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The Clinical Evidence in Support of HIZENTRA for Primary Immunodeficiency (PI)

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Important Safety Information

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Hizentra: 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.

Hizentra: Important Safety Information

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.

About Primary Immunodeficiency

WHAT IS IT?

Inherited disorders of the immune system predisposing individuals to infection, immune dysregulation with autoimmune disease and malignancy[1]

DISEASE OVERVIEW

Increased susceptibility to severe, recurrent infections which can occur in any part of the body, including the skin, sinuses, throat, ears, lungs, brain or spinal cord, urinary or intestinal tracts[2]

EPIDEMIOLOGY

>450 types of PI are recognized by the International Union of Immunological Societies[2]

1 in 1200 people diagnosed with PI in the United States[3]

National Institute of Health estimates 500,000 individuals affected in US[4]

PI, primary immunodeficiency.

1. Bonilla FA et al. *Ann Allergy Asthma Immunol.* 2005;94:S1-S63. **2.** Immune Deficiency Foundation. https://primaryimmune.org/about-primary-immunodeficiencies. Accessed February 21, 2023. **3.** McCusker et al. *Allergy Asthma Clin Immunol*. 2018; 14:61. **4.** National Institutes of Health. https://www.niaid.nih.gov/diseases-conditions/primary-immune-deficiency-diseases-pidds. Accessed February 21, 2023.

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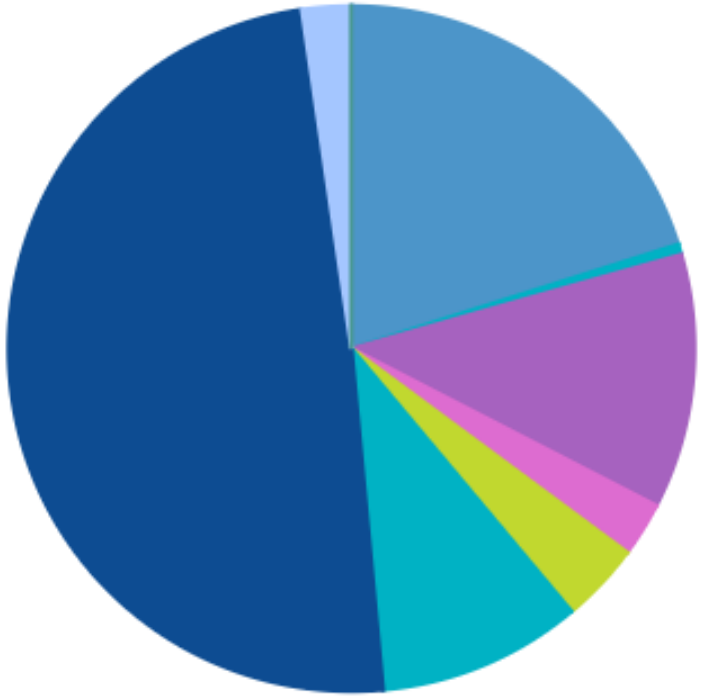
Major Categories of PI (US)

Distribution of PIDs registered in the USID database



Category	Examples
Predominantly Antibody Deficiencies	• CVID • Agammaglobulinemia
Combined immunodeficiencies with associated or syndromic features	• DiGeorge Syndrome • Wiskott-Aldrich Syndrome
Congenital defects of phagocyte number or function	• Chronic Granulomatous Disease
Immunodeficiencies affecting cellular and humoral immunity	• Severe Combined Immune Deficiency (SCID) • Hyper IgM Syndrome
Diseases of Immune Dysregulation	• HLH, including XLP and Pigmentary disorders • Autoimmune lymphoproliferative syndrome (ALPS)
Defects in Intrinsic and Innate Immunity	• Mucocutaneous candidiasis • NK Cell Defect
Other	• Other immune deficiency – known/unknown cause
Complement Deficiencies	• Complement Deficiency

USIDNET Patient Registry. Available at: https://usidnet.org/registry-data/stats-registry-enrollment/ . Accessed February 28, 2023.

