Patient Discharge Instructions for Hizentra

These are suggestions to guide you in discussing discharge instructions with your patients and should be amended according to individual practice standards along with guidance from the prescribing information.

Observed adverse reactions: The most common side effects observed in the clinical trials for Hizentra include local infusion-site reactions (redness, swelling, itching, and/or bruising 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. Refer to the accompanying prescribing information for full list of reactions. Advise patients to tell their doctor about any side effect that concerns them.

Local Site Reactions

- Local site reactions can be expected during the infusion and diminish as the drug is absorbed over the following 1–2 days. As patients are infusing liquid under the skin in each infusion site, puffiness or swelling where the drug is infused can be expected. Redness, blanching, or itching are also possible.
- In the pivotal clinical trials, patients reported that most local site reactions were mild.
- Discuss with patients how to alleviate discomfort associated with local site reactions.

Emphasize to patients that they should report severe or unusual site reactions to their healthcare provider, such as extreme pain or discomfort, blistering, urticaria (hives), or spreading redness.

Discuss with patients what reactions should prompt them to seek help.

- Patients should be instructed to check with their physician before infusing SCIg if they do not feel well, if they’re unable to self-infuse, or have infused in the wrong area and to proceed as their physician advises.
- Discuss with patients when to call Emergency–911 for assistance.

Refer to accompanying prescribing information for full list of reactions.

Important Safety Information

• 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.
**Important Safety Information (continued)**

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin (Ig) or components of Hizentra (e.g., 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 (e.g., 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 (CJD) 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, migraine, 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.

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.**

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.

**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. (1.1)
- Maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP). (1.2)

**DOSAGE AND ADMINISTRATION**
For subcutaneous infusion only.

**Dose (2.2)**

<table>
<thead>
<tr>
<th>PI</th>
<th>Before switching to HIZENTRA, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td>Start HIZENTRA 1 week after last Immune Globulin Intravenous (Human) (IGIV) infusion.</td>
</tr>
<tr>
<td>Initial weekly dose = Previous IGIV dose (in grams) x 1.37</td>
<td></td>
</tr>
<tr>
<td>No. of weeks between IGIV doses</td>
<td></td>
</tr>
<tr>
<td>Biweekly (every 2 weeks)</td>
<td>Start HIZENTRA 1 or 2 weeks after the last IGIV infusion or 1 week after the last IGIVSC infusion. Administer twice the calculated weekly dose.</td>
</tr>
<tr>
<td>Frequent dosing (2 to 7 times per week)</td>
<td>Start HIZENTRA 1 week after the last IGIV or IGIVSC infusion. Divide the calculated weekly dose by the desired number of times per week.</td>
</tr>
<tr>
<td>Adjust the dose based on clinical response and serum IgG trough levels.</td>
<td></td>
</tr>
</tbody>
</table>

| 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. |

**DOSAGE FORMS AND STRENGTHS**
0.2 g per mL (20%) protein solution for subcutaneous infusion. (3)

**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**
- Aseptic meningitis syndrome has been reported with IGIV or IGIVSC, including HIZENTRA treatment. (5.3)
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of acute renal failure. (5.4)
- Monitor for signs and symptoms of hemolysis. (5.5)
- Monitor for pulmonary adverse reactions (tracheal-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 ≥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

**RECENT MAJOR CHANGES**

| Indications (1.2) | 3/2018
| Dosage and Administration (2.2, 2.3) | 3/2018

**DOSAGE FORMS AND STRENGTHS**

<table>
<thead>
<tr>
<th>Infusion Parameters*</th>
<th>1st Infusion</th>
<th>Subsequent Infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL/site)</td>
<td>≤15</td>
<td>≤25</td>
</tr>
<tr>
<td>Rate (mL/hr/site)</td>
<td>≤15</td>
<td>≤25</td>
</tr>
</tbody>
</table>

* As tolerated

**RECENT MAJOR CHANGES**

**Recent Major Changes**

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**References**

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 products13, including HIZENTRA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors [see Warnings and Precautions (5.2), and Patient Counseling Information (17)].
- For patients at risk of thrombosis, administer HIZENTRA at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see Warnings and Precautions (5.2)].

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

1.1 Primary Immunodeficiency (PI)
HIZENTRA is indicated as a 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:
  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 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)].
  Initial HIZENTRA dose = Previous IGIV dose (in grams) x 1.37
  Number of weeks between IGIV doses
- To convert the HIZENTRA dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 5.
- 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 Clinical Pharmacology (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 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 starting 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)].

