CSL Behring

Hizentra® P&T summary

CSL Behring's leading SCIg therapy

Indications

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, 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 Important Safety Information on page 38 and full prescribing information for Hizentra including boxed warning.

Healthcare Systems

Hizentra®
Immune Globulin Subcutaneous (Human) 20% Liquid

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Hizentra®
Immune Globulin Subcutaneous (Human) 20% Liquid

Burden of PI and CIDP

Disease state overview

Primary immunodeficiency (PI)

PI is composed of 485 genetic disorders characterized by impaired or absent immune system function, leading to an increased risk of severe, persistent, and recurrent infections throughout the body.[1-4] Approximately 500,000 people in the United States are affected by PI,[5] with 39% experiencing permanent functional impairment before diagnosis.[6] The most diagnosed PI is common variable immunodeficiency (CVID), accounting for 62% of cases, followed by hypogammaglobulinemia at 10% of cases.[6]

PI can result from various genetic pathways affecting immune system components, such as the humoral response, cell-mediated immunity, complement system, or phagocytic cell function.[7] In CVID, a common characteristic is low immunoglobulin (Ig) G, IgA, and IgM levels, leading to susceptibility to infections, autoimmunity, granulomatous disease, and cancer.[8,9] The symptoms of PI vary depending on the type of disease.[10]

Chronic inflammatory demyelinating polyneuropathy (CIDP)

CIDP is a progressive, disabling autoimmune disease that affects the peripheral nervous system.[11,12] CIDP occurs when the immune system attacks and destroys myelin, a material that protects the nerve fibers (axons), which transmit electrical signals throughout the body.[13,14] Demyelination results in signaling impairment, leading to loss of strength and sensation in the arms and legs.[11,14,15] Symptoms develop progressively over at least 2 months, including symmetric muscle weakness, impaired function, numbness, and tingling. Most cases of CIDP are idiopathic; however, there have been reported instances of preceding respiratory and gastrointestinal infections. For now, no causative organism has been identified.[16] Although most patients respond to treatment, if left untreated, 30% of CIDP patients would progress to wheelchair dependence.[14]

Epidemiology

Primary immunodeficiency

PI is a global health concern, affecting more than 6,000,000 people worldwide, of whom 70% to 90% remain undiagnosed. The worldwide prevalence is approximately 1 in 10,000 people.[10]

In the United States, there are approximately 500,000 people affected by PI, with a prevalence rate of 1 in 2000 individuals.[5,17] According to the global Jeffrey Modell Centers Network, physician-reported prevalence of patients with PI increased by 96.3% in the United States and 86.1% globally from 2013 to 2021. During the same period, the overall use of Ig therapy in all forms increased by 36.5% in the United States and 110% globally, with subcutaneous immunoglobulin (SCIg) therapy increasing by 134.3% in the United States.[18]

Common symptoms of PI include increased susceptibility to infection and persistent disease.[10] Warning signs may include frequent ear and sinus infections and recurrent pneumonia.[18] Initial assessment often involves measuring serum Ig levels.

Epidemiology (continued)

Chronic inflammatory demyelinating polyneuropathy

CIDP is a treatment-responsive neuropathy, although not all patients have a sustained response or recover their prediagnosis functioning.[19] Prevalence estimates range from approximately 1 to 9 cases per 100,000 people worldwide.[19-21] Although CIDP can occur at any age, the prevalence increases with advancing age. The mean age of onset ranges from 40 to 60 years. CIDP was 1.4 to 4.7 times more common in males than females in multiple population-based studies.[20] A relapsing course of CIDP is more common in younger patients (aged 10-49 years) and a chronic nonrelapsing course is more common in older patients (aged 40-69 years).[22] Prevalence rates may be incorrectly estimated since the clinical presentation of CIDP can vary, leading to underdiagnosis or misdiagnosis.[23,24]

Diagnosis of CIDP involves a combination of clinical, electrophysiological, and laboratory criteria.[12]

Disease burden

Primary immunodeficiency

Patients with PI often suffer from other serious chronic diseases, with allergic rhinitis being the most common, followed by asthma, according to one study. Another study found that patients with PI who did not receive intravenous immunoglobulin (IVIg) treatment spent a median of 21 more days in the hospital per year compared with patients in the control group. However, patients treated with IVIg had a similar number of hospitalization days per year as the control patients (0.22 days vs 0 days). PI also leads to frequent school and work absences, further adding to the burden on patients and their families.[25]

Chronic inflammatory demyelinating polyneuropathy

CIDP significantly affects physical health, with patients commonly experiencing pain, fatigue, and reduced physical function.[26] Since patients often experience initial symptoms affecting the lower limbs, walking may be impaired, limiting both mobility and independence. The combination of limb weakness, loss of grip strength, and sensory dysfunction causes many patients to require help with activities of daily living, such as eating, bathing, dressing, getting out of bed, and using the bathroom.[27,28] In addition, the impairment of functional capacity by CIDP can result in patients being unable to be professionally active, demonstrating the socioeconomic impact of CIDP. In a 2009 study by Kuitwaard et al, pain and fatigue were evaluated in 76 patients using the Numeric Pain Rating Scale and Fatigue Severity Scale.[29] The results revealed that 17% of the patients reported severe pain, while 74% reported severe fatigue. Not only does CIDP affect patients physically, but it may also affect their mental health. Two studies, one conducted in the Netherlands and one in Germany, reported 9% and 12% of CIDP patients had depression, respectively.[26]

Economic burden

Primary immunodeficiency

Undiagnosed patients with PI face frequent infections, leading to more extended hospital stays, increased emergency department visits, more days on antibiotics, and more missed school/workdays. This results in an annual cost of $124,404 per patient. In contrast, diagnosed PI patients who require fewer medical services incur a yearly cost of $36,516 with IgG therapy. The post-diagnosis annual savings is $87,888, the total per patient treated with IgG (the impact of IgG treatment weighted for 32% of identified patients [average annual cost of IgG ($30,000) x 32%]).[18]

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Economic burden (continued)

Chronic inflammatory demyelinating polyneuropathy

In a retrospective case-control analysis conducted using data from the IQVIA® Real-World Data Adjudicated Claims on adults newly diagnosed with CIDP, healthcare resource use, costs, and clinical characteristics were assessed and compared over a 2-year follow-up. More patients with CIDP experienced ≥1 hospitalization compared with the matched control group of non-CIDP patients (26.2% vs 9.0%, respectively). CIDP patients also had a higher average number of outpatient prescription fills (62.8 vs 32.0; $p<0.0001$) and physician office visits (34.7 vs 13.0; $p<0.0001$). Additionally, patients with CIDP incurred mean total costs that were 7.5 times higher than control patients ($116,330 vs $15,586; $p<0.0001$).[30]

