Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer such as polysorbate 80.

4 CONTRAINDICATIONS

Hizentra is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80.

Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (see Description [11]).

Hizentra is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (see Description [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur to human immune globulin or components of Hizentra, such as polysorbate 80. In case of hypersensitivity, discontinue the Hizentra infusion immediately and institute appropriate treatment.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Hizentra. Hizentra contains ≤50 mcg/mL IgA (see Description [11]).

5.2 Reactions Reported to Occur With IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGIV treatment, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter.

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.1 If renal function deteriorates, consider discontinuing Hizentra. 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 or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Hizentra at the minimum rate practicable.

Thrombotic Events

Thrombotic events may occur with use of human immune globulin products.2-4 Patients at increased 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 hypersensitivity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hypersensitivity, including those with cryoglobulins, fasting chylomicronemia markedly high triglycerides (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Hizentra at the minimum rate practicable.

Aseptic Meningitis Syndrome (AMS)

AMS may occur with use of human immune globulin products.5 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 frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Conduct a thorough neurological examination, including CSF studies, to rule out other causes of meningitis in patients exhibiting signs and symptoms of AMS. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis

Hizentra 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 (Coombs’) test result and hemolysis.5,6 Delayed hemolytic anemia can develop subsequently to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.9 Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If these are present after a Hizentra infusion, perform appropriate confirmatory laboratory testing.

If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Hizentra, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.10,11 TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor Hizentra recipients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient’s serum.

5.3 Transmissible Infectious Agents

Because Hizentra is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of current virus infections, and including virus inactivation/removal steps in the manufacturing process for Hizentra.

Report all infections thought to be possibly transmitted by Hizentra to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.4 Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most common adverse reactions (ARs), observed in ≥25% of subjects receiving Hizentra, were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, AR rates observed in clinical studies of a product cannot be directly compared to rates in the clinical studies of another product and may not reflect the rates observed in clinical practice.

The safety of Hizentra was evaluated in a clinical study for 15 months in subjects with PI who had been treated previously with IGIV every 3 or 4 weeks. The safety analyses included 49 subjects in the intention-to-treat (ITT) population. The ITT population consisted of all subjects who received at least one dose of Hizentra (see Clinical Studies [14]).

Subjects were treated with Hizentra at weekly doses ranging from 66 to 331 mg/kg body weight during the wash-in/wash-out period and from 72 to 379 mg/kg during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

No deaths or serious ARs occurred during the study. Two subjects withdrew from the study due to ARs. One subject experienced a severe injection-site reaction one day after the third weekly infusion, and the other subject experienced moderate myositis. Both reactions were judged to be “at least possibly related” to the administration of Hizentra.

Table 2 summarizes the most frequent adverse events (AEs) (experienced by at least 4 subjects), irrespective of causality. Included are all AEs and those considered temporally associated with the Hizentra infusion, i.e., occurring during or within 72 hours after the end of an infusion. Local reactions were the most frequent AEs observed, with injection-site reactions (i.e., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

Table 2: Incidence of Subjects With Adverse Events (AEs)* ( Experienced by 4 or More Subjects) and Rate per Infusion, Irrespective of Causality (ITT Population)

<table>
<thead>
<tr>
<th>AE (≥4 Subjects)</th>
<th>All AEs*</th>
<th>AEs* Occurring During or Within 72 Hours of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of Subjects (n=49))</td>
<td>Number (Rate) of AEs (n=2264 Infusions)</td>
<td>Number (% of Subjects (n=49))</td>
</tr>
<tr>
<td>Local reactions</td>
<td>49 (100)</td>
<td>1340 (0.592)</td>
</tr>
</tbody>
</table>
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.