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 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>Difference From Target Serum IgG Trough Level (mg/dL)</th>
<th>Dosing Frequency</th>
<th>Weight Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 to &lt;30 kg</td>
<td>&gt;30 to &lt;50 kg</td>
<td>&gt;50 to &lt;70 kg</td>
</tr>
<tr>
<td>50</td>
<td>Weekly†</td>
<td>n/a</td>
</tr>
<tr>
<td>100</td>
<td>Biweekly†</td>
<td>5</td>
</tr>
<tr>
<td>200</td>
<td>Biweekly†</td>
<td>5</td>
</tr>
</tbody>
</table>

† 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.

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 100 mg/kg.

**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)

Administer a minimum total weekly HIZENTRA dose of 0.2 g/kg body weight for 2 consecutive weeks if a patient is at risk of measles exposure (i.e., due to an outbreak in the U.S. or travel to endemic areas outside of the U.S.). For biweekly dosing, one infusion of a minimum at 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.

#### Measles Exposure

Administer a minimum total weekly HIZENTRA dose of 0.2 g/kg body weight for 2 consecutive weeks if a patient is at risk of measles exposure (i.e., due to an outbreak in the U.S. or travel to endemic areas outside of the U.S.). For biweekly dosing, one infusion of a minimum at 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.

<table>
<thead>
<tr>
<th><strong>2.3 Administration</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIZENTRA is for subcutaneous infusion only.</td>
</tr>
</tbody>
</table>

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 can be increased to 25 mL per infusion site for patients with PI or up 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><strong>Assemble supplies</strong> – 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.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Clean surface – Thoroughly clean a flat surface using an alcohol wipe.</td>
</tr>
<tr>
<td><strong>2.</strong> Wash hands – Thoroughly wash and dry hands. The use of gloves when preparing and administering HIZENTRA is optional.</td>
</tr>
<tr>
<td><strong>3.</strong> 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>
</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.
4 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.
- Hyperprolinemia 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)].

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,
and/or symptoms of hemolysis are present after HIZENTRA infusion, perform appropriate
tests for the presence of anti-neutrophil antibodies in both the product
and patient’s serum.

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 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.1 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)].

Periodic monitoring of renal function and urine output is particularly important in patients
d 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.19 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.10

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.3 TRALI is characterized by severe respiratory distress, pulmonary edema,
hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours
following transfusion. Patients with TRALI may be managed using oxygen therapy with
adequate ventilatory support.

Monitor HIZENTRA recipients for pulmonary adverse reactions. If TRALI is suspected,
perform appropriate tests for the presence of anti-neutrophil antibodies in both the product
and patient’s serum.

5.7 Transmissible Infectious Agents

Because HIZENTRA is made from human 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. All infections suspected by a physician
immediately to be 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, hematoma 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, 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 Immunodeficiency (PI)

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 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)].

Table 2 summarizes the most frequent adverse reactions (ARs) (experienced by ≥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.

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

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

1 Excluding infections.
2 Rate of ARs per infusion.
3 Includes infusion-site reactions as well asbruising, scabbing, pain, irritation, cysts, eczema, and nodules at the infusion site.
4 The ratio of infusions with ARs, including local reactions, to all infusions was 1303 to 2264 (57.6%). Excluding local reactions, the corresponding ratio was 56 to 2264 (2.5%).
5 Table 3 summarizes infusion-site reactions based on investigator assessments 15 to 45 minutes after the end of the 683 infusions administered during regularly scheduled visits (every 4 weeks).
site reactions. Local reactions were more frequent among subjects who received the 0.4 g/kg body weight dose group compared to the 0.2 g/kg body weight dose group after adjusting for the greater mean duration of exposure to HIZENTRA in the 0.4 g/kg body weight dose group (129 days) compared to that of the 0.2 g/kg body weight dose group (119 days). All 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.

**PI European Study**

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

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

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

**Table 3. Investigator Assessment* of In infusion-Site Reactions by Infusion, PI U.S. Study**

<table>
<thead>
<tr>
<th>In infusion-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>

* 13 to 45 minutes following infusions administered at regularly scheduled visits (every 4 weeks).

† For multiple infusion sites, every site was judged, but only the site with the strongest reaction was recorded.

‡ Rate of infusion-site reactions per infusion.

§ Number of infusions administered during regularly scheduled visits.

