Hizentra Coding Information

Diagnosis and ICD-10-CM® 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% SC Ig 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 (e.g., CPT coding). Because government and other third-party payer coding requirements change periodically, please verify current coding requirements directly with the payer being billed.

ICD-10-CM Diagnosis Codes
The following ICD-10-CM codes may be used to identify patient medical conditions typically associated with Hizentra use.

<table>
<thead>
<tr>
<th>G61</th>
<th>Chronic inflammatory demyelinating polyneuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>G61.81</td>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td>G61.85</td>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td>G61.86</td>
<td>Polyradiculoneuropathy (multiple nerve disorder)</td>
</tr>
<tr>
<td>G61.87</td>
<td>Polyradiculoneuropathy, chronic inflammatory demyelinating</td>
</tr>
<tr>
<td>G61.88</td>
<td>Polyradiculoneuropathy, chronic inflammatory demyelinating, unspecified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D88</th>
<th>Immunodeficiency with predominantly antibody defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D88.0</td>
<td>Hereditary hypogammaglobulinemia</td>
</tr>
<tr>
<td>D88.01</td>
<td>Autosomal recessive agammaglobulinemia (Swiss type)</td>
</tr>
<tr>
<td>D88.02</td>
<td>X-linked agammaglobulinemia (Bruton)</td>
</tr>
<tr>
<td>D88.03</td>
<td>Agammaglobulinemia with immunoglobulin-bearing B-lymphocytes</td>
</tr>
<tr>
<td>D88.04</td>
<td>Common variable agammaglobulinemia (CVID/AGamma)</td>
</tr>
<tr>
<td>D88.05</td>
<td>Hypogammaglobulinemia NODS</td>
</tr>
<tr>
<td>D88.06</td>
<td>Selective deficiency of immunoglobulin A (IgA)</td>
</tr>
<tr>
<td>D88.07</td>
<td>Selective deficiency of immunoglobulin G (IgG) subclasses</td>
</tr>
<tr>
<td>D88.08</td>
<td>Selective deficiency of immunoglobulin M (IgM)</td>
</tr>
<tr>
<td>D88.09</td>
<td>Immunodeficiency with increased immunoglobulin M (IgM)</td>
</tr>
<tr>
<td>D88.10</td>
<td>Antibody deficiency with near-normal immunoglobulins</td>
</tr>
<tr>
<td>D88.11</td>
<td>Antibody deficiency with near-normal immunoglobulins, or with hyperimmunoglobulinemia</td>
</tr>
<tr>
<td>D88.12</td>
<td>Selective deficiency of immunoglobulin A (IgA)</td>
</tr>
<tr>
<td>D88.13</td>
<td>Selective deficiency of immunoglobulin G (IgG) subclasses</td>
</tr>
<tr>
<td>D88.14</td>
<td>Selective deficiency of immunoglobulin M (IgM)</td>
</tr>
<tr>
<td>D88.15</td>
<td>Immunodeficiency with increased immunoglobulin M (IgM)</td>
</tr>
<tr>
<td>D88.16</td>
<td>Antibody deficiency with near-normal immunoglobulins</td>
</tr>
<tr>
<td>D88.17</td>
<td>Antibody deficiency with near-normal immunoglobulins, or with hyperimmunoglobulinemia</td>
</tr>
<tr>
<td>D88.18</td>
<td>Selective deficiency of immunoglobulin A (IgA)</td>
</tr>
<tr>
<td>D88.19</td>
<td>Selective deficiency of immunoglobulin G (IgG) subclasses</td>
</tr>
<tr>
<td>D88.20</td>
<td>Selective deficiency of immunoglobulin M (IgM)</td>
</tr>
</tbody>
</table>

| D88.21 | Immunodeficiency with predominantly antibody defects |
| D88.22 | Kappa light chain deficiency |
| D88.23 | Combined immunodeficiency, unspecified |

<table>
<thead>
<tr>
<th>D81</th>
<th>Combined immunodeficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>D81.0</td>
<td>Severe combined immunodeficiency (SCID)</td>
</tr>
<tr>
<td>D81.1</td>
<td>Severe combined immunodeficiency (SCID) with low T- and B-cell numbers</td>
</tr>
<tr>
<td>D81.2</td>
<td>Severe combined immunodeficiency (SCID) with low T- and B-cell numbers</td>
</tr>
<tr>
<td>D81.3</td>
<td>Severe combined immunodeficiency (SCID) with low T- and B-cell numbers</td>
</tr>
<tr>
<td>D81.4</td>
<td>Nezelof’s syndrome</td>
</tr>
<tr>
<td>D81.6</td>
<td>Major histocompatibility complex class I deficiency</td>
</tr>
<tr>
<td>D81.8</td>
<td>Combined immunodeficiency</td>
</tr>
</tbody>
</table>

| D88.3 | Combined immunodeficiency |
| D88.4 | Combined immunodeficiency |
| D88.5 | Combined immunodeficiency |
| D88.6 | Combined immunodeficiency |
| D88.7 | Combined immunodeficiency |
| D88.8 | Combined immunodeficiency |
| D88.9 | Combined immunodeficiency |

