<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D80</td>
<td>Immunodeficiency with predominantly antibody defects</td>
</tr>
<tr>
<td>D80.0*</td>
<td>Hereditary hypogammaglobulinemia&lt;br&gt;Autosomal recessive agammaglobulinemia (Swiss type)&lt;br&gt;X-linked agammaglobulinemia (Bruton) (with growth hormone deficiency)</td>
</tr>
<tr>
<td>D80.1</td>
<td>Nonfamilial hypogammaglobulinemia&lt;br&gt;Agammaglobulinemia with immunoglobulin-bearing B-lymphocytes&lt;br&gt;Common variable agammaglobulinemia [CVAgamma]&lt;br&gt;Hypogammaglobulinemia NOS</td>
</tr>
<tr>
<td>D80.2</td>
<td>Selective deficiency of immunoglobulin A [IgA]</td>
</tr>
<tr>
<td>D80.3</td>
<td>Selective deficiency of immunoglobulin G [IgG] subclasses</td>
</tr>
<tr>
<td>D80.4</td>
<td>Selective deficiency of immunoglobulin M [IgM]</td>
</tr>
<tr>
<td>D80.5*</td>
<td>Immunodeficiency with increased immunoglobulin M [IgM]</td>
</tr>
<tr>
<td>D80.6</td>
<td>Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia</td>
</tr>
<tr>
<td>D80.7</td>
<td>Transient hypogammaglobulinemia of infancy</td>
</tr>
<tr>
<td>D80.8</td>
<td>Other immunodeficiencies with predominantly antibody defects&lt;br&gt;Kappa light chain deficiency</td>
</tr>
<tr>
<td>D80.9</td>
<td>Immunodeficiency with predominantly antibody defects, unspecified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D81</td>
<td>Combined immunodeficiencies</td>
</tr>
<tr>
<td>D81.0*</td>
<td>Severe combined immunodeficiency [SCID] with reticular dysgenesis</td>
</tr>
<tr>
<td>D81.1*</td>
<td>Severe combined immunodeficiency [SCID] with low T- and B-cell numbers</td>
</tr>
<tr>
<td>D81.2*</td>
<td>Severe combined immunodeficiency [SCID] with low or normal B-cell numbers</td>
</tr>
<tr>
<td>D81.4</td>
<td>Nezelof's syndrome</td>
</tr>
<tr>
<td>D81.6*</td>
<td>Major histocompatibility complex class I deficiency&lt;br&gt;Bare lymphocyte syndrome</td>
</tr>
<tr>
<td>D81.7*</td>
<td>Major histocompatibility complex class II deficiency</td>
</tr>
<tr>
<td>D81.89*</td>
<td>Other combined immunodeficiencies</td>
</tr>
<tr>
<td>D81.9*</td>
<td>Combined immunodeficiency, unspecified&lt;br&gt;Severe combined immunodeficiency disorder [SCID] NOS</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>D82</td>
<td>Immunodeficiency associated with other major defects</td>
</tr>
<tr>
<td></td>
<td>Excludes: ataxia telangiectasia [Louis-Bar] (G11.3)</td>
</tr>
<tr>
<td>D82.0*</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td></td>
<td>Immunodeficiency with thrombocytopenia and eczema</td>
</tr>
<tr>
<td>D82.1</td>
<td>Di George’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Pharyngeal pouch syndrome</td>
</tr>
<tr>
<td></td>
<td>Thymic alymphoplasia</td>
</tr>
<tr>
<td></td>
<td>Thymic aplasia or hypoplasia with immunodeficiency</td>
</tr>
<tr>
<td>D82.2</td>
<td>Immunodeficiency with short-limbed stature</td>
</tr>
<tr>
<td>D82.3</td>
<td>Immunodeficiency following hereditary defective response to Epstein-Barr virus</td>
</tr>
<tr>
<td></td>
<td>X-linked lymphoproliferative disease</td>
</tr>
<tr>
<td>D82.4</td>
<td>Hyperimmunoglobulin E [IgE] syndrome</td>
</tr>
<tr>
<td>D82.8</td>
<td>Immunodeficiency associated with other specified major defects</td>
</tr>
<tr>
<td>D82.9</td>
<td>Immunodeficiency associated with major defect, unspecified</td>
</tr>
<tr>
<td>D83</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>D83.0*</td>
<td>Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function</td>
</tr>
<tr>
<td>D83.1*</td>
<td>Common variable immunodeficiency with predominant immunoregulatory T-cell disorders</td>
</tr>
<tr>
<td>D83.2*</td>
<td>Common variable immunodeficiency with autoantibodies to B- or T-cells</td>
</tr>
<tr>
<td>D83.8*</td>
<td>Other common variable immunodeficiencies</td>
</tr>
<tr>
<td>D83.9*</td>
<td>Common variable immunodeficiency, unspecified</td>
</tr>
</tbody>
</table>

*Medicare Part B–approved diagnosis codes for treatment with Hizentra in the home.

ICD=International Classification of Diseases

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HIZENTRA safely and effectively. See full prescribing information for HIZENTRA.

HIZENTRA, Immune Globulin Subcutaneous (Human), 20% Liquid
Initial U.S. Approval: 2010

WARNING: THROMBOSIS

See full prescribing information for complete boxed warning.

• Thrombosis may occur with immune globulin products, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoaguable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.

• For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older (1).

DOSAGE AND ADMINISTRATION

For subcutaneous infusion only.

Administer at regular intervals from daily up to every two weeks (biweekly).

Dosage (2.2)

Before switching to Hizentra, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments.

• Weekly: Start Hizentra 1 week after last IGIV infusion
  Initial weekly dose = Previous IGIV dose (in grams) x 1.37
  No. of weeks between IGIV doses

  1st

  2nd to 4th

  5th

  6th and above

  ≤ 15

  15 ≤ 20

  20 ≤ 25

• Biweekly: Start Hizentra 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly Hizentra/IGSC infusion. Administer twice the calculated weekly dose.