A claims database analysis of patients diagnosed with CIDP in the United States showed that patients with CIDP use a variety of healthcare resources, with pharmacy claims being the largest portion of costs, at an estimated mean of $31,899 per patient per year.[27]

Table 1. Mean health plan paid costs for CIDP patients in 2011[27]

	Mean health plan paid cost per patient per year
Attributed to medical cost	$25,054 ± $6840
Attributed to pharmacy claims	$31,899 ± $7375
Total mean cost	**$56,953 ± $10,282**

A database analysis of hospitalization burden was conducted in adults with CIDP in the United States from 2010 to 2012. A total of 31,451 hospital discharges in patients with CIDP were evaluated. From 2010 to 2012, the total economic burden of CIDP hospitalizations was $2.1 billion. The mean hospital charge related to CIDP hospitalization was $68,231. Compared with matched non-CIDP hospitalizations, CIDP hospitalizations were associated with 50% longer length of stay and higher total charges.[31]

Treatment options

Primary immunodeficiency

Treatment for PI depends on the specific type of disease. Common treatments include prophylactic antimicrobials, such as antibiotics and antifungals tailored to the age and clinical status of the patient.[32,33] Most PI patients with antibody production defects receive Ig replacement therapy. Hematopoietic stem cell transplantation (HSCT) is another option for some patients.[10,32]

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Treatment options (continued)

Chronic inflammatory demyelinating polyneuropathy

The goal of treatment of CIDP is to improve symptoms, reduce disability, and achieve and maintain long-term disease control.[3,4] First-line induction treatment options include IVIg, corticosteroids, plasma exchange, and anti-FcRn therapy. Although comparative data between these modalities are sparse, for patients with moderate or severe disability, the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline states that IVIg, corticosteroids, or plasma exchange should be offered, with all being strongly recommended. IVIg is specifically recommended as the initial treatment in pure motor CIDP (Good Practice Point). SCIg has been strongly recommended as a maintenance treatment option in CIDP patients stabilized on IVIg.[12]

In addition to patient characteristics such as past medical history and current comorbid conditions, initial choice of therapy may be based on safety profile, time to response, availability, ease of administration, and cost profile. If the first-line treatment options (either alone or in combination) are not effective, chemotherapeutic or immunosuppressive agents may be considered.[12,34]

Product introduction[35]

Hizentra is the most prescribed SCIg for PI in the United States. It was approved by the US Food and Drug Administration (FDA) in March 2010 for the treatment of PI in patients aged 2 years and older.

In March 2018, Hizentra became the first FDA-approved SCIg treatment for adults with CIDP to prevent relapse of neuromuscular disability and impairment.

Hizentra has a proven track record of safety, efficacy, and tolerability. Available in a variety of prefilled syringe sizes, Hizentra also offers the convenience of at-home self-administration for people living with PI and CIDP. Patients should receive training from their healthcare providers prior to independently self-administering subcutaneous infusions in the home or other appropriate setting.

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WARNING: THROMBOSIS

- **Thrombosis may occur with immune globulin products,[36-38] 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**
- **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 the following conditions:

- **Primary immunodeficiency**
  Hizentra is indicated as replacement therapy for PI in adults and pediatric patients aged 2 years and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, CVID, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies
- **Chronic inflammatory demyelinating polyneuropathy**
  Hizentra is indicated for the treatment of adult patients with CIDP as maintenance therapy to prevent relapse of neuromuscular disability and impairment

Limitation 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.

Dosage and administration

For subcutaneous infusion only.

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 prefilled syringe or 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 prefilled syringe or vial label. Do not use beyond the expiration date
- Do not mix Hizentra with other products
- Do not shake the prefilled syringe or vial
- Use aseptic technique when preparing and administering this product
- Both the Hizentra prefilled syringe and vial are single-dose containers. Multiple Hizentra prefilled syringes or vials can be administered to achieve the prescribed dose. Discard all used administration supplies and any unused product immediately after each infusion in accordance with local requirements

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Dosage and administration (continued)

Dose

Primary immunodeficiency

- 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 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

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 (eg, 3 or 4); then multiply this by the dose adjustment factor of 1.37
  - 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
- 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 (eg, 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 (eg, 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 weekly IGSC infusion

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Dosage and administration (continued)

Dose (continued)

Dosage 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.

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

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.

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 2 (first column) 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 2 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 2. Incremental adjustment (mL)* of the Hizentra dose† based on the difference (±mg/dL) from the target serum IgG trough level

Difference from target serum IgG trough level (mg/dL)	Dosing frequency	Weight-adjusted dose increment (mL)*				
		Weight group				
		>10 to ≤30 kg	>30 to ≤50 kg	>50 to ≤70 kg	>70 to ≤90 kg	>90 kg
50	Weekly‡	N/A	2.5	5	5	10
	Biweekly	5	5	10	10	20
100	Weekly‡	2.5	5	10	10	15
	Biweekly	5	10	20	20	30
200	Weekly‡	5	10	15	20	30
	Biweekly	10	20	30	40	60

*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.

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Dosage and administration (continued)

Dose (continued)

Dose adjustment (continued)

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

Monitor the patient's clinical response and repeat the dose adjustment as needed. Dosage requirements for patients switching to Hizentra from another IGSC product: If a patient on Hizentra does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of the previous IGSC treatment, the physician may want to adjust the dose. For such patients, Table 2 also provides guidance for dose adjustment if their desired IGSC trough level is known.

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 (ie, due to an outbreak in the United States or travel to endemic areas outside of the United States). 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.

Chronic inflammatory demyelinating polyneuropathy

- Initiate therapy with Hizentra 1 week after the last IGIV infusion
- The recommended subcutaneous dose is 0.2 g/kg (1 mL/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 in preventing CIDP relapse
- If CIDP symptoms worsen on 0.2 g/kg (1 mL/kg) body weight per week, consider increasing the Hizentra dose from 0.2 g/kg (1 mL/kg) to 0.4 g/kg (2 mL/kg) body weight per week, administered in 2 sessions per week over 1 or 2 consecutive days
  - If CIDP symptoms worsen on the 0.4 g/kg body weight per week dose, consider reinitiating 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

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Review of Hizentra Prescribing Information (continued)

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 1 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, either as prefilled syringe(s) or vial(s).

