Local site reactions

- Local site reactions can be expected during the infusion and diminish as the drug is absorbed over the following 1–2 days. As patients are infusing up to 25 mL (vol of liquid under the skin) in each infusion site, purpura or swelling where the drug is infused can be expected. Bleeding at the site, blanching, or itching are also possible.

- In the two pivotal clinical trials, most local site reactions were mild.

- Local reactions for SCIg therapy are common and expected, and reports decrease over time.

- Injection-site bleeding

- Shortness of breath

- Chest, shoulder, arm, or leg pain

- Local site reactions for SCIg therapy are common and expected, and reports decrease over time. Adjust ancillary supplies accordingly and infusion parameters based on patient tolerability. Urchiga and blistering are not normal reactions, and Hizenta should be discontinued in those instances.

- Gentle massage and warm/cool compresses can be used to decrease discomfort.

- Local reactions can be expected during the infusion and diminish as the drug is absorbed over the following 1–2 days. As patients are infusing up to 25 mL (vol of liquid under the skin) in each infusion site, purpura or swelling where the drug is infused can be expected. Bleeding at the site, blanching, or itching are also possible.

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- Gentle massage and warm/cool compresses can be used to decrease discomfort.
Hizentra is indicated as replacement therapy for patients with primary humoral immunodeficiency (PI), age 2 and older. 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.

**WARNING: THROMBOSIS**
Thrombosis may occur with immune globulin products, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogen, indwelling vascular needles, 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. See full prescribing information for complete boxed warning.

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin preparations or components of Hizentra, such as polysorbate 80. Because it contains the stabilizer L-proline, Hizentra is contraindicated in patients with hyperprolinemia. Hizentra should be administered subcutaneously.

**Hypersensitivity reactions**
- Shortness of breath
- Chest, shoulder, arm, or leg pain
- Hypertension
- Urticaria
- Rash
- Angioedema

**Other medications and suggested treatments (eg, warm/cold compress)**
- Acetaminophen (eg, Tylenol®) 1000 mg PO every 4 to 6 hours PRN pre- or post-infusion
- Diphenhydramine (eg, Benadryl®) 25–50 mg PO every 4 to 6 hours PRN pre- or post-infusion
- EpiPen is a registered trademark of Mylan Inc. Benadryl and Tylenol are registered trademarks of McNeil Consumer Healthcare.

**Important Safety Information for Hizentra**
- Administration may be followed by aseptic meningitis syndrome (AMS).
- Post-infusion reactions have been reported with the use of subcutaneous administration of immune globulin (SCIg).
- Local reactions for SCIg therapy are common and expected, and reports decrease over time.
- In the two pivotal clinical trials, most local site reactions were mild.
- Local site reactions can be expected during the infusion and diminish as the drug is absorbed over the following 1–2 days. As patients are infusing up to 25 mL of liquid under the skin in each infusion site, puffiness or swelling where the drug is infused can be expected. Redness, blanching, or itching are also possible 1–2 days post-infusion.
- Local site reactions are common and expected, and reports decrease over time.
- Most common adverse reactions observed in 5% or more of study subjects receiving Hizentra were local reactions (ie, swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, extremity pain, cough, pharyngitis, vomiting, upper abdominal pain, and rash.

**Emphasize to patients that they should report severe or unusual site reactions, such as extreme pain or discomfort,**
- Gentle massage and warm/cool compresses can be used to decrease discomfort.
- After an infusion, patients might experience headache of varying severity.
- Local reactions for SCIg therapy are common and expected, and reports decrease over time.

**Contact Information:**
- Phone number: [insert phone number]
- To report any side effects:
- Phone number: [insert phone number]
- To report any infusion/set/pump issues:
- Phone number: [insert phone number]

**Date**

**Appointment date**

**Next scheduled evaluation with physician in**

**weeks**

**months**

**Next follow-up visit with nurse and specialty pharmacist**
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, hypercoagulable 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
- 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 or Hizentra/IGSC infusion. Divide the calculated weekly dose by the desired number of times per week.
- 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>1st</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

ADVERSE REACTIONS

The most common adverse reactions observed in ≥5% of study subjects were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain (6).

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.

DRUG INTERACTIONS

The passive transfer of antibodies may interfere with the response to live virus vaccines (7.1), and lead to misinterpretation of the results of serological testing (5.8, 7.2).

USE IN SPECIFIC POPULATIONS

- Pediatric: No specific dose requirements are necessary to achieve the desired serum IgG levels (8.4).