Warning Signs of Primary Immunodeficiency

Children

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within 1 year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections including septicemia
10. A family history of PI

Adults

1. Two or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year, in the absence of allergy
3. One pneumonia per year for more than1 year
4. Chronic diarrhea with weight loss
5. Recurrent viral infections (colds, herpes, warts, condyloma)
6. Recurrent need for intravenous antibiotics to clear infections
7. Recurrent, deep abscesses of the skin or internal organs
8. Persistent thrush or fungal infection on skin or elsewhere
9. Infection with normally harmless tuberculosis-like bacteria
10. A family history of PI

Jeffrey Modell Foundation. https://info4pi.org/library/educational-materials/. Accessed March 3, 2023

Presentation of Primary Immunodeficiency

- Clinical presentation is highly variable and may present at any age[1]
- Individuals with PI are predisposed to severe and frequent infections[1]
- PI's may present as routine infections, often of the sinuses, ears and lungs, and go undetected in the primary care setting[1]
  - These recurrent and severe infections can lead to lung damage and shorten lifespan[2]
- Early diagnosis is critical for preventing disease-associated morbidity and mortality[1]
  - PI, particularly Common Variable Immunodeficiency (CVID), is also associated with:
    - Immune dysregulation and autoimmune disease[3]
    - Malignancy[4]

1. McCusker C, Warrington R. *Allergy, Asthma Clin Immunol.* 2011;7(Suppl 1):S11. **2**. Kobrynski L. *Biologics.* 2012;6:277–287. **3**. Agarwal S et al. *Ann Allergy Asthma Immunol*. 2019;123(5):454-460.
4. Shapiro RS. *Am J Hematol.* 2011;86:49–55.

PI Diagnostic Challenges: Comorbid Conditions

Comorbidities may confound diagnosis of PI

Respiratory

- Most common organ specific complication, particularly in CVID[1]
- High prevalence of lung disease is likely due to recurrent sinopulmonary infections that occur in PI patients[1]
- Inflammatory lung disease occurs in 30-60% of CVID patients[2]

Autoimmune/Autoinflammatory

- In CVID, usually manifests as autoimmune cytopenia, with immune thrombocytopenic purpura (ITP) and sometimes autoimmune hemolytic anemia (AIHA)[2]
- Autoimmune cytopenia diagnosis precedes a PI diagnosis in 60% of patients[1]
- Gastrointestinal inflammatory conditions are common[2]
- Chronic infection (e.g., with mycoplasma) has been identified in the synovial fluid of some patients[4-6]

Malignancy

- PIs are associated with a higher prevalence of malignancy (lymphoma and gastric carcinoma)[1]
- Cited as the second leading cause of death after infections in PI patients[3]

1. Dilley M, et al. *Allergy Asthma Proc* 2021 42:78-86. **2**. Agarwal S, et al. *Ann Allergy Asthma Immunol.* 2019;123(5):454-460. **3.** Shapiro RS, et al. *Am J Hematol*. 2011;86(1):48-55. **4**. Azizi G, et al. *Scand J Immunol.* 2018; 87(5):e12663. 5. Kitcharoensakkul M and Cooper MA. *Curr Opin Allergy Clin Immunol.* 2019;19(6):545-552. **6**. Gutierrez MJ, et al. *Semin Arthritis Rheum.* 2018;48(2):318-326.

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Pivotal Trials in Primary Immunodeficiency

Efficacy and Safety of a New 20% Immunoglobulin Preparation for Subcutaneous Administration, IgPro20, in Patients With Primary Immunodeficiency (US Trial)

AND

Efficacy and safety of Hizentra® in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy (EU Trial)

Pivotal Trials in PI: Study Design

	US Study[1]	EU Study[2]
Objective	To evaluate the efficacy and safety of Hizentra in patients with primary immunodeficiency (PI)	
Clinical Sites	12	15
Eligible PIDs	• Common variable immunodeficiency (CVID) or X-linked agammaglobulinemia (XLA) • The EU Trial also allowed patients with autosomal recessive agammaglobulinemia (ARAG)	
Patient Ages	5–72 years	2–65 years
Other Inclusion Criteria	• Regular IVIg therapy every 3 to 4 weeks for at least 3 months prior to enrollment • The EU study also allowed patients using weekly SCIg therapy for at least the preceding 6 months • Documented serum IgG trough level(s) of ≥5 g/L during this time	
Exclusion Criteria	• Newly diagnosed PID (previously untreated with IVIG) • Evidence of an active serious infection • Malignancies of lymphoid cells and immunodeficiency with thymoma • Known hyperprolinemia, hypoalbuminemia, protein-losing enteropathies, or proteinuria • Allergic reactions to immunoglobulins or other blood products • Known antibodies to IgA • Treatment with steroids or other immunosuppressants • Pregnancy or breast feeding	
Study Type	Phase III, open-label, prospective, multicenter, single-arm	
No. of Patients Enrolled	49	51
Dose Adjustment Coefficient	1.53	1.0
Treatment Duration	15 months	10 months

1. Hagan JB, et al. *J Clin Immunol.* 2010;30:734-745. **2**. Jolles S, et al. *Clin Immunol.* 2011:141:90-102.

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Pivotal Trials in PI: Endpoints