1. Assemble supplies: Gather the Hizentra prefilled syringe(s) or vial(s), all supplies, and infusion log book.

2. Clean surface: Clean a table or other flat surface.

3. Wash hands: Thoroughly wash and dry hands.

4. Check prefilled syringe(s) or vial(s):

- If using prefilled syringes, carefully peel back the transparent covering from the tray and inspect the protective cap. Peel back the outer layer of the wrap-around label to allow for viewing of Hizentra through the fully transparent inner layer, but don't remove the label completely
- If using vials, inspect the protective cap of the vials

Carefully inspect each prefilled syringe(s) or vial(s) of Hizentra. Hizentra is a clear and pale yellow to light brown solution. **Do not use the prefilled syringe or vial if:** it is damaged; the liquid looks cloudy, contains particles, or has changed color; the protective cap of the prefilled syringe or the vial is missing or defective; or the expiration date on the label has passed.

5. Preparation of Hizentra for infusion: If using Hizentra prefilled syringes, go to Step 5.1. If using Hizentra vials, go to Step 5.2.

5.1. Hizentra prefilled syringe(s):

- The 5 mL, 10 mL, 20 mL, and 50 mL prefilled syringes are supplied and ready to use. The 5 mL and 10 mL prefilled syringes are fully assembled. For the 20 mL and 50 mL prefilled syringes, screw the plunger rod onto the prefilled syringe stopper prior to use
- Hizentra prefilled syringes can be placed directly in the infusion pump if the prefilled syringe size matches the pump requirements. If the prefilled syringe can be placed directly in the infusion pump, then go to Step 6

NOTE: An additional adapter may be required for the Hizentra prefilled syringes to fit properly in the infusion pump. Check with the provider of your supplies for the appropriate adapter and installation instructions.

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Administration (continued)

- If the Hizentra prefilled syringe size does not match the infusion pump requirements, transfer the contents of the prefilled syringe to another syringe of a size specific for the infusion pump by following the directions below:
  - Use a syringe-to-syringe transfer device (tip-to-tip connector) to transfer the contents of the prefilled syringe to the empty syringe specific for the infusion pump
  - Remove the protective cap from the prefilled syringe. Attach the transfer device (tip-to-tip connector) by twisting it onto the prefilled syringe. Attach the empty syringe by screwing it onto the other side of the transfer device
  - Make sure you transfer the amount needed to achieve the prescribed dose
    - Measure dose from the top of the stopper
  - Push the plunger of the prefilled syringe (eg, using your fingers, thumb, or the palm of your hand) to transfer Hizentra from the prefilled syringe to the empty syringe
    - Repeat this step if multiple prefilled syringes are necessary to achieve the prescribed dose. Remove the emptied prefilled syringe and attach another prefilled syringe to the transfer device (tip-to-tip connector)
  - After the transfer is complete, remove the emptied prefilled syringe and the transfer device (tip-to-tip connector) by unscrewing them from the syringe specific for your pump. Connect the filled syringe to the infusion tubing

Go to step 6.

5.2. Transfer Hizentra from vial to syringe:

- Take the protective cap off the vial
- Clean the vial stopper with an alcohol wipe. Let the stopper 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 out the plunger of the syringe to fill the syringe with air. Make sure that 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
  - 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 prescribed dose, repeat this step

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Review of Hizentra Prescribing Information (continued)

Administration (continued)

6. Prepare infusion pump and tubing:

- Prior to preparing the pump(s), make sure you have the prescribed dose in the syringe(s) and the infusion tubing is attached
- Prepare the infusion pump following the manufacturer's instructions, including attaching any necessary adapters
- Do not remove the needle caps until you are ready to infuse
  - Prime (fill) the infusion. To prime the tubing, connect the syringe filled with Hizentra to the infusion tubing and gently push on the syringe plunger (eg, using your fingers or thumb or the palm of your hand) to fill the tubing with Hizentra
  - Stop priming before Hizentra fluid reaches the capped needle
  - Insert the syringe filled with Hizentra into the infusion pump

7. Prepare infusion site(s):

- Select an area on your abdomen, thigh, upper arm, or side of upper leg/hip for the infusion. The number and location of infusion sites depends on the volume of the total dose
- Never infuse into areas where the skin is tender, bruised, red, or hard. Avoid infusing into scars or stretch marks
- Infuse Hizentra into a maximum of 8 sites simultaneously, or up to 12 consecutively per infusion. Infusion sites should be at least 2 inches apart
- Clean the skin at each infusion site with an antiseptic skin prep. Let the skin dry

8. Insert needle(s):

- Use just 1 needle per site. If injecting in more than 1 site, the following steps should be completed for each needle, one at a time
- Remove the needle cap
- Using 2 fingers, pinch together the skin around the infusion site. With a quick dart-like motion, insert the needle straight into the skin
- Put sterile gauze and tape or a transparent dressing over the infusion site to hold the needle in place

9. Start infusion:

- Follow the manufacturer's instructions to turn on the infusion pump and start the infusion

10. Complete infusion and record treatment:

- When all the Hizentra has been infused, turn off the infusion pump
- Remove the needle(s) from the skin
- Once you have removed the needle(s), remove the empty syringe from the infusion pump
- Disconnect the infusion set from the empty syringe
- Cover the infusion site(s) with a protective dressing
- Peel off the removable part of the label for each prefilled syringe or vial used. Affix it to the patient's log book with the date and time of infusion, or scan the prefilled syringe or vial if recording the infusion electronically

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Administration (continued)

11. Clean up:

- If applicable, remove adapter from the infusion pump following the manufacturer's instructions
- Throw away the empty Hizentra prefilled syringe(s) or vial(s), along with the used disposable supplies, in the sharps container in accordance with local requirements
- Clean and store the infusion pump, following the manufacturer's instructions

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

Dosage forms and strengths

Hizentra is a 0.2 g/mL (20%) protein solution for subcutaneous infusion available in a single-dose, prefilled syringe (5 mL, 10 mL, 20 mL, and 50 mL) or tamper-evident vial (5 mL, 10 mL, 20 mL, and 50 mL).

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
- IgA-deficiency with antibodies against IgA and a history of hypersensitivity

Warnings and precautions

Hypersensitivity

Severe hypersensitivity reactions may occur due 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.

Thrombosis

Thrombosis may occur following treatment with immune globulin products,[36-38] including Hizentra. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triglycerides, or monoclonal gammopathies. For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

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Warnings and precautions (continued)

Aseptic meningitis syndrome

Aseptic meningitis syndrome (AMS) has been reported with use of IGIV[39] 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.

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.[40] 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 preexisting renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs, monitor renal function and consider lower, more frequent dosing.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[41] 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.

Hemolysis

Hizentra can contain blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with Ig, causing a positive direct antiglobulin (Coombs') test result and hemolysis.[42,43] 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.[44]

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.