### Table 2: (Continued)

<table>
<thead>
<tr>
<th>AE (≥ 2 Subjects)</th>
<th>All AEs*</th>
<th>AEs* Occurring During or Within 72 Hours of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (% of Subjects (n=49))</td>
<td>Number (Rate†) of AEs (n=2264 Infusions)</td>
</tr>
<tr>
<td>Other AEs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (26.5)</td>
<td>40 (0.018)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (16.3)</td>
<td>9 (0.004)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (14.3)</td>
<td>8 (0.004)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (12.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (10.2)</td>
<td>11 (0.005)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (10.2)</td>
<td>5 (0.002)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>5 (10.2)</td>
<td>5 (0.002)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (10.2)</td>
<td>7 (0.003)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4 (8.2)</td>
<td>7 (0.003)</td>
</tr>
<tr>
<td>Migraine</td>
<td>4 (8.2)</td>
<td>5 (0.002)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (8.2)</td>
<td>5 (0.002)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4 (8.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>4 (8.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (8.2)</td>
<td>5 (0.002)</td>
</tr>
</tbody>
</table>

* Excluding infections.
† Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.
‡ Rate of AEs per infusion.
§ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

The following adverse reactions have been identified and reported during the postmarketing use of IVIG products:
- **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.
- **Renal:** Acute renal dysfunction/failure, osmotic nephropathy.
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm.
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension.
- **Neurological:** Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome.
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis).
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs’) test.
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain.
- **General/Body as a Whole:** Pyrexia, rigors.

Table 4 summarizes injection-site reactions based on investigator assessments 15 to 45 minutes after the end of the 683 infusions administered during regularly scheduled visits (every 4 weeks).

### Table 3: Incidence of Subjects With Adverse Reactions (Experienced by 2 or More Subjects) to Hizentra and Rate per Infusion (ITT Population)

<table>
<thead>
<tr>
<th>Adverse Reaction (≥2 Subjects)</th>
<th>Number (%) of Subjects (n=49)</th>
<th>Number (Rate†) of Reactions (n=2264 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions1</td>
<td>49 (100)</td>
<td>1338 (0.591)</td>
</tr>
<tr>
<td>Other AEs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 (24.5)</td>
<td>36 (0.016)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Contusion</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Migraine</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (4.1)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>2 (4.1)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4.1)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4.1)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (4.1)</td>
<td>2 (&lt;0.001)</td>
</tr>
</tbody>
</table>

1 Rate of AEs per infusion.
2 Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.
3 Number of infusions administered during regularly scheduled visits.

6.3 Postmarketing Experience

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.

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* Based on March 2010 version
Immune Globulin Subcutaneous (Human) 16% Liquid

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

1 INDICATIONS AND USAGE

Vivaglobin is an Immune Globulin Subcutaneous (Human) (IGSC), 16% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the primary immunodeficiency in common variable immunodeficiency (CVI/D), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

4 CONTRAINDICATIONS

Vivaglobin is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of Immune Globulin (Human). Vivaglobin is contraindicated in IgA-deficient patients with antibodies against IgA or a history of hypersensitivity (see Description [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Severe hypersensitivity reactions may occur (see Patient Counseling Information [17.2]). In case of hypersensitivity, discontinue the Vivaglobin infusion immediately and institute appropriate treatment. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Vivaglobin contains ≤1.7 mg/mL IgA (see Description [11]). The minimum concentration of IgA that will provoke a hypersensitivity reaction is not known; therefore all IgG preparations carry the risk of inducing an anaphylactic reaction to IgA.

5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with IGIV treatment and with Vivaglobin treatment. 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 frequently show 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. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

5.3 Reactions Reported with IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

Renal Dysfunction/Failure

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Vivaglobin and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients treated with IGIV. Renal function deterioration, consider discontinuing Vivaglobin. 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 or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Vivaglobin at the minimum rate practicable.

Hemolysis

Vivaglobin may 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 (Coombs') test result and hemolysis. Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported. Monitor recipients of Vivaglobin for clinical signs and symptoms of hemolysis. If these are present after Vivaglobin infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Vivaglobin, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor recipients of Vivaglobin for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.4 Transmissible Infectious Agents

Because Vivaglobin is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob (CJID) agent. No cases of transmission of viral diseases or CJID have been associated with the use of Vivaglobin. Report all infections thought possibly to have been transmitted by Vivaglobin to the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient (see Patient Counseling Information [17.2]).