<table>
<thead>
<tr>
<th>D82</th>
<th>Immunodeficiency associated with other major defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D82.0</td>
<td>Severe combined immunodeficiency with predominant abnormalities of B-cell numbers and function</td>
</tr>
<tr>
<td>D82.1</td>
<td>Immunodeficiency with thymocytopenia and eczema</td>
</tr>
<tr>
<td>D82.2</td>
<td>Immunodeficiency with short-limbed stature</td>
</tr>
<tr>
<td>D82.3</td>
<td>Immunodeficiency following hereditary defective response to Epstein-Barr virus</td>
</tr>
<tr>
<td>D82.4</td>
<td>Immunodeficiency with autoimmune disease</td>
</tr>
<tr>
<td>D82.5</td>
<td>Immunodeficiency with predominant immunoregulatory T-cell disorders</td>
</tr>
<tr>
<td>D82.6</td>
<td>Immunodeficiency with autoimmune disease</td>
</tr>
<tr>
<td>D82.7</td>
<td>Immunodeficiency with predominant immunoregulatory T-cell disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D83</th>
<th>Common variable immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>D83.0</td>
<td>Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function</td>
</tr>
<tr>
<td>D83.1</td>
<td>Common variable immunodeficiency with predominant immunoregulatory T-cell disorders</td>
</tr>
<tr>
<td>D83.2</td>
<td>Common variable immunodeficiency with autoimmune disease</td>
</tr>
<tr>
<td>D83.3</td>
<td>Common variable immunodeficiency, unspecified</td>
</tr>
</tbody>
</table>

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 forms; use the payer’s designated procedure for submitting documentation with electronic claim forms.
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.

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

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Hizentra), 100 mg</td>
</tr>
</tbody>
</table>

Certain payers may require the entry of NDC information to the claim form, as 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.

CPT Code
<table>
<thead>
<tr>
<th>Code</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 Durable Medical Equipment Medicare Administrative Contractors (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.

External Infusion Pump

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E0779</td>
<td>Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater</td>
</tr>
</tbody>
</table>

E0779 is the only reimbursable pump code for infusion of Hizentra under Medicare Part B. Other pump codes may be used to bill other payers, depending on the pump that is used and the payer’s pump coverage policy. The codes below are not covered by Medicare. Other pump codes may include:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E0781</td>
<td>Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient</td>
</tr>
<tr>
<td>E0791</td>
<td>Parenteral infusion pump, stationary, single or multichannel</td>
</tr>
</tbody>
</table>

Billing for External Pumps and Supplies

When the billing provider furnishes supplies for the patient’s use with the external infusion pump, the following codes may be appropriate for the supplies if they meet the requirements of the code description and payer coverage policies.

External Infusion Pump Supplies

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

*All 3 codes are needed to bill for infusion pump supplies.

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

B Field 24D (CPT/HCPCS)
- Enter HCPCS code J1559 for Hizentra if appropriate
- Enter HCPCS codes for pump and related supplies
  - Pump: Enter appropriate code (Medicare will cover only E0779)
  - Supplies: Enter code that best describes supplies provided (eg, K0552 or A4421)
- 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.

C 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 (F2 [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.

D Field 24D (Modifier)
For Medicare claims, enter Modifier -JB (administered subcutaneously) on the same line as Hizentra (eg, 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).

E Field 24E (Diagnosis Pointer)
Enter the line letter(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.

F Field 24G (Days or Units)
- Hizentra: Enter the number of 100-mg billing units used to treat the patient. For example, if 40,000 mg are dispensed (eg, four 50-mL vials), 400 would be reported in Field 24G (40,000/100 = 400)
- Pump: Enter one billing unit
- Supplies: Enter one per unit described by the corresponding HCPCS code

CMS-1500 Claim Example
Call Us Now for Reimbursement Support

Hizentra reimbursement support is available free of charge through IgIQ, CSL Behring’s single source for Ig solutions.

IgIQ™
Your single source for Ig solutions

1-877-355-IGIQ (4447)
Monday—Friday 8 AM to 8 PM ET


Important Safety Information

Hizentra is indicated for:

- Treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years and older.
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to prevent relapse of neuromuscular disability and impairment.

  - Limitation of Use: Maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Continued maintenance beyond these periods should be individualized based on patient response and need for continued therapy.

For subcutaneous infusion only.

- 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.

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin (Ig) or components of Hizentra (eg, polysorbate 80), as well as in patients with immunoglobulin A deficiency with antibodies against IgA and a history of hypersensitivity. Because Hizentra contains L-proline as stabilizer, use in patients with hyperprolinemia is contraindicated.

IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions. Thrombosis may occur following treatment with Ig products, including Hizentra.

Monitor patients for aseptic meningitis syndrome (AMS), which may occur following treatment with Ig products, including Hizentra. In patients at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output. In addition, monitor patients for clinical signs of hemolysis or pulmonary adverse reactions (eg, transfusion-related acute lung injury [TRALI]).