	US Study	EU Study[1]
Primary Endpoint	Annual rate of serious bacterial infections* (aSBI)	Serum IgG trough levels at steady state
Secondary Endpoints	• Rate of serious bacterial infections in the ITT population • Number of infection episodes • Number of days missed from work/school/day care or inability to perform normal activities due to infections • Number of days of hospitalization due to infections • Use of antibiotics for infection prophylaxis or treatment • Trough serum IgG levels	• Rate of documented serious bacterial infections • Number of infection episodes • Number of days missed from work/school/kindergarten/day care or inability to perform normal activities due to infections • Number of days of hospitalization due to infections • Use of antibiotics for infection prophylaxis or treatment

*Serious bacterial infections defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess

1. Jolles S, et al. *Clin Immunol.* 2011:141:90-102

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Pivotal Trials in PI: Efficacy

Endpoints		US Study (n=38)	EU Study[1‡] (n=46)
Events per Patient-Year	Serious bacterial infection	0.00	0.00
	Any infection	2.76	5.18
Days per Patient-Year	Unable to perform usual activities or days missed from work/school	2.06	8.00
	Hospitalized due to infections	0.2	3.48
	Use of antibiotics for prophylaxis or treatment	48.5	72.75
Mean trough IgG level†, mg/dL		1253	810

†Mean of individual median levels during the study treatment period.

‡Data include 1 patient who suffered from recurrent pneumonias. Inclusion of these data affected the overall rates reported above. Annual rates per subject year excluding this subject were as follows: all infection episodes 5.16; days missed from school/work 5.25; hospitalized due to infections 0.95; use of antibiotics 66.62.

1. Jolles S, et al. *Clin Immunol.* 2011:141:90-102

Safety and Tolerability: US Trial

		% of Patients (n=49)	Rate, % of infusions† (n=2264 infusions)
Serious ARs* Considered at Least Possibly Related		0	0
Local Reactions‡		100	58.4
Systemic ARs* Observed in ≥5% of Study Patients Occurring During or Within 72h After Completion of an Infusion	Headache	24.5	1.4
	Diarrhea	10.2	0.3
	Fatigue	8.2	0.2
	Back Pain	8.2	0.2
	Nausea	8.2	0.2
	Cough	8.2	0.2
	Pain in Extremity	8.2	0.3
	Vomiting	6.1	0.1
	Upper Abdominal Pain	6.1	0.1
	Migraine	6.1	0.2
	Pain	6.1	0.2

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

Safety and Tolerability: EU Trial

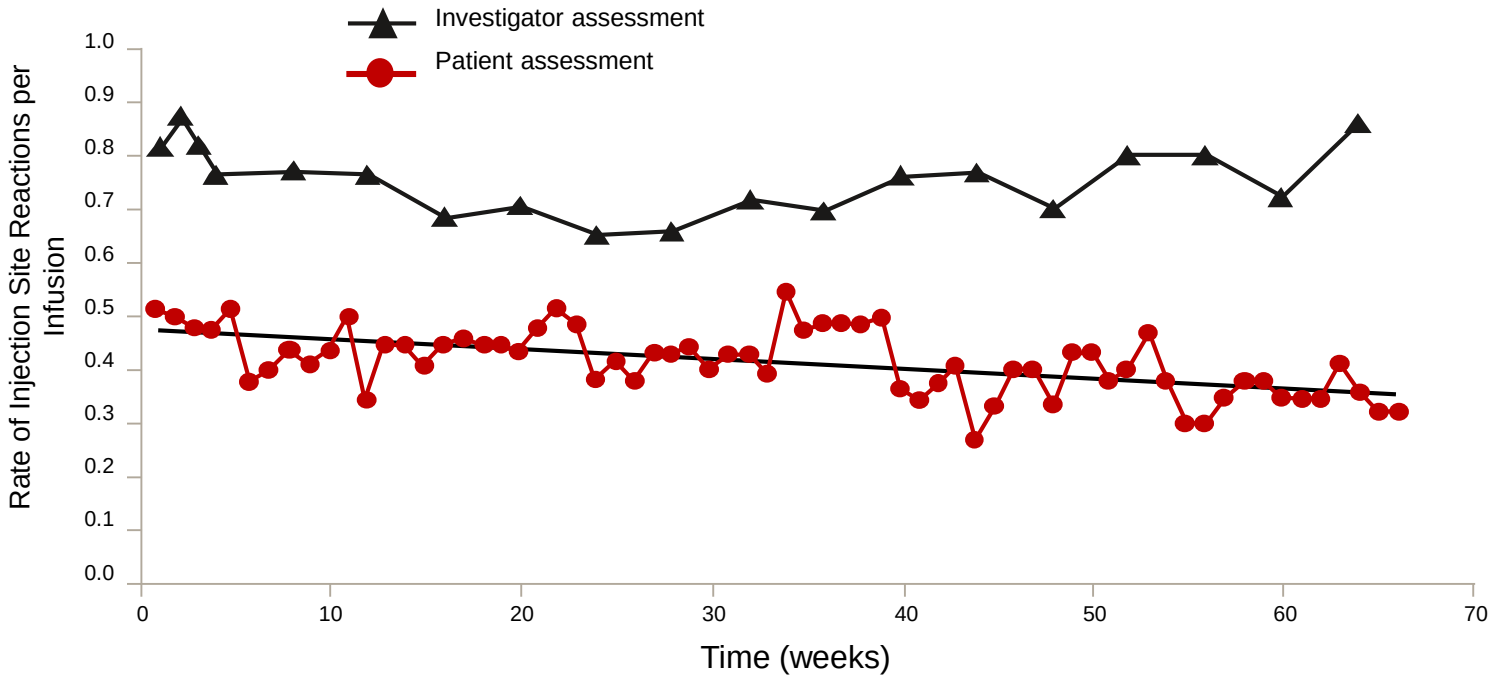
		% of Patients (n=51)	Rate, % of infusions† (n=1831 infusions)
Serious ARs* Considered at Least Possibly Related		0	0
Local Reactions‡		47.1	5.7
Systemic ARs* Observed in ≥5% of Study Patients Occurring During or Within 72h After Completion of an Infusion	Headache	17.6	1.1
	Rash	7.8	0.2
	Pruritus	7.8	0.7
	Fatigue	5.9	0.3