• Frequent dosing (2 to 7 times per week): Start Hizentra 1 week after the last IGIV infusion or 1 week after the last subsequent dose adjustments.

• Adjust the dose based on clinical response and serum IgG trough levels (see Dose Adjustment).

Administration (2.3)

• Infusion sites – 1 to 4 injection sites simultaneously, with at least 2 inches between sites.

<table>
<thead>
<tr>
<th>Infusion Parameters*</th>
<th>Infusion Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Volume (mL/site)</td>
<td>≤ 15</td>
</tr>
<tr>
<td>Rate (mL/hr/site)</td>
<td>15</td>
</tr>
</tbody>
</table>

* As tolerated

See 17 for PATIENT COUNSELING INFORMATION and the accompanying FDA-approved patient labeling

Revised: 10/2016

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**Dosage for patients switching to Hizentra from IGSC**
- The previous weekly IGSC dose should be maintained.
- For biweekly dosing, multiply the previous weekly dose by 2.
- For frequent dosing (2 to 7 times per week), divide the previous weekly dose by the desired number of times per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

**Start Hizentra treatment:**
- For weekly or frequent dosing, start treatment with Hizentra 1 week after the patient’s last IGIV infusion or Hizentra/IGSC infusion.
- For biweekly dosing, start treatment 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly Hizentra/IGSC infusion.

**Dose Adjustment**
Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level, irrespective of the frequency of administration. To determine if a dose adjustment should be considered, measure the patient’s serum IgG trough level 2 to 3 months after switching to Hizentra.

**Weekly dosing:** When switching from IGIV to weekly Hizentra dosing, the target serum IgG trough level is projected to be approximately 16% higher than the last trough level during prior IGIV therapy [see Pharmacokinetics (12.3)].

**Biweekly dosing:** When switching from IGIV to biweekly Hizentra dosing, the target serum IgG trough level is projected to be approximately 10% higher than the last IGIV trough level. When switching from weekly to biweekly Hizentra dosing, the target trough is projected to be approximately 5% lower than the last trough level on weekly therapy [see Pharmacokinetics (12.3)].

**Frequent dosing:** When switching from weekly dosing to more frequent Hizentra dosing, the target serum IgG trough level is projected to be approximately 3 to 4% higher than the last trough level on weekly therapy [see Pharmacokinetics (12.3)].

To adjust the dose based on serum trough levels, calculate the difference (in mg/dL) between the patient’s serum IgG trough level and the target IgG trough level for weekly or biweekly dosing. Then find this difference in Table 1 (Column 1) and, based on the Hizentra dosing frequency (for weekly or biweekly) and the patient’s body weight, locate the corresponding adjustment amount (in mL) by which to increase (or decrease) the dose. For frequent dosing, add the weekly increment from Table 1 to the weekly-equivalent dose and then divide by the number of days of dosing.

**Use the patient’s clinical response as the primary consideration in dose adjustment. Additional dosage increments may be indicated based on the patient’s clinical response (infection frequency and severity).**

**Table 1. Incremental Adjustment (mL)* of the Hizentra Dose† Based on the Difference (±mg/dL) from the Target Serum IgG Trough Level**

<table>
<thead>
<tr>
<th>Difference From Target Serum IgG Trough Level (mg/dL)</th>
<th>Dosing Frequency</th>
<th>Weight Adjusted Dose Increment (mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Weight Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;10 to 30 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;30 to 50 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 to 70 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;70 to 90 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;90 kg</td>
</tr>
<tr>
<td>50</td>
<td>Weekly*</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>2.5, 5</td>
</tr>
<tr>
<td>100</td>
<td>Weekly</td>
<td>2.5, 5, 10, 15</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>5, 10, 20, 30</td>
</tr>
<tr>
<td>200</td>
<td>Weekly</td>
<td>5, 10, 15, 20, 30</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>10, 20, 30, 40</td>
</tr>
</tbody>
</table>

* Incremental adjustments based on slopes of the pharmacometric model-predicted relationship between serum IgG trough level and Hizentra dose increments of 1 mg/kg per week.
† Includes biweekly, weekly or frequent dosing.
‡ To determine the dose increment for frequent dosing, add the weekly increment to the weekly-equivalent dose and then divide by the number of days of dosing.

For example, if a patient with a body weight of 70 kg has an actual IgG trough level of 900 mg/dL and the target trough level is 1000 mg/dL, this results in a difference of 100 mg/dL. Therefore, increase the weekly dose of Hizentra by 10 mL. For biweekly dosing, increase the biweekly dose by 20 mL. For 2 times per week dosing, increase the dose by 5 mL.

**Monitor the patient’s clinical response, and repeat the dose adjustment as needed.**

**Dosage requirements for patients switching to Hizentra from another IGSC product:** If a patient on Hizentra does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of the previous IGSC treatment, the physician may want to adjust the dose. For such patients, Table 1 also provides guidance for dose adjustment if their desired IGSC trough level is known.

**Measles Exposure**
Administer a minimum total weekly Hizentra dose of 200 mg/kg body weight for two consecutive weeks if a patient is at risk of measles exposure (i.e., due to an outbreak in the US or travel to endemic areas outside of the US). For biweekly dosing, one infusion of a
Follow the steps below and use aseptic technique to administer Hizentra.

1. Assemble supplies – Gather the Hizentra vial(s), disposable supplies (not provided with Hizentra), and other items (infusion pump, sharps or other container, patient’s treatment diary/log book) needed for the infusion.

2. Clean surface – Thoroughly clean a flat surface using an alcohol wipe.

3. Wash hands – Thoroughly wash and dry hands. The use of gloves when preparing and administering Hizentra is optional.

4. Check vials – Carefully inspect each vial of Hizentra. Do not use the vial if the liquid looks cloudy, contains particles, or has changed color, if the protective cap is missing, or if the expiration date on the label has passed.