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

The most common adverse reactions (observed in ≥5% of study subjects) were local infusion-site reactions, as well as headache, diarrhea, fatigue, back pain, nausea, extremity pain, cough, upper respiratory tract infection, rash, pruritus, vomiting, upper abdominal pain, migrane, arthralgia, pain, fall, and nasopharyngitis.

The passive transfer of antibodies can interfere with response to live virus vaccines and lead to misinterpretation of serologic test results.

Please see enclosed full prescribing information for Hizentra.
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.

RECENT MAJOR CHANGES
Indications (1.2)
Dosage and Administration (2.2, 2.3)
3/2018

INDICATIONS AND USAGE
HIZENTRA is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for:
- Primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. (1.1)
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP). (1.2)

DOSAGE AND ADMINISTRATION
For subcutaneous infusion only.
Dose (2.2)
PI
Before switching to HIZENTRA, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments.
- Weekly: Start HIZENTRA 1 week after last Immune Globulin Intravenous (Human) (IGIV) infusion. Initial weekly dose = Previous IGIV dose (in grams) x 1.37
  No. of weeks between IGIV doses
- Biweekly (every 2 weeks): Start HIZENTRA 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly 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 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.

CIDP
- Initiate therapy with HIZENTRA 1 week after the last IGIV infusion.
- Recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) body weight (bw) per week:
  - in the clinical study after transitioning from IGIV to HIZENTRA, a dose of 0.4 g/kg (2 mL/kg) bw per week was also safe and effective to prevent CIDP relapse.
- If CIDP symptoms worsen, consider re-initiating treatment with an IGIV approved for the treatment of CIDP, while discontinuing HIZENTRA.
  - If improvement and stabilization are observed during IGIV treatment, consider re-initiating HIZENTRA at 0.4 g/kg bw per week, while discontinuing IGIV.
  - If CIDP symptoms worsen on 0.4 g/kg bw per week, consider re-initiating therapy with IGIV, while discontinuing HIZENTRA.
- Monitor patient’s clinical response and adjust duration of therapy based on patient need.

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1.1 Primary Immunodeficiency (PI)
1.2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
2 DOSAGE AND ADMINISTRATION
2.1 Preparation and Handling
2.2 Dose
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

Administration (2.3)
- PI: Administer at regular intervals from daily up to every 2 weeks.
- CIDP: Administer weekly.
- Infusion sites — Up to 8 infusion sites are allowed simultaneously, with at least 2 inches between sites.

<table>
<thead>
<tr>
<th>Administration in PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (2.2)</td>
</tr>
<tr>
<td>1st Infusion</td>
</tr>
<tr>
<td>Volume (mL/site)</td>
</tr>
<tr>
<td>Rate (mL/hr/site)</td>
</tr>
</tbody>
</table>

As tolerated

DOSAGE FORMS AND STRENGTHS

<table>
<thead>
<tr>
<th>Dosage Form and Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 g per mL (20%) protein solution for subcutaneous infusion. (3)</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS
- Anaphylactic or severe systemic reaction to human immune globulin or inactive ingredients of HIZENTRA, such as polysorbate 80. (4)
- Hyperprolinemia Type I or II (HIZENTRA contains stabilizer L-proline). (4)
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity. (4)

WARNINGS AND PRECAUTIONS
- IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions. (5.1)
- Thrombosis may occur following treatment with immune globulin products, including HIZENTRA. (5.2)
- Aseptic meningitis syndrome has been reported with IGIV or IGSC, including HIZENTRA treatment. (5.3)
- Monitor for clinical signs and symptoms of hemolysis. (5.5)
- Monitor for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.6)
- HIZENTRA is made from human blood and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.7)

ADVERSE REACTIONS
The most common adverse reactions observed in at least 5% of study subjects were local infusion site reactions, headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, upper respiratory tract infection, rash, pruritus, vomiting, abdominal pain (upper), migraine, arthralgia, pain, fall and nasopharyngitis. (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)

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

Revised: March 2018

7 DRUG INTERACTIONS
7.1 Live Virus Vaccines
7.2 Serological Testing

8 USE IN SPECIFIC POPULATIONS
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8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use

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12.1 Mechanism of Action
12.2 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
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14.2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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16 HOW SUPPLIED/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 products12, including HIZENTRA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogen(s), 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 USEAGE

HIZENTRA is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of the following conditions:

1.1 Primary Immunodeficiency (PI)

HIZENTRA is 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.

1.2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

HIZENTRA is indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.

Limitations of Use:

HIZENTRA maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Maintenance therapy beyond these periods should be individualized based upon the patient’s response and need for continued therapy [see Dose and Administration (2)].

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 vial.
- Use aseptic technique when preparing and administering this product.
- The HIZENTRA vial is for single use only. Discard all used administration supplies and any unused product immediately after each infusion in accordance with local requirements.

