PRODUCT MONOGRAPH

Privigen®

Immunoglobulin Intravenous (Human)

10 % Solution for infusion

Passive Immunizing Agent

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Privigen®

Immunoglobulin Intravenous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	10% Solution for infusion	L-proline *For a complete listing see Dosage form, Composition and Packaging section.*

DESCRIPTION

Privigen®, Immunoglobulin Intravenous (Human), 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, combined with a filter aid-assisted depth filtration, and anion exchange chromatography. The Privigen manufacturing process includes an immunoaffinity chromatography step that specifically reduces blood group A and B antibodies (isoagglutinins A and B) (see section PHARMACEUTICAL INFORMATION).

INDICATIONS AND CLINICAL USE

Privigen® (Immunoglobulin Intravenous (Human)) is indicated for:

- The treatment of patients with primary immune deficiency (PID) and secondary immune deficiency (SID). This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, secondary hypogammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
- The treatment of patients with immune thrombocytopenic purpura (ITP) to rapidly raise platelet counts to prevent bleeding.
- Immunomodulation in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Geriatrics:
See subsection **Special Populations,** under section **WARNINGS AND PRECAUTIONS.**

Pediatrics:
See subsection **Special Populations**, under section **WARNINGS AND PRECAUTIONS.**

CONTRAINDICATIONS

Privigen®, Immunoglobulin Intravenous (Human), is contraindicated in individuals with selective IgA deficiency with known anti-IgA antibodies. Privigen® contains trace amounts of no more than 25 mcg/mL of IgA levels.

Privigen® is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immunoglobulin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Intravenous Immunoglobulin (Human) (IVIG) 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, IVIG 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 IVIG products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Privigen® does not contain carbohydrates as stabilizers (e.g., sucrose, maltose) (see sections **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS** for important information intended to reduce the risk of acute renal failure).

There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins.

Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus).

Thrombosis may occur even in the absence of known risk factors (see "**WARNING AND PRECAUTIONS"**–" **Thromboembolism**" sub-section.)

General

Privigen®, Immunoglobulin Intravenous (Human), 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 removing certain viruses during manufacturing through a four step process: octanoic acid fractionation combined with a filter aid-assisted depth filtration, virus filtration and inactivation by pH 4 incubation as well as additional depth filtration (see subsection **Viral Inactivation/Removal** under section **PHARMACEUTICAL INFORMATION**).

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 1-613-783-1892. The physician should discuss the risks and benefits of this product with the patient.

Because Privigen contains the stabilizer L-proline, caution should be considered in patients with hyperprolinemia (type I and II). Physicians should weigh the risk/benefit of use in these patients on an individual basis.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies. IVIG is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

Rarely, human normal immunoglobulin can cause a fall in blood pressure with anaphylactoid reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Thromboembolism

Thromboembolic events such as myocardial infraction, stroke, pulmonary embolism and deep vein thrombosis have been associated with the use of immunoglobulins.

Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. Privigen® should be administered at the minimum dose and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration of immunoglobulins.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed.

Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus).

Hematologic

IVIG products can contain blood group antibodies (e.g. isoagglutinins A and B) that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction[5-7] and rarely, hemolysis. The Privigen manufacturing process includes an immunoaffinity chromatography step (IAC) that specifically reduces blood group A and B antibodies (isoagglutinins A and B). Clinical data with Privigen manufactured with the IAC step is not yet available.

Delayed hemolytic anemia can develop subsequent to Privigen® therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported[8].

Isolated cases of hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred.

The following risk factors may be associated with the development of hemolysis: high doses, whether given as a single administration or divided over several days; non-O blood group; and underlying inflammatory state.[9] As this event was commonly reported in non-O blood group patients receiving high doses for non-PID/SID indications, increased vigilance is recommended. Hemolysis has rarely been reported in patients given replacement therapy for PID/SID.

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.

IVIG recipients should be closely monitored for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after IVIG infusion, appropriate confirmatory laboratory testing should be performed. If transfusion is indicated for patients who develop hemolytic anemia after receiving IVIG, cross-matching should be performed.

Neurologic

Aseptic Meningitis Syndrome (AMS) has been reported to occur infrequently in association with IVIG treatment. The syndrome usually begins within several hours to 2 days following IVIG 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 granulocyte 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 bw) and/or rapid infusion of IVIG. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.[10]

Renal

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IVIG products, particularly those containing sucrose.[1] Privigen® does not contain any sugar such as sucrose, maltose or glucose. 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 because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus, sepsis, paraproteinemia, or hypovolemia, those who are obese, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), Privigen® should be administered at the minimum rate of infusion practicable (see section **DOSAGE AND ADMINISTRATION**). If renal function deteriorates, consider discontinuing Privigen®.

Respiratory

There have been reports of noncardiogenic pulmonary edema in patients administered IVIG.[11] Transfusion-related Acute Lung Injury (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. IVIG recipients should be monitored for pulmonary adverse reactions. 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 product and the patient's serum.

Special Populations

Pregnant Women: The safety of Privigen® for use in human pregnancy has not been established in controlled clinical trials. IVIG products have been shown to cross the placenta, increasingly during the third trimester. Privigen® should only be used in pregnant women when the benefits outweigh the risks associated with its use.

Nursing Women: Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry. Privigen® should only be used in nursing women when the benefits outweigh the risk associated with its use.

Fertility: No human data are available to indicate the presence or absence of drug associated risk. Animal reproduction studies have not been conducted with Privigen®.

Pediatrics (3-16 years of age):

Treatment of Primary and Secondary Immune Deficiency

In the pivotal study, Privigen® was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PID. In the extension study, there were 21 pediatric subjects evaluated (13 children and 8 adolescents) of which 19 were carried forward from the pivotal study. 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 efficacy of Privigen® has not been established in pediatric subjects with PID who are under the age of 3.

Treatment of Immune Thrombocytopenic Purpura

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

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

The safety and effectiveness of Privigen® has not been established in pediatric subjects with CIDP, who are under the age of 18.

However, the dosage and administration in children and adolescents should not differ from that of adults as the dosage for each indication is given by body weight and adjusted to the clinical outcome.

Geriatrics:

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 **Warnings and Precautions** under section **WARNINGS AND PRECAUTIONS**). For those patients with the risk of renal insufficiencies, Privigen® must be infused at the minimum practicable rate.

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

Monitoring and Laboratory Tests

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. 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical trials undertaken with Privigen®, Immunoglobulin Intravenous (Human), the most serious adverse reaction observed in patients receiving Privigen® for the PID was hypersensitivity in one subject. The most serious adverse reactions observed in patients receiving Privigen® for ITP were aseptic meningitis syndrome in one subject and anemia in two other ITP subjects (see section **WARNINGS AND PRECAUTIONS**). The most serious adverse reactions observed in patients receiving Privigen for CIDP were Hemolysis in two subjects. The most common adverse reaction observed for PID, ITP and CIDP was headache. In general, reported adverse reactions to Privigen® in subjects with PID, ITP or CIDP were similar in kind and frequency to those observed with other IVIG products.