5. Transfer Hizentra from vial(s) to syringe
   - Remove the protective cap from the vial to expose the central portion of the rubber stopper of the Hizentra vial.
   - Clean the stopper with an alcohol wipe and allow it to dry.
     - If using a transfer device, follow the instructions provided by the device manufacturer.
     - If using a needle and a syringe to transfer Hizentra, follow the instructions below.
       - Attach a sterile transfer needle to a sterile syringe. Pull back on the plunger of the syringe to draw air into the syringe that is equal to the amount of Hizentra to be withdrawn.
       - Insert the transfer needle into the center of the vial stopper and, to avoid foaming, inject the air into headspace of the vial (not into the liquid).
       - Withdraw the desired volume of Hizentra.

6. Prepare infusion pump and tubing – Follow the manufacturer’s instructions for preparing the pump, using subcutaneous administration sets and tubing, as needed. Be sure to prime the tubing with Hizentra to ensure that no air is left in the tubing.

7. Prepare injection site(s)
   - The number and location of injection sites depends on the volume of the total dose. Infuse Hizentra into a maximum of 4 sites simultaneously; or up to 12 consecutively per infusion. Injection sites should be at least 2 inches apart.

8. Insert needle(s)
   - Using an antiseptic skin preparation, clean each site beginning at the center and working outward in a circular motion. Allow each site to dry before proceeding.
   - Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue.
   - If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.

9. Start infusion – Follow the manufacturer’s instructions to turn on the infusion pump.

10. Record treatment – Remove the peel-off portion of the label from each vial used, and affix it to the patient’s treatment diary/log book or scan the vial if recording the infusion electronically.

11. Clean up – After administration is complete, turn off the infusion pump. Take off the tape or dressing and remove the needle set from the injection site(s). Disconnect the tubing from the pump. Immediately discard any unused product and all used disposable supplies in accordance with local requirements. Clean and store the pump according to the manufacturer’s instructions.

For self-administration, provide the patient with instructions and training for subcutaneous infusion in the home or other appropriate setting.

3 DOSE FORMS AND STRENGTHS
Hizentra is a 0.2 g/mL (20%) protein solution for subcutaneous injection.

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 (type I or II) 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. If a hypersensitivity reaction occurs, 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 Thrombosis
Thrombosis may occur following treatment with immune globulin products1-3, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammapathies. For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see Boxed Warning and Patient Counseling Information (17)].
5.3 Aseptic Meningitis Syndrome (AMS)
AMS has been reported with use of IGIV<sup>4</sup> or IGSC. The syndrome usually begins within several hours to 2 days following immune globulin treatment. AMS is characterized by the following signs and symptoms: 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 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 immune globulin product.

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

5.4 Renal Dysfunction/Failure
Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death may occur with use of human immune globulin products, especially those containing sucrose.<sup>5</sup> Hizentra does not contain sucrose. Ensure that patients are not volume depleted before administering Hizentra.

For patients judged to be at risk for developing renal dysfunction, including 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, monitor renal function and consider lower, more frequent dosing [see Dosing and Administration (2.3)].

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.<sup>6</sup> Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Hizentra.

5.5 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.<sup>7,8</sup> 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.<sup>9</sup>

Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after Hizentra infusion, perform appropriate laboratory testing.

5.6 Transfusion-Related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.<sup>11</sup> 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/or patient's serum.

5.7 Transmissible Infectious Agents
Because Hizentra is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of Hizentra. All infections suspected by a physician possibly to have been transmitted by Hizentra should be reported to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.8 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 ≥5% of study subjects receiving Hizentra were local reactions (e.g., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigued, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain.

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.

US Study
The safety of Hizentra was evaluated in a clinical study in the US for 15 months (3-month wash-in/wash-out period followed by a 12-month efficacy period) 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 median doses ranging from 66 to 331 mg/kg body weight (mean: 181.4 mg/kg) during the wash-in/wash-out period and from 72 to 379 mg/kg (mean: 213.2 mg/kg) during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

Table 2 summarizes the most frequent adverse reactions (ARs) (experienced by at least 2 subjects) occurring during or within 72 hours after the end of an infusion. Local reactions were assessed by the investigators 15 to 45 minutes post-infusion and by the subjects 24 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments. Local reactions were the most frequent ARs observed, with injection-site reactions (e.g., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

### Table 2. Incidence of Subjects with Adverse Reactions (ARs)* (Experienced by 2 or More Subjects) and Rate per Infusion (ITT Population), US Study

<table>
<thead>
<tr>
<th>AR (≥2 Subjects)</th>
<th>Number (%) of Subjects (n=49)</th>
<th>Number (Rate&lt;sup&gt;†&lt;/sup&gt;) of ARs (n=2264 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12 (24.5)</td>
<td>32 (0.014)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (10.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (8.2)</td>
<td>5 (0.002)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4 (8.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Migraine</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Contusion</td>
<td>2 (4.1)</td>
<td>4 (0.001)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (4.1)</td>
<td>2 (&lt; 0.001)</td>
</tr>
</tbody>
</table>

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

The ratio of infusions with ARs, including local reactions, to all infusions was 1303 to 2264 (57.6%). Excluding local reactions, the corresponding ratio was 56 to 2264 (2.5%).

Table 3 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. Investigator Assessment of Injection-Site Reactions by Infusion, US Study

<table>
<thead>
<tr>
<th>Injection-Site Reaction</th>
<th>Number&lt;sup&gt;‡&lt;/sup&gt; of Reactions (n=683 Infusions)&lt;sup&gt;§&lt;/sup&gt;</th>
<th>Number (Rate&lt;sup&gt;†&lt;/sup&gt;) of Reactions (n=683 Infusions)&lt;sup&gt;§&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/induration</td>
<td>467 (0.68)</td>
<td>467 (0.68)</td>
</tr>
<tr>
<td>Erythema</td>
<td>346 (0.51)</td>
<td>346 (0.51)</td>
</tr>
<tr>
<td>Local heat</td>
<td>108 (0.16)</td>
<td>108 (0.16)</td>
</tr>
<tr>
<td>Local pain</td>
<td>88 (0.13)</td>
<td>88 (0.13)</td>
</tr>
<tr>
<td>Itching</td>
<td>64 (0.09)</td>
<td>64 (0.09)</td>
</tr>
</tbody>
</table>

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

Most local reactions were either mild (93.4%) or moderate (6.3%) in intensity.