2.2 Dose

Primary Immunodeficiency (PI)

- HIZENTRA can be administered at regular intervals from daily up to every 2 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:
  - Ensure that patients have received Immune Globulin Intravenous (Human) (IGIV) treatment at regular intervals for at least 3 months.
  - 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 IGIV

- Establish the initial weekly dose of HIZENTRA by converting the monthly IGIV dose into a weekly equivalent and increasing it using the 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.

- 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 Clinical Pharmacology (12.3, Table 7)].

\[
\text{Initial HIZENTRA dose (in grams)} = \frac{\text{Previous IGIV dose (in grams)}}{\text{Number of weeks between IGIV doses}} \times 1.37
\]

- For biweekly dosing, multiply the calculated HIZENTRA 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 IGSC infusion.
- For biweekly dosing, start treatment 1 or 2 weeks after the last IGIV infusion or 1 week after the last IGSC infusion.

Dose Adjustment

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 Clinical Pharmacology (12.3)].

- Bivweekly 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 IgG trough level. When switching from weekly to biweekly dosing, the target trough is projected to be approximately 5% lower than the last trough level on weekly therapy [see Clinical Pharmacology (12.3)].

Frequent dosing: When switching from weekly dosing to more frequent 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 Clinical Pharmacology (12.3)].

To adjust the dose based on serum trough levels, calculate the difference (in mg/dL) between the patient’s IgG trough level obtained 2 to 3 months following the switch from IGIV or the last IGSC dose adjustment 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</th>
<th>&gt;10 to &lt;30</th>
<th>&gt;30 to &lt;50</th>
<th>&gt;50 to &lt;70</th>
<th>&gt;70 to &lt;90</th>
<th>&gt;90 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Weekly</td>
<td>n/a</td>
<td>2.5</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>Weekly</td>
<td>2.5</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>200</td>
<td>Weekly</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>60</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.

n/a, not applicable.
Follow the steps below and use aseptic technique to administer HIZENTRA.

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.

**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

- Initiate therapy with HIZENTRA 1 week after the last IGIV infusion.
- The recommended subcutaneous dose is 0.2 g/kg body weight per week, administered in 1 or 2 sessions over 1 or 2 consecutive days.
  - In the clinical study after transitioning from IGIV to HIZENTRA treatment, a dose of 0.4 g/kg (2 mL/kg) body weight per week was also safe and effective to prevent CIDP relapse.
- If CIDP symptoms worsen, consider re-initiating treatment with an IGIV approved for the treatment of CIDP, while discontinuing HIZENTRA.
  - If improvement and stabilization are observed during IGIV treatment, consider re-initiating HIZENTRA at the dose of 0.4 g/kg body weight per week, administered in 2 sessions per week over 1 or 2 consecutive days, while discontinuing IGIV.
  - If CIDP symptoms worsen on the 0.4 g/kg body weight per week dose, consider re-initiating therapy with an IGIV product approved for treatment of CIDP, while discontinuing HIZENTRA.
- Monitor the patient’s clinical response and adjust the duration of therapy based on patient need.

### 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.

- Infusion sites – A HIZENTRA dose may be infused into multiple infusion sites. Use up to 8 infusion sites in parallel. More than one infusion device can be used simultaneously. Infusion sites should be at least 2 inches apart. Change the actual site of infusion with each administration.
- Volume (as tolerated) – For the first infusion of HIZENTRA, do not exceed a volume of 15 mL per infusion site in patients with PI or up to 20 mL per infusion site in patients with CIDP. For subsequent infusions, the volume may be increased to 25 mL per infusion site for patients with PI or to 50 mL per site for patients with CIDP.
- Rate (as tolerated) – For the first infusion of HIZENTRA, the recommended flow rate is up to 15 mL per hour per infusion site in patients with PI or up to 20 mL per hour per site in patients with CIDP. For subsequent infusions, the flow rate may be increased to 25 mL per hour per site in patients with PI or up to 50 mL per hour per site in patients with CIDP.

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Instructions</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, has changed color, the protective cap is missing, or 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.</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 infusion site(s) • The number and location of infusion sites depends on the volume of the total dose. Infuse HIZENTRA into a maximum of 8 sites simultaneously. Infusion sites should be at least 2 inches apart. • 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>8.</td>
<td>Insert needle(s) • 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.</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 infusion.
CONTRAINDICATIONS
HIZENTRA is contraindicated in patients with:
• History of anaphylactic or severe systemic reaction to human immune globulin or inactive ingredients of HIZENTRA, such as polysorbate 80.
• Hyperprolactinemia Type I or II because it contains L-proline as a stabilizer (see Description (11)).
• IgA-deficiency with antibodies against IgA and a history of hypersensitivity (see Description (11)).

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.

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.

5.3 Aseptic Meningitis Syndrome (AMS)
AMS has been reported with use of IGIV or IGSC, including HIZENTRA. 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 products. 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.

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. 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.

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.