Transfusion-related acute lung injury

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.[45] Transfusion-related acute lung injury (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 antineutrophil antibodies in both the product and patient's serum.

Please see Important Safety Information on page 38 and full prescribing information for Hizentra including boxed warning.

Warnings and precautions (continued)

Transmissible infectious agents

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

Laboratory tests

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

Adverse reactions

The most common adverse reactions (ARs) observed in ≥5% of study subjects receiving Hizentra were local reactions (eg, 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, fall, and nasopharyngitis.

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 with rates in the clinical studies of another product and may not reflect the rates observed in clinical practice.

Treatment of PI

PI US study

The safety of Hizentra was evaluated in a clinical study in the United States 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 1 dose of Hizentra.

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 3 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 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 (eg, swelling, redness, heat, pain, and itching at the site of infusion) comprising 98% of local reactions.

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Adverse reactions (continued)

Clinical trials experience (continued)

Table 3. Incidence of subjects with ARs* (experienced by 2 or more subjects) and rate per infusion (ITT population), PI US study

AR (≥2 subjects)	ARs occurring during or within 72 hours of infusion	
	Number (%) of subjects (n=49)	Number (rate†) of ARs (n=2264 infusions)
Local reactions‡	**49 (100)**	**1322 (0.584)**
Other ARs		
Headache	12 (24.5)	32 (0.014)
Diarrhea	5 (10.2)	6 (0.003)
Fatigue	4 (8.2)	4 (0.002)
Back pain	4 (8.2)	5 (0.002)
Nausea	4 (8.2)	4 (0.002)
Pain in extremity	4 (8.2)	6 (0.003)
Cough	4 (8.2)	4 (0.002)
Vomiting	3 (6.1)	3 (0.001)
Abdominal pain, upper	3 (6.1)	3 (0.001)
Migraine	3 (6.1)	4 (0.002)
Pain	3 (6.1)	4 (0.002)
Arthralgia	2 (4.1)	3 (0.001)
Contusion	2 (4.1)	3 (0.001)
Rash	2 (4.1)	3 (0.001)
Urticaria	2 (4.1)	2 (<0.001)

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

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Adverse reactions (continued)

Clinical trials experience (continued)

The ratio of infusions with ARs, including local reactions, to all infusions was 1303 to 2264 (57.6%). Excluding local reactions, the corresponding ratio was 56 to 2264 (2.5%). Table 4 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).

Table 4. Investigator assessment* of infusion-site reactions by infusion, PI US study

Infusion-site reaction	Number† (rate‡) of reactions (n=683 infusions§)
Edema/induration	467 (0.68)
Erythema	346 (0.51)
Local heat	108 (0.16)
Local pain	88 (0.13)
Itching	64 (0.09)

*15 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.

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 1 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 5 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.

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Adverse reactions (continued)

Clinical trials experience (continued)

Table 5. Incidence of subjects with ARs* (experienced by 2 or more subjects) and rate per infusion, PI European study

	ARs occurring during or within 72 hours of infusion	
AR (≥2 subjects)	**Number (%) of subjects (n=51)**	**Number (rate†) of ARs (n=1831 infusions)**
Local reactions‡	**24 (47.1)**	**105 (0.057)**
Other ARs		
Headache	9 (17.6)	20 (0.011)
Rash	4 (7.8)	4 (0.002)
Pruritus	4 (7.8)	13 (0.007)
Fatigue	3 (5.9)	5 (0.003)
Abdominal pain, upper	2 (3.9)	3 (0.002)
Arthralgia	2 (3.9)	2 (0.001)
Erythema	2 (3.9)	4 (0.002)
Abdominal discomfort	2 (3.9)	3 (0.002)
Back pain	2 (3.9)	2 (0.001)
Hematoma	2 (3.9)	3 (0.002)
Hypersensitivity	2 (3.9)	4 (0.002)

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

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Adverse reactions (continued)

Clinical trials experience (continued)

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

Three subjects withdrew from the study due to ARs of mild to moderate intensity. One subject experienced infusion-site pain and infusion-site pruritus; the second subject experienced infusion-site reaction, fatigue, and feeling cold; and the third subject experienced infusion-site reaction and hypersensitivity.

Biweekly (every 2 weeks) or frequent (2 to 7 times per week) dosing

No data regarding ARs are available for these alternative Hizentra dosing regimens because no clinical trials using these regimens were conducted.

Treatment of CIDP

PATH study

The safety of 2 doses of Hizentra (0.2 g/kg body weight or 0.4 g/kg body weight) vs placebo was evaluated in the 24-week subcutaneous treatment period of the Polyneuropathy And Treatment with Hizentra (PATH) study in subjects with CIDP who had been treated previously with IGIV. The dose was administered once a week in 2 infusion sessions conducted on 1 or 2 consecutive day(s). The safety population included 172 subjects.

Table 6 summarizes the most frequent ARs that occurred in ≥5% of subjects treated with Hizentra and at a higher frequency than placebo. The overall AR rates were similar in the 0.2 g/kg body weight and 0.4 g/kg body weight Hizentra dose groups (50.9% and 46.6%, respectively) and higher than placebo (33.3%). The most frequent ARs were local infusion-site reactions. Local reactions were more frequent among subjects who received the 0.4 g/kg body weight dose than among subjects who received the 0.2 g/kg body weight dose (29.3% and 19.3%, respectively). The exposure-adjusted rate of local reactions per subject remained greater in the 0.4 g/kg body weight dose group compared with 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 with 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 [94.5%]) or moderate (interferes somewhat with routine activities and may have warranted intervention [5.5%]) in intensity and the frequency tended to decrease over time. No subject withdrew because of local reaction.

One serious AR, allergic dermatitis, was reported in the 0.2 g/kg body weight Hizentra group. It started at subcutaneous Week 9 and lasted 15 days. One subject withdrew from the study due to a nonserious AR, fatigue.