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 myostitis. Both reactions were judged to be “at least possibly related” to the administration of Hizentra.

European Study
In a clinical study conducted in Europe, the safety of Hizentra was evaluated for 10 months (3-month wash-in/wash-out period followed by a 7-month efficacy period) in 51 subjects with PI who had been treated previously with IGIV every 3 or 4 weeks or with IGSC weekly.

Subjects were treated with Hizentra at weekly median doses ranging from 59 to 267 mg/kg body weight (mean: 118.8 mg/kg) during the wash-in/wash-out period and from 59 to 243 mg/kg (mean: 120.1 mg/kg) during the efficacy period. The 51 subjects received a total of 1831 weekly infusions of Hizentra.

Table 4 summarizes the most frequent ARs (experienced by at least 2 subjects) occurring during or within 72 hours after the end of an infusion. Local reactions were assessed by the subjects between 24 and 72 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments.
Table 4. Incidence of Subjects with Adverse Reactions (ARS)* (Experienced by 2 or More Subjects) and Rate per Infusion, European Study

<table>
<thead>
<tr>
<th>AR (≥2 Subjects)</th>
<th>ARS* Occurring During or Within 72 Hours of Infusion</th>
<th>Number (% of Subjects)</th>
<th>Number (Rate) of ARS</th>
<th>ARS (n=1831 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions†</td>
<td>24 (47.1)</td>
<td>105 (0.057)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other ARs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (17.6)</td>
<td>20 (0.011)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4 (7.8)</td>
<td>4 (0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (7.8)</td>
<td>13 (0.007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.9)</td>
<td>5 (0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>2 (3.9)</td>
<td>3 (0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (3.9)</td>
<td>2 (0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (3.9)</td>
<td>4 (0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (3.9)</td>
<td>3 (0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3.9)</td>
<td>2 (0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (3.9)</td>
<td>3 (0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2 (3.9)</td>
<td>4 (0.002)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Excluding infections.
† Rate of ARs per infusion.
‡ Includes infusion-related reaction, infusion-site mass, infusion-site erythema, hematoma, induration, inflammation, edema, pain, pruritus, rash, reaction, swelling, injection-site extravasation, nodule, puncture-site reaction.

The proportion of subjects reporting local reactions decreased over time from approximately 20% following the first infusion to <5% by the end of the study.

Three subjects withdrew from the study due to ARs of mild to moderate intensity. One subject experienced injection-site pain and injection-site pruritus; the second subject experienced injection-site reaction, fatigue, and feeling cold; and the third subject experienced injection-site reaction and hypersensitivity. All reactions were judged by the investigator to be "at least possibly related" to the administration of Hizentra.

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.

Hizentra

The following adverse reactions have been identified during postmarketing use of Hizentra. This list does not include reactions already reported in clinical studies with Hizentra [see Adverse Reactions (6.1)].

- **Infusion reactions:** Allergic-anaphylactic reactions such as swollen face or tongue and pharyngeal edema, periorbital edema, angioedema, urticaria, skin rash, flushing, urticaria, hypotension, anaphylaxis, chills, dizziness, hypotension, angioedema, dyspnea, chest pain, injection-site pain, pharyngeal rash, and injection-site pain. These reactions are usually transient and resolve after discontinuing the infusion. The use of pretreatment with antihistamines may prevent these reactions.

- **Cardiovascular:** Chest discomfort (including chest pain).

- **Respiratory:** Dyspnea.

- **Neurological:** Tremor, burning sensation.

- **General disorders and administration site conditions:** Injection-site ulcer.

The following adverse reactions have been reported during postmarketing use of immune globulin products:

- **Infusion reactions:** Tachycardia, flushing, wheezing, rigors, myalgia.

- **Respiratory:** Osmotic nephropathy.

- **Respiratory:** Acute Respiratory Distress Syndrome (ARDS), cyanosis, hypoxemia, pulmonary edema, bronchospasm.

- **Cardiovascular:** Cardiac arrest, vascular collapse, hypotension.

- **Neurological:** Loma, loss of consciousness, seizures, aseptic meningitis syndrome.

- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatosis).

- **Hematological:** Panocytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs’) test.

- **Gastrointestinal:** Hepatic dysfunction.

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 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

**Risk Summary**

No human data are available to indicate the presence or absence of drug-associated risk. 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. Immune globulins cross the placenta from maternal circulation increasing after 30 weeks of gestation. Hizentra should be given to pregnant women only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15.2%, respectively.

8.2 Lactation

**Risk Summary**

No human data are available to indicate the presence or absence of drug associated risk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Hizentra and any potential adverse effects on the breastfed infant from Hizentra or from the underlying maternal condition.

8.4 Pediatric Use

**Clinical Studies (Weekly Dosing)**

The safety and effectiveness of weekly Hizentra have been established in the pediatric age groups 2 to 16. 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 pharmacokinetics, safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

**Pharmacokinetic Modeling and Simulation (Bieweekly or more Frequent Dosing)**

The bieweekly (every two weeks) or more frequent dosing (2 to 7 times per week) regimens, developed from population PK-based modeling and simulation, included 57 pediatric subjects (32 from Hizentra clinical studies [see Pharmacokinetics (12.3)]). Hizentra dosing is adjusted to body weight. No pediatric-specific dose requirements are necessary for these regimens.

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 US 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. The clinical study of Hizentra in Europe did not include subjects over the age of 65.