VERSEREATIONS
49 (100) 1322 (0.584)

Table 2. Incidence of Subjects with Adverse Reactions (ARs)† (Experienced by 2 or More Subjects) and Rate of Infusion (ITT Population), PI U.S. Study

<table>
<thead>
<tr>
<th>AR (≥2 Subjects)</th>
<th>ARs† Occurring During or Within 72 Hours of Infusion</th>
<th>Number (%) of Subjects</th>
<th>Number (Rate) of ARs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions‡</td>
<td>49 (100)</td>
<td>1322 (0.584)</td>
<td></td>
</tr>
<tr>
<td>Other ARs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 (24.5)</td>
<td>32 (0.014)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (10.2)</td>
<td>6 (0.003)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (8.2)</td>
<td>5 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4 (8.2)</td>
<td>6 (0.003)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (4.1)</td>
<td>2 (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

† Rate of ARs per infusion.
‡ Includes infusion-site reactions as well as bruising, chapping, pain, irritation, cysts, eczema, and nodules at the infusion site.
§ Includes ARs per infusion.
‡ Each AR was counted only once.
¶ Rate of ARs per infusion.

5.7 Transmissible Infectious Agents
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. 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.

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, hemotoma and itching at the infusion site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, upper respiratory tract infection, rash, pruritus, vomiting, abdominal pain (upper), migraine, arthralgia, pain, fall and nasopharyngitis.

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.

TREATMENT OF PRIMARY IMMUNE DEFICIENCY (PI)

U.S. Study
The safety of HIZENTRA was evaluated in a clinical study in the U.S. 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 449 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 infusion-site reactions (e.g., swelling, redness, heat, pain, and itching at the site of infusion) comprising 98% of local reactions.

Pharmacovigilance at 1-866-915-6958.

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 to possibly have been transmitted by HIZENTRA should be reported to CSL Behring Pharmacovigilance at 1-866-915-6958.
Most local reactions were either mild (does not interfere with routine activities (93.4%) or moderate (interferes somewhat with routine activities and may have warranted intervention (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 infusion-site reaction one day after the third weekly infusion, and the other subject experienced moderate myositis.

### PLI 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 PLI who had been treated previously with IGIV every 3 or 4 weeks or with IGSC weekly.

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

Table 4 summarizes the most frequent ARs (experienced by at least 2 subjects) occurring during or within 72 hours after the end of an infusion. Local reactions were assessed by the subjects between 24 and 72 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments.

### Table 4. Incidence of Subjects with Adverse Reactions (ARs)* (Experienced by 2 or More Subjects) and Rate per Infusion, PLI European Study

<table>
<thead>
<tr>
<th>AR (+2 Subjects)</th>
<th>Number (%) of Subjects (n=151)</th>
<th>Number of Rate† of ARs (n=1831 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions†</td>
<td>24 (14.7) 105 (0.057)</td>
<td></td>
</tr>
<tr>
<td>Other ARs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4 (7.0) 7 (0.005) 11 (19.3) 54 (0.027) 17 (29.3) 49 (0.022)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3 (4.2) 2 (0.001) 4 (7.0) 5 (0.002) 4 (6.9) 4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (1.8) 1 (&lt;0.001) 3 (5.3) 3 (0.001) 2 (3.4) 2 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.8) 1 (0.01) 5 (8.8) 5 (0.002) 0 0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.5) 2 (0.001) 3 (5.3) 3 (0.001) 2 (3.4) 2 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>9 (17.6) 20 (0.011)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (7.8) 4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (7.8) 13 (0.007)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>3 (5.9) 5 (0.003)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (3.9) 2 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (3.9) 4 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (3.9) 3 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3.9) 2 (0.001)</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (3.9) 3 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2 (3.9) 4 (0.002)</td>
<td></td>
</tr>
</tbody>
</table>

† Includes infusion-site erythema, infusion-site swelling, infusion-site pain, infusion-site induration, infusion-site warmth, infusion-site hematoma, and infusion-site pruritus.

Hypersensitivity was reported in 2 subjects (3.5%) in the 0.2 g/kg HIZENTRA group, 2 subjects (3.4%) in the 0.4 g/kg group, and zero subjects in the placebo group. Systemic adverse reactions in the 13-week single-arm IGIV Restabilization Period of the study for subjects also randomized and treated with HIZENTRA during the 24-week subcutaneous treatment period (N=115) occurred at a rate of 0.098 (956 infusions) relative to a rate of 0.027 (4225 infusions) during treatment with HIZENTRA in the IGSC period of the study. The systemic adverse reaction per infusion for HIZENTRA was 3.6-fold lower than the corresponding rate for IGIV.

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, tachycardia, flushing.
- **Cardiovascular**: Chest discomfort (including chest pain)
- **Respiratory**: Dyspnea
- **Neurological**: Tremor, burning sensation
- **General disorders and administration site conditions**: Infusion-site ulcer, infusion-site necrosis

### Table 3. Investigator Assessment* of Infusion-Site Reactions by Infusion, PLI U.S. Study

<table>
<thead>
<tr>
<th>Infusion-Site Reaction</th>
<th>Number† (%) of Reactions (n=683 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/infiltration</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>

† Includes infusion-related reaction; infusion-site mass; infusion/injection-site erythema, hematoma, induration, inflammation, edema, pain, pruritus, rash, reaction, swelling; infusion-site extravasation; nodular; puncture-site reaction.
The following adverse reactions have been reported during postmarketing use of immune globulin products:

- Infusion reactions: 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: Pancreatitis, leukopenia, hemolysis, positive direct antiglobulin (Coombs’ test)
- Gastrointestinal: Hepatic dysfunction

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella (see Patient Counseling Information (17)).