Clinical Trial Adverse Drug Reactions

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 and Secondary Immune Deficiency

Pivotal study

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PID received median doses of Privigen® ranging from 200 to 888 mg/kg bw every 3 weeks (median dose 428.3 mg/kg bw) or 4 weeks (median dose 440.6 mg/kg bw) for up to 12 months (see section **CLINICAL TRIALS**).

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.

The safety endpoint of the study was the proportion of infusions with one or more temporally associated AEs. Temporally associated AEs are those occurring during or within 72 hours after the end of an infusion, irrespective of causality.

A target for this safety endpoint is an upper 1-sided confidence limit of less than 40%. 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%, thus well below the target for this safety endpoint.

Table 1 summarizes the proportion of Privigen® infusions resulting in temporally associated AEs and the number and rate of temporally associated AEs, *irrespective of causality.*

Table 1: Privigen® Infusions With Temporally Associated Adverse Events* (TAAEs) in Subjects With PID, *Irrespective of Causality*

Total number of infusions: 1038	**TAAEs* occurring during or within the specified number of hours after the end of an infusion**		
	24 hours	**48 hours**	**72 hours**
Proportion of infusions with TAAEs	16%	19%	21%
Upper bound of 1-sided 97.5% confidence interval for the proportion of infusions with TAAEs	18.7%	21.5%	23.8%
Total number of TAAEs	282	353	396
Rate of TAAEs (per total number of infusions)	0.27	0.34	0.38

*Including infections.

Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects during or within 72 hours after the end of a Privigen® infusion, irrespective of causality.

Table 2: Temporally Associated Adverse Events* (TAAEs) in >5% of Subjects With PID During or Within 72 Hours After the End of an Privigen® Infusion, *Irrespective of Causality*

TAAE*	**Subjects (%) (n=80)**	**Infusions (%) (n=1038)**
Headache	35 (43.8)	90 (8.7)
Fatigue	13 (16.3)	29 (2.8)
Nausea	10 (12.5)	22 (2.1)
Chills	9 (11.3)	15 (1.4)
Back pain	8 (10.0)	14 (1.3)
Pain	7 (8.8)	14 (1.3)
Vomiting	7 (8.8)	13 (1.3)
Pyrexia	6 (7.5)	11 (1.1)
Cough	5 (6.3)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)

*Excluding infections.

Table 3 lists the related temporally associated AEs that occurred in more than 5% of subjects with PID during or within 72 hours after the end of a Privigen® infusion. Related AEs were defined as those judged by the investigators to be "at least possibly" causally related to the infusion of Privigen®.

Table 3: Related Temporally Associated Adverse Events (TAAEs) in >5% of Subjects With PID During or Within 72 Hours After the End of a Privigen® Infusion

Related TAAE	Subjects (%) (n=80)	Infusions (%) (n=1038)
Headache	23 (28.8)	64 (6.2)
Nausea	9 (11.3)	20 (1.9)
Fatigue	9 (11.3)	18 (1.7)
Chills	9 (11.3)	15 (1.4)
Pain	5 (6.3)	9 (0.9)

Sixteen subjects (20%) experienced 38 serious AEs. Five of these were severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that occurred in one subject. All five were related to Privigen® 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). One subject died due to multiple organ system failure, which was not related to Privigen®.

Of the 1330 AEs reported, the investigators judged 215 to be related to the infusion of Privigen® (including the five serious, severe AEs described above). Of the 210 non-serious AEs, 104 were mild, 89 were moderate, 16 were severe, and 1 was not ranked ("unknown").

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).

Extension study

During an extension of the pivotal study, higher infusion rates were permitted and additional efficacy, safety and tolerability data were collected. This study included original subjects from the pivotal study (n=45) and new subjects who were previously receiving another IVIG product (n=10). Only subjects who continued from the pivotal study were permitted to receive a Higher Infusion Rate (HIR) at the discretion of the investigator. Twenty-three of 45 subjects (51.1%) received 265 (38.4%) infusions at a maximum rate greater than 8 mg/kg/min (median: 12 mg/kg/min; maximum: 16 mg/kg/min) with 97% of infusions in the HIR group reaching a maximum infusion rate of 12 mg/kg/min.

When analyzed by infusion rate class (i.e., LIR vs. HIR), the proportion of infusions with TAAEs (72 hours) was considerably lower with HIR infusions than with LIR infusions (0.072 vs. 0.192), as was also seen in the rate of TAAEs per infusion. Overall, this reflects both the study design and the clinical practice to increase the infusion rate according to patient tolerance.

Twenty-two subjects remained on the high infusion rate; one subject withdrew from the study due to urticaria, which was mild, but was considered drug-related. Due to the small population size in the clinical trial, the safety and tolerability of Privigen® administered at a higher infusion rate of 12mg/kg/min should be monitored by users.

Treatment of Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with ITP received a 2 g/kg bw dose of Privigen® administered as two 1 g/kg bw intravenous infusions on two consecutive days (see section **CLINICAL TRIALS**).

Two of the 57 ITP subjects experienced hemolysis. These cases resolved uneventfully. Six other subjects experienced laboratory signs for hemolysis without clinical relevance. All 8 subjects developed a transient positive direct Coombs´ test.

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

Table 4 lists the temporally associated AEs that occurred in more than 5% of subjects with ITP during or within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen®, *irrespective of causality*.

Table 4: Temporally Associated Adverse Events (TAAEs) in >5% Subjects With ITP During or Within 72 Hours After the End of a Treatment Cycle* With Privigen®, *Irrespective of Causality*

TAAE	Subjects (%) (n=57)
Headache	37 (64.9)
Pyrexia	14 (24.6)
Nausea	6 (10.5)
Vomiting	6 (10.5)
Epistaxis	6 (10.5)
Hyperthermia	5 (8.8)
Bilirubin conjugated increased	5 (8.8)
Blood bilirubin unconjugated increased	5 (8.8)
Hyperbilirubinemia	3 (5.3)
Hematocrit decreased	3 (5.3)

* Two consecutive infusions.

Table 5 lists all related AEs that occurred in more than 5% of subjects with ITP during and/or following a treatment cycle with Privigen®. Related AEs were defined as those judged by the investigators to be "at least possibly" causally related to the infusion of Privigen®.

Table 5: Related Adverse Events* in >5% of Subjects With ITP During and/or Following a Treatment Cycle† With Privigen®

Related AE*	Subjects (%) (n=57)
Headache	37 (64.9)
Pyrexia	14 (24.6)
Anemia	6 (10.5)
Hyperthermia	5 (8.8)
Nausea	5 (8.8)
Vomiting	5 (8.8)
Bilirubin conjugated increased	5 (8.8)
Blood bilirubin unconjugated increased	5 (8.8)
Blood lactate dehydrogenase increased	3 (5.3)
Coombs' direct test positive	3 (5.3)
Coombs' test positive	3 (5.3)
Hematocrit decreased	3 (5.3)
Hyperbilirubinemia	3 (5.3)

* Includes all related AEs, including those beyond 72 hours after end of last infusion.
† Two consecutive infusions.