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Adverse reactions (continued)

Clinical trials experience (continued)

Table 6. CIDP subcutaneous treatment period—ARs occurring in ≥5% of subjects treated with Hizentra and at a higher frequency than placebo-treated subjects

	Placebo		0.2 g/kg Hizentra		0.4 g/kg Hizentra	
	Number (%) of subjects (n=57)	Number of events (rate/ infusion) (n=1514*)	Number (%) of subjects (n=57)	Number of events (rate/ infusion) (n=2007*)	Number (%) of subjects (n=58)	Number of events (rate/ infusion) (n=2218*)
Local reactions†	**4 (7.0)**	**7 (0.005)**	**11 (19.3)**	**54 (0.027)**	**17 (29.3)**	**49 (0.022)**
Headache	2 (3.5)	2 (0.001)	4 (7.0)	5 (0.002)	4 (6.9)	4 (0.002)
Nasopharyngitis	1 (1.8)	1 (<0.001)	4 (7.0)	6 (0.003)	2 (3.4)	2 (<0.001)
Fatigue	1 (1.8)	1 (<0.001)	5 (8.8)	5 (0.002)	0	0
Upper respiratory tract infection	2 (3.5)	2 (0.001)	3 (5.3)	3 (0.001)	2 (3.4)	2 (<0.001)
Fall	0	0	3 (5.3)	8 (0.004)	1 (1.7)	1 (<0.001)
Back pain	1 (1.8)	1 (<0.001)	3 (5.3)	4 (0.002)	1 (1.7)	1 (<0.001)
Arthralgia	1 (1.8)	1 (<0.001)	3 (5.3)	4 (0.002)	1 (1.7)	1 (<0.001)
Pain in extremity	0	0	1 (1.8)	1 (<0.001)	3 (5.2)	3 (0.001)

*Number of infusions.
†Includes infusion-site erythema, infusion-site swelling, infusion-site pain, infusion-site induration, infusion-site warmth, infusion-site hematoma, 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 ARs in the 13-week 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 AR rate per infusion for Hizentra was 3.6-fold lower than the corresponding rate for IGIV.

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Adverse reactions (continued)

Clinical trials experience (continued)

The exposure-adjusted rate for systemic ARs 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 AR 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.

PATH extension study

The PATH extension study was a multicenter, 48-week, open-label extension study that evaluated the long-term safety and efficacy of Hizentra 0.2 g/kg and 0.4 g/kg doses, per body weight, in the maintenance treatment of CIDP in subjects who either completed or were being successfully rescued from CIDP relapse with IGIV in the PATH study. A total of 82 subjects were enrolled. Of these, 66 (80.5%) subjects completed the study, and 16 (19.5%) subjects discontinued.

In the study, 30.1% of subjects in the Hizentra 0.2 g/kg group and 51.4% of subjects in the 0.4 g/kg group experienced ARs. Similar to the PATH study, the most frequent ARs were local infusion-site reactions, and local reactions were more frequent among subjects who received the 0.4 g/kg body weight dose than among subjects who received the 0.2 g/kg body weight dose (18.1% and 9.6%, respectively). Of all the local reactions, 1 subject had 3 severe reactions (interrupts routine activities or may require intensive therapeutic intervention [7.5%]) with the 0.4 g/kg dose; the rest were either mild (85.0%) or moderate (7.5%). Two subjects withdrew because of local reactions.

The total exposure was 25.1 subject years in the Hizentra 0.2 g/kg group and 38.7 subject years in the 0.4 g/kg group. The mean duration of exposure was 125.8 (range: 1 to 330) days in the Hizentra 0.2 g/kg group and 196.1 (range: 1 to 330) days in the 0.4 g/kg group.

Post-marketing experience

Because post-marketing reporting of ARs 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 ARs have been identified during post-marketing use of Hizentra. This list does not include reactions already reported in clinical studies with Hizentra:

- 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

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Adverse reactions (continued)

Post-marketing experience (continued)

Immune globulin products

The following ARs have been reported during post-marketing use of immune globulin products[40]:

- Infusion reactions: wheezing, rigors, myalgia
- Renal: osmotic nephropathy
- Respiratory: apnea, acute respiratory distress syndrome, cyanosis, hypoxemia, pulmonary edema, bronchospasm
- Cardiovascular: cardiac arrest, vascular collapse, hypotension
- Neurological: coma, loss of consciousness, seizures, AMS
- Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (eg, bullous dermatitis)
- Hematologic: pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- Gastrointestinal: hepatic dysfunction

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

Drug interactions

Live virus vaccines

The passive transfer of antibodies with Ig administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella.

Serological testing

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

Use in specific populations

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 increasingly after 30 weeks of gestation. Hizentra should be given to pregnant women only if clearly needed. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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Use in specific populations (continued)

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.

Pediatric use

Treatment of PI

Clinical studies (weekly dosing)

The safety and effectiveness of weekly Hizentra have been established in the pediatric groups aged 2 to 16 years. Hizentra was evaluated in 10 pediatric subjects with PI (3 children and 7 adolescents) in a study conducted in the United States and in 23 pediatric subjects with PI (18 children and 5 adolescents) in Europe. There were no differences in the pharmacokinetics or safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Pharmacokinetic (PK) 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). 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 years have not been established.

Treatment of CIDP

The safety and effectiveness of Hizentra have not been established in patients with CIDP who are under the age of 18 years.

Geriatric use

Treatment of PI

Of the 49 subjects evaluated in the US clinical study of Hizentra, 6 subjects were aged 65 years or older. No overall differences in safety or efficacy were observed between these subjects and subjects aged 18 to 65 years. The clinical study of Hizentra in Europe did not include subjects over the age of 65 years.

Treatment of CIDP

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

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Review of Hizentra Prescribing Information (continued)

Description

Hizentra 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, octanoic acid fractionation, and anion exchange chromatography. The IgG proteins are not subjected to heating or to chemical or enzymatic modification. The Fc and Fab functions of the IgG molecule are retained. Fab functions tested include antigen-binding capacities, and Fc functions tested include complement activation and Fc-receptor–mediated leukocyte activation (determined with complexed IgG). The IgG subclass distribution is similar to that of normal human plasma. 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 (eg, sucrose, maltose), and no preservative.

Plasma units used in the manufacture of Hizentra are tested using FDA-licensed serological assays for hepatitis B virus (HBV) 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 not to exceed 10^4 IU of B19V DNA per mL.

The manufacturing process for Hizentra includes 3 steps to reduce the risk of virus transmission. Two of these are dedicated virus clearance steps: pH 4 incubation to inactivate enveloped viruses, and virus filtration to remove, by size exclusion, both enveloped and nonenveloped viruses as small as approximately 20 nanometers. In addition, a depth filtration step contributes to the virus reduction capacity.[46]

These steps have been independently validated in a series of in vitro experiments for their capacity to inactivate and/or remove both enveloped and nonenveloped viruses. Table 7 shows the virus clearance during the manufacturing process for Hizentra, expressed as the mean $\log_{10}$ reduction factor.

