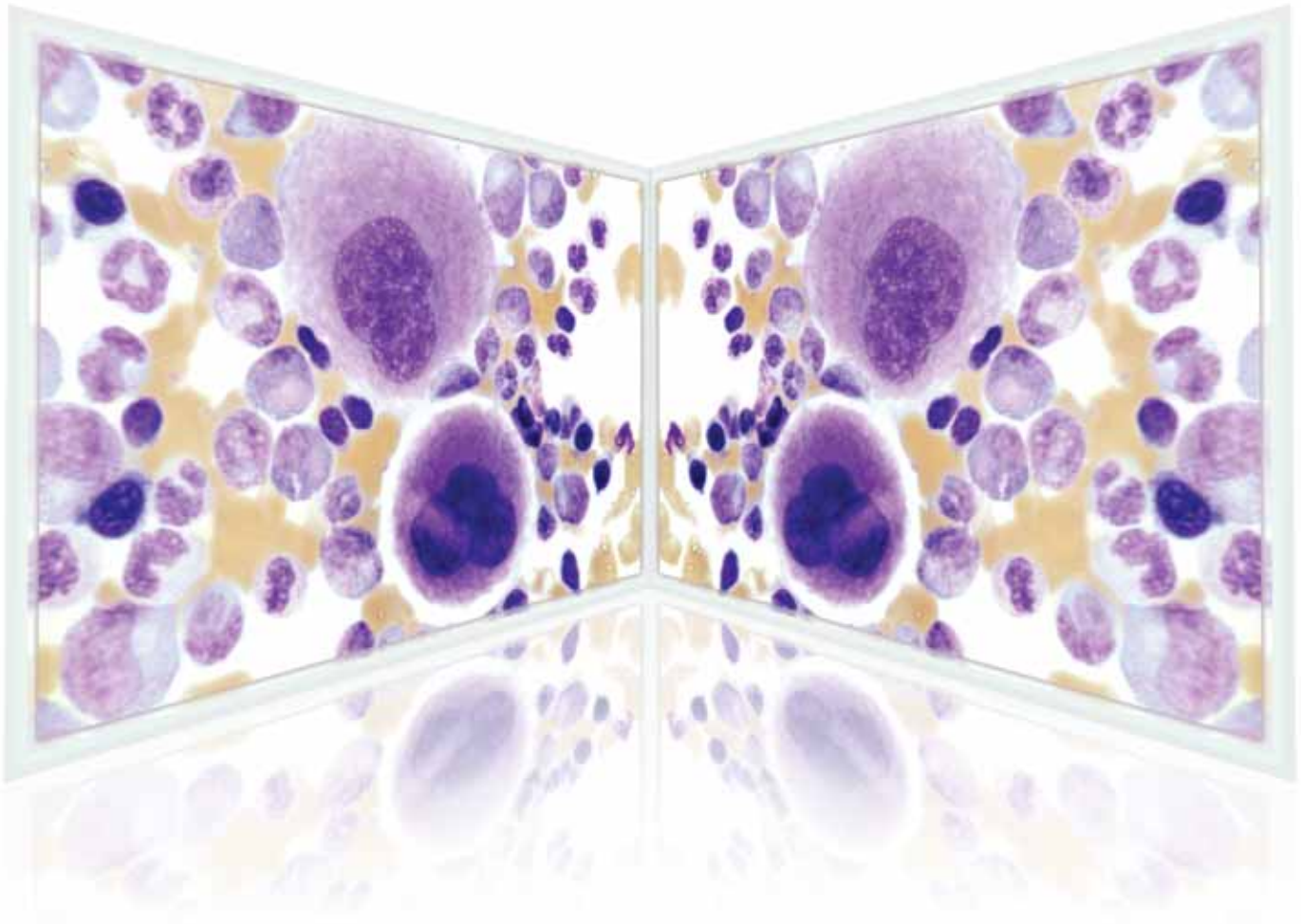

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

CSL Behring

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

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

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.

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 1-866-915-6958. (*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 Immune Globulin Intravenous (Human), 10% Liquid 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.

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