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®. Two subjects experienced transient drug-related non-serious hemolytic reactions manifested as anemia and a positive direct Coombs' test.

Of the 270 AEs reported, 256 (94.8%) were mild to moderate in severity and transient in nature. The investigators judged 174 of the 270 AEs reported to be related to the infusion of Privigen®.

In a prospective, multicenter, open-label, single-arm study to investigate the efficacy and safety of Privigen® in the treatment of CIDP, 28 patients received Privigen® induction dose of 2 g/kg bw divided over 2 to 5 consecutive days, followed by 6 maintenance doses of 1 g/kg bw over 1 to 2 consecutive days every 3 weeks (see Section **CLINICAL TRIALS**).

AEs occurred after 108 of the 259 infusions administered in this study, resulting in an AE rate per infusion of 0.417. The rate of AEs that were considered at least possibly related to the study drug was 0.189 (49 events). The rate of temporally associated AEs occurring between the start of an infusion and within 72 h after the end of infusion was 0.255 (66 events). No infusion had to be stopped due to an AE.

Four subjects experienced a total of 4 SAEs (hemolysis in two subjects; deterioration of CIDP in one subject and worsening of chronic sigmoid diverticulitis in one subject). The SAE of deterioration of CIDP started before the first infusion of Privigen®. The 2 hemolysis cases (0.008 case per infusion), were considered by the investigator to be at least possibly related to the study product. Both cases were observed in the induction phase of the study, at the dose of 2 g/kg bw. There were no cases of hemolysis in the maintenance phase of the study, at a dose of 1g/kg bw. Please refer to section **WARNINGS AND PRECAUTIONS** for additional details on the risk factors.

Of these 4 observed SAEs, one SAE (hemolysis) was severe in intensity, one SAE was moderate in intensity (chronic inflammatory demyelinating polyradiculoneuropathy), and two SAEs were mild in intensity (hemolysis and diverticulitis). All SAEs resolved without sequelae.

There were no deaths in this Study.

Table 6 lists the temporally associated AEs occurring during an infusion or within 72 h after the end of infusion in more than 5% of subjects.

Table 6: Temporally Associated Adverse Events in >5% Subjects with CIDP (Within 72 h), Irrespective of Causality

TAAE	**Subjects (%) (n=28)**	**Infusions (%) (n=259)**
Headache	8 (28.6)	19 (0.073)
Hypertension	4 (14.3)	6 (0.023)
Asthenia	4 (14.3)	4 (0.015)
Pain in extremity	3 (10.7)	3 (0.012)
Nausea	3 (10.7)	3 (0.012)
Influenza like illness	2 (7.1)	2 (0.008)
Hemolysis	2 (7.1)	2 (0.008)

The most common AE considered to be at least possibly related overall during the study was headache, which was reported by 8 subjects (28.6%) in total (7 subjects [25.0%] during induction period; 4 subjects [14.3%] during maintenance period)**.**

Table 7: Related Adverse Events in >5% of Subjects With CIDP during treatment period (Induction Period, Maintenance Period and Total)

Preferred term	**Induction period**		**Maintenance period**		**Total**	
	Number (%) of subjects (N=28)	**Number of AEs (rate per infusion) (N=73)**	**Number (%) of subjects (N=28)**	**Number of AEs (rate per infusion) (N=186)**	**Number (%) of subjects (N=28)**	**Number of AEs (rate per infusion) (N=259)**
Any preferred term	13 (46.4)	27 (0.370)	11 (39.3)	22 (0.118)	17 (60.7)	49 (0.189)
Headache	7 (25.0)	7 (0.096)	4 (14.3)	11 (0.059)	8 (28.6)	18 (0.069)
Hypertension	3 (10.7)	3 (0.041)	2 (7.1)	2 (0.011)	4 (14.3)	5 (0.019)
Asthenia	3 (10.7)	3 (0.041)	1 (3.6)	1 (0.005)	4 (14.3)	4 (0.015)
Nausea	2 (7.1)	2 (0.027)	1 (3.6)	1 (0.005)	3 (10.7)	3 (0.012)
Influenza-like illness	2 (7.1)	2 (0.027)	0	0	2 (7.1)	2 (0.008)
Hemolysis	2 (7.1)	2 (0.027)	0	0	2 (7.1)	2 (0.008)
Leukopenia	0	0	2 (7.1)	2 (0.011)	2 (7.1)	2 (0.008)
Rash	1 (3.6)	1 (0.014)	1 (3.6)	1 (0.005)	2 (7.1)	2 (0.008)
AE = Adverse event;; N = Total number of subjects or infusions in the study.						

Post-Market Adverse Drug Reactions

Privigen®

The following adverse reactions have been identified during post-marketing use of Privigen:

- *Infusion reactions:* Hypersensitivity (e.g., anaphylactic shock, anaphylaxis), changes in blood pressure, dyspnea, chills and fever, tachycardia, chest discomfort/pain, flushing
- *Hematologic:* Hemolytic anemia, jaundice/hyperbilirubinemia, hemoglobinuria/hematuria/chromaturia, acute renal failure, decreased neutrophil count
- *Neurological:* Headache, aseptic meningitis, photophobia, dizziness
- *Integumentary:* Urticaria, pruritus, rash
- *Respiratory:* Transfusion-related Acute Lung Injury (TRALI)

General

The following adverse reactions have been identified and reported during the post approval use of immunoglobulin products.[12]

- *Infusion Reactions:* Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *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
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test, haemolytic anaemia
- *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 drug exposure. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

DRUG INTERACTIONS

Overview

Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella/chickenpox for a period of at least 6 weeks and up to 3 months. An interval of 3 months should elapse before vaccination with live attenuated vaccines. In the case of measles vaccinations, the decrease in efficacy may persist for up to a year. Patients given measles vaccine should therefore have their antibody status checked.The immunizing physician should be informed of recent therapy with Privigen® so that appropriate measures may be taken.

Drug-Drug Interactions

See subsection Overview.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

See subsection Monitoring and Laboratory Tests under section **WARNINGS AND PRECAUTIONS**.

DOSAGE AND ADMINISTRATION

Ensure that patients with pre-existing renal insufficiency and those predisposed to acute renal failure are not volume depleted before administering Privigen®, Immunoglobulin Intravenous (Human) (see section **WARNINGS AND PRECAUTIONS**).

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. If the symptoms subside promptly, the infusion may then be resumed at a lower rate that is comfortable for the patient. The treatment required depends on the nature and severity of the adverse reaction. In case of shock, standard medical measures for shock should be implemented.

Recommended Dose and Dosage Adjustment

Treatment of Primary and Secondary Immune Deficiency

The usual dose of Privigen® for patients with PID and SID is 200 to 800 mg/kg body weight (bw), administered every 3 to 4 weeks. A target serum immunoglobulin G (IgG) trough level of at least 5 g/L has been proposed.[13, 14] However, an optimum level in patients with PID/SID has not been established in randomized, controlled clinical studies. Doses should be adjusted to achieve the desired serum trough levels and clinical responses.