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with HIZENTRA. It is not known whether HIZENTRA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasing after 30 weeks of gestation. HIZENTRA should be given to pregnant women only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Treatment of Primary Immunodeficiency

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 U.S. [see Clinical Studies (14)] and in 23 pediatric subjects with PI (18 children and 5 adolescents) in Europe. There were no differences in the pharmacokinetics, safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired IgG levels.

Pharmacokinetic Modeling and Simulation (Biweekly or more Frequent Dosing)

The biweekly (every 2 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 Clinical Pharmacology (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.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

The safety and effectiveness of HIZENTRA have not be established in patients with CIDP who are under the age of 18.

8.5 Geriatric Use

Treatment of Primary Immunodeficiency

Of the 49 subjects evaluated in the U.S. 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 subjects 18 to 65 years of age. The clinical study of HIZENTRA in Europe did not include subjects over the age of 65.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

Of the 172 subjects evaluated in the SC treatment period of a global study (HIZENTRA vs placebo), 50 subjects were >65 years of age (34 HIZENTRA and 16 placebo subjects). No overall differences in safety or efficacy were observed between these subjects and subjects 18 to 65 years of age.

11 DESCRIPTION

HIZENTRA, Immune Globulin Subcutaneous (Human), 20% Liquid, is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyvalent human immunoglobulin G (IgG) for subcutaneous administration. HIZENTRA is manufactured from large pools of human plasma by a combination of cold alcohol fractionation, octanoc 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 (detected with complexed IgG).

HIZENTRA has a purity of ≥98% IgG and a pH of 4.6 to 5.2. This product contains approximately 250 mmol/L (range: 210 to 290 mmol/L) 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, 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 10^14 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.10 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 6 shows the virus clearance during the manufacturing process for HIZENTRA, expressed as the mean log_{10} reduction factor (LRF).

Table 6. Virus Inactivation/Removal in HIZENTRA*
For the 19 subjects completing the wash-in/wash-out period, the average dose adjustment for HIZENTRA was 153% (range: 126% to 187%) of the previous weekly-equivalent IVIG dose. After 12 weeks of treatment with HIZENTRA at this individually adjusted dose, the final steady-state AUC determinations were made in 18 of the 19 subjects. The geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for HIZENTRA vs IVIG treatment was 1.002 (range: 0.77 to 1.20) with a 90% confidence limit of 0.951 to 1.055 for the 18 subjects.

With HIZENTRA, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved with IVIG while trough levels are generally higher (1448 vs 1127 mg/dL). In contrast to IVIG administered every 3 to 4 weeks, weekly subcutaneous administration results in relatively stable steady-state serum IgG levels.13,14 After the subjects had reached steady state with weekly administration of HIZENTRA, peak serum IgG levels were observed after a mean of 2.9 days (range: 0 to 7 days) in 18 subjects.

Table 8 summarizes PK parameters at steady state for pediatric subjects (age groups: 6 to <12 years and 12 to <16 years) and adult 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.

Table 7. Pharmacokinetics Parameters of HIZENTRA and IVIG, PI U.S. Study

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AUC* (PRIVIGEN®)</th>
<th>Number of subjects</th>
<th>HIZENTRA</th>
<th>IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Range</td>
<td>18</td>
<td>18</td>
<td>228</td>
<td>152</td>
</tr>
<tr>
<td>IgG peak levels (mg/dL) Mean Range</td>
<td>141-381</td>
<td>86-254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG trough levels (mg/dL) Mean Range</td>
<td>1616</td>
<td>2564</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Range</td>
<td>1090-2825</td>
<td>2046-3456</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (day x mg/dL) Mean Range</td>
<td>1448</td>
<td>1127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Range</td>
<td>952-2623</td>
<td>702-1810</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (mL/day/kg) Mean Range</td>
<td>2.2</td>
<td>1.3*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Range</td>
<td>1.2-3.7</td>
<td>0.9-2.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; CL, clearance.

* For IVIG: weekly-equivalent dose.

† Standardized to a 7-day period.

‡ Apparent clearance (CL/F) for HIZENTRA (F = bioavailability).

§ Based on n = 25 from the U.S. PRIVIGEN PI study.

