immunodeficiency

The usual dose of Privigen™ for patients with PI is 200 to 800 mg/kg, administered every 3 to 4 weeks. An optimum target serum immunoglobulin G (IgG) trough level has not been established in randomized, controlled clinical studies. Doses should be adjusted to achieve the desired serum trough levels and clinical responses.

The recommended initial infusion rate is 0.5 mg/kg/min (0.005 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk of renal dysfunction or thrombotic events, Privigen™ should be administered at the minimum infusion rate practicable (*see Warnings and Precautions [5.1, 5.5]*).

2.3 Treatment of Chronic Immune Thrombocytopenic Purpura

The usual dose of Privigen™ for patients with chronic ITP is 1 g/kg administered daily for 2 consecutive days, resulting in a total dosage of 2 g/kg.

The recommended initial infusion rate is 0.5 mg/kg/min (0.005 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 4 mg/kg/min (0.04 mL/kg/min). For patients judged to be at risk of renal dysfunction or thrombotic events, Privigen™ should be administered at the minimum infusion rate practicable (*see Warnings and Precautions [5.1, 5.5]*).

2.4 Administration

Privigen™ is for intravenous (IV) administration and should be given by a separate infusion line. An infusion pump may be used to control the rate of administration. The Privigen™ infusion line can be flushed with Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP.

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.

Ensure that patients with pre-existing renal insufficiency and those predisposed to acute renal failure are not volume depleted before administering Privigen™ (*see Boxed Warning, Warnings and Precautions [5.1]*).

The patient's vital signs should be observed and monitored carefully throughout the infusion. If side effects occur, the infusion should be slowed or stopped until the symptoms subside. The infusion may then be resumed at a lower rate that is comfortable for the patient.

3 DOSAGE FORMS AND STRENGTHS

5 g in 50 mL solution
10 g in 100 mL solution
20 g in 200 mL solution

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 individuals with selective IgA deficiency because they can develop antibodies to IgA and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Privigen™ contains trace amounts of IgA (*see Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Acute Renal Dysfunction and Acute Renal Failure

Patients should not be volume depleted prior to the initiation of the infusion of Privigen™. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, should be assessed before the initial infusion of Privigen™ and at appropriate intervals thereafter. For patients judged to be at risk of developing renal dysfunction, Privigen™ should be administered at the minimum rate of infusion practicable (*see Dosage and Administration [2.2, 2.3]*). If renal function deteriorates, consider discontinuing Privigen™. (*See Patient Counseling Information [17.1]*).

5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with Privigen™ and other IGIV treatments. The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including 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. Patients exhibiting such signs and symptoms should receive a thorough neurological examination, 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. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.² (See *Patient Counseling Information [17.2]*.)

5.3 Hemolysis

IGIV products can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.³⁻⁵ Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (extravascular hemolysis) or intravascular RBC destruction (intravascular hemolysis).⁶

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen™ in the ITP study. These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (*see Patient Counseling Information [17.3]*). If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be performed. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, adequate cross-matching should be performed to avoid exacerbating on-going hemolysis.

5.4 Transfusion-related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema in patients administered IGIV.⁷ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours following transfusion. IGIV recipients should be monitored for pulmonary adverse reactions (*see Patient Counseling Information [17.4]*). Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and the patient's serum.

5.5 Thrombotic Events

Thrombotic events have been reported with Privigen™ and other IGIV treatments.⁸⁻¹⁰ Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk

factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies in all patients for whom IGIV administration is being considered.

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk of hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

5.6 Transmissible Infectious Agents

Privigen™ is made from human plasma. Products made from human plasma may contain infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing through pH 4 incubation, depth filtration, and virus filtration (*see Description [11]*).

Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434. (*See Patient Counseling Information [17.5]*.)

5.7 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.

5.8 Interference With Live Virus Vaccines

Immunoglobulin administration may transiently impair the efficacy of live virus vaccines such as measles, mumps, and rubella. The immunizing physician should be informed so that appropriate measures may be taken (*see Drug Interactions [7.1], Patient Counseling Information [17.6]*).

6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen™ for PI was hypersensitivity in one subject. The most serious adverse reactions observed in 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 [5.2, 5.3]*).