Treatment of Immune Thrombocytopenic Purpura

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

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

The recommended starting dose* is 2 g/kg bw divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw over 1 to 2 consecutive days every 3 weeks.

Missed Dose

A missed dose should be administered as soon as possible to ensure an adequate IgG serum level.

* The dose is based on the dose used in the clinical study conducted with Privigen. The duration of treatment beyond 24 weeks should be subject to the physician's discretion based upon the patient response and maintenance response in the long-term. The dosing and intervals may have to be adapted according to the individual course of the disease.

Administration

Infusion Rate

The recommended initial infusion rate of Privigen® is 0.5 mg/kg/min (0.3 mL/kg/hr). If well tolerated, the rate of administration may gradually be increased up to an infusion rate of 12 mg/kg/min (7.2 mL/kg/hr).

As with other IgG products, patients who are receiving IgG for the first time, who have received another IgG, or who have not received IgG in more than 8 weeks may be at risk of developing systemic reactions (mimicking symptoms of an inflammatory response or infection) on rapid infusion of Privigen® (greater than 4 mg/kg/min [2.4 mL/kg/hr]). These patients should be started at a slow rate of infusion (e.g., 0.5 mg/kg/min [0.3 mL/kg/hr] or less) for at least 30 min. and gradually advanced to the maximum rate as tolerated. When high doses (≥1g/kg bw) are administered it is recommended not to exceed the rate of 8 mg/kg/min.The initial infusion rate for patients who have previously received Privigen® for three or more consecutive infusions can be individualized based on the rate the patient previously tolerated.

For patients judged to be at risk of renal dysfunction or thrombotic events, Privigen® should be administered at the minimum infusion rate practicable (see section WARNINGS AND PRECAUTIONS).

Infusion Parameters

Privigen® is for intravenous administration and should be given by a separate infusion line. An infusion pump may be used to control the rate of administration.

Do not mix Privigen® with other IVIG products or other intravenous medications. If necessary, Privigen® can be diluted with D5W. As well Privigen® can be flushed with D5W or 0.9% Sodium Chloride for injection, USP.

If large doses of Privigen® are to be administered, several vials may be pooled using aseptic technique. Because the solution contains no preservative, discard partially used product after 24 hours.

Reconstitution

Not applicable. Privigen® is a ready to use solution of human immunoglobulin for intravenous infusion.

OVERDOSAGE

Overdose can lead to fluid volume overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Treatment of Primary and Secondary Immune Deficiency

Privigen®, Immunoglobulin Intravenous (Human), contains a broad spectrum of antibody specificities against bacterial, viral, parasitic, and mycoplasma agents that are capable of both opsonization and neutralization of pathogens and toxins. Appropriate doses of Privigen® should restore abnormally low IgG levels to the normal range and thus help protect patients against infections.

Treatment of Immune Thrombocytopenic Purpura

The mechanism of action of immunoglobulins in the treatment of 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.[15]Another proposed mechanism is the down-regulation of platelet autoantibody-producing B cells by anti-idiotypic antibodies in IVIG.[16]

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

CIDP is an immune-mediated disease and is characterized by progressive or relapsing motor and/or sensory symptoms and signs in more than 1 limb, developing over at least 2 months. Sensory disturbances are usually slight, but are a common finding in CIDP subjects. Proximal and distal parts of the limbs are usually affected symmetrically. Atrophy is less marked than weakness. Loss of reflexes is found in almost all subjects, but may be confined to the ankles. Cranial nerve involvement, sometimes preceding the neuropathy, has been reported infrequently.

IVIG are beneficial in treating neuropathies by suppressing the immune-mediated processes that are directed against myelin or axonal antigenic targets. Although no specific mechanism of action has conclusively been proven to be the dominating pathway it appears that there are several possible modes of action that act together, essentially the inhibition of the complement pathway, Fc receptor modulation on macrophages (e.g inhibition of FcyRI and III or upregulation of FcyRII) inhibits macrophage-mediated demyelination, the suppression of pathogenic cytokines, the interaction with intercellular adhesion molecules to modulate cell migration, T-cell modulation and direct effects on remyelination.

Pharmacokinetics

Treatment of Primary and Secondary Immune Deficiency

In the clinical study assessing the efficacy and safety of Privigen® in 80 subjects with PID (see section **CLINICAL TRIALS**), serum concentrations of total IgG and IgG subclasses were measured in 25 subjects (ages 12 to 65) 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. Blood samples were taken 10 to 30 minutes before the infusion and 3 to 20 minutes, 24±2 hours, 3 days, 7 days, 10 days, 14±1 days, and 21±1 days after the infusion. For subjects on the 4-week dosing interval, an additional sample was taken 28±1 days after the infusion.

Table 8 presents the pharmacokinetic parameters of Privigen®, measured as serum concentrations of total IgG.

Table 8: Pharmacokinetic Parameters of Privigen®

Parameter	No. of Subjects	Median (Range)
C_{max} (peak, mg/dL)	25	2340 (1040-3460)
C_{min} (trough, mg/dL)	25	1023 (579-1469)
$t_{½}$ (days)	25	36.6 (20.6-96.6)
AUC_{0-t} (day × mg/dL)*		
3-week dosing interval	3	29,860 (28,580-40,010)
4-week dosing interval	22	36,670 (19,680-44,340)

C_{max}, maximum serum concentration; C_{min}, trough (minimum level) serum concentration;
$t_{½}$, 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® of 36.6 days is representative of half-lives in the PID patient population receiving immunoglobulins.

The IgG subclass levels observed in the pharmacokinetic population were consistent with a physiologic distribution pattern (mean trough values): IgG_1, 564.91 mg/dL; IgG_2, 394.15 mg/dL; IgG_3, 30.16 mg/dL; IgG_4, 10.88 mg/dL.

In the extension study, mean trough levels of total IgG serum concentrations achieved in subjects with PID were 1115 ± 297 mg/dL for the 3-week dosing interval and 931 ± 181 mg/dL for the 4-week dosing interval, comparable to the results from the pivotal study.

Treatment of Immune Thrombocytopenic Purpura

Pharmacokinetic studies with Privigen® were not performed in patients with chronic ITP.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

Pharmacokinetic studies with Privigen® were not performed in patients with CIDP.

STORAGE AND STABILITY

Privigen®, Immunoglobulin Intravenous (Human), can be stored either in the refrigerator or at room temperature (at +2°C to +25°C) until 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. The shelf life of Privigen® is 36 months.