5.5 Laboratory Tests

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

6 ADVERSE REACTIONS

The most common adverse reactions (those AEs considered by the investigator to be at least possibly related to Vivaglobin administration) observed in ≥5% of study subjects receiving Vivaglobin were local injection-site reactions (swelling, redness, and itching), headache, nausea, rash, and gastrointestinal disorder.

6.1 Clinical Studies Experience

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

US-Canada Study

The safety of Vivaglobin was evaluated in a clinical study in the US and Canada for 12 months in 65 subjects with PI who had been previously treated with IGIV every 3 or 4 weeks (see Clinical Studies [14.1]). After 3 months, subjects were switched from IGIV to weekly subcutaneous administration of Vivaglobin for 12 months. Subjects were treated weekly with Vivaglobin at a mean dose of 158 mg/kg body weight (range: 34 to 352 mg/kg). The 65 subjects received a total of 3,656 infusions of Vivaglobin.

Table 2 shows the number of subjects who withdrew from the US-Canada study due to adverse events (AEs) and the AEs leading to discontinuation.

Table 2: Subjects with Adverse Events (AEs) Leading to Discontinuation, US-Canada Study

<table>
<thead>
<tr>
<th>AEs</th>
<th>Subjects with AEs At Least Possibly Related</th>
<th>Subjects with AEs Irrespective of Causality</th>
<th>Total Number (%) of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least 1 AE leading to discontinuation</td>
<td>4</td>
<td>1</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>3</td>
<td>–</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>–</td>
<td>1</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>1*</td>
<td>–</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1*</td>
<td>–</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

* One subject experienced hyperventilation and tachycardia.

Table 3 summarizes the most frequent AEs (experienced by more than 5% of subjects), irrespective of causality. It includes all AEs and those considered temporally associated with the Vivaglobin infusion, i.e., occurring during the infusion or within 72 hours after the end of the infusion.
Table 3: Incidence of Subjects With Adverse Events (AEs)\(^*\) (Experienced by >5% of Subjects) and Rate\(^*\) per Infusion, Irrespective of Causality, in the US-Canada Study

<table>
<thead>
<tr>
<th>AEs(^*) (&gt;5% of Subjects)</th>
<th>Number (Rate(^*)) of Subjects (n=65)</th>
<th>Number (Rate(^*)) of AEs per Infusion (n=3656)</th>
<th>Number (Rate(^*)) of Subjects (n=65)</th>
<th>Number (Rate(^*)) of AEs Per Infusion (n=3656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs at the injection site(^a)</td>
<td>60 (92%)</td>
<td>1789 (0.49)</td>
<td>60 (92%)</td>
<td>1767 (0.4848)</td>
</tr>
</tbody>
</table>

Other AEs

- Headache: 31 (48%)\(^*\)
- Gastrointestinal disorder: 24 (37%)\(^*\)
- Fever: 16 (25%)\(^*\)
- Nausea: 12 (18%)\(^*\)
- Rash: 11 (17%)\(^*\)
- Sore throat: 10 (15%)\(^*\)
- Allergic reaction: 7 (11%)\(^*\)
- Pain: 6 (9%)\(^*\)
- Diarrhea: 6 (9%)\(^*\)
- Cough increased: 6 (9%)\(^*\)
- Gastrointestinal pain: 5 (8%)\(^*\)
- Migraine: 5 (8%)\(^*\)
- Skin disorder: 5 (8%)\(^*\)
- Asthma: 5 (8%)\(^*\)
- Arthralgia: 4 (6%)\(^*\)
- Asthenia: 4 (6%)\(^*\)
- Malaise: 4 (6%)\(^*\)

\(^*\) Excluding infections. \(^\dagger\) Rate, number of AEs per infusion. \(^\ddagger\) Includes injection-site inflammation.

The total number of AEs, irrespective of causality, including injection-site reactions, that began during or within 72 hours after the end of an infusion was 2262 (a rate of 0.62 AEs per infusion); excluding injection-site reactions, the rate of AEs per infusion was 0.14.

