Hizentra Coding Information

Diagnosis and ICD-10-CM¹ billing codes for 20% subcutaneous Ig (SCIg) therapy

Please see full Important Safety Information on back and enclosed full prescribing information for Hizentra, including boxed warning.
Hizentra Coding Information
Diagnosis and billing codes for 20% SCIg therapy

This resource provides information from a complex and evolving medical coding system. The treating physician is solely responsible for diagnosis coding and determination of the appropriate ICD-10-CM codes that describe the patient’s condition and are supported by the medical record. All codes listed in this guide are for informational purposes and are not an exhaustive list. The CPT, HCPCS, and ICD-10-CM codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT coding). Because government and other third-party payer coding requirements change periodically, please verify current coding requirements directly with the payer being billed.

Medicare, Medicaid, and most insurers cover Hizentra for the treatment of patients with primary immunodeficiency disease. Hizentra is covered as a Medicare Part B benefit with claims considered for payment by the 4 regional Durable Medical Equipment Medicare Administrative Contractors (DME MACs). Medicaid coverage policy varies by state. Coverage by other payers varies by payer and provider contract.

### ICD-10-CM Diagnosis Codes

The following ICD-10-CM codes may be used to identify patient medical conditions typically associated with primary immunodeficiency disease.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D80.0</td>
<td>Hereditary hypogammaglobulinemia (Swiss type)</td>
</tr>
<tr>
<td>D80.1</td>
<td>Nonfamilial hypogammaglobulinemia</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</td>
</tr>
<tr>
<td>D80.9</td>
<td>Transient hypogammaglobulinemia of infancy</td>
</tr>
</tbody>
</table>

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

### Prior Authorization

When a payer requires prior authorization:

- Request the approval and authorization reference code in writing
- Insert the authorization reference code into Field 23 of the CMS-1500 claim form when billing for services. Enter the authorization reference code in the equivalent field on the electronic claim form (ASC 837P, Loop 2300, Segment REF01, with the Qualifier G1 entered to Segment REF01), unless otherwise directed by the payer
- If required by the payer, attach a copy of the authorization approval letter to the paper claim form; use the payer’s designated procedure for submitting documentation with electronic claim forms

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Please see full Important Safety Information on back and enclosed full prescribing information for Hizentra, including boxed warning.
Billing Codes
The following HCPCS codes describe supplies (including drugs) rendered by the billing provider. CMS publishes and maintains the HCPCS code set.
These codes are entered to paper claim form CMS-1500 in Field 24; or, to electronic claim form ASC 837P in Loop 2400, Segment SV101-2, with the Qualifier “HC” entered to Segment SV101-1, unless otherwise directed by the payer.

**Ready-to-Use Hizentra Vial Sizes**

<table>
<thead>
<tr>
<th>Grams Protein</th>
<th>Fill Size</th>
<th>NDC Number to Use on All Claim Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g</td>
<td>5 mL</td>
<td>44206-0451-01</td>
</tr>
<tr>
<td>2 g</td>
<td>10 mL</td>
<td>44206-0452-02</td>
</tr>
<tr>
<td>4 g</td>
<td>20 mL</td>
<td>44206-0454-04</td>
</tr>
<tr>
<td>10 g</td>
<td>50 mL</td>
<td>44206-0455-10</td>
</tr>
</tbody>
</table>

If the billing provider performs administration services in conjunction with a patient’s infusion, the following administration codes may be used to bill for this service if the service meets the requirements of the code description.

<table>
<thead>
<tr>
<th>CPT Code³</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96369</td>
<td>Subcutaneous injection for therapy or prophylaxis; initial, up to one hour, including pump setup and establishment of subcutaneous infusion site(s)</td>
</tr>
<tr>
<td>96370</td>
<td>Each additional hour</td>
</tr>
<tr>
<td>96371</td>
<td>Additional pump setup with establishment of new subcutaneous infusion site(s)</td>
</tr>
</tbody>
</table>


Billing for Medicare DME MACs
The Medicare benefit for subcutaneous immune globulin administered by DME MACs applies only to those products that are specifically labeled as subcutaneous administration products. Intravenous immune globulin products administered via the subcutaneous route are not covered by Medicare DME MACs (refer to Local Coverage Decision for External Infusion Pumps, effective 2/4/2011).