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

Revised: 10/2016

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines
7.2 Serological Testing

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 US Study
14.2 European Study

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
Hizentra®
Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid

FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS
• Thrombosis may occur with immune globulin products1–5, 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 [see Warnings and Precautions (5.2), and Patient Counseling Information (17)].
• 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 Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE
Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. 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.

2 DOSAGE AND ADMINISTRATION
For subcutaneous infusion only.

2.1 Preparation and Handling
Hizentra is a clear and pale yellow to light brown solution. Do not use if the solution is cloudy or contains particulates.
• Prior to administration, visually inspect each vial of Hizentra for particulate matter or discoloration, whenever the solution and container permit.
• Do not freeze. Do not use any solution that has been frozen.
• Check the product expiration date on the vial label. Do not use beyond the expiration date.
• Do not mix Hizentra with other products.
• Do not shake the Hizentra vial.
• Use aseptic technique when preparing and administering Hizentra.
• The Hizentra vial is for single-use only. Discard all unused administration supplies and any unused product immediately after each infusion in accordance with local requirements.

2.2 Dosage
• Hizentra can be administered at regular intervals from daily up to every two weeks (biweekly).
• Individualize the dose based on the patient’s clinical response to Hizentra therapy and serum immunoglobulin G (IgG) trough levels.
• Before receiving treatment with Hizentra:
  o Ensure that patients have received Immune Globulin Intravenous (Human) (IGIV) treatment at regular intervals for at least 3 months.
  o Obtain the patient’s serum IgG trough level to guide subsequent dose adjustments [see below under Dose Adjustment].

Dosage for patients switching to Hizentra from Immune Globulin Intravenous (Human) (IGIV)
• Establish the initial weekly dose of Hizentra by converting the monthly IGIV dose into a weekly equivalent and increasing it using a dose adjustment factor. The goal is to achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC]) not inferior to that of the previous IGIV treatment.
  o To calculate the initial weekly dose of Hizentra, divide the previous IGIV dose in grams by the number of weeks between doses during the patient’s IGIV treatment (e.g., 3 or 4); then multiply this by the dose adjustment factor of 1.37 [see Pharmacokinetics (12.3, Table 8)].

  Initial Hizentra dose = Previous IGIV dose (in grams) x 1.37
  Number of weeks between IGIV doses
  o To convert the Hizentra dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 5.
  o Provided the total weekly dose is maintained, any dosing interval from daily up to biweekly can be used and will result in systemic serum IgG exposure that is comparable to the previous IGIV or weekly Hizentra treatment [see Pharmacokinetics (12.3)].
  o For biweekly dosing, multiply the calculated Hizentra weekly dose by 2.
  o For frequent dosing (2 to 7 times per week), divide the calculated weekly dose by the desired number of times per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

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 trough level 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>Weight Group</th>
<th>Weight Adjusted Dose Increment (mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 kg</td>
<td>n/a</td>
</tr>
<tr>
<td>10 to 30 kg</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;30 to 50 kg</td>
<td>5</td>
</tr>
<tr>
<td>&gt;50 to 70 kg</td>
<td>10</td>
</tr>
<tr>
<td>&gt;70 to 90 kg</td>
<td>20</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>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

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

<table>
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<td>&gt;90 kg</td>
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</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
minimum of 400 mg/kg is recommended. If a patient has been exposed to measles, ensure this minimum dose is administered as soon as possible after exposure.

### 2.3 Administration

Hizentra is for subcutaneous infusion only.

Hizentra is intended for subcutaneous administration using an infusion pump. Infuse Hizentra in the abdomen, thigh, upper arm, and/or lateral hip.

- **Injection sites** – A Hizentra dose may be infused into multiple injection sites. Use up to 4 sites simultaneously or up to 12 sites consecutively per infusion. Injection sites should be at least 2 inches apart. Change the actual site of injection with each administration.
- **Volume** – For the first infusion of Hizentra, do not exceed a volume of 15 mL per injection site. The volume may be increased to 20 mL per site for the fifth infusion and then to 25 mL per site as tolerated.
- **Rate** – For the first infusion of Hizentra, the recommended flow rate is 15 mL per hour per site. For subsequent infusions, the flow rate may be increased to 25 mL per hour per site as tolerated.

Follow the steps below and use aseptic technique to administer Hizentra.

