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1. INDICATIONS AND USAGE

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.

1.1 Treatment of Primary Immunodeficiency

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) in response to IgA components contained in IgG. Privigen® contains trace amounts of IgA (see Description [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Acute Renal Dysfunction and Acute Renal Failure

Patients with an experienced history of hypotension before the initial 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 creatinine (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, but not limited to, 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. (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. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (extravascular hemolysis) or intravascular RBC destruction (intraocular hemolysis).

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen® in the ITP study. These cases resolved spontaneously. 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 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.

5.5 Thrombotic Events

Thrombotic events have been reported with Privigen® and other IGIV treatments. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac function, diabetes mellitus, age greater than 65, volume depletion, renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, and/or known or suspected hypertension. 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 triglycerides (triglycerides), or monosodium gout.

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 the manufacturing process. Passage of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

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

Immune globulin 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]).

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 (20%) had 1-sided 97.5% confidence interval for the proportion of Immune Globulin Intravenous (Human), 10% Liquid patients who received premedication prior to the infusion of Privigen® and/or 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]).

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 every 4 weeks (median dose 440.6 mg/kg) for up to 12 months (see Clinical Studies [14.1]). Routine predemication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by predemication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received predemication 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. The total number of temporally associated AEs was 397 (a rate of 0.69 events per IgG infusion dose).

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

<table>
<thead>
<tr>
<th>TAAE</th>
<th>No. Subjects Reporting TAAE (% of Subjects [n=80])</th>
<th>No. TAAEs Reported (as % Rate of Infusions [n=1038])</th>
<th>No. Infusions With TAAE (% of Infusions [n=1038])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>35 (43.8)</td>
<td>90 (8.7)</td>
<td>82 (7.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>20 (25.0)</td>
<td>51 (4.9)</td>
<td>44 (4.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (16.3)</td>
<td>29 (2.8)</td>
<td>27 (2.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (12.5)</td>
<td>22 (2.1)</td>
<td>19 (1.8)</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (11.3)</td>
<td>15 (1.4)</td>
<td>15 (1.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (8.8)</td>
<td>13 (1.3)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (7.5)</td>
<td>11 (1.1)</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (6.3)</td>
<td>5 (0.5)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (6.3)</td>
<td>5 (0.5)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>5 (6.3)</td>
<td>5 (0.5)</td>
<td>5 (0.5)</td>
</tr>
</tbody>
</table>

* Two consecutive daily infusions.

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 150 related to the infusion of Privigen®, 5 related to aseptic meningitis). The safety and effectiveness of Privigen® has not been established in pediatric subjects with chronic ITP who are under the age of 15. Privigen® should be used with caution in patients over 65 years of age who have limited renal function. 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.

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, arthritis, 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:

- Respiratory: Atelectasis, 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
- Hematological: Purpura, 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, co-administered 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. Immunoglobulins cross the placenta from a pregnant woman or can affect reproduction capacity. Privigen® should be given to a pregnant woman only if clearly needed. Immunoglobulins may also cross the placenta from maternal circulation increasing after 30 weeks of gestation.

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 increasing after 30 weeks of gestation.

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.

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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