SPECIAL HANDLING INSTRUCTIONS

Privigen®, Immunoglobulin Intravenous (Human), is a clear or slightly opalescent, colorless to pale yellow solution. As with all parenteral solutions, 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 IVIG products or other intravenous medications. If necessary, Privigen® can be diluted with 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, discard partially used product after 24 hours. Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Privigen®, Immunoglobulin Intravenous (Human), 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:

Fill Size	Grams IgG
25 mL	2.5 g
50 mL	5 g
100 mL	10 g
200 mL	20 g
400 mL	40 g

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

Composition:

Human immunoglobulin:	100 g/L
L-proline:	28.8 g/L (250 mmol/L)
HCl and/or NaOH:	for pH adjustment to 4.8
Water for Injection, USP:	q.s.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Immunoglobulin Intravenous (Human)

Chemical name: Immunoglobulin Intravenous (Human)

Molecular formula and molecular mass: 146,000 Da (IgG_1, IgG_2, and IgG_4), 170,000 Da (IgG_3)

Structural formula: IgG has two identical light polypeptide chains and two identical heavy polypeptide chains, which are linked together with disulphide bonds. There are two intra-chain disulphide bonds in the light chain, one in the variable region and one in the constant region. There are four such bonds in the heavy chain. Each disulphide bond encloses a peptide loop of 60-70 amino acid residues. These result in a series of globular regions with very similar secondary and tertiary structure. The peptide loops enclosed by the disulphide bonds represent the central portion of a domain of about 110 amino acid residues. In both the heavy and light chains the first of these domains corresponds to the variable region. In the light chain there is one additional domain and in the heavy chain three additional domains which make up the constant portion of the chain. It is variations in the amino acid sequence of the variable domains of the light and heavy chains that confer the specificity of immunoglobulins. The number and distribution of interchain disulphide bonds differ between the IgG subclasses with two for IgG_1 and IgG_4, four for IgG_2, and fifteen for IgG_3.

Physicochemical properties:

IgG-subclass distribution
IgG_1 69%
IgG_2 26%
IgG_3 3%
IgG_4 2%

Product Characteristics

Privigen®, Immunoglobulin Intravenous (Human), 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 combined with a filter aid-assisted depth filtration, and anion exchange chromatography. In addition, the Privigen manufacturing process includes an immunoaffinity chromatography step that specifically reduces blood group A and B antibodies (isoagglutinins A and B). 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, assessed with biochemical or biological assays. Fc functions tested include complement activation and Fc-receptor-mediated leukocyte activation (determined with complexed IgG). Scavenging/inhibition of immune complex-induced complement activation, an anti-inflammatory function of IVIGs, were greater *in vitro* with Privigen® than with other marketed IVIG products. Privigen® does not activate the complement system or prekallikrein in an unspecific manner.

Privigen® has a purity of at least 98% IgG, with trace amounts of IgA (no more than 25 mcg/mL of IgA levels), as well as other plasma proteins. The distribution of IgG subclasses is similar to that found in normal human plasma (see **IgG-subclass distribution**). Privigen® is isotonic, with an osmolality of 320 mOsmol/kg. Privigen® contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative, and it has a low sodium content (1 mEq/L or less).
Privigen® has a pH of 4.8 and contains 250 mmol/L of L-proline (a nonessential amino acid) as a stabilizer. The low pH and the presence of L-proline inhibit oxidative reactions (which cause discoloration) and IgG dimer formation (which is important for product tolerability). The IgG dimer content in IgG formulated with either 250 mmol/L L-proline (Privigen®) or 250 mmol/L glycine at a pH of 4.8 was evaluated after being stored at room temperature (+25ºC) for 60 days. The percentage of IgG dimers was 7.9% in Privigen® and 11% in product formulated with glycine, representing a decrease in dimer content of approximately 30% in Privigen®.

All plasma used in the manufacture of Privigen® is tested using FDA-licensed serological assays for hepatitis B surface antigen (HBsAg) 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).

Viral Inactivation/Removal

The manufacturing process for Privigen® includes four steps that have been shown to reduce the risk of virus transmission in an additive manner. Octanoic acid fractionation, combined with a filter aid-assisted depth filtration, effectively eliminates enveloped viruses that are potentially present in the starting material. Dedicated virus clearance steps include pH 4 incubation to inactivate enveloped viruses and B19V[17] and virus filtration to remove by size exclusion both enveloped and non-enveloped viruses as small as approximately 20 nanometers. An additional depth filtration step removes residual non-IgG proteins and 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 9** shows the virus clearance during the manufacturing process for Privigen®, expressed as the mean $\log_{10}$ reduction factor (LRF).

Table 9: Virus Inactivation/Removal in Privigen®

	HIV-1	**PRV**	**BVDV**	**WNV**	**EMCV**	**MVM [B19V]**
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**					
Octanoic acid fractionation	≥4.6*	≥6.3*	≥6.0*	>7.4*	1.0**	1.4**
pH 4 incubation	≥5.4	≥5.9	4.6	>7.8	nt	[>5.0]†
Depth filtration	≥5.3	≥6.3	2.1	3.0	4.2	2.2
Virus filtration	≥4.6	≥5.5	≥5.4	>5.9	≥5.4	≥5.5
Overall reduction ($\log_{10}$ units)	**≥15.3**	**≥17.7**	**≥12.1**	**>16.7**	**≥9.6**	**≥7.7**

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); B19V, B19 virus; LRF, $\log_{10}$ reduction factor; nt: not tested.
* Given that the octanoic acid fractionation includes depth filtration, partitioning at this step and the step designated depth filtration shares partially overlapping mechanisms. Hence, these values were not accounted for in the overall LRF.
** Values less than 1.5 $\log_{10}$ are not considered a significant reduction and are not accounted for in the overall LRF.
† The B19V value[18] is not accounted for in the overall LRF.

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.[18] Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanoic acid fractionation combined with a filter aid-assisted depth filtration (>6.4 $\log_{10}$), depth filtration (2.6 $\log_{10}$), and virus filtration (>5.8 $\log_{10}$). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

CLINICAL TRIALS

Treatment of Primary and Secondary Immune Deficiency

Pivotal Study

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and pharmacokinetics of Privigen® in adult and pediatric subjects with PID, 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 IVIG 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 bw per infusion. The median dose for the 3-week interval was 428.3 mg/kg bw per infusion; the median dose for the 4-week interval was 440.6 mg/kg bw per infusion. 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 in 69% (716) of infusions was 7 mg/kg/min or greater, and the maximum rate in 17% (176) of infusions was greater than 8 mg/kg/min.

The primary endpoint was 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 endpoints, including rate of other infections, days out of work/school/day care or days unable to perform normal activities due to illness, days of hospitalization, use of antibiotics, and overall feeling of well being.

During the 12-month study period, the aSBI rate was 0.08 (with an upper 1-sided 97.5% confidence interval of 0.182), which met the FDA requirement 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 abcess. None of these aSBIs were related to Privigen®, and all 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; only 16 (6.3%) of 255 infections in 10 subjects were considered severe.

Table 10 summarizes the efficacy results for all 80 subjects; similar results were seen in the 70 per-protocol subjects.

Table 10: Summary of Efficacy Results in Subjects With PID

Number of Subjects	80
Infections Annual rate of confirmed aSBIs* Annual rate of other infections	 0.08 aSBIs /subject year† 3.55 infections/subject year
Total Number of Subject Days	26,198
Out of work/school/ day care or unable to perform normal activities due to illness Number of days (%) Annual rate	 570 (2.17%) 7.94 days/subject year
Hospitalization Number of days (%) Annual rate	 166 (0.63 %) 2.31 days/subject year
Antibotic use Number of subjects (%) Annual rate	 64 (80%) 87.4 days/subject year
Overall feeling of well being‡, mean (range)	2.1 (1.0-5.0)§

* Defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.
† Upper 1-sided 97.5% confidence interval: 0.182.
‡ Level of well being: 1=very well; 2=well; 3=fair; 4=poor; 5=very poor.
§ Average scores per infusion.

