

Finally! On-Demand Treatment

for Acute Abdominal or
Facial Attacks of HAE*
in Adults and Adolescents



On-demand means treating patients with Berinert® when an acute abdominal or facial attack occurs.

For example, if a patient has 7 abdominal or facial attacks in a year, you treat the patient 7 times.

*Hereditary angioedema.

Important Safety Information

Berinert®, C1 Esterase Inhibitor (Human) is a plasma-derived concentrate of C1 Esterase Inhibitor (Human), indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients. The safety and efficacy of Berinert® for prophylactic therapy have not been established.

Berinert® is contraindicated in individuals who have experienced an anaphylactic or severe systemic reaction to C1 esterase inhibitor preparations.

Monitor patients for early signs of allergic or hypersensitivity reactions

(including hives, generalized urticaria, chest tightness, wheezing, hypotension, and anaphylaxis). If hypersensitivity is suspected, immediately discontinue administration and initiate appropriate treatment. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reactions.

Thrombotic events have occurred in patients receiving off-label high doses of Berinert®. Monitor patients with known risk factors for thrombotic events.

Berinert® is derived from human plasma. The risk of transmission of infectious

agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

The most serious adverse reaction reported in subjects in clinical studies who received Berinert® is an increase in the severity of pain associated with HAE. The most common adverse reactions observed in more than 4% of subjects after Berinert® treatment were headache, abdominal pain, nausea, muscle spasms, pain, diarrhea, and vomiting.

Berinert® has not been evaluated in pregnant women or nursing mothers; benefits of

treatment should be weighed against potential risks in pregnant women, and Berinert® should be given to nursing mothers only if clearly needed. The safety and efficacy of Berinert® have not been established in children (ages 0 through 12) or in the geriatric population.

Please see Brief Summary of Prescribing Information on following pages.

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BERINERT®
C1 Esterase Inhibitor, Human
On-Demand Treatment

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Berinert®, C1 Esterase Inhibitor (Human) is for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients. The safety and efficacy of Berinert® for prophylactic therapy have not been established.



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BERINERT[®]
C1 Esterase Inhibitor, Human
On-Demand Treatment

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Biotherapies for Life[™] **CSL Behring**

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Berinert® [C1 Esterase Inhibitor (Human)]
Freeze-dried powder

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

1 INDICATIONS AND USAGE

Berinert is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients. The safety and efficacy of Berinert for prophylactic therapy have not been established.

4 CONTRAINDICATIONS

Berinert is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction (see Patient Counseling Information [17]). The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of Berinert. Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered. In case of suspected hypersensitivity, immediately discontinue administration of Berinert and institute appropriate treatment.

5.2 Thrombotic Events

Thrombotic events have been reported in association with Berinert when used off-label and at higher than labeled doses.¹ Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor products² (see Overdosage [10] and Animal Toxicology and/or Pharmacology [13.2]).

5.3 Transmission of Infectious Agents

Because Berinert is made from human blood, it may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing (see Description [11] and Patient Counseling Information [17]).

Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Since 1979, a few suspected cases of viral transmission have been reported with the use of Berinert outside the US, including cases of acute hepatitis C. From the incomplete information available from these cases, it was not possible to determine with certainty if the infections were or were not related to prior administration of Berinert. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient. (See Patient Counseling Information [17.1]).

All infections thought by a physician possibly to have been transmitted by Berinert should be reported by lot number, by the physician, or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

6 ADVERSE REACTIONS

The most serious adverse reaction reported in subjects enrolled in clinical studies who received Berinert was an increase in the severity of pain associated with HAE. The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert in clinical studies were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasms, pain, diarrhea and vomiting.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Placebo-controlled Clinical Study

In the placebo-controlled clinical study, referred to as the randomized clinical trial (RCT) (see Clinical Studies [14]), 124 subjects experiencing an acute moderate to severe abdominal or facial HAE attack were treated with Berinert (either a 10 unit per kg body weight or a 20 unit per kg body weight dose), or placebo (physiological saline solution). The treatment-emergent serious adverse reactions/events that occurred in 5 subjects in the RCT were laryngeal edema, facial attack with laryngeal edema, swelling (shoulder and chest), exacerbation of hereditary angioedema, and laryngospasm.

