BRIEF SUMMARY OF PRESCRIBING INFORMATION

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid

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

1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

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.

3.3 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur with IGIV treatment. The most common adverse reactions (ARs), observed in ≥5% of subjects receiving Hizentra, were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

5.5 Laboratory Tests

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

6 ADVERSE REACTIONS

The most common adverse reactions (ARs) observed in ≥5% 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.

Thrombotic Events

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

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. 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 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. 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.

5.4 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 certain 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.

5.3 Reactions Reported to Occur 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 deplete and assess renal function, 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. 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.
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 (&gt;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>3404 (0.592)</td>
</tr>
<tr>
<td>Other AEs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (26.5)</td>
<td>40 (0.18)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (16.3)</td>
<td>9 (0.04)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>7 (14.3)</td>
<td>8 (0.04)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (12.2)</td>
<td>6 (0.03)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (10.2)</td>
<td>11 (0.05)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (10.2)</td>
<td>5 (0.02)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>5 (10.2)</td>
<td>5 (0.02)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (10.2)</td>
<td>7 (0.03)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4 (8.2)</td>
<td>7 (0.03)</td>
</tr>
<tr>
<td>Migraine</td>
<td>4 (8.2)</td>
<td>5 (0.02)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (8.2)</td>
<td>5 (0.02)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4 (8.2)</td>
<td>6 (0.03)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>4 (8.2)</td>
<td>6 (0.03)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (8.2)</td>
<td>5 (0.02)</td>
</tr>
</tbody>
</table>

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

The ratio of infusions with temporally associated AEs, including local reactions, to all infusions was 1338 to 2264 (59.1%; upper 95% confidence limit of 62.4%). Excluding local reactions, the corresponding ratio was 173 to 2264 (7.6%; upper 95% confidence limit of 9.8%).

Table 3 summarizes the most frequent ARs (i.e., those AEs considered by the investigators to be “at least possibly related” to Hizentra administration) experienced by at least 2 subjects.

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</th>
<th>Number (%) of Subjects: (n=49)</th>
<th>Number (Rate) of AEs (n=2264 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions‡</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 (0.16)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.1)</td>
<td>3 (0.01)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (6.1)</td>
<td>4 (0.02)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (6.1)</td>
<td>3 (0.01)</td>
</tr>
<tr>
<td>Confusion</td>
<td>2 (4.1)</td>
<td>3 (0.01)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (4.1)</td>
<td>3 (0.01)</td>
</tr>
<tr>
<td>Migraine</td>
<td>2 (4.1)</td>
<td>3 (0.01)</td>
</tr>
<tr>
<td>Diahrea</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>

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 4: Investigator Assessments* of Injection-Site Reactions by Infusion

<table>
<thead>
<tr>
<th>Injection-Site Reaction</th>
<th>Number (Rate) of Reactions (n=683 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/induration</td>
<td>467 (0.68)</td>
</tr>
<tr>
<td>Erythema</td>
<td>346 (0.50)</td>
</tr>
<tr>
<td>Local heat</td>
<td>108 (0.16)</td>
</tr>
<tr>
<td>Local pain</td>
<td>88 (0.13)</td>
</tr>
<tr>
<td>Itching</td>
<td>64 (0.09)</td>
</tr>
</tbody>
</table>

* 15 to 45 minutes after the end of infusions administered at regularly scheduled visits (every 4 weeks).
† For multiple injection sites, every site was judged, but only the site with the strongest reaction was recorded.
‡ Rate of injection-site reactions per infusion.
§ Number of infusions administered during regularly scheduled visits.

Manufacturer by: CSL Behring AG
Distributed by: CSL Behring LLC
Bein, Switzerland
Kankakee, IL 60901 USA
US License No. 1766
Based on February 2011 revision

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.

The following adverse reactions have been identified and reported during the postmarketing use of IGIV products:1:
- **Infusion reactions**: Hypersensitivity (e.g., anaphylaxis), headache, diaphoresis, 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, deramatis (e.g., bullous dermatitis)
- **Hematologic**: Pancreatitis, leukopenia, hemolysis, positive direct antiglobulin (Coombs’) test
- **Gastrointestinal**: Hepatic dysfunction, abdominal pain
- **General/Body as a Whole**: Pyrexia, rigors

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6938 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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]).

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 Hizentra. It is not known whether Hizentra can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hizentra should be given to pregnant women only if clearly needed.

8.3 Nursing Mothers
Hizentra has not been evaluated in nursing mothers.

8.4 Pediatric Use
The safety and effectiveness of Hizentra have been established in the pediatric age groups 2 to 16, as supported by evidence from adequate and well-controlled studies. Hizentra was evaluated in 10 pediatric subjects with PI (3 children and 7 adolescents) in a study conducted in the US (see Clinical Studies [14]) and in 23 pediatric subjects with PI (18 children and 5 adolescents) in Europe. There were no differences in the safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Safety and effectiveness of Hizentra in pediatric patients below the age of 2 have not been established.

8.5 Geriatric Use
Of the 49 subjects evaluated in the clinical study of Hizentra, 6 subjects were 65 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger subjects.
If you live with primary immunodeficiency disease (PIDD)...

Make the leap to Hizentra

The Sub-Q Ig therapy that fits your life

Hizentra is a subcutaneous immune globulin (Sub-Q Ig) therapy that was deliberately designed to give you freedom and flexibility with your Ig treatment.

- The 20% concentration delivers an Ig dose in half the volume of 10% solutions
- Convenient room temperature storage for up to 30 months
- Always ready for immediate use

*Based on an equivalent dose in grams.

To learn about the benefits of Hizentra, visit www.LearnAboutHizentra.com
Ask your doctor about Hizentra today.

Important Safety Information

Hizentra is 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 Hizentra should not be used.

**Hizentra is to be infused under your skin only, do not inject into a blood vessel.**

Hypersensitivity reactions may occur with Hizentra. 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 is 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 (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.

Your physician will monitor for potentially serious reactions associated with intravenous immunoglobulin treatment that might also occur with Hizentra, including renal dysfunction/failure, osmotic nephropathy, thrombotic events, aseptic meningitis syndrome (AMS), 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.

Please see brief summary of full prescribing information for Hizentra 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.