Extension Study

An extension study to the pivotal study was conducted in 55 adult and pediatric subjects with PI to study higher infusion rates and to collect additional efficacy, safety and tolerability data. This study included original subjects from the pivotal study (n=45) and new subjects who were receiving another IVIG product (n=10). Only subjects who continued from the pivotal study received infusions at a higher rate (median: 12 mg/kg/min; maximum of 16 mg/kg/min). This HIR was safely administered in slightly more than half of the eligible subjects, with 97% of infusions in the HIR group administered at 12 mg/kg/min (maximum of 16 mg/kg/min). Subjects were treated with Privigen® at doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months; 12 subjects were on a 3-week treatment schedule and 43 on a 4-week schedule. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female; 41 (74.5%) were Caucasian, 9 (16.4%) were Hispanic, and 5 (9.1%) were African-American. In this extension study, the annualized rate of acute serious bacterial infections was 0.018 with an upper 1-sided 99% confidence interval of 0.117. Other efficacy results, including the serum IgG trough levels, were similar to those observed during the pivotal study.

Treatment of 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 x 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 bw dose of Privigen® administered as two 1 g/kg bw intravenous infusions on two consecutive days and were observed for 29 days. Fifty-three (93%) subjects received Privigen® at the maximum infusion rate allowed (4 mg/kg/min [2.4 mL/kg/hr]).

The primary endpoint was the response rate defined as the percentage of subjects with an increase in platelet counts to at least 50 x 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 x 10^9/L at any point within the study period, the duration of that response, and the regression 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 x 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 x 10^9/L within 7 days after the first infusion. The lower bound of the 95% confidence interval for the response rate (69.2%) was well above the predefined response rate of 50%, demonstrating a clinically relevant platelet response. Similar results were seen in the 56 per-protocol subjects.

An increase from baseline in median platelet counts was observed on all subsequent visits. The highest median increase was seen 7 days after the first infusion (123 x 10^9/L). The median maximum platelet count achieved was 154 x 10^9/L. The median time to reach a platelet response of more than 50 x 10^9/L was 2.5 days after the first infusion. Forty-three percent of the 57 subjects reached this response after Day 1 (i.e., on Day 2 prior to second dosing) and 75% reached this response after Day 5.

Duration of platelet response was analyzed for the subjects who achieved a response any time after the first infusion. The median duration of platelet response was 15.4 days (range: 1 to greater than 82), at least 8.8 days in 75% of subjects and at least 21.9 days in 25% of subjects. Five (9%) subjects maintained a response up to Day 29. Four subjects (7%) maintained a response up to Day 57 and when measured again at Day 85 had a median platelet count of 72 (range: 6 to 242) x 10^9/L.

A regression of hemorrhage was seen in 31 (86.1%) of the 36 subjects who had skin bleeding at baseline and in all 11 subjects who had bleeding in the oral cavity. The overall regression rate in subjects who had bleeding in the genitourinary tract at baseline was 77.8% (7 of 9 subjects).

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

A prospective, multicenter, open-label, single-arm study investigated the efficacy and safety of Privigen in 28 patients with CIDP. Subjects ranged in age from 22 to 79 years, 18 (64.3 %) were males and 10 (35.7 %) were females; all were Caucasians.

Subjects received 2 g/kg bw induction dose divided over 2 to 5 days followed by 6 maintenance dose of 1g/kg bw divided over 1 to 2 days every 3 weeks. Infusions were to be started at a rate of 0.5 mg/kg bw/min (0.3 mL/kg bw/h). If well tolerated within 30 minutes, the rate could be increased in a first step to 1.0 mg/kg bw/min (0.6 mL/kg bw/h) for another 30 minutes. If well tolerated, a stepwise increase to a maximum of 8 mg/kg bw/min (4.8 mL/kg bw/h) was allowed at the discretion of the investigator.

The adjusted 10-point INCAT score was used as the primary endpoint to determine response to Privigen treatment. The adjustment was introduced to correct for improvement in the upper limbs only - a change from 1 to 0 or from 0 to 1 solely due to upper limbs score was not considered to be clinically relevant. Responders were defined as patients with a initial clinically meaningful improvement (decrease of ≥1 point in the adjusted INCAT score) that was maintained to study completion at Week 25. In addition, 2 measures of impairment in muscle strength (Grip strength and MRC sum score) were implemented as secondary endpoints.

In the Intention to Treat (ITT) analysis, the responder rate (with response sustained over 25 weeks) was 46.4% [95% CI – 29.53, 64.19]. The re-analysis of the primary efficacy endpoint stratified by IVIG pre-treatment status are shown in **Table 11**:

Table 11: Primary Efficacy Endpoint Stratified by IVIG Pre-treatment

					Wilson Score 95% CI	
Study population	**IVIG pre-treatment**	**Number of subjects**	**Number of responders**	**Responder rate [%]**	**Lower limit**	**Upper limit**
FAS	IVIG-pretreated	13	7	53.8	0.291	0.768
FAS	IVIG-untreated	15	6	40.0	0.198	0.643
FAS = Full analysis set						

In the Per Protocol (PP) analysis, 11 out of 22 subjects responded to Privigen treatment, i.e. a response rate of 50% [95%CI: 30.72 to 69.28%]

Maximum grip strength and MRC sum score which are outcome measures of impairment measuring muscle strength, supported the findings of the primary analysis.

DETAILED PHARMACOLOGY

See section **ACTION AND CLINICAL PHARMACOLOGY.**

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single and repeat-dose toxicity

Repeated-dose toxicity studies were conducted in rats involving 7-hour continuous i.v. administration of 120 mmol/L and 300 mmol/L L-proline on 5 or 28 consecutive days. The maximum amount of L-proline infused was 1449 mg/kg/day. This dose corresponds to 42 mL L-proline solution/kg bw and represents the maximal daily dose (volume) that can be infused in the animals. There were no unscheduled deaths or treatment-related clinical signs. Slight (statistically not significant) reductions in body weight gain and reduced food consumption was observed only in the 28-day high dose male group. No obvious influence of treatment was observed on the hematology parameters. Variances between groups in serum clinical chemistry parameters were considered incidental (not dose related) and all individual values fell within the historical control range. No organ weight changes were found nor were treatment related macroscopic or microscopic changes in the tissues (including brain tissue) observed. A No Observed Adverse Effect Level (NOAEL) at the high-dose of 1449 mg/kg/day L-proline could be established.