Table 1: Adverse Reactions* Occurring up to 4 hours After Initial Infusion in More Than 4% of Subjects, Irrespective of Causality[†]

Adverse Reactions	Number (%) of Subjects Reporting Adverse Reactions Berinert 20 units/kg (n = 43)	Number (%) of Subjects Reporting Adverse Reactions Placebo Group (n = 42)
Nausea [†]	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	0 (0)
Abdominal Pain [†]	2 (4.7%)	3 (7.1%)
Vomiting [†]	1 (2.3%)	3 (7.1%)
Diarrhea [†]	0 (0)	4 (9.5%)
Headache	0 (0)	2 (4.8%)

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).
[†] The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.

Table 2: Adverse Reactions* Occurring in More Than 4% of Subjects up to 72 hours After Infusion of Initial or Rescue Medication[†] by Intent-to-Treat, Irrespective of Causality

Adverse Reactions	Number (%) of Subjects Reporting Adverse Reactions* [†] Berinert 20 units/kg (n = 43)	Number (%) of Subjects Reporting Adverse Reactions* [†] Placebo Group (n = 42)
Nausea	3 (7%)	11 (26.2%)
Headache	3 (7%)	5 (11.9%)
Abdominal Pain	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	1 (2.4%)
Vomiting	1 (2.3%)	7 (16.7%)
Pain	1 (2.3%)	4 (9.5%)
Muscle spasms	1 (2.3%)	4 (9.5%)
Diarrhea	0 (0)	8 (19%)
Back pain	0 (0)	2 (4.8%)
Facial pain	0 (0)	2 (4.8%)

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).
[†] If a subject experienced no relief or insufficient relief of symptoms within 4 hours after infusion, investigators had the option to administer a blinded second infusion ("rescue" treatment) of Berinert (20 units/kg for the placebo group or 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group).
[‡] Adverse reactions following either initial treatment and/or blinded "rescue" treatment. Because more subjects in the placebo randomization group than in the Berinert randomization group received rescue treatment, the median observation period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive Berinert.

Table 3 lists the adverse events that occurred in more than 4% of the subjects 7 to 9 days after the end of a Berinert infusion, irrespective of causality.

Table 3: Adverse Events Occurring in More Than 4% of Subjects* Receiving Berinert at Either 10 Units/kg or 20 units/kg 7 to 9 Days after Infusion, Irrespective of Causality

Adverse Events	Number (%) of Subjects Reporting Adverse Events (n=108)
Hereditary angioedema	12 (11.1%)
Headache	12 (11.1%)
Abdominal pain [†]	7 (6.5%)
Nausea [†]	7 (6.5%)
Muscle spasms	6 (5.6%)
Pain	6 (5.6%)
Diarrhea [†]	5 (4.6%)
Vomiting [†]	5 (4.6%)

* Includes subjects in the placebo group who received Berinert 20 units/kg as rescue study medication.
[†] These symptoms were identified in the protocol as related to the underlying disease. Any increase in intensity or new occurrence of these symptoms after study medication administration was considered to be an adverse event.

Subjects were tested at baseline and after 3 months for possible exposure to Parvovirus B19, hepatitis B, hepatitis C, and HIV-1 and HIV-2. No subject who underwent testing evidenced seroconversion or treatment-emergent positive polymerase chain reaction testing for these pathogens.

Extension Study

In an interim safety analysis, of the ongoing open-label extension study, 56 subjects with 559 acute moderate to severe abdominal, facial, peripheral and/or laryngeal attacks received a 20 unit/kg body weight dose of Berinert (see Clinical Studies [14]). This study

provides additional safety data in subjects who received multiple infusions of the product for sequential HAE attacks (one infusion per attack).

Table 4 lists the adverse events that occurred in this interim safety analysis of the ongoing open-label extension study in more than 4% of subjects up to 72 hours or 9 days after the end of a Berinert infusion, *irrespective of causality*.