Table 7. Virus inactivation/removal in Hizentra*

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
Virus property						
Genome	RNA	DNA	RNA	RNA	RNA	DNA
Envelope	Yes	Yes	Yes	Yes	No	No
Size (nm)	80-100	120-200	50-70	50-70	25-30	18-24
Manufacturing step	**Mean LRF**					
pH 4 incubation	≥5.6	≥6.1	4.6	≥7.8	NT	NT
Depth filtration	≥6.7	≥5.7	3.5±0.2	3.0±0.4	5.7±0.2	3.7±0.3
Virus filtration	≥4.7	≥5.8	≥4.6	≥6.8	≥6.3	≥6.5
Overall reduction ($\log_{10}$ units)	**≥17.0**	**≥17.6**	**≥12.7**	**≥17.6**	**≥12.0**	**≥10.2**

*The virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. The estimated LRF obtained was ≤5.6.

BVDV=bovine viral diarrhea virus, a model for hepatitis C virus; EMCV=encephalomyocarditis virus, a model for hepatitis A virus; HIV-1=human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; LRF=$\log_{10}$ reduction factor; MVM=minute virus of mice, a model for a small highly resistant nonenveloped DNA virus (eg, parvovirus); NT=not tested; PRV=pseudorabies virus, a nonspecific model for large enveloped DNA viruses (eg, herpes virus); WNV=West Nile virus.

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Clinical pharmacology

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.

Pharmacokinetics

Treatment of PI

Clinical studies

The pharmacokinetics of Hizentra were evaluated in a PK substudy of subjects with PI (14 adults, 1 pediatric subject aged 6 to <12 years, and 3 adolescent subjects aged 12 to <16 years) participating in the 15-month efficacy and safety study. 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 (AUC IgG) not inferior to that of the previous weekly-equivalent IGIV dose. Table 8 summarizes PK parameters for subjects in the substudy following treatment with Hizentra and IGIV.

Table 8. Pharmacokinetics parameters of Hizentra and IGIV, PI US study

	Hizentra	IGIV* (Privigen)
Number of subjects	**18**	**18**
Dose* (mg/kg)		
Mean	228	152
Range	141-381	86-254
IgG peak levels (mg/dL)		
Mean	1616	2564
Range	1090-2825	2046-3456
IgG trough levels (mg/dL)		
Mean	1448	1127
Range	952-2623	702-1810
AUC† (day x mg/dL)		
Mean	10560	10320
Range	7210-18670	8051-15530
Clearance‡ (mL/day/kg)		
Mean	2.2	1.3§
Range	1.2-3.7	0.9-2.1

*For IGIV: weekly-equivalent dose.
†Standardized to a 7-day period.
‡Apparent clearance (CL/F) for Hizentra (F=bioavailability).
§Based on n=25 from the US Privigen PI study.

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Clinical pharmacology (continued)

Pharmacokinetics (continued)

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

With Hizentra, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved with IGIV while trough levels are generally higher (1448 vs 1127 mg/dL). In contrast to IGIV administered every 3 to 4 weeks, weekly subcutaneous administration results in relatively stable steady-state serum IgG levels.[47,48] 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 9 summarizes PK parameters at steady-state for pediatric subjects (age groups: 6 to <12 years and 12 to <16 years) and adult subjects (aged ≥16 years) in the European Hizentra study following weekly treatment. Pediatric PK parameters are similar to those of adult subjects; thus no pediatric-specific dose requirements are needed for Hizentra dosing.

Table 9. Pediatric pharmacokinetics parameters of Hizentra, PI European study

	Age group			
	6 to <12 years (n=9)	12 to <16 years (n=3)	16 to <65 years (n=11)	Total (n=23)
Dose (mg/kg)				
Mean	120	115	117	118
Range	71-170	72-150	87-156	71-170
IgG trough levels (mg/dL)				
Mean	731	764	754	746
Range	531-915	615-957	505-898	505-957
$AUC_{0\text{-}7days}$ (day x mg/dL)				
Mean	5230	5491	5452	5370
Range	3890-6950	4480-6750	3860-6810	3860-6950
Clearance* (mL/day/kg)				
Mean	2.19	2.17	2.30	2.23
Range	1.57-3.05	1.38-3.34	1.82-3.01	1.38-3.34

*Apparent clearance (CL/F) (F=bioavailability).
$AUC_{0\text{-}7days}$=area under the curve for the 7-day dosing interval.

Please see **Important Safety Information** on page 38 and full **prescribing information** for Hizentra including boxed warning.

Clinical pharmacology (continued)

PK modeling and simulation

Biweekly (every 2 weeks) or more frequent dosing

PK 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 4 clinical studies of IGIV (Privigen) and/or Hizentra. Of the 151 subjects, 94 were adult subjects (63 from Hizentra clinical studies) and 57 were pediatric subjects (32 from Hizentra clinical studies). Compared with weekly administration, PK modeling and simulation predicted that administration of Hizentra on a biweekly basis at double the weekly dose results in comparable IgG exposure (equivalent AUCs, with a slightly higher IgG peak [C_{max}] and slightly lower trough [C_{min}]). 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 [C_{max}] and slightly higher trough [C_{min}]). Frequent dosing reduces the peak-to-trough variation in Hizentra serum levels, thus resulting in more sustained IgG exposures. See Table 10 (columns for AUC, C_{max}, and C_{min}).

Dose adjustment factor

Using data from 4 clinical studies, results of model-based simulations demonstrated that weekly or biweekly Hizentra dosing regimens with an IGIV:IGSC dose adjustment factor of 1:1.37 adequately maintain median $AUC_{0\text{-}28days}$ and C_{min} ratios at ≥90% of values observed with 4-weekly IGIV dosing. See Table 10 (top 2 rows).

Prediction of trough levels following regimen changes

PK modeling and simulation also predicted changes in trough levels after switching from (a) monthly IGIV to weekly or biweekly Hizentra dosing, (b) weekly to biweekly Hizentra dosing, or (c) weekly to more frequent dosing. Table 10 (last column) shows the predicted changes in steady-state IgG trough levels after switching between the various dosing regimens.