11 DESCRIPTION

Hizentra, Immune Globulin Subcaneous (Human), 20% Liquid, is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyclonal human immunoglobulin G (IgG) for subcaneous administration. Hizentra is manufactured from large pools of human plasma by a combination of cold alcohol fractionation, octanoic acid fractionation, and anion exchange chromatography. 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, and Fc functions tested include complement activation and Fc receptor-mediated leukocyte activation (determined with complexed IgG). Hizentra has a purity of ≥98% IgG and a pH of 4.6 to 5.2. Hizentra contains approximately 250 mg/mL (range: 210 to 290 mg/mL) L-proline (a nonessential amino acid) as a stabilizer, 8 to 30 mg/L polysorbate 80, and trace amounts of sodium. Hizentra contains ≤50 mcg/mL IgA. Hizentra contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative.

Plasma units used in the manufacture of Hizentra are tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to human immunodeficiency virus (HIV)-1/2 and hepatitis C virus (HCV) as well as FDA-licensed Nucleic Acid Testing (NAT) for HBV, HCV and HIV-1. All plasma units have been found to be nonreactive (negative) in these tests. In addition, the plasma has been tested for B19 virus (B19V) DNA by NAT. Only plasma that passes virus screening is used for production, and the limit for B19V in the fractionation pool is set to not exceed 10^4 IU of B19V DNA per mL.

The manufacturing process for Hizentra includes three steps to reduce the risk of virus transmission. Two of these are dedicated virus clearance steps: pH 4 incubation to inactivate enveloped viruses; and virus filtration to remove, by size exclusion, both enveloped and nonenveloped viruses as small as approximately 20 nanometers. In addition, a depth filtration step 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 5 shows the virus clearance during the manufacturing process for Hizentra, expressed as the mean log reduction factor (LRF).
subjects were treated previously with Privigen®, Immune Globulin Intravenous (Human), 10% participating in the 15-month efficacy and safety study pediatric subject aged 6 to <12 years, and 3 adolescent subjects aged 12 to <16 years) with PI Clinical Studies

Hizentra supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against 12 CLINICAL PHARMACOLOGY

6.4 log10), depth filtration (2.6 log 10), and virus filtration ≥

To decrease infectivity of an experimental TSE model agent. TSE reduction steps include

model for CJD and its variant (vCJD).12 Several of the production steps have been shown

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for CJD and its variant (vCJD).13 Several of the production steps have been shown to decrease infectivity of an experimental TSE model agent. TSE reduction steps include

stable steady-state serum IgG levels.13,14 After the subjects had reached steady-state with

With Hizentra, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved with

≤ 12 years) with PI Clinical Studies

95% of values observed with 4-weekly IGIV dosing. See Table 8 (column for AUC, Cmax and Cmin).

PK modeling and simulation predicted that for the same total weekly dose, Hizentra infusions given 2, 3, 5, or 7 times per week (weekly dosing) produce IgG exposures comparable to weekly dosing (equivalent AUCs, with a slightly lower IgG peak (Cmax) and slightly longer trough (Cmin)). Frequent dosing reduces the peak-to-trough variation in Hizentra exposure, thus resulting in more sustained IgG exposures. See Table 8 (column for AUC, Cmax and Cmin).

Dose Adjustment Factor

Using data from four clinical studies, results of model-based simulations demonstrated that weekly or biweekly Hizentra dosing regimens with an IGIV:IGSC dose adjustment factor of 1.137 adequately maintain median AUC0-28d and Cmin ratios at ≥90% of values observed with 4-weekly IGIV dosing. See Table 8 (top two rows).

Prediction of Trough Levels Following Regimen Changes

PK modeling and simulation also predicted changes in trough levels after switching from (a) monthly IGIV to weekly or biweekly Hizentra dosing, (b) weekly to biweekly Hizentra dosing, or (c) weekly to more frequent dosing. Table 8 (last column) shows the predicted changes in steady-state IgG trough levels after switching between the various dosing regimens.

Table 7 summarizes PK parameters at steady state for pediatric subjects (age groups: 6 to <12 years and 12 to <16 years) and adults subjects (≥16 years) in the European Hizentra study following weekly treatment [see Clinical Studies (14.2)]. Pediatric PK parameters are similar to those of adult subjects; thus no pediatric specific dose requirements are needed for Hizentra dosing.

Pharmacokinetic Modeling and Simulation

Biweekly (Every Two Weeks) or More Frequent Dosing

Pharmacokinetic characterization of biweekly or more frequent dosing of Hizentra was undertaken using population PK-based modeling and simulation. Serum IgG concentration data consisted of 3837 samples from 151 unique pediatric and adult subjects with PI from four clinical studies of IGIV (Privigen®) and/or Hizentra. Of the 151 subjects, 94 were adult subjects (63 from Hizentra clinical studies) and 57 were pediatric subjects (32 from Hizentra clinical studies). Compared with weekly administration, PK modeling and simulation predicted that administration of Hizentra on a biweekly basis at double the weekly dose results in comparable IgG exposure (equivalent AUCs, with a slightly higher IgG peak (Cmax) and slightly lower trough (Cmin)). In addition, PK modeling and simulation predicted that for the same total weekly dose, Hizentra infusions given 2, 3, 5, or 7 times per week (weekly dosing) produce IgG exposures comparable to weekly dosing (equivalent AUCs, with a slightly lower IgG peak (Cmax) and slightly higher trough (Cmin)). Frequent dosing reduces the peak-to-trough variation in Hizentra exposure, thus resulting in more sustained IgG exposures. See Table 8 (columns for AUC, Cmax and Cmin).

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For the 19 subjects completing the wash-in/wash-out period, the average dose adjustment for Hizentra was 153% (range: 126% to 187%) of the previous weekly-equivalent IGIV dose. After 12 weeks of treatment with Hizentra at this individually adjusted dose, the final steady-state AUC determinations were made in 18 of the 19 subjects. The geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for Hizentra vs IGIV treatment was 1.002 (range: 0.77 to 1.20) with a 90% confidence limit of 0.951 to 1.055 for the 18 subjects. With Hizentra, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved with IGIV while trough levels are generally higher (1448 vs 1127 mg/dL). In contrast to IGIV, Hizentra is administered every 3 to 4 weeks, weekly subcutaneous administration results in relatively stable steady-state serum IgG levels.13,14 After the subjects had reached steady-state with weekly administration of Hizentra, peak serum IgG levels were observed after a mean of 2.9 days (range: 0 to 7 days) in 18 subjects.