Previously, lower levels of L-proline (up to 960 mg/kg/day) administered to rats together with L-nicotinamide with or without isoleucine and L-leucine have been studied involving up to 28 consecutive days of infusions. There were some findings which were either not considered toxicologically significant (moderately high ALAT levels with a lack of corroborating liver pathology or liver weight increase) or likely to be methodological artifacts (moderately low platelet counts in female rats). Kidney pathology findings were also observed in this 28-day i.v. rat study, but not in the 2-day and 7-day rat studies and, most importantly, not in the studies assessing L-proline alone at higher doses than the L-proline dose used in the studies with the combination of the three components. The findings obtained using L-proline in combinations with L-isoleucine and nicotinamide are therefore not attributed to L-proline.

Genotoxicity

Immunoglobulins such as human IgGs cannot interact directly with DNA or chromosomes. Therefore, testing of such molecules is not appropriate.

The absence of direct genotoxicity has been demonstrated for L-proline in combination with nicotinamide and L-isoleucine using a variety of assays such as the Ames test, *in vitro* cytogenicity assay, a bacterial stress gene (Pro-Tox) assay and a bone marrow micronucleus assay in mice. Published literature substantiates that L-proline is not mutagenic in the Ames test, a microsomal mutagenesis assay or a host-mediated assay.

Carcinogenicity

Carcinogenicity studies are not appropriate for IgG molecules found in Privigen® or the excipient L-proline because they are both endogenously available and repeated dosing of human IgGs would cause immunological reactions in heterologous species. In addition, carcinogenicity studies are not required for medicinal products for short-term use like Privigen® (ICH guideline S1A). Limited data are available for L-proline from the published literature. It has been shown that L-proline has no influence on the progression of hamster bile duct carcinoma.

Reproductive and developmental toxicity

Segment I (fertility and early embryonic development) and III (peri and post-natal development, including maternal function) reproductive toxicity studies have not been conducted on L-proline which is endogenously bioavailable in humans and used extensively in products for humans. In addition, in the four week toxicity study there were no histopathological findings on reproductive organs of rats treated up to the top dose level at the Day 28 kill.

A Segment II (teratogenicity and embryo toxicity) reproduction toxicity study in rats has been carried out with L-proline at a dose of 1449 mg/kg/day administered i.v. during 7 hours/day during Days 6 to 17 of gestation. This dose corresponds to 42 mL L-proline solution/kg bw and represents the maximal daily dose that can be infused in the animals. There was no indication of maternal or embryo-toxicity, and the dose tested was a NOEL.

Additional Segment II (teratogenicity and embryo toxicity) reproduction toxicity studies in rats have been carried out previously with L-proline at doses up to 575 mg/kg/day administered i.v. during 7 hours/day during Days 6 to 15 or 17 of gestation in a fixed combination with L-isoleucine and nicotinamide. Except for slight maternal and fetal effects on weight gain and food consumption, no evidence of teratogenic or fetotoxic activity was observed.

Local tolerance

A local tolerance study in rabbits was conducted with Privigen® to assess putative local reactions at sites after i.v., p.v. and i.a. application. Erythema and edema formation induced by test article and saline injection were slight and similar in incidence and severity after i.v. and i.a. application, and slightly pronounced, but in a tolerable range, after test article injection compared to saline in the p.v. group.

In a second local tolerance study in rabbits Privigen® was administered subcutaneously at single doses of 0.5 mL and 2.5 mL/kg. Besides Privigen®, other test articles were assessed, i.e. the marketed comparator product Beriglobin P (16% protein solution), IgPro16, IgPro18 and IgPro20. All IgPros tested represent other investigational products of CSL Behring that were formulated the same way as Privigen® except that their protein concentration was higher, according to their designation (e.g., 18% protein in IgPro18). Finally the excipient solution (L-proline 0.25 mmol/L, pH 4.8) was also assessed. Privigen®, IgPro16 and the excipient solution, showed less erythema formation than the comparator test article Beriglobin P. The degree of erythema development after IgPro20 and IgPro18 administration was comparable to that of the comparator test article. No notable differences were observed between the two Privigen® doses tested. The frequency and intensity of edema formation augmented with the increasing test article dosing (protein concentration differences of test articles)**.** No major difference in pain reactions could be observed between test articles and no abnormality was detected histologically after s.c. injection of Privigen®.

Single-Dose Toxicity

No single-dose toxicity studies are available for either Privigen® or its excipient L-proline.

Repeat-Dose Toxicity (including supportive toxicokinetics evaluation)

The testing of human immunoglobulin preparations in animal models of limited value because immunoglobulins are immunologically active and contain xenoreactive antibodies [19, 20,21] which may cause effects in animals that are not relevant for humans. In addition, human IgG formulations have well established clinical safety and efficacy in patients, based on extensive use over many years. For these reasons no repeat dose toxicity studies were therefore conducted with Privigen®.

The other toxicity data concentrate on L-proline. Because of the clinical knowledge of L-proline toxicity studies were performed in only one animal species, in rats. The data were collected during development of Privigen®, or during development of Sandoglobulin Liquid where excipient mixtures were assessed which contained L-proline. The studies were designed to provide results, which are directly relevant to the Privigen® clinical dosing regimens. In particular, the dosing regimen in animals was the intravenous route with a dosing time of 7 hours/day thus simulating a human high-dose IVIG infusion. The limitation of dosing to 28 days is justified in view of the proposed clinical dosing regimens of 1 dose (0.2 – 0.8 g Privigen®/kg bw) every 3 or 4 weeks for PID patients or 1 g Privigen®/kg bw administered for 2 consecutive days for ITP patients. In studies carried out during development of Privigen®, glycine was also studied in addition to L-proline. Glycine is a commonly used excipient in liquid IVIGs and was also a candidate excipient for Privigen® early in development of the product. Using the formulation with L-proline, the dimer content at room temperature storage could be reduced by 30% as compared to a formulation with glycine. A low dimer content is important for product tolerability.

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PART III: CONSUMER INFORMATION

Privigen®
Immunoglobulin Intravenous (Human)

This leaflet is part III of a three-part "Product Monograph" published when Privigen® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Privigen®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Privigen® is a highly purified product, called an immunoglobulin, made from human plasma. Privigen® contains the antibody immunoglobulin G (IgG), which is found in the blood of healthy individuals to help combat germs, such as bacteria and viruses. Because it helps the body rid itself of these bacteria and viruses, IgG is important in helping the body fight disease and illness.

What the medication is used for:

Privigen® is a medication used to treat adults and children:

- Who need antibody replacement therapy due to primary or secondary immune deficiency. Primary Immune Deficiency (PID) patients are born with a reduced ability or inability to produce immunoglobulins. Secondary Immune Deficiency (SID) patients develop or acquire a reduced ability or inability to produce immunoglobulins due to environmental factors, certain diseases or certain therapies;
- Who do not have enough blood platelets and who are at high risk of bleeding (immune thrombocytopenic purpura, ITP);
- Who suffer from chronic inflammatory demyelinating polyneuropathy (CIDP) which is a chronic disease characterised by inflammation of the peripheral nerves that causes muscle weakness and / or numbness mainly in the legs and upper limbs.

Privigen® is supplied as a sterile liquid in single-use vials and is given by intravenous infusion.