Billing for External Pumps and Supplies
When the billing provider furnishes an external infusion pump for patient use, the following code may be used to bill for the pump if it meets the requirements of the code description.

<table>
<thead>
<tr>
<th>External Infusion Pump Supplies</th>
</tr>
</thead>
<tbody>
<tr>
<td>K0552 Supplies for external drug infusion pump, syringe-type cartridge, sterile, each</td>
</tr>
<tr>
<td>A4221 Supplies for maintenance of drug infusion catheter, per week</td>
</tr>
<tr>
<td>A4222 Infusion supplies for external drug infusion pump, per cassette or bag</td>
</tr>
</tbody>
</table>

Modifier -JB for Medicare Billing
Medicare requires the addition of Modifier -JB (administered subcutaneously) to the HCPCS code for Hizentra (J1559) to confirm subcutaneous administration. Example: J1559-JB.
Modifier -JB should also be added to the HCPCS code for the covered infusion pump (E0779) following the modifier that indicates whether the pump is being rented (RR) or purchased (NU). Example: E0779-RR-JB or E0779-NU-JB.
CMS-1500 Claim Example

Field 21
Enter all appropriate ICD-10-CM diagnosis codes, starting on Field 21, Line 1. This field allows the entry of 1 character indicator and 12 diagnosis codes at a maximum of 7 characters in length.

Field 24D (Modifier)
For Medicare claims, enter Modifier -JB (administered subcutaneously) on the same line as Hizentra (ie, J1559-JB). Modifier -JB must also be added to the line for the pump following the modifier that indicates whether the pump is a rental (RR) or a purchase (NU) (eg, E0779-RR-JB or E0779-NU-JB).

Field 24E (Diagnosis Pointer)
Enter the line number(s) from Field 21 that best describes the medical necessity for the service listed in Field 24D. For Medicare claims, only one line number from Field 21 should be entered in Field 24E for each HCPCS code reported in Field 24D.

Field 24G (Days or Units)

- Hizentra: Enter the number of 100-mg billing units used to treat the patient. For example, if 28,000 mg are dispensed (eg, seven 20-mL vials), 280 would be reported in Field 24G (28,000/100 = 280).
- Pump: Enter one billing unit
- Supplies: Enter one per unit described by the corresponding HCPCS code

Field 24D (Shaded Area)
For Medicaid claims, and for Medicare claims that will cross over to Medicaid as the secondary payer, NDC information in a specific format is required in the shaded area above the line on which Hizentra is reported in 24D. The various Medicaid plans and Medicare have different reporting formats for this information. In general, the billing entity will need to supply the NDC (in HIPAA-compliant 11-digit format) preceded by the Modifier N4 (eg, N499999999999). This is typically followed by the NDC unit of measure (I2 [international unit], GR [gram], ML [milliliter], or UN [unit]) and the numeric quantity of the NDC that was dispensed. Other payers may require similar information. Check with your payer for specific requirements related to reporting the information required in the shaded areas of Field 24.

Field 24D (CPT/HCPCS)
- Enter HCPCS code J1559 for Hizentra
- Enter HCPCS codes for pump and related supplies:
  - Pump: Medicare will cover only E0779
  - Supplies: Enter code that best describes supplies provided (eg, K0552 or A4221)
- If the billing provider is eligible for coverage of subcutaneous infusion, enter CPT code 96369 for the establishment of infusion sites, pump setup, and the first hour of infusion. If the patient is monitored beyond the first hour, CPT code 96370 may be appropriate. Additional pump setup with establishment of new subcutaneous infusion sites is reported with CPT code 96371.

Field 24D (Modifier)
For Medicare claims, enter Modifier -JB (administered subcutaneously) on the same line as Hizentra (ie, J1559-JB). Modifier -JB must also be added to the line for the pump following the modifier that indicates whether the pump is a rental (RR) or a purchase (NU) (eg, E0779-RR-JB or E0779-NU-JB).