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.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>0.2 g/kg HIZENTRA</th>
<th>0.4 g/kg HIZENTRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reactions*</td>
<td>Number (% of Subjects)</td>
<td>Number of Events (Rate/Infusion)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.5)</td>
<td>2 (&lt;0.001)</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>4 (0.002)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.9)</td>
<td>3 (0.006)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
</tbody>
</table>

* Includes infusion-related reaction, infusion-site maculopapular rash, infusion-site urticaria, infusion-site injection-site erythema, infusion-site induration, infusion-site warmth, infusion-site edema, and infusion-site pruritus.

During the 24-week subcutaneous treatment period of the study, the exposure-adjusted systemic adverse reaction rate for HIZENTRA was 31% lower than the corresponding rate for IGIV. However, this difference should be interpreted with caution, because there was no parallel group of subjects receiving placebo during the period of IGIV treatment.

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

<table>
<thead>
<tr>
<th>AR (≥2 Subjects)</th>
<th>Number (% of Subjects)</th>
<th>Number (Rate') of ARs (n=1231 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions†</td>
<td>24 (47.1)</td>
<td>105 (0.057)</td>
</tr>
<tr>
<td>Other ARs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (17.6)</td>
<td>20 (0.011)</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>4 (0.002)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5.9)</td>
<td>3 (0.006)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2 (3.9)</td>
<td>2 (&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AR (≥2 Subjects)</th>
<th>Number (% of Subjects)</th>
<th>Number (Rate') of ARs (n=1151 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2 (3.5)</td>
<td>4 (0.007)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (1.8)</td>
<td>1 (&lt;0.001)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.8)</td>
<td>1 (&lt;0.001)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (3.5)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (1.8)</td>
<td>1 (&lt;0.001)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>0 (0.0)</td>
<td>0 (&lt;0.001)</td>
</tr>
</tbody>
</table>

| AR = adverse reaction; SC = subcutaneous.
| † Number of infusions.
| ‡ Includes infusion-related reaction, infusion-site maculopapular rash, infusion-site urticaria, infusion-site induration, infusion-site warmth, infusion-site edema, and infusion-site pruritus.

Hypertension 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 rate per infusion for HIZENTRA was 3.6-fold lower than the corresponding rate for IGIV.

The exposure-adjusted rate for 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) was 0.075 reactions per week, relative to an exposure-adjusted rate of 0.052 reactions per week during treatment with HIZENTRA in the IGSC period of the study. The exposure-adjusted systemic adverse reaction rate for HIZENTRA was 31% lower than the corresponding rate for IGIV. However, this difference should be interpreted with caution, because there was no parallel group of subjects receiving placebo during the period of IGIV treatment.

### 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.
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, dermatis (e.g., bullous dermatisitis)
- 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

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 serum 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 Demineralizing Polynuropathy

The safety and effectiveness of HIZENTRA have not been 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 Demineralizing Polynuropathy

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 10^4 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.1

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*

<table>
<thead>
<tr>
<th>Virus Property</th>
<th>HIV-1</th>
<th>PRV</th>
<th>BVDV</th>
<th>WNV</th>
<th>EMCV</th>
<th>MVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Envelope</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Size (nm)</td>
<td>80-100</td>
<td>120-200</td>
<td>50-70</td>
<td>50-70</td>
<td>25-30</td>
<td>18-24</td>
</tr>
</tbody>
</table>

<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>≥5.3</td>
</tr>
<tr>
<td>Overall Reduction (Log_{10} Units)</td>
<td>≥16.0</td>
</tr>
</tbody>
</table>

| HIV-1: Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; PRV: pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpesviruses); BVDV: bovine viral diarrhea virus, a model for hepatitis C virus; WNV: West Nile virus; EMCV: encephalomyocarditis virus, a model for hepatitis A virus; MVM: minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parovirus); LRF, log_10 reduction factor; nt, not tested; na, not applicable.

The virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. The estimated LRF obtained was ≥5.3.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for CJD and its variant (vCJD).1 Several of the production steps have been shown to decrease infectivity of an experimental TSE model agent. TSE reduction steps include octanoc acid fractionation (≥6.4 log_{10}), depth filtration (2.6 log_{10}), and virus filtration (≥5.8 log_{10}). These steps provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HIZENTRA supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action has not been fully elucidated, but may include immunomodulatory effects.