Table 8. Pediatric Pharmacokinetics Parameters of HIZENTRA, PI European Study

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total (n=23)</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>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg) Mean Range</td>
<td>120</td>
<td>71-170</td>
<td>115</td>
<td>72-150</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL) Mean Range</td>
<td>731</td>
<td>531-915</td>
<td>764</td>
<td>615-957</td>
</tr>
<tr>
<td>AUC Cmin (day x mg/dL) Mean Range</td>
<td>5230</td>
<td>3890-6950</td>
<td>5491</td>
<td>4480-6750</td>
</tr>
<tr>
<td>CL (mL/day/kg) Mean Range</td>
<td>2.19</td>
<td>1.57-3.05</td>
<td>2.30</td>
<td>1.38-3.44</td>
</tr>
</tbody>
</table>

AUC Cmin, area under the curve for the 7-day dosing interval; CL, apparent clearance (CL/F) (F = bioavailability).

Pharmacokinetic Modeling and Simulation

Biweekly (Every 2 Weeks) or more Frequent Dosing

Pharmacokinetic characterization of biweekly or more frequent dosing of HIZENTRA was undertaken using population PK-based modeling and simulation. Serum IgG concentration data consisted of 3837 samples from 151 unique pediatric and adult subjects with PI from four clinical studies of IVIG (PRIVIGEN®) and 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 serum levels, thus resulting in more sustained IgG exposures. See Table 9 (columns for AUC, Cmax and Cmin).

Dose Adjustment Factor

Using data from four clinical studies, results of model-based simulations demonstrated that weekly or biweekly HIZENTRA dosing regimens with an IVIG/IVIG dose adjustment factor of 1:1.37 adequately maintain median AUC Cmax and Cmin ratios at ≥90% of values observed with 4-weekly IVIG dosing. See Table 9 (top two rows).

Prediction of Trough Levels Following Regimen Changes

PK modeling and simulation also predicted changes in trough levels after switching from (a) monthly IVIG to weekly or biweekly HIZENTRA dosing, (b) weekly to biweekly HIZENTRA dosing, or (c) weekly to a more frequent dosing period. Table 9 (last column) shows the predicted changes in steady-state IgG trough levels after switching between the various dosing regimens.

Table 9. Predicted Ratios* [Median (5%, 95% percentiles)] of AUC, Cmax and Cmin and Changes in IgG Trough Levels after Switching Between IgG Dosing Regimens for Primary Humoral Immune Deficiency

<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>IVIG</td>
<td>Weekly HIZENTRA†</td>
<td>0.97 (0.90, 1.04)</td>
<td>0.68 (0.60, 0.76)</td>
<td>1.16 (1.07, 1.26)</td>
<td>16% increase</td>
</tr>
<tr>
<td>Biweekly HIZENTRA‡</td>
<td>0.97 (0.91, 1.04)</td>
<td>0.71 (0.63, 0.78)</td>
<td>1.0 (1.02, 1.08)</td>
<td>10% increase</td>
<td></td>
</tr>
<tr>
<td>Weekly HIZENTRA‡</td>
<td>1.00 (0.98-1.03)</td>
<td>1.06 (1.02-1.09)</td>
<td>0.95 (0.93-0.98)</td>
<td>5% increase</td>
<td></td>
</tr>
<tr>
<td>Biweekly HIZENTRA‡</td>
<td>1.00 (0.98-1.03)</td>
<td>0.99 (0.96-1.02)</td>
<td>1.03 (1.00-1.06)</td>
<td>3% increase</td>
<td></td>
</tr>
<tr>
<td>Weekly HIZENTRA‡</td>
<td>1.01 (0.98-1.03)</td>
<td>0.99 (0.96-1.02)</td>
<td>1.04 (1.01-1.07)</td>
<td>4% increase</td>
<td></td>
</tr>
<tr>
<td>Weekly HIZENTRA‡</td>
<td>1.01 (0.98-1.03)</td>
<td>0.99 (0.97-1.01)</td>
<td>1.04 (1.01-1.06)</td>
<td>4% increase</td>
<td></td>
</tr>
</tbody>
</table>

* Ratios are based on comparison of second regimen vs. first regimen.
† Approximate change in trough based on predicted median Cmin ratio.
‡ Weekly dose based on dose adjustment factor of 1.37 when switching from IVIG.
§ Biweekly dose = 2x weekly dose, based on dose adjustment factor of 1.37 when switching from IVIG.

PK-based modeling and simulation results indicate that, similar to observations from the clinical study with weekly HIZENTRA dosing (Table 8), body weight-adjusted biweekly dosing accounted for age-related (~3 years) differences in clearance of HIZENTRA, thereby maintaining systemic IgG exposure (AUC values) in the therapeutic range.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effects of HIZENTRA or its effects on fertility.

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.13 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 less than 60 times higher than the L-proline dose that would result from the administration of HIZENTRA once weekly, no effects on learning and memory were observed. The clinical relevance of these studies is not known.

14 CLINICAL STUDIES

14.1 Primary Immunodeficiency (PI)

U.S. Study

A prospective, open-label, multicenter, single-arm, clinical study conducted in the U.S. evaluated the efficacy, tolerability, and safety of HIZENTRA in 49 adult and pediatric subjects with PI. Subjects previously receiving monthly treatment with IVIG 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 IVIG dose (see Clinical Pharmacology (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 infusion sites per infusion ranged from 1 to 12. In 73% of infusions, the number of infusion sites was 4 or fewer. Up to 4 simultaneous infusion 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 infusion 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 10 summarizes the efficacy results for subjects in the efficacy period (MITT population) of the study. No subjects experienced an SBI in this study.