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- Pump: Enter one billing unit
- Supplies: Enter one per unit described by the corresponding HCPCS code

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Please see full Important Safety Information on back and enclosed full prescribing information for Hizentra, including boxed warning.
IgA-deficient patients with anti-IgA antibodies may be at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Hizentra. If hypersensitivity occurs or anaphylactic reactions are suspected, discontinue administration immediately and treat as medically appropriate.

Monitor patients for aseptic meningitis syndrome (AMS), which has been reported with SCIg. In patients at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output. Also monitor patients for clinical signs of hemolysis or transfusion-related acute lung injury (TRALI).

Hizentra is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

The most common 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, rash, pruritus, vomiting, upper abdominal pain, migraine and pain.

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Hizentra is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

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.

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Ig administration can transiently impair the efficacy of live attenuated virus vaccines, such as measles, mumps and rubella. It can also lead to misinterpretation of serologic testing.

Please see enclosed full prescribing information for Hizentra, including boxed warning.

Important Safety Information

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 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. 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 is also contraindicated in patients with immunoglobin A deficiency who have antibodies against IgA and a history of hypersensitivity.

Hizentra should be administered subcutaneously only. Do not administer intravenously.

References:
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

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**RECENT MAJOR CHANGES**

Dosage and Administration (2.2) 01/2015

**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. Do not inject into a blood vessel. Administer at regular intervals from daily up to every other week (bideweekly).

**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) $\times 1.37$
  - 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.

**Infusion Parameters**

<table>
<thead>
<tr>
<th>Infusion Number</th>
<th>Infusion Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (mL/site)</td>
</tr>
<tr>
<td></td>
<td>Rate (mL/hr/site)</td>
</tr>
<tr>
<td>1st</td>
<td>≤ 15</td>
</tr>
<tr>
<td>2nd to 4th</td>
<td>≤ 20</td>
</tr>
<tr>
<td>5th</td>
<td></td>
</tr>
<tr>
<td>6th and above</td>
<td></td>
</tr>
</tbody>
</table>

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**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**

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- 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: January 2015

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**FULL PRESCRIBING INFORMATION: CONTENTS**

**WARNING: THROMBOSIS**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Preparation and Handling
  2.2 Dosage
  2.3 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Hypersensitivity
  5.2 Thrombosis
  5.3 Aseptic Meningitis Syndrome (AMS)
  5.4 Renal Dysfunction/Failure
  5.5 Hemolysis
  5.6 Transfusion-Related Acute Lung Injury (TRALI)
  5.7 Transmissible Infectious Agents
  5.8 Laboratory Tests
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience
7 DRUG INTERACTIONS
  7.1 Live Virus Vaccines
  7.2 Serological Testing
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
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 products1-3, 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 (see Warnings and Precautions [5.2]).
- 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. Do not inject into a blood vessel.

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)].
  For biweekly dosing, multiply the calculated Hizentra weekly dose by 2.
  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 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 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 (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>&gt;10 to 30 kg</td>
<td>Weight Group</td>
<td></td>
</tr>
<tr>
<td>Weekly†</td>
<td>&gt;30 to 50 kg</td>
<td></td>
</tr>
<tr>
<td>Biweekly</td>
<td>&gt;50 to 70 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;70 to 90 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;90 kg</td>
<td></td>
</tr>
</tbody>
</table>

| 50                                                     | Weekly          | 2.5                                       |
|                                                      | Biweekly        | 5                                         |
| 100                                                    | Weekly          | 5                                         |
|                                                      | Biweekly        | 5                                         |
| 200                                                    | Weekly          | 10                                        |
|                                                      | Biweekly        | 10                                        |

n/a, not applicable.† 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.

Dose adjustment 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. Do not inject into a blood vessel.

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.

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

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.
   - Before starting the infusion, attach a sterile syringe to the end of the primed administration tubing and gently pull back on the plunger to make sure no blood is flowing back into the tubing. If blood is present, remove and discard the needle and tubing. Repeat the process beginning with step 6 (priming) using a new needle, new infusion tubing, and a different injection site.

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 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.

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 products, 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 gammopathies. 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, 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.5 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.6 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.7,8 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.9 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 confirmatory laboratory testing.