Table 4 summarizes the severity of local AEs by infusion, irrespective of causality.

Table 4: Severity of Local Adverse Events (AEs) by Infusion, Irrespective of Causality, in the US-Canada Study

<table>
<thead>
<tr>
<th>AEs(^*) (Number of infusions: 3656)</th>
<th>Number (Rate(^*)) of AEs</th>
<th>Number (Rate(^*)) of AEs Occurring During or Within 72 Hours of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs at the injection site(^a)</td>
<td>1789 (0.49)</td>
<td>1767 (0.4848)</td>
</tr>
<tr>
<td>Mild(^a)</td>
<td>1112 (0.30)</td>
<td>1100 (0.30)</td>
</tr>
<tr>
<td>Moderate(^a)</td>
<td>601 (0.16)</td>
<td>593 (0.16)</td>
</tr>
<tr>
<td>Severe(^a)</td>
<td>65 (0.02)</td>
<td>64 (0.02)</td>
</tr>
<tr>
<td>Unknown severity</td>
<td>11 (&lt;0.01)</td>
<td>10 (&lt;0.01)</td>
</tr>
</tbody>
</table>

Discontinuations due to AEs at the injection site\(^a\) 3 subjects

\(^a\) Rate, number of AEs per infusion.
\(^\dagger\) Defined as those reactions that did not interfere with routine activities.
\(^\ddagger\) Defined as those reactions that interfered with routine activities.

Of the three subjects who discontinued the study due to injection-site reactions, one withdrew on Day 1 (Infusion 1) of the wash-in/wash-out period after a moderate injection-site reaction and a mild headache; one withdrew on Day 22 (Infusion 4) of the wash-in/wash-out period following severe injection-site reactions for two weeks; and one withdrew on Day 78 following a mild injection-site reaction.

Local reactions decreased substantially after repeated use.

Table 5 summarizes the most frequent adverse reactions (experienced by at least 3% of subjects) and considered by the investigator to be at least possibly related to Vivaglobin administration.

Table 5: Incidence of Subjects With Adverse Reactions (Experienced in ≥3% of Subjects) and Rate\(^*\) Per Infusion in the US-Canada Study

<table>
<thead>
<tr>
<th>Related Adverse Reactions (≥3% Subjects)</th>
<th>Number (Rate(^*)) of Subjects (n=65)</th>
<th>Number (Rate(^*)) of AEs per Infusion (n=3656)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions at the injection site(^a)</td>
<td>60 (92%)</td>
<td>1787 (0.49)</td>
</tr>
<tr>
<td>Other Adverse reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 (32%)</td>
<td>59 (0.016)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (11%)</td>
<td>9 (0.002)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (6%)</td>
<td>9 (0.002)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (5%)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>3 (5%)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (3%)</td>
<td>2 (0.001)</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>2 (3%)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (3%)</td>
<td>2 (0.001)</td>
</tr>
<tr>
<td>Urine abnormality</td>
<td>2 (3%)</td>
<td>3 (0.001)</td>
</tr>
</tbody>
</table>

\(^a\) Rate, number of adverse reactions per infusion. \(^\dagger\) Includes injection-site inflammation.

Europe-Brazil Study

In a clinical study conducted in Europe and Brazil, the efficacy and safety of Vivaglobin were evaluated for 10 months in 60 subjects with PI. Subjects were treated weekly with Vivaglobin at a mean dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% of their previous weekly IVIG or ISIG dose (see Clinical Studies [14.2]). Study subjects received a total of 2,297 infusions of Vivaglobin.

The AEs and their rates reported in this study were similar to those reported in the US-Canada study, with two exceptions: no episodes of headache were reported; and 18 (a rate of 0.008 per infusion) episodes of fever were judged to be related to the administration of Vivaglobin. One subject discontinued due to repeated local reactions of moderate severity.

6.2 Postmarketing Experience

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.