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>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.</td>
</tr>
<tr>
<td>2.</td>
<td>Clean surface – Thoroughly clean a flat surface using an alcohol wipe.</td>
</tr>
<tr>
<td>3.</td>
<td>Wash hands – Thoroughly wash and dry hands. The use of gloves when preparing and administering Hizentra is optional.</td>
</tr>
<tr>
<td>4.</td>
<td>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.</td>
</tr>
<tr>
<td>5.</td>
<td>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. When using multiple vials to achieve the desired dose, repeat this step.</td>
</tr>
<tr>
<td>6.</td>
<td>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.</td>
</tr>
<tr>
<td>7.</td>
<td>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.</td>
</tr>
<tr>
<td>8.</td>
<td>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.</td>
</tr>
<tr>
<td>9.</td>
<td>Start infusion – Follow the manufacturer’s instructions to turn on the infusion pump.</td>
</tr>
<tr>
<td>10.</td>
<td>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.</td>
</tr>
<tr>
<td>11.</td>
<td>Clean up – After administration is complete, turn off the infusion pump. Take off the tape or dressing and remove the needle set from the infusion 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.</td>
</tr>
</tbody>
</table>

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

### 3 DOSAGE 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 for 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 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. 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. 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’s) 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 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. 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.

5.7 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, fatigue, 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 at 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 (&gt;2 Subjects)</th>
<th>Number (%) of Subjects (n=49)</th>
<th>Number (Rate) 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>3 (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.
§ Number of infusions administered during regularly scheduled visits (every 4 weeks).

The ratio of infections 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 (%) 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 (0.51)</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 following 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.

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 myositis. 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 24 and 72 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments.
globulin products: The following adverse reactions have been reported during postmarketing use of immune
Patient Counseling Information (17)
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)).
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). Several of the production steps have been shown to decrease infectivity of an experimental TSE model agent. TSE reduction steps include octanionic acid fractionation (≥6.4 log10), depth filtration (2.6 log10), and virus filtration (≥5.8 log10). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Hizentra supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action in PI has not been fully elucidated.

12.3 Pharmacokinetics

Clinical Studies
The pharmacokinetics (PK) of Hizentra were evaluated in a PK substudy of subjects (14 adults, 1 pediatric subject aged 6 to <12 years, and 3 adolescent subjects aged 12 to <16 years) with PI.

The PK parameters are similar to Privigen® in adults with PI aged 18 years or older, and to Privigen® in pediatric subjects aged 6 to <12 years, and to IGIV in adult subjects aged 18 years or older. PK parameters for subjects in the substudy following treatment with Hizentra and IGIV are shown in Table 6. 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 trough levels after switching between the various dosing regimens.

<table>
<thead>
<tr>
<th>Table 5. Virus Inactivation/Removal in Hizentra*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>HIV-1</td>
</tr>
<tr>
<td>PRV</td>
</tr>
<tr>
<td>BVDV</td>
</tr>
<tr>
<td>WNV</td>
</tr>
<tr>
<td>EMCV</td>
</tr>
<tr>
<td>MVM</td>
</tr>
</tbody>
</table>

* η: apparent reduction factor; nt: not tested; na: not applicable.

The estimated LRF obtained was ≥5.3. The virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. 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). Several of the production steps have been shown to decrease infectivity of an experimental TSE model agent. TSE reduction steps include octanionic acid fractionation (≥6.4 log10), depth filtration (2.6 log10), and virus filtration (≥5.8 log10). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

Table 6. Pharmacokinetics Parameters of Hizentra, European 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)</td>
<td>228</td>
</tr>
<tr>
<td>Mean Range</td>
<td>141-281</td>
</tr>
<tr>
<td>IgG peak levels (mg/dL)</td>
<td>1616</td>
</tr>
<tr>
<td>Mean Range</td>
<td>1090-2825</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL)</td>
<td>1448</td>
</tr>
<tr>
<td>Mean Range</td>
<td>952-2623</td>
</tr>
<tr>
<td>AUC‡ (day x mg/dL)</td>
<td>1.00E+08</td>
</tr>
<tr>
<td>Mean Range</td>
<td>1.00E+08</td>
</tr>
<tr>
<td>CL§ (ml/d/kg)</td>
<td>2.57</td>
</tr>
<tr>
<td>Mean Range</td>
<td>0.95-2.1</td>
</tr>
</tbody>
</table>

‡ Weekly dose based on dose adjustment factor of 1.37 when switching from IGIV. § Bioavailability.

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 trough levels after switching between the various dosing regimens.