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Clinical pharmacology (continued)

PK modeling and simulation (continued)

Table 10. Predicted ratios* (median [5th, 95th percentiles]) of AUC, C_{max}, and C_{min} and changes in IgG trough levels after switching between IgG dosing regimens for primary humoral immune deficiency

IgG dosing regimen switch					
From	**To**	**AUC**	**C_{max}**	**C_{min}**	**Predicted change in trough†**
IGIV	Weekly Hizentra‡	0.97 (0.90, 1.04)	0.68 (0.60, 0.76)	1.16 (1.07, 1.26)	16% increase
IGIV	Biweekly Hizentra§	0.97 (0.91, 1.04)	0.71 (0.63, 0.78)	1.10 (1.02, 1.18)	10% increase
Weekly Hizentra	Biweekly Hizentra§	1.00 (0.98, 1.03)	1.06 (1.02, 1.09)	0.95 (0.92, 0.98)	5% increase
Weekly Hizentra	2 times per week Hizentra	1.01 (0.98, 1.03)	0.99 (0.96, 1.02)	1.03 (1.00, 1.06)	3% increase
Weekly Hizentra	3 times per week Hizentra	1.01 (0.98, 1.03)	0.99 (0.96, 1.02)	1.04 (1.01, 1.07)	4% increase
Weekly Hizentra	5 times per week Hizentra (daily for 5 days)	1.01 (0.98, 1.03)	0.99 (0.97, 1.01)	1.04 (1.01, 1.06)	4% increase
Weekly Hizentra	Daily Hizentra (7 times per week)	1.00 (0.98, 1.03)	0.98 (0.95, 1.01)	1.04 (1.02, 1.08)	4% increase

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

AUC=area under the curve calculated as $AUC_{0\text{-}28days}$ for the IGIV to Hizentra switches, $AUC_{0\text{-}14days}$ for the weekly to biweekly Hizentra switch, and $AUC_{0\text{-}7days}$ for weekly to more frequent Hizentra switches; C_{max}=maximum IgG concentration; C_{min}=minimum IgG concentration during a 28-day period (for the IGIV to Hizentra switches), a 14-day period (for the weekly to biweekly Hizentra switch), or a 7-day period (for the weekly to more frequent Hizentra switches).

PI pediatric pharmacokinetics

PK-based modeling and simulation results indicate that, similar to observations from the clinical study with weekly Hizentra dosing (Table 9), 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.

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Clinical pharmacology (continued)

PK modeling and simulation (continued)

Treatment of CIDP

PATH study

In the PATH study, subjects (n=172) achieved sustained trough levels over a period of 24 weeks when receiving weekly doses of 0.2 g/kg body weight and 0.4 g/kg body weight, respectively. The mean (SD) IgG trough concentration after 24 weeks of Hizentra treatment in the 0.2 g/kg body weight group was 15.3 (2.57) g/L and in the 0.4 g/kg body weight group was 20.8 (3.23) g/L.

PATH extension study

A total of 82 subjects were enrolled in the PATH extension study. The mean serum IgG concentration remained stable at approximately 20 g/L until Week 33; after this period it decreased to 17.1 g/L. The Week 33 decrease in IgG level matched the level in subjects being down-titrated from 0.4 g/kg to 0.2 g/kg at Week 25. The mean IgG level decreased by 19% from enrollment into the extension study for subjects who remained stable after down-titrating to 0.2 g/kg vs the 0.4 g/kg dosing. The mean IgG level decreased by 27% from enrollment into the extension study for subjects who relapsed after down-titrating to 0.2 g/kg vs 0.4 g/kg dosing. The mean (SD) IgG level increased to 20.2 (3.59) g/L at the end of the study for subjects who relapsed on 0.2 g/kg and up-titrated to 0.4 g/kg dosing.

Nonclinical toxicology

Carcinogenesis, mutagenesis, impairment of fertility

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

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.[49] 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 (ie, rats) dosed with the same amount of L-proline with a dosing interval relevant to IGSC treatment (ie, on 5 consecutive days on Days 9 to 13, or once weekly on Days 9, 16, and 23), no effects on learning and memory were observed. The clinical relevance of these studies is not known.

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Clinical studies

Primary immunodeficiency

US study

A prospective, open-label, multicenter, single-arm, clinical study conducted in the United States evaluated the efficacy, tolerability, and safety of Hizentra in 49 adult and pediatric subjects with PI. Subjects previously receiving monthly treatment with IGIV were switched to weekly subcutaneous administration of Hizentra for 15 months. Following a 3-month wash-in/wash-out period, subjects received a dose adjustment to achieve an equivalent AUC to their previous IGIV dose 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 1 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 1 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/daycare or unable to perform normal activities due to infections, hospitalizations due to infections, and serum IgG trough levels.

Table 11 summarizes the efficacy results for subjects in the efficacy period (MITT population) of the study. No subjects experienced an SBI in this study.

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Clinical studies (continued)

Primary immunodeficiency (continued)

Table 11. Summary of efficacy results (MITT population)

Number of subjects (efficacy period)	38
Total number of subject days	12,697
Infections Annual rate of SBIs* Annual rate of any infections	 0 SBIs/subject year† 2.76 infections/subject year‡
Antibiotic use for infections (prophylaxis or treatment) Number of subjects (%) Annual rate	 27 (71.1) 48.5 days/subject year
Total number of subject days	12,605
Days out of work/school/kindergarten/daycare or unable to perform normal activities due to infections Number of days (%) Annual rate	 71 (0.56) 2.06 days/subject year
Hospitalizations due to infections Number of days (%) Annual rate	 7 (0.06)§ 0.2 days/subject year

*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.

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Clinical studies (continued)