12.3 Pharmacokinetics

Treatment of Primary Immunodeficiency

Clinical Studies

The pharmacokinetics (PK) of HIZENTRA was evaluated in a PK substudy of subjects (14 adults, 1 pediatric subject aged 6 to <12 years, and 3 adolescent subjects aged 12 to <16 years) with PI participating in the 15-month efficacy and safety study [see Clinical Studies (14)]. All PK subjects were treated previously with PRIVIGEN®, Immune Globulin Intravenous (Human), 10% Liquid and were switched to weekly subcutaneous treatment with HIZENTRA. After a 3-month wash-in/wash-out period, doses were adjusted individually with the goal of providing a systemic serum IgG exposure (area under the IgG serum concentration vs time curve; AUC) not inferior to that of the previous weekly-equivalent IGIV dose. Table 7 summarizes PK parameters for subjects in the substudy following treatment with HIZENTRA and IGIV.
needed for HIZENTRA dosing. Dose requirements are similar to those of adult subjects; thus no pediatric specific dose requirements are needed for HIZENTRA dosing.

For the 19 subjects completing the wash-in/wash-out period, the average dose adjustment for HIZENTRA was 153% (range: 126% to 187%) of the previous weekly-equivalent IGIV dose. After 12 weeks of treatment with HIZENTRA at this individually adjusted dose, the final steady-state AUC determinations were made in 18 of the 19 subjects. The geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for HIZENTRA vs IGIV treatment was 1.02 (range: 0.77 to 1.20) with a 90% confidence limit of 0.951 to 1.055 for the 18 subjects.

With HIZENTRA, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved with IGIV while trough levels are generally higher (1448 vs 1127 mg/dL). In contrast to IGIV, the mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for HIZENTRA vs IGIV treatment was 1.00 (95% CI: 0.98-1.03) for a 1:1.37 dose adjustment factor. 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.
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 year¹</td>
</tr>
<tr>
<td>Annual rate of any infections</td>
<td>2.76 infections/subject year⁴</td>
</tr>
<tr>
<td>Antibiotic use for infection (prophylaxis or treatment)</td>
<td></td>
</tr>
<tr>
<td>Number of subjects (%)</td>
<td>27 (71.1)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>48.5 days/subject year</td>
</tr>
<tr>
<td>Total number of subject days</td>
<td>12,605</td>
</tr>
<tr>
<td>Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>71 (0.56)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>2.06 days/subject year</td>
</tr>
<tr>
<td>Hospitalizations due to infections</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>7 (0.06)§</td>
</tr>
<tr>
<td>Annual rate</td>
<td>0.2 days/subject year</td>
</tr>
</tbody>
</table>

* Defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess.

† Upper 99% confidence limit: 0.132.

‡ 95% confidence limits: 2.235; 3.370.

§ Based on 1 subject.

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

### European Study

In a prospective, open-label, multicenter, single-arm, clinical study conducted in Europe, 51 adult and pediatric subjects with PI switched from monthly IGIV (31 subjects) or weekly IGSC (20 subjects) to weekly treatment with HIZENTRA. For the 46 subjects in the efficacy analysis, the weekly mean dose in the efficacy period was 120.1 mg/kg (range 59 to 243 mg/kg), which was 104% of the previous weekly equivalent IGIV or weekly IGSC dose. None of the subjects had an SBI during the efficacy period, resulting in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infections was 5.18 infections per subject for the efficacy period.

### 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 52-Week 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.
Storage and Handling

- Keep HIZENTRA in its original carton to protect it from light.
- Each vial label 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.

17 PATIENT COUNSELING INFORMATION

Advise 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), HIZENTRA contains antibodies called immunoglobulin G (IgG). People with vCJD, 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 immobile for some time. These things may increase your risk of having a blood clot after using HIZENTRA. Also, tell your doctor what drugs you are using, as some drugs, such as those that contain the hormone estrogen (for example, birth control pills), may increase your risk of developing a blood clot.

How should I take HIZENTRA?

You will take HIZENTRA through an infusion, only under your skin. You will place up to 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 2 weeks. For CIDP, infusions are given once weekly (in 1 or 2 sessions) 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.

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), HIZENTRA contains antibodies called immunoglobulin G (IgG). People with vCJD, 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.

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...
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. Keep HIZENTRA in the storage box at room temperature.

**Step 1: Assemble supplies**

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

- Infusion administration tubing
- Needle or catheter sets (for subcutaneous infusion)
- Y-site connectors (if needed)
- Alcohol wipes
- Antiseptic skin prep
- 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.

When using multiple vials to achieve the desired dose, repeat this step.
**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](http://www.fda.gov/medwatch).

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