Table 7. Pediatric Pharmacokinetics Parameters of Hizentra, European Study

<table>
<thead>
<tr>
<th>Age Group</th>
<th>6 to &lt;12 years</th>
<th>12 to &lt;16 years</th>
<th>16 to &lt;18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>120</td>
<td>115</td>
<td>117</td>
</tr>
<tr>
<td>Mean</td>
<td>71-170</td>
<td>72-150</td>
<td>87-156</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL)</td>
<td>731</td>
<td>764</td>
<td>754</td>
</tr>
<tr>
<td>Mean</td>
<td>531-915</td>
<td>615-957</td>
<td>505-898</td>
</tr>
<tr>
<td>AUC‡ (day x mg/dL)</td>
<td>5230</td>
<td>5491</td>
<td>5452</td>
</tr>
<tr>
<td>Mean</td>
<td>3800-6750</td>
<td>4480-6750</td>
<td>3800-6810</td>
</tr>
<tr>
<td>CL§ (ml/d/kg)</td>
<td>2.19</td>
<td>2.17</td>
<td>2.30</td>
</tr>
<tr>
<td>Mean</td>
<td>1.57-3.05</td>
<td>1.38-3.34</td>
<td>1.82-3.34</td>
</tr>
</tbody>
</table>

‡ Weekly dose based on dose adjustment factor of 1.37 when switching from IGIV. § Bioavailability.

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 trough levels after switching between the various dosing regimens.

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>(0.90-1.04)</td>
<td>0.68</td>
<td>(0.60-0.76)</td>
</tr>
<tr>
<td>IGIV</td>
<td>Biweekly Hizentra§</td>
<td>0.97</td>
<td>(0.91-1.04)</td>
<td>0.71</td>
<td>(0.63-0.78)</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>Biweekly Hizentra§</td>
<td>1.00</td>
<td>(0.98-1.03)</td>
<td>0.99</td>
<td>(0.96-1.01)</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>1 times per week Hizentra</td>
<td>1.01</td>
<td>(0.98-1.03)</td>
<td>0.99</td>
<td>(0.96-1.01)</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>3 times per week Hizentra</td>
<td>1.00</td>
<td>(0.98-1.03)</td>
<td>0.99</td>
<td>(0.97-1.01)</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>5 times per week Hizentra</td>
<td>1.00</td>
<td>(0.98-1.03)</td>
<td>0.99</td>
<td>(0.97-1.01)</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>Daily Hizentra (7 times per week)</td>
<td>1.00</td>
<td>(0.98-1.03)</td>
<td>0.99</td>
<td>(0.95-1.01)</td>
</tr>
</tbody>
</table>

† Ratios are based on comparison of second regimen vs. first regimen. § Appropriate change in trough based on predicted median Cmin ratio. ‡ Weekly dose based on dose adjustment factor of 1.37 when switching from IGIV.
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 hyperprolinemia. In this study, rats received daily subcutaneous injections with L-proline from day 6 to day 28 of life. 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-臂, 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/septicemia, 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/septicemia, 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 Description  | Components
--- | --- | ---
5 mL  | 44206-451-01 Vial containing 1 gram of protein (NDC 44206-451-90)  | NDC Number Components
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  | 0.2 days/subject year

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.
discomfort that worsens on deep breathing, unexplained rapid pulse, or numbness or weakness on one side of the body (see Warnings and Precautions [5.2]).

- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (see Warnings and Precautions [5.3]).
- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (see Warnings and Precautions [5.4]).
- Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine (see Warnings and Precautions [5.5]).
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever (see Warnings and Precautions [5.6]).

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.

Instruct patients to scan the vial if recording the infusion electronically and keep a diary/log book that includes information about each infusion such as, the time, date, dose, lot number(s) and any reactions.

Inform the patient that mild to moderate local injection-site reactions (e.g., swelling and redness) are a common side effect of subcutaneous therapy, but to contact their healthcare professional if a local reaction increases in severity or persists for more than a few days.

Inform patients of the importance of having an infusion needle long enough to reach the subcutaneous tissue and of changing the actual site of injection with each infusion. Explain that Hizentra is for subcutaneous infusion only.

Inform patients to consider adjusting the infusion-site location, volume per site, and rate of infusion based on how infusions are tolerated.

Inform patient to interrupt or terminate the Hizentra infusion if a hypersensitivity reaction occurs.

Inform patients that they should be tested regularly to make sure they have the correct levels of Hizentra (IgG) in their blood. These tests may result in adjustments to the Hizentra dose.

Ensure the patient understands the importance of adhering to their prescribed administration schedule to maintain appropriate steady IgG levels.

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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 100°F. 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.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9
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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