Table 5. Virus Inactivation/Removal in Hizentra*

<table>
<thead>
<tr>
<th>Virus Property</th>
<th>Genome</th>
<th>RNA</th>
<th>DNA</th>
<th>RNA</th>
<th>RNA</th>
<th>RNA</th>
<th>DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PRV</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BVDV</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>WNv</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EMCV</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MVM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 6. Pharmacokinetics Parameters of Hizentra and IGIV, US Study

<table>
<thead>
<tr>
<th>Hizentra</th>
<th>IGIV* (Privigen®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>18</td>
</tr>
<tr>
<td>Dose (mg/kg) Mean Range</td>
<td>228-1414</td>
</tr>
<tr>
<td>IgG peak levels (mg/dL) Mean Range</td>
<td>1616-1090</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL) Mean Range</td>
<td>1448-952</td>
</tr>
<tr>
<td>AUC (day x mg/dL) Mean Range</td>
<td>10560-7210</td>
</tr>
<tr>
<td>CL (ml/kg/day) Mean Range</td>
<td>2.2-6.7</td>
</tr>
</tbody>
</table>

Table 7. Pediatric Pharmacokinetics Parameters of Hizentra, European Study

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose (mg/kg)</th>
<th>Mean Range</th>
<th>AUC</th>
<th>Cmax</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to &lt;12 years (n=9)</td>
<td>120-71</td>
<td>115-75</td>
<td>117-90</td>
<td>118-70</td>
<td></td>
</tr>
<tr>
<td>12 to &lt;16 years (n=3)</td>
<td>731-531</td>
<td>764-615</td>
<td>754-505</td>
<td>746-505</td>
<td></td>
</tr>
<tr>
<td>16 to &lt;15 years (n=11)</td>
<td>5230-3800</td>
<td>5491-3800</td>
<td>5452-3800</td>
<td>5370-3800</td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Predicted Ratios* [Median (5th, 95th percentiles)] of AUC, Cmax and Cmin Changes in IgG Trough Levels after Switching Between IgG Dosing Regimens

<table>
<thead>
<tr>
<th>From:</th>
<th>To:</th>
<th>AUC</th>
<th>Cmax</th>
<th>Cmin</th>
<th>Predicted Change in Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGIV</td>
<td>Weekly Hizentra</td>
<td>0.97</td>
<td>0.68</td>
<td>1.16</td>
<td>16% increase</td>
</tr>
<tr>
<td>IGIV</td>
<td>Biweekly Hizentra</td>
<td>0.97</td>
<td>0.68</td>
<td>1.16</td>
<td>10% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>Biweekly Hizentra</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>5% decrease</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>2 times per week Hizentra</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>3% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>3 times per week Hizentra</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>4% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>5 times per week Hizentra (daily for 5 days)</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>4% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>Daily Hizentra (5 times per week)</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
<td>4% increase</td>
</tr>
</tbody>
</table>

*Ratios are based on comparison of second regimen vs. first regimen. 1:1.37 adequately maintain median AUC0-28d and Cmin ratios at ≥90% of values observed with 4-weekly IGIV dosing. See Table 8 (top two rows).
PK-based modeling and simulation results indicate that, similar to observations from the clinical study with weekly Hizentra dosing (Table 7), body weight-adjusted biweekly dosing accounted for age-related (>3 years) differences in clearance of Hizentra, thereby maintaining systemic IgG exposure (AUC values) in the therapeutic range.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Long- and short-term memory loss was seen in juvenile rats in a study modeling hyperprolactinemia. In this study, rats received daily subcutaneous injections with L-proline from day 6 to day 28 of life.12 The daily amounts of L-proline used in this study were more than 60 times higher than the L-proline dose that would result from the administration of 400 mg/kg body weight of Hizentra once weekly. In unpublished studies using the same animal model (i.e., rats) dosed with the same amount of L-proline with a dosing interval relevant to IGSC treatment (i.e., on 5 consecutive days on days 9 to 13, or once weekly on days 9, 16, and 23), no effects on learning and memory were observed. The clinical relevance of these studies is not known.

14 CLINICAL STUDIES

14.1 US Study

A prospective, open-label, multicenter, single-arm, clinical study conducted in the US evaluated the efficacy, tolerability, and safety of Hizentra in 49 adult and pediatric subjects with PI. Subjects previously receiving monthly treatment with IGIV were switched to weekly subcutaneous administration of Hizentra for 15 months. Following a 3-month wash-in/wash-out period, subjects received a dose adjustment to achieve an equivalent AUC to their previous IGIV dose (see Pharmacokinetics (12.3)) and continued treatment for a 12-month efficacy period. The efficacy analyses included 38 subjects in the modified intention-to-treat (MITT) population. The MITT population consisted of subjects who completed the wash-in/wash-out period and received at least one infusion of Hizentra during the efficacy period.

Although 5% of the administered doses could not be verified, the weekly median doses of Hizentra ranged from 72 to 379 mg/kg body weight during the efficacy period. The mean dose was 213.2 mg/kg, which was 149% of the previous IGIV dose.

In the study, the number of injection sites per infusion ranged from 1 to 12. In 73% of infusions, the number of injection sites was 4 or fewer. Up to 4 simultaneous injection sites were permitted using 2 pumps; however, more than 4 sites could be used consecutively during one infusion. The infusion flow rate did not exceed 50 mL per hour for all injection sites combined. During the efficacy period, the median duration of a weekly infusion ranged from 1.6 to 2.0 hours.

The study evaluated the annual rate of serious bacterial infections (SBIs), defined as bacterial pneumonia, bacteremia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess. The study also evaluated the annual rate of any infections, the use of antibiotics for infection (prophylaxis or treatment), the days out of work/school/kindergarten/day care or unable to perform normal activities due to infections, hospitalizations due to infections, and serum IgG trough levels.