5.6 Transfusion-Related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.10 TRALI is characterized by severe respiratory distress, pulmonary edema, hypoaxemia, 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 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>ARs∗ Occurring During or Within 72 Hours of Infusion</th>
<th>ARs∗ of Subjects (n=49)</th>
<th>Number (Rate) of ARs (n=2264 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions†</td>
<td>49 (100)</td>
<td>1322 (0.584)</td>
</tr>
</tbody>
</table>

| Other ARs:                      |                        |                                      |
| Headache                      | 12 (24.5)             | 32 (0.014)                          |
| Diarrhea                      | 5 (10.2)              | 6 (0.003)                           |
| Fatigue                       | 4 (8.2)               | 4 (0.002)                           |
| Back pain                     | 4 (8.2)               | 5 (0.002)                           |
| Nausea                        | 4 (8.2)               | 4 (0.002)                           |
| Pain in extremity             | 4 (8.2)               | 6 (0.003)                           |
| Cough                         | 4 (8.2)               | 6 (0.003)                           |
| Vomiting                      | 3 (6.1)               | 3 (0.001)                           |
| Abdominal pain, upper         | 3 (6.1)               | 3 (0.001)                           |
| Migraine                      | 3 (6.1)               | 4 (0.002)                           |
| Pain                          | 3 (6.1)               | 4 (0.002)                           |
| Arthralgia                    | 2 (4.1)               | 3 (0.001)                           |
| Contusion                     | 2 (4.1)               | 3 (0.001)                           |
| Rash                          | 2 (4.1)               | 3 (0.001)                           |
| Urticaria                     | 2 (4.1)               | 2 (< 0.001)                         |

Excluding infections.
† Rate of ARs per infusion.
‡ 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 3: Investigator Assessments∗ of Injection-Site Reactions by Infusion, US Study

<table>
<thead>
<tr>
<th>Injection-Site Reaction</th>
<th>Number (Rate) of Reactions (n=683 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/induration</td>
<td>467 (0.68)</td>
</tr>
<tr>
<td>Erythema</td>
<td>346 (0.51)</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>

Excluding infections.
∗ 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.
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>Number (%) of Subjects (n=51)</th>
<th>Number (Rate') of ARs (n=1831 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9 (17.6)</td>
<td>20 (0.111)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (7.8)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (7.8)</td>
<td>13 (0.007)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.9)</td>
<td>5 (0.003)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>2 (3.9)</td>
<td>3 (0.002)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (3.9)</td>
<td>2 (0.001)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (3.9)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (3.9)</td>
<td>3 (0.002)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3.9)</td>
<td>2 (0.001)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (3.9)</td>
<td>3 (0.002)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2 (3.9)</td>
<td>4 (0.002)</td>
</tr>
</tbody>
</table>

* Excluding infections.
† Rate of ARs per infusion.
‡ Includes infusion-related reaction; infusion-site mass; infusion/injection-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, pyrexia, chills, dizziness, hypertension/changes in blood pressure, malaise.
- **Cardiovascular:** Chest discomfort (including chest pain)
- **Respiratory:** Dyspnea
- **Neurological:** Tremor, burning sensation

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

- **Infusion reactions:** Tachycardia, flushing, wheezing, rigors, myalgia
- **Renal:** Osmotic nephropathy
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), cyanosis, hypoxemia, pulmonary edema, bronchospasm
- **Cardiovascular:** Cardiac arrest, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, aseptic meningitis syndrome
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs’) test
- **Gastrointestinal:** Hepatic dysfunction

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

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

#### 8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

### 8.4 Pediatric Use

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 (14.1)] 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 (Biweekly or more Frequent Dosing)

The biweekly (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 Subcutaneous (Human), 20% Liquid, is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyclonal human immunoglobulin G (IgG) for subcutaneous administration. Hizentra is manufactured from large pools of human plasma by a combination of cold alcohol fractionation, octanionic 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 mU/mL (range: 210 to 290 mU/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 non-enveloped 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_{10} reduction factor (LRF).
Table 5: Virus Inactivation/Removal in Hizentra*