What it does:

Privigen® increases your levels of antibodies (in cases of Primary or Secondary Immune Deficiency or Immune Thrombocytopenia Purpura).

Privigen® is known as antibody replacement therapy, because it replaces the missing and much-needed IgG antibodies in people who have low levels of these infection-fighting proteins. By replacing these important antibodies, Privigen® helps make people with primary and secondary immune deficiency better able to avoid infections and fight them when they do occur.

The precise action of Privigen® in immune thrombocytopenic purpura is unknown, but it is believed to block platelet removal and therefore increase their number.

Likewise, the precise action of Privigen® in chronic inflammatory demyelinating polyneuropathy is not clear but it is believed to modify the pathway that leads to muscle weakness and / or numbness.

When it should not be used:

People who have a history of severe allergic reactions to immunoglobulin treatment or have a condition known as selective IgA deficiency should not use Privigen®. Tell your doctor if you have ever had an allergic reaction due to either of these conditions. If a serious allergic reaction occurs at any time, stop the Privigen® treatment and contact your doctor or an emergency medical professional immediately.

Because clinical studies with pregnant women have not been conducted, if you are pregnant or think you may be pregnant, discuss with your doctor whether Privigen® is clearly needed. Please also consult your doctor about the use of this product if you are a nursing mother.

What the medicinal ingredient is:

Immunoglobulin Intravenous (Human).

What the important nonmedicinal ingredients are:

L-proline.
For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Privigen® is a solution for intravenous infusion.

It is supplied in 2.5 g (25 mL bottle), 5 g (50 mL bottle), 10 g (100 mL bottle), 20 g (200 mL bottle) or 40 g (400 mL bottle) . The concentration of the active ingredient is 10% or 100 g/L.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Immunoglobulin Intravenous (Human) (IVIG) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death, particularly in patients predisposed to acute renal failure.
- There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins.
- Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus).
- Thrombosis may occur even in the absence of known risk factors.

BEFORE you use Privigen® talk to your doctor or pharmacist if:

- you are pregnant or think that you may be pregnant;
- you are nursing;
- you have a history of allergic or other adverse reactions to immunoglobulins;
- you recently have been vaccinated;
- you have been previously advised that you have IgA deficiency;
- you have a kidney disease;
- you have Hyperprolinemia (high levels of proline in the blood);

- You receive this medicine in high doses either on 1 day or over several days and you have a blood group A, B or AB and/or you have an underlying inflammatory condition. In these circumstances, it has been commonly reported that immunoglobulins increase the risk of breakdown of red blood cells (hemolysis).

INTERACTIONS WITH THIS MEDICATION

Privigen® can impair the efficacy of certain virus vaccines, such as measles, mumps,rubella (also known by its abbreviation "MMR"), and varicella/chickenpox. Inform the immunizing physician of recent treatment with Privigen® so appropriate precautions can be taken.

Other products must not be mixed with the Privigen® solution.

PROPER USE OF THIS MEDICATION

How do I use Privigen®?

Privigen® is injected intravenously.

Your doctor will determine the appropriate dose for your treatment.

Usual dose:

The usual dose of Privigen® for patients with Primary and Secondary Immune Deficiency is 200 to 800 mg/kg body weight, every 3 to 4 weeks.

The usual dose of Privigen® for patients with Immune Thrombocytopenic Purpura is 1g/kg body weight for 2 consecutive days.
The usual starting dose of Privigen® for patients with chronic inflammatory demyelinating polyneuropathy is 2 g/kg bw divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw over 1 to 2 consecutive days every 3 weeks.

Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels.

Overdose:

Overdose can lead to fluid volume overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

Missed Dose:

Inform your doctor if you missed a dose. Your next dose should be administered as soon as possible to ensure an adequate efficacy.

POSSIBLE SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

The following symptoms are common. If any of the listed symptoms occur, are severe or if they worry you, talk to your doctor or pharmacist:

- Headache
- High Blood Pressure (hypertension)
- Fever
- Nausea
- Fatigue/tiredness
- Chills
- Anemia
- Influenza (flu) like symptoms
- Pain
- Vomiting
- Physical weakness (asthenia)
- Skin disorder (rash, itching, hives)
- Hypersensitivity
- Diarrhea

Routine laboratory tests may uncommonly reveal changes to liver or kidney functions as well changes in blood count.

If the following symptoms occur, stop your medication and call your doctor or pharmacist without delay:

- Anaphylactic shock: A rapid occurring severe allergic reaction that involves the whole body. The symptoms to watch for are: Hives, swelling of the lips, tongue or throat, difficulty in breathing, low blood pressure, faintness, abdominal pain, nausea and vomiting.
- Hemolytic anemia/hemolysis (where you have too few red blood cells caused either by red blood cells dying early or dying because their cell membrane has been disrupted). The symptoms to watch for include: Fatigue, weakness, dizziness, headache, rapid heartbeat, ringing in the ears.

The following symptoms occur rarely but if they occur, you need to talk to your doctor or pharmacist about them:

- Aseptic meningititis: This is an inflammation of the membrane that envelops the brain and spinal cord, which is not caused by bacteria. The symptoms to watch for include: Malaise, fever, headache which can be severe, stiffness of the neck and back, nausea, vomiting, drowsiness, photophobia, painful eye movement.
- Blood clots (thromboembolism): if you are overweight, are elderly, have diabetes, have been bedridden for a long time, have high blood pressure, have low blood volume, have problems with your blood vessels, have an increased tendency for blood clotting or have a disease or a condition which causes your blood to thicken. In these circumstances, immunoglobulins may increase the risk of heart attack, stroke, blood clots in the lung, or blockage of a blood vessel in the leg, although only very rarely.
- Transfusion-related Acute Lung Injury (TRALI): Non-heart related accumulation of fluid in the air spaces of the lungs causing severe difficulty in breathing, chest pain, chest discomfort, painful respiration typically appearing within 1 to 6 hours after receiving treatment.
- Acute renal failure: if you have or had previously problems with your kidneys or take medicinal products that may harm your kidneys. In these circumstances, immunoglobulins may increase the risk of serious rapid loss of kidney function although only very rarely.
- Abnormally low level of specific white blood cells called neutrophils (decreased neutrophils counts).

This is not a complete list of side effects. For any unexpected effects while taking Privigen®, contact your doctor or pharmacist.

HOW TO STORE IT

Privigen® is supplied in single-use vials. It contains no preservatives, so any unused portion should be discarded immediately after injection. When stored either in the refrigerator or at room temperature (at +2°C to +25°C), Privigen® can be used until the expiration date on its label. Do not use after the expiration date. *Do not freeze Privigen®*. Keep the vial in its box during storage.

Keep Privigen® and all other medications out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Address Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

****We recommend that CSL Behring Canada be copied when reporting suspected side effects, at the following address:***

adversereporting@cslbehring.com

or be informed by pager
Pager Number: 1-613-783-1892

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at:

http://www.cslbehring.ca

or by contacting the sponsor, CSL Behring Canada, Inc. at: 1-613-783-1892.

This leaflet was prepared by CSL Behring Canada, Inc.

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