Table 9 summarizes the efficacy results for subjects in the efficacy period (MITT population) of the study. No subjects experienced an SBI in this study.

Table 9. Summary of Efficacy Results (MITT Population)

<table>
<thead>
<tr>
<th>Number of subjects (efficacy period)</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subject days</td>
<td>12,697</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Annual rate of SBIs*</td>
<td>0 SBIs per subject year*</td>
</tr>
<tr>
<td>Annual rate of any infections</td>
<td>2.76 infections/subject year*</td>
</tr>
<tr>
<td>Antibiotic use for infection (prophylaxis or treatment)</td>
<td></td>
</tr>
<tr>
<td>Number of subjects (%)</td>
<td>27 (71.1)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>48.5 days/subject year</td>
</tr>
<tr>
<td>Total number of subject days</td>
<td>12,605</td>
</tr>
<tr>
<td>Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>71 (0.56)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>2.06 days/subject year</td>
</tr>
<tr>
<td>Hospitalizations due to infections</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>7 (0.06)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>0.2 days/subject year</td>
</tr>
</tbody>
</table>

* Defined as bacterial pneumonia, bacteremia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess.
† Upper 99% confidence limit: 0.132.
‡ 95% confidence limits: 2.235; 3.370.
§ Based on 1 subject.

The mean IgG trough levels increased by 24.2%, from 1009 mg/dL prior to the study to 1253 mg/dL during the efficacy period.

14.2 European Study

In a prospective, open-label, multicenter, single-arm, clinical study conducted in Europe, 51 adult and pediatric subjects with PI switched from monthly IGIV (31 subjects) or weekly IGSC (20 subjects) to weekly treatment with Hizentra. For the 46 subjects in the efficacy analysis, the weekly mean dose in the efficacy period was 120.1 mg/kg (range 59 to 243 mg/kg), which was 104% of the previous weekly equivalent IGIV or weekly IGSC dose.

None of the subjects had an SBI during the efficacy period, resulting in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

• Hizentra is supplied in a single-use, tamper-evident vial containing 0.2 grams of protein per mL of preservative-free liquid.

Each product presentation includes a package insert and the following components:

Presentation Carton NDC Number Components
5 mL 44206-451-01 Vial containing 1 gram of protein (NDC 44206-451-90)
10 mL 44206-452-02 Vial containing 2 grams of protein (NDC 44206-452-91)
20 mL 44206-454-04 Vial containing 4 grams of protein (NDC 44206-454-92)
50 mL 44206-455-10 Vial containing 10 grams of protein (NDC 44206-455-93)

16.2 Storage and Handling

• Keep Hizentra in its original carton to protect it from light.

• Each vial contains a peel-off strip with the vial size and product lot number for use in recording doses in a patient treatment record.

• When stored at room temperature (up to 25°C [77°F]), Hizentra is stable for up to 30 months, as indicated by the expiration date printed on the outer carton and vial label.

• Do not shake.

• Do not freeze. Do not use product that has been frozen.

• The components used in the packaging for Hizentra contain no latex.

17 PATIENT COUNSELING INFORMATION

Advising the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients to immediately report the following signs and symptoms to their healthcare provider:

• Hypersensitivity reactions to Hizentra (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) (see Warnings and Precautions [5.1]).

• Pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or
You will take Hizentra through an infusion, only under your skin. You will control pills, may increase your risk of developing a blood clot.

Inform patients that because Hizentra is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (see Warnings and Precautions [5.7] and Description [11]).

Inform patients that Hizentra may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella) and to notify their immunizing physician of recent therapy with Hizentra (see Drug Interactions [7]).

Home Treatment for Primary Humoral Immunodeficiency with Subcutaneous Administration

If self-administration is deemed to be appropriate, ensure that the patient receives clear instructions and training on subcutaneous administration in the home or other appropriate setting and has demonstrated the ability to independently administer subcutaneous infusions.

Hizentra
Immune Globulin Subcutaneous (Human), 20% Liquid

Information for Patients
This patient package insert summarizes important information about Hizentra. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare professional, and it does not include all of the important information about Hizentra. If you have any questions after reading this, ask your healthcare professional.

What is the most important information I should know about Hizentra?

Hizentra is supposed to be infused under your skin only. DO NOT inject Hizentra into a blood vessel (vein or artery).

What is Hizentra?
Hizentra (Hi – ZEN – tra) is a prescription medicine used to treat primary immune deficiency (PI). Hizentra is made from human plasma. It contains antibodies, called immunoglobulin G (IgG), that healthy people have to fight germs (bacteria and viruses). People with PI get a lot of infections. Hizentra helps lower the number of infections you will get.

Who should NOT take Hizentra?
Do not take Hizentra if you have too much proline in your blood (called “hyperprolinemia”) or if you have had reactions to polysorbate 80.

Tell your doctor if you have had a serious reaction to other immune globulin medicines or if you have been told that you also have a deficiency of the immunoglobulin called IgA.

Tell your doctor if you have a history of heart or blood vessel disease or blood clots, have thick blood, or have been immobile for some time. These things may increase your risk of having a blood clot after using Hizentra. Also tell your doctor what drugs you are using, as some drugs, such as those that contain the hormone estrogen (for example, birth control pills), may increase your risk of developing a blood clot.

How should I take Hizentra?
You will take Hizentra through an infusion, only under your skin. You will place up to 4 needles into different areas of your body each time you use Hizentra. The needles are attached to a pump with an infusion tube. You can have infusions as often as every day up to every two weeks. For weekly infusions, it can take about 1 to 2 hours to complete an infusion; however, this time may be shorter or longer depending on the dose and frequency your doctor has prescribed for you.

Inform patients that Hizentra are at the end of this patient package insert (see “How do I use Hizentra?”). Do not use Hizentra by yourself until you have been taught how by your doctor or healthcare professional.