Chronic inflammatory demyelinating polyneuropathy

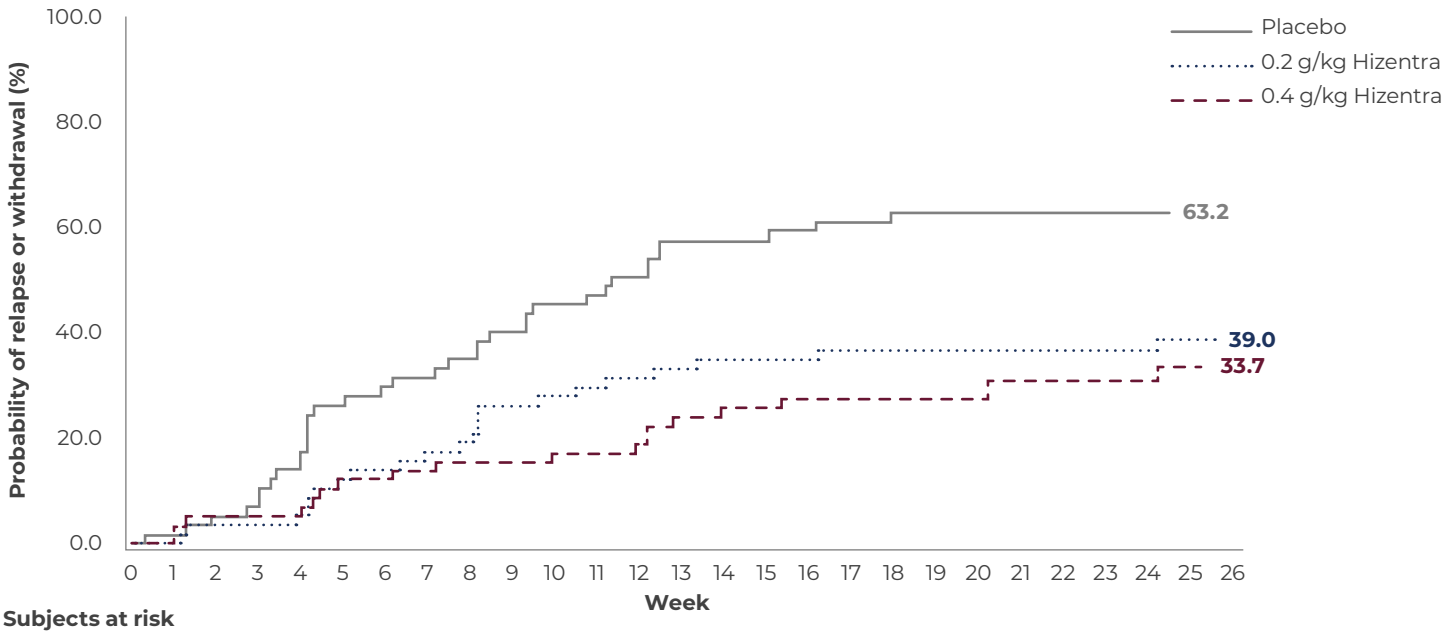
PATH study

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) vs 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 subcutaneous 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 at risk

Placebo	57	49	38	29	24	22	18
0.2	57	55	46	40	38	37	34
0.4	58	55	50	48	43	43	34

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Clinical studies (continued)

Chronic inflammatory demyelinating polyneuropathy (continued)

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.

PATH extension study

The PATH extension study was a multicenter, 48-week, open-label extension study that evaluated the long-term safety and efficacy of Hizentra 0.2 g/kg and 0.4 g/kg doses in the maintenance treatment of CIDP in subjects who either completed or were being successfully rescued from CIDP relapse with IGIV treatment in the PATH study.

A total of 82 subjects were enrolled. In the study, subjects who started on a Hizentra 0.2 g/kg dose were up-titrated to 0.4 g/kg dose if they relapsed. In the case of no relapse, subjects remained at a dose of 0.2 g/kg. Subjects who started on a Hizentra 0.4 g/kg dose were down-titrated to 0.2 g/kg dose after 24 weeks of treatment and subjects who relapsed on a Hizentra 0.2 g/kg dose were up-titrated to a 0.4 g/kg dose. Due to the study design, the same subject could have received both doses during the study; 72 subjects received doses of 0.4 g/kg, and 73 subjects received doses of 0.2 g/kg during the efficacy evaluation period.

Subjects who completed the PATH study without relapse on a 0.4 g/kg dose and initially received this dose in the PATH extension study had a relapse rate of 5.6% (1/18 subjects). Subjects who completed the PATH study without relapse on a 0.2 g/kg dose and initially received this dose in the extension study had a relapse rate of 50% (3/6 subjects).

For all subjects who received 0.4 g/kg in the PATH extension study, 9.7% (7/72 subjects) had a relapse. For all subjects who received 0.2 g/kg in the PATH extension study, 47.9% (35/73 subjects) had a relapse.

After down-titrating from Hizentra 0.4 g/kg to 0.2 g/kg, 50% (26/52) of subjects relapsed, of whom 92% (24/26) recovered after returning to Hizentra 0.4 g/kg. A total of 35 subjects relapsed on Hizentra 0.2 g/kg dose, of which 89% (31/35) subjects recovered after returning to 0.4 g/kg dose.

Both the PATH and PATH extension studies demonstrated that Hizentra 0.2 g/kg or 0.4 g/kg dose was effective in preventing CIDP relapse when administered weekly, with the Hizentra 0.4 g/kg dose more likely to prevent relapse.

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How supplied, storage, and handling

Hizentra is supplied in a prefilled syringe or a 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.

Each product presentation includes a package insert and the components described in Table 12.

Table 12. How supplied

Prefilled syringe presentation	Carton NDC number	Components
5 mL	44206-456-21	Prefilled syringe containing 1 gram of protein (NDC 44206-456-94)
10 mL	44206-457-22	Prefilled syringe containing 2 grams of protein (NDC 44206-457-95)
20 mL	44206-458-24	Prefilled syringe containing 4 grams of protein (NDC 44206-458-96) with plunger rod
50 mL	44206-455-25	Prefilled syringe containing 10 grams of protein (NDC 44206-455-97) with plunger rod

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

NDC=National Drug Code.

Storage and handling

- Store the Hizentra prefilled syringe or vial in its original carton to protect it from light
- Each prefilled syringe or vial label contains a peel-off strip with the prefilled syringe or 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 of the prefilled syringe or vial label
- Do not shake the Hizentra prefilled syringe or vial
- Do not freeze. Do not use product that has been frozen
- Discard any unused product and all used disposable supplies after each infusion

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Patient counseling information

Advise the patient to read the FDA-approved patient labeling (Information for Patients and Instructions for Use).

Inform the patient 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)
- 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
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting
- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath
- Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever

Inform the patient that because Hizentra is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Inform the patient that Hizentra may interfere with the response to live virus vaccines (eg, measles, mumps, rubella, and varicella) and to notify their immunizing physician of recent therapy with Hizentra.

Home treatment with subcutaneous administration

- If self-administration is deemed to be appropriate, ensure that the patient receives clear instructions and training on subcutaneous administration in the home or other appropriate setting and has demonstrated the ability to independently administer subcutaneous infusions
- Ensure the patient understands the importance of adhering to their prescribed administration schedule to maintain appropriate steady IgG levels
- Instruct the patient to scan the prefilled syringe or vial if recording the infusion electronically and keep a diary/log book that includes information about each infusion such as the time, date, dose, lot number(s), and any reactions
- Inform the patient that mild to moderate local infusion-site reactions (eg, swelling and redness) are a common side effect of subcutaneous therapy, but to contact their healthcare professional if a local reaction increases in severity or persists for more than a few days
- Inform the patient of the importance of having an infusion needle long enough to reach the subcutaneous tissue and of changing the actual site of infusion with each infusion. Explain that Hizentra is for subcutaneous infusion only
- Inform the patient to consider adjusting the infusion-site location, volume per site, and rate of infusion based on how infusions are tolerated
- Inform the patient to interrupt or terminate the Hizentra infusion if a hypersensitivity reaction occurs
- Inform PI patients that they should be tested regularly to make sure they have the correct levels of Hizentra (IgG) in their blood. These tests may result in adjustments to the Hizentra dose

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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.

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 (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.

Indications

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, 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 full prescribing information for Hizentra including boxed warning.

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

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