<table>
<thead>
<tr>
<th>Manufacturing Step</th>
<th>Mean LRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 4 incubation</td>
<td>≥5.4</td>
</tr>
<tr>
<td>Depth filtration</td>
<td>≥5.3</td>
</tr>
<tr>
<td>Virus filtration</td>
<td>≥5.5</td>
</tr>
<tr>
<td>Overall Reduction</td>
<td>≥16.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Pharmacokinetics Parameters</th>
<th>Hizentra</th>
<th>IGIV* (Privigen®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Dose (mg/kg) Mean Range</td>
<td>228</td>
<td>141-281</td>
</tr>
<tr>
<td>IgG peak levels (mg/dL)</td>
<td>1616</td>
<td>1090-2825</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL)</td>
<td>1448</td>
<td>952-2623</td>
</tr>
<tr>
<td>AUC* (day x mg/dL) Mean</td>
<td>10560</td>
<td>7210-18670</td>
</tr>
<tr>
<td>CL (ml/kg/day) Mean</td>
<td>2.2</td>
<td>1.2-3.7</td>
</tr>
</tbody>
</table>

Table 7: Comparative Pharmacokinetics of Hizentra, European Study

<table>
<thead>
<tr>
<th>Age Group</th>
<th>6 to &lt;12 years (n=9)</th>
<th>12 to &lt;16 years (n=3)</th>
<th>16 to &lt;65 years (n=11)</th>
<th>Total (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg) Mean Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGIV</td>
<td>120</td>
<td>71-170</td>
<td>115</td>
<td>117</td>
</tr>
<tr>
<td>Hizentra§</td>
<td>731</td>
<td>531-915</td>
<td>764</td>
<td>749</td>
</tr>
<tr>
<td>AUC0-7 days (mg x mL/dL)</td>
<td>5230</td>
<td>3806-6950</td>
<td>5491</td>
<td>5370</td>
</tr>
<tr>
<td>CL (mL/day/kg) Mean</td>
<td>2.19</td>
<td>1.57-3.05</td>
<td>1.38-3.34</td>
<td>2.23</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: To:</th>
<th>AUC</th>
<th>Cmax</th>
<th>Cmin</th>
<th>Predicted Change in Trough†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly IGIV</td>
<td>0.97</td>
<td>0.68</td>
<td>1.16</td>
<td>16% increase</td>
</tr>
<tr>
<td>Biweekly Hizentra§</td>
<td>0.97</td>
<td>0.71</td>
<td>0.95</td>
<td>10% increase</td>
</tr>
<tr>
<td>Daily Hizentra</td>
<td>1.00</td>
<td>1.06</td>
<td>1.04</td>
<td>5% decrease</td>
</tr>
<tr>
<td>Weekly Hizentra biweekly</td>
<td>1.01</td>
<td>0.99</td>
<td>1.01</td>
<td>3% increase</td>
</tr>
<tr>
<td>Weekly Hizentra weekly</td>
<td>1.01</td>
<td>0.99</td>
<td>1.04</td>
<td>4% increase</td>
</tr>
<tr>
<td>Weekly Hizentra daily 5 days</td>
<td>1.01</td>
<td>0.99</td>
<td>1.04</td>
<td>4% increase</td>
</tr>
<tr>
<td>Weekly Hizentra daily 7 days</td>
<td>1.00</td>
<td>0.98</td>
<td>1.04</td>
<td>4% increase</td>
</tr>
</tbody>
</table>

Table 7 summarizes PK parameters at steady state for pediatric subjects (age groups: 6 to <12 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 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 (frequent 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).

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.
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 intent-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 abscesses. 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 abscesses.
† Upper 99% confidence limit: 0.132.
‡ 95% confidence limits: 2.235, 3.370.
§ Based on 1 subject.

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) SIBs 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
- 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
Advis 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
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

Immunoglobulin 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. Make sure that the infusion is not into a blood vessel. 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.

Instructions for using 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 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.

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.

Make sure you are not injecting Hizentra into a blood vessel. To test for this, attach a sterile syringe to the end of the infusion tubing. Pull the plunger back gently (Figure 12). If you see any blood flowing back into the tubing, take the needle out of the injection site. Throw away the tubing and needle. Start the infusion over at a different site with new infusion tubing and a new needle.

Step 9: Start infusion

Follow the manufacturer’s instructions to turn on the infusion pump (Figure 13).

Step 10: Record treatment (Figure 14)

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 15) 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.