The most common adverse reactions observed in subjects with PI were headache, pain, nausea, fatigue, and chills. The most common adverse reactions observed in subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia.

In general, reported adverse reactions to Privigen™ in subjects with either PI or chronic ITP were similar in kind and frequency to those observed with other IGIV products.

6.1 Clinical Studies Experience

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

Treatment of Primary Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI received median doses of Privigen™ ranging from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg) for up to 12 months (*see Clinical Studies [14.1]*).

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 with temporally associated AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint.¹¹ The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion).

Table 1 lists the temporally associated AEs that occurred in more than 5% of subjects within 72 hours after the end of a Privigen™ infusion, *irrespective of causality*.

Table 1: Temporally Associated Adverse Events* (TAAEs) in >5% of Subjects With PI Within 72 Hours After the End of a Privigen™ Infusion, *Irrespective of Causality*

TAAE	No. Subjects Reporting TAAE (% of Subjects [n=80])	No. TAAEs Reported (as % Rate of Infusions [n=1038])	No. Infusions With TAAE (% of Infusions [n=1038])
Headache	35 (43.8)	90 (8.7)	82 (7.9)
Pain	20 (25.0)	51 (4.9)	44 (4.2)
Fatigue	13 (16.3)	29 (2.8)	27 (2.6)
Nausea	10 (12.5)	22 (2.1)	19 (1.8)
Chills	9 (11.3)	15 (1.4)	15 (1.4)
Vomiting	7 (8.8)	13 (1.3)	13 (1.3)
Pyrexia	6 (7.5)	11 (1.1)	10 (1.0)
Cough	5 (6.3)	5 (0.5)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)	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™ (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 received a 2 g/kg dose of Privigen™ administered daily as two 1 g/kg intravenous infusions for 2 consecutive days (*see Clinical Studies [14.2]*).

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 2 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen™, *irrespective of causality*.

Table 2: Temporally Associated Adverse Events (TAAEs) in >5% Subjects With Chronic ITP Within 72 hours After the End of a Treatment Cycle* With Privigen™, Irrespective of Causality

TAAE	No. Subjects Reporting TAAE (% of Subjects [n=57])	No. TAAEs Reported (as % Rate of Infusions [n=114])	No. Infusions With TAAE (% of Infusions [n=114])
Headache	37 (64.9)	48 (42.1)	41 (36.0)
Pyrexia/hyperthermia	21 (36.8)	23 (20.2)	22 (19.3)
Nausea	6 (10.5)	8 (7.0)	6 (5.3)
Epistaxis	6 (10.5)	8 (7.0)	6 (5.3)
Vomiting	6 (10.5)	7 (6.1)	6 (5.3)
Blood unconjugated bilirubin increased	6 (10.5)	6 (5.3)	6 (5.3)
Blood conjugated bilirubin increased	5 (8.8)	5 (4.4)	5 (4.4)
Blood total bilirubin increased	4 (7.0)	4 (3.5)	4 (3.5)
Hematocrit decreased	3 (5.3)	3 (2.6)	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

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 postapproval use of IGIV products.¹²

- *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
- *Integumentary*: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic*: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *General/Body as a Whole*: Pyrexia, rigors
- *Musculoskeletal*: Back pain
- *Gastrointestinal*: Hepatic dysfunction, abdominal pain

Because postmarketing reporting of adverse reactions is voluntary and 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. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, and rubella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response.¹³ The immunizing physician should be informed of recent therapy with Privigen™ so that appropriate measures may be taken (*see Patient Counseling Information [17.6]*).

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

Privigen™ has not been evaluated in nursing mothers.

8.4 Pediatric Use

Treatment of Primary Immunodeficiency

Privigen™ was evaluated in 19 children and 12 adolescents with PI. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen™ has not been established in pediatric subjects with PI who are under the age of 3.

Treatment of Chronic Immune Thrombocytopenic Purpura

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

8.5 Geriatric Use

Privigen™ should be used with caution in patients over 65 years of age who are judged to be at increased risk of developing renal insufficiency (*see Boxed Warning, Warnings and*

Precautions [5.1]). Recommended doses should not be exceeded, and the infusion rate selected should be the minimum practicable. Privigen™ should be infused at a rate less than 2 mg/kg/min (0.02 mL/kg/min).