### Table 10. 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 infections</td>
<td>12,697</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>0 days/subject year</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>0 days/subject year</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>0 days/subject year</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.

**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.

### 14.2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

A multicenter, double-blind, randomized, placebo-controlled, parallel-group phase 3 study evaluated the efficacy, safety, and tolerability of 2 different weekly doses of HIZENTRA (0.4 g/kg body weight and 0.2 g/kg body weight) versus placebo in 172 adult subjects with CIDP and previously treated with IGIV (PATH study). The mean treatment duration was 129 days in the 0.4 g/kg HIZENTRA group and 118.9 days in the 0.2 g/kg HIZENTRA group (treatment duration up to 166 and 167 days in each group, respectively). Subjects generally used 4 infusion sites in parallel (maximum: 8 sites in parallel). Subjects infused an average of 20 mL per infusion site (maximum: 50 mL/site) with an infusion rate of 20 mL/h (maximum: 50 mL/h) and volumes up to 140 mL per infusion session. The infusion time was approximately 1 hour.

The main endpoint was the percentage of subjects who had a CIDP relapse or were withdrawn for any other reason during the SC Treatment Period. CIDP relapse was defined as a ≥ 1 point increase in adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score compared with baseline. Both HIZENTRA doses demonstrated superiority over placebo for the main endpoint (32.8% for 0.4 g/kg HIZENTRA and 38.6% for 0.2 g/kg HIZENTRA compared with 63.2% for placebo, p<0.001 or p=0.007, respectively), with no statistically significant difference between the doses. When only considering relapse, the CIDP relapse rates were 19.0% for 0.4 g/kg HIZENTRA and 33.3% for 0.2 g/kg HIZENTRA compared with 56.1% for placebo (p<0.001 or p=0.012, respectively), with no statistically significant difference between the doses. Eighty-one percent (81%) and 67% of HIZENTRA-treated subjects remained relapse-free (0.4 g/kg body weight and 0.2 g/kg body weight, respectively); 44% of placebo subjects remained relapse-free for up to 24 weeks. A Kaplan-Meier Plot of time to CIDP relapse or withdrawal for any other reason is shown in Figure 1.

**Figure 1. Kaplan-Meier Plot Time to CIDP Relapse or Withdrawal for Any Other Reason**

Subjects in both HIZENTRA dose groups remained relatively stable while subjects in the placebo group deteriorated in mean INCAT score, mean grip strength, mean Medical Research Council sum score, and mean Rasch-built Overall Disability Scale (R-ODS) centile score.

### 15 REFERENCES


16. How Supplied/Storage and Handling

**How Supplied**

HIZENTRA is supplied in a single-use, tamper-evident vial containing 0.2 grams of protein per mL of preservative-free liquid. The HIZENTRA packaging components are not made with natural rubber latex.
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 is a prescription medicine used to treat primary immune deficiency (PI) and chronic inflammatory demyelinating polyneuropathy (CIDP). HIZENTRA is made from human blood. HIZENTRA contains antibodies called immunoglobulin G (IgG). People with PI get a lot of infections, and IgG fights germs (bacteria and viruses). People with CIDP have a form of autoimmune disease where it is believed the body’s defenses attack the nerves and cause muscle weakness and numbness mainly in the legs and arms. IgG is believed to help protect the nerve from being attacked.

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 immobilized 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 8 needles into different areas of your body each time you use HIZENTRA. The needles are attached to a pump with an infusion tube. For PI, you can have infusions as often as every day up to every two (2) weeks. For CIDP, infusions are given once weekly (in 1 or 2 sessions conducted on 1 day or 2 consecutive days). 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 infusion site
- Headache/migraine
- Nausea and/or vomiting
- Pain (including pain in the chest, back, joints, arms, legs)
- Fatigue
- Diarrhea
- Stomach ache/bloating
- Cough, cold or flu symptoms
- Rash (including hives)
- Itching
- Fever and/or chills
- Shortness of breath
- Dizziness
- Fall
- Runny or stuffy nose

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
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.

**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 infusion 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.
- You can use up to 8 infusion sites at the same time. If you are using more than one infusion site, be sure the infusion sites are at least 2 inches apart. More than one infusion device can be used simultaneously.
- 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 infusion site. Insert the needle under the skin (Figure 10).
- Put sterile gauze and tape or a transparent dressing over the infusion site (Figure 11). This will keep the needle from coming out.

**Step 8: Insert needle(s)**

- 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.

**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.

**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.**

**Do not use the vial if:**

- The protective cap is missing.
- The liquid looks cloudy, contains particles, or has changed color.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a blood problem.
- 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.

**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.**

**If you have been told to wear gloves when preparing your infusion,** put the gloves on.

**New sites should be at least 1 inch from a previous site.**
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 infusion site. Disconnect the tubing from the pump.
- Throw away any HIZENTRA that is leftover in the singleuse 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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