What should I avoid while taking Hizentra?
Vaccines may not work well for you while you are taking Hizentra. Tell your doctor or healthcare professional that you are taking Hizentra before you get a vaccine.

Tell your doctor or healthcare professional if you are pregnant or plan to become pregnant, or if you are nursing.

What are possible side effects of Hizentra?
The most common side effects with Hizentra are:

- Redness, swelling, itching, and/or bruising at the injection site
- Headache/migraine
- Nausea and/or vomiting
- Pain (including pain in the chest, back, joints, arms, legs)
- Fatigue
- Diarrhea
- Stomach ache/bloating
- Cough
- Rash (including hives)
- Itching
- Fever and/or chills
- Shortness of breath
- Dizziness

Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Tell your doctor right away if you have any of the following symptoms. They could be signs of a serious problem.

- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, or numbness or weakness on one side of the body. These could be signs of a blood clot.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity
to light. These could be signs of a brain swelling called meningitis.

• Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a blood problem.

• Chest pains or trouble breathing.

• Fever over 100ºF. This could be a sign of an infection.

Tell your doctor about any side effects that concern you. You can ask your doctor to give you more information that is available to healthcare professionals.

**How do I use Hizentra?**

Infuse Hizentra only after you have been trained by your doctor or healthcare professional. Below are step-by-step instructions to help you remember how to use Hizentra. Ask your doctor or healthcare professional about any instructions you do not understand.

**Instructions for use**

Hizentra comes in single-use vials.

Keep Hizentra in the storage box at room temperature.

**Step 1: Assemble supplies**

Gather the Hizentra vial(s), the following disposable supplies (not provided with Hizentra), and other items (infusion pump, sharps or other container, treatment diary or log book):

- Infusion administration tubing
- Needle or catheter sets (for subcutaneous infusion)
- Y-site connectors (if needed)
- Alcohol wipes
- Antiseptic skin preps
- Syringes
- Transfer device or needle(s)
- Gauze and tape, or transparent dressing
- Gloves (if recommended by your doctor)

**Step 2: Clean surface**

Thoroughly clean a table or other flat surface using one of the alcohol wipes.

**Step 3: Wash hands**

- Thoroughly wash and dry your hands (Figure 1).
- If you have been told to wear gloves when preparing your infusion, put the gloves on.

**Step 4: Check vials**

Carefully look at the liquid in each vial of Hizentra (Figure 2). Hizentra is a pale yellow to light brown solution. Check for particles or color changes. Do not use the vial if:

- The liquid looks cloudy, contains particles, or has changed color.
- The protective cap is missing.
- The expiration date on the label has passed.

**Step 5: Transfer Hizentra from vial(s) to syringe**

- Take the protective cap off the vial (Figure 3). Clean the vial stopper with an alcohol wipe (Figure 4). Let the stopper dry.
- Attach a needle or transfer device to a syringe tip, using aseptic technique. If using a transfer device, follow the instructions provided by the device manufacturer. If using a needle and a syringe to transfer Hizentra, follow the instructions below.
  - Attach a sterile transfer needle to a sterile syringe (Figure 5).
  - Pull out the plunger of the syringe to fill the syringe with air. Make sure the amount of air is the same as the amount of Hizentra you will transfer from the vial.
  - Put the Hizentra vial on a flat surface. Keeping the vial upright, insert the transfer needle into the center of the rubber stopper.
  - Check that the tip of the needle is not in the liquid. Then, push the plunger of the syringe down. This will inject the air from the syringe into the airspace of the vial.
  - Leaving the needle in the stopper, carefully turn the vial upside down (Figure 6).
  - Slowly pull back on the plunger of the syringe to fill the syringe with Hizentra.
  - Take the filled syringe and needle out of the stopper. Take off the needle and throw it away in the sharps container.

When using multiple vials to achieve the desired dose, repeat this step.

**Step 6: Prepare infusion pump and tubing**

Prepare the infusion pump (following the manufacturer’s instructions) and prime (fill) the infusion tubing. To prime the tubing, connect the syringe filled with Hizentra to the infusion tubing and gently push on the syringe plunger to fill the tubing with Hizentra (Figure 7).

**Step 7: Prepare injection site(s)**

- Select an area on your abdomen, thigh, upper arm, or side of upper leg/hip for the infusion (Figure 8).
- Use a different site from the last time you infused Hizentra. New sites should be at least 1 inch from a previous site.

Never infuse into areas where the skin is tender, bruised, red, or hard. Avoid infusing into scars or stretch marks.

- If you are using more than one injection site, be sure the injection sites are at least 2 inches apart.
- During an infusion, do not use more than 4 injection sites at the same time.

Clean the skin at each site with an antiseptic skin prep (Figure 9). Let the skin dry.
Step 8: Insert needle(s)
- With two fingers, pinch together the skin around the injection site. Insert the needle under the skin (Figure 10).

- Put sterile gauze and tape or a transparent dressing over the injection site (Figure 11). This will keep the needle from coming out.

Step 9: Start infusion
Follow the manufacturer’s instructions to turn on the infusion pump (Figure 12).

Step 10: Record treatment (Figure 13)
Peel off the removable part of the label of the Hizentra vial. Put this label in your treatment diary or log book with the date and time of the infusion. Also include the exact amount of Hizentra that you infused. Scan the vial if recording the infusion electronically.

Step 11: Clean up
- When all the Hizentra has been infused, turn off the pump.
- Take off the dressing and take the needle out of the injection site. Disconnect the tubing from the pump.
- Throw away any Hizentra that is leftover in the single-use vial, along with the used disposable supplies, in the sharps or other container (Figure 14) as recommended by your healthcare professional.
- Clean and store the infusion pump, following the manufacturer’s instructions.

Be sure to tell your doctor about any problems you have doing your infusions. Your doctor may ask to see your treatment diary or log book, so be sure to take it with you each time you visit the doctor’s office.

Call your doctor for medical advice about side effects. You can also report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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