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

11 DESCRIPTION

Privigen™ is a ready-to-use, sterile, 10% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous administration. 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.

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 ≤ 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.

All plasma units used in the manufacture of Privigen™ are tested 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.

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 3 shows the virus clearance during the manufacturing process for Privigen™, expressed as the mean log₁₀ reduction factor (LRF).

Table 3: 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	nd	≥2.7	≥5.9	≥3.7	≥5.5
Overall reduction (log₁₀ units)	≥16.0	≥12.2	≥9.4	≥16.7	≥7.9	≥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; nd, not determined; nt, not tested.

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 Immunodeficiency

Privigen™ contains a broad spectrum of antibody specificities. Appropriate doses of Privigen™ should restore abnormally low IgG levels to the normal range.

Treatment of Chronic Immune Thrombocytopenic Purpura

The mechanism of action of immunoglobulins in the treatment of chronic ITP is not fully understood. One possible mechanism may be the inhibition of the elimination of autoantibody-reacted platelets from the blood circulation by IgG-induced Fc-receptor blockade of phagocytes.¹⁷ Another proposed mechanism is the down-regulation of platelet autoantibody-producing B cells by anti-idiotypic antibodies in IGIV.¹⁸

12.3 Pharmacokinetics

Treatment of Primary 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. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively.

Table 4 summarizes the pharmacokinetic parameters of Privigen™, measured as serum concentrations of total IgG.

Table 4: 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)
Clearance (mL/day/kg)*	1.3 (0.1)	1.3 (1.1-1.4)	1.3 (0.3)	1.3 (0.9-2.1)

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.

* 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 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 female and 42.5% were male; 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. The median dose for the 3-week interval was 428.3 mg/kg; the median dose for the 4-week interval was 440.6 mg/kg. Subjects received a total of 1038 infusions of Privigen™, 272 in the 3-week dosing interval and 766 in the 4-week dosing interval. 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 endpoint was 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 endpoints included days out of work/school/day care or days unable to perform normal activities due to illness, days of hospitalization, and use of antibiotics.

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 5 summarizes the efficacy results for all 80 subjects.

Table 5: 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 $20 \times 10^9/L$ 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 dose of Privigen™ administered daily as two 1 g/kg intravenous infusions 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 endpoint was 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 endpoints included 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 x 10⁹/L). The median maximum platelet count achieved was 154 x 10⁹/L. The median time to reach a platelet response of more than 50 x 10⁹/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 dosage forms 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 24 months, as indicated by the expiration date printed on the outer carton and vial label. Do not freeze. Keep Privigen™ in its original carton to protect it from light.

17 PATIENT COUNSELING INFORMATION

17.1 Renal Dysfunction

Instruct patients to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath. Such symptoms may suggest kidney damage (*see Boxed Warning, Warnings and Precautions [5.1]*).

17.2 Aseptic Meningitis Syndrome (AMS)

Instruct patients to immediately report signs and symptoms of AMS. These symptoms include severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (*see Warnings and Precautions [5.2]*).

17.3 Hemolysis

Instruct patients to immediately report signs and symptoms of hemolysis. These symptoms include fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine (*see Warnings and Precautions [5.3]*).

17.4 Transfusion-Related Acute Lung Injury (TRALI)

Instruct patients to immediately report signs and symptoms of TRALI, which is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. TRALI typically occurs within 1 to 6 hours following transfusion (*see Warnings and Precautions [5.4]*).

17.5 Transmissible Infectious Agents

Inform patients that Privigen™ is made from human plasma (part of the 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 the donated plasma for certain virus infections, and by inactivating and/or removing certain viruses during manufacturing (*see Warnings and Precautions [5.6]*).

17.6 Live Virus Vaccines

Inform patients that administration of IgG may transiently impair the effectiveness of live virus vaccines (e.g., measles, mumps, and rubella) and to notify their immunizing physician of recent therapy with Privigen™ (*see Drug Interactions [7.1]*).

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