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

1. Jolles S, et al. *J Clin Immunol.* 2011;141:90-102.

Local Reactions

Occurrence of Local Reactions as Assessed by Patients and Investigators in a US study[1]*



% of local reactions reported as mild

93.4% US clinical study[1]

87.3% EU clinical study[2]

Withdrawal due to local reactions
US clinical trial: 2%
EU clinical trial: 5.9%

*Investigator assessments: performed 15 to 45 minutes post infusion at the study site, every 4 weeks; patient assessment: 24 ±3 hours post each infusion until completion of the study (completion visit, week 66). The number of infusions with available data decreased from 49 at week 1 to 28 at week 64 for both patient and investigator assessments.
Reprinted with permission from Hagan JB et al. *J Clin Immunol.* 2010;30:734-745.

1. Hagan JB et al. *J Clin Immunol*. 2010;30:734-745. **2.** Jolles S et al. *Clin Immunol*. 2011:141:90-102.

Hizentra (20% SCIg) PI Pivotal Trial Results for US, EU

FDA predefined success rate of <1 aSBI per subject year

	US Study (n=49)	EU Study[1] (n=51)
Dose	1:1.53	1:1
Duration, weeks	64	40
Infections		
Annual rate of SBI per subject year	0	0
Annual rate for any infection per subject year	2.76	5.18
Adverse Reactions		
Any adverse events per infusion	0.773	0.288
Local reactions per infusion	0.584	0.060

aSBI: acute SBI; SBI: serious bacterial infection (defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess); FDA: US Food and Drug Administration; PI: primary immunodeficiency; SCIg: subcutaneous immunoglobulin.

1. Jolles S, et al. *Clin Immunol.* 2011:141:90-102

Hizentra Overview

Hizentra Dosing in PI

PI

- Obtain patient's serum IgG trough level
- Start Hizentra 1–2 weeks after last IVIg infusion or 1 week after the last SCIg infusion
- Initial dosing calculations:
  - **Weekly dose:** $\frac{\textit{Monthly IVIg dose in g}}{\textit{Number of weeks between infusions}} \times 1.37$
  - **Every 2 weeks:** $Weekly\ dose \times 2$
  - **Frequent dosing*:** $\frac{\textit{Weekly dose in g}}{\textit{Number of days to infuse per week}}$
- Adjust the dose based on clinical response and IgG trough levels
- To convert the dose from grams to milliliters, multiply the calculated dose in grams by 5

*2–7 times per week.

Hizentra Administration in PI

Hizentra is intended for subcutaneous administration using an infusion pump

INFUSION PUMP Daily up to every 2 weeks		
Infusion parameters*	**1st infusion**	**Subsequent infusions**
Volume (mL/site)	≤15	≤25
Rate (mL/h/site)	≤15	≤25
Infusion sites	Up to 8 infusion sites allowed simultaneously, with at least 2 inches between sites	

*As tolerated.

Hizentra: Additional Information

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.

Storage and Handling

- Keep HIZENTRA in its original carton to protect it from light
- Each prefilled syringe or vial 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 25ºC [77ºF]), 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 the HIZENTRA prefilled syringe or vial
- Do not freeze