Vivaglobin Adverse reactions identified during worldwide postmarketing use of Vivaglobin for treatment of PI are allergic-anaphylactic reactions (including dyspnea, pruritis, urticaria, rash, edema and other cutaneous reactions, wheezing, syncope, hypotension, and throat swelling), generalized reactions (including flu-like symptoms, myalgia, chills, fever, tachycardia, arthralgia, nausea and vomiting, diarrhea, gastrointestinal cramping, stomach pain, back pain, headache, headache possibly caused by increased blood pressure, and chest tightness), migraine, and injection-site reactions.

General

The following adverse reactions have been identified and reported during the postmarketing use of IVIG products:\(^1\):

- Renal: Acute renal dysfunction/failure, osmotic nephropathy
- Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension
- Neurological: Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- Hematologic: Pancreatitis, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- General/Body as a Whole: Pyrexia, rigors
- Musculoskeletal: Back pain
- Gastrointestinal: Hepatic dysfunction, abdominal pain

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles/mumps/rubella and varicella (see Patient Counseling Information [17.2]).

7.2 Serological Testing

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Vivaglobin. It is also not known whether Vivaglobin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vivaglobin should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

Vivaglobin has not been evaluated in nursing mothers.

8.4 Pediatric Use

- In the US-Canada study, Vivaglobin was evaluated in 6 children (ages 5 through 11) and 4 adolescents (ages 13 through 16). In the Europe-Brazil study, Vivaglobin was evaluated in 16 children (ages 3 through 11) and 6 adolescents (ages 13 through 16).
- The safety and efficacy of Vivaglobin were not studied in pediatric subjects under 2 years of age.
- There were no differences in the safety and efficacy profiles as compared with adult subjects.
- No pediatric-specific dosing requirements were necessary to achieve the desired serum IgG levels.
- For recommendations on the number of simultaneous injection sites for pediatric patients who weigh less than 45 kg (99 pounds), see Administration (2.4).

8.5 Geriatric Use

The clinical studies of Vivaglobin did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. For recommendations on the number of simultaneous injection sites for geriatric patients, see Administration (2.4).

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Based on April 2010 Revision.
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Ask your doctor about Hizentra today.

Important Safety Information
Hizentra and Vivaglobin are indicated for the treatment of various forms of primary immunodeficiency (PI).
If you have a history of anaphylactic or severe systemic response to immune globulin preparations or selective immunoglobulin A deficiency, check with your physician, as you should not use Hizentra or Vivaglobin.
Hizentra and Vivaglobin are to be infused under your skin only; do not inject into a blood vessel.
Hypersensitivity reactions may occur with Hizentra or Vivaglobin. If you have antibodies to IgA, you face a greater risk of developing severe hypersensitivity or going into shock. If your physician suspects you are having a negative reaction or are going into shock, treatment will be discontinued. Because Hizentra contains proline, you cannot be treated with Hizentra if you have hyperprolinemia (a high level of proline in your blood).
Hizentra and Vivaglobin are derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

The most common drug-related adverse reactions with Hizentra (seen in 5% or more of subjects in the clinical trial) were local reactions (swelling, redness, heat, pain and itching at the injection site), headache, vomiting, pain, and fatigue. The most common drug-related adverse reactions with Vivaglobin (seen in 5% or more of subjects in the clinical trial) were injection-site reactions (eg, swelling, redness, and itching), headache, nausea, rash, reduced strength and energy, and gastrointestinal disorders.
Your physician will monitor for potentially serious reactions associated with intravenous immunoglobulin treatment that might also occur with Hizentra or Vivaglobin, including aseptic meningitis syndrome (AMS), renal dysfunction/failure, osmotic nephropathy, thrombotic events, hemolysis, and transfusion-related acute lung injury (TRALI).
Ig administration may impair the effect of virus vaccines, such as measles, mumps and rubella. Before getting any vaccination, inform your doctor that you are using Hizentra or Vivaglobin.
Please see brief summary of full Prescribing Information for Hizentra and Vivaglobin, including the Patient Product Information for each, on previous pages.
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.