Table 4: Incidence of Adverse Events by Descending Frequency Occurring in More Than 4% of Subjects Receiving Berinert up to 72 Hours or 9 Days After Infusion, Irrespective of Causality

Adverse Events	Number (%) of Subjects Reporting Adverse Events up to 72 hours (n=56)	Number (%) of Subjects Reporting Adverse Events up to 9 Days (n=56)
Headache	3 (5.4%)	4 (7.1%)
Abdominal pain	3 (5.4%)	3 (5.4%)
Hereditary angioedema	2 (3.6%)	4 (7.1%)
Nasopharyngitis	2 (3.6%)	3 (5.4%)

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. Adverse reactions reported in Europe since 1979 in patients receiving Berinert for treatment of HAE include hypersensitivity/anaphylactic reactions, a few suspected cases of viral transmission, including cases of acute hepatitis C, injection-site pain, injection-site redness, chills, and fever.

The following adverse reactions, identified by system organ class, have been attributed to Berinert during post-approval use outside the US.

- *Immune System Disorder: Hypersensitivity/anaphylactic reactions, and shock*
- *General/Body as a Whole: Pain on injection, redness at injection site, chills, and fever*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

only if clearly needed. In a retrospective case collection study, 20 pregnant women ranging in age from 20 to 35 years received Berinert with repeated doses up to 3,500 units per attack; these women reported no complications during delivery and no harmful effects on their 34 neonates.

8.2 Labor and Delivery

The safety and effectiveness of Berinert administration prior to or during labor and delivery have not been established. Use only if clearly needed.

8.3 Nursing Mothers

It is not known whether Berinert is excreted in human milk. Because many drugs are excreted in human milk, use only if clearly needed when treating a nursing woman.

8.4 Pediatric Use

Safety and efficacy of Berinert in children (ages 0 through 12) have not been established. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from older subjects. The safety and efficacy of Berinert were evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16) (*see Pharmacokinetics [12.3]*).

8.5 Geriatric Use

Safety and efficacy of Berinert in the geriatric population have not been established. Clinical studies with Berinert included four subjects older than 65 years. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from younger subjects.

15 REFERENCES

1. German Medical Profession's Drugs Committee. Severe thrombus formation of Berinert® HS. *Deutsches Ärzteblatt*. 2000;97:B-864.
2. Horstick G *et al.* Application of C1-Esterase Inhibitor During Reperfusion of Ischemic Myocardium: Dose-Related Beneficial Versus Detrimental Effects. *Circulation*. 2002;104:3125-3131.

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Privigen delivers IVIg therapy that is:

Simple.

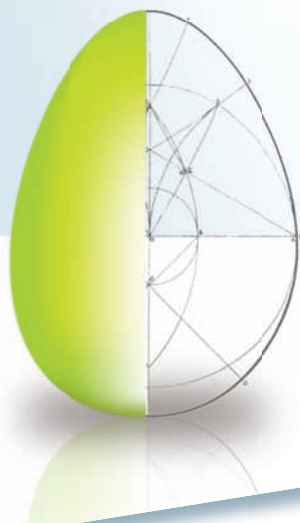
- Ready-to-use 10% liquid IVIg
- Room temperature storage up to 24 months

Sophisticated.

- First and only IVIg stabilized with proline
- Sucrose-free
- IgA ≤ 25 mcg/mL

Safe.

- In clinical trials, 97% of related adverse events were non-serious; 95% of 1038 infusions were administered without premedication
- 3-step virus inactivation/removal process, including nanofiltration to 20 nanometers, minimizes the risk of pathogen transmission



For more information about Privigen, visit **www.Privigen.com**.


privigen®
Immune Globulin Intravenous
(Human), 10% Liquid
IVIg therapy made simple

Important Safety Information

Privigen is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

WARNING: Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with the administration of Immune Globulin Intravenous (Human) (IVIg) products in predisposed patients. Administer IVIg products at the minimum infusion rate possible. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIg products containing sucrose. Privigen does not contain sucrose. See full Prescribing Information for complete Boxed Warning.

Privigen is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin, in patients with hyperprolinemia, and in patients with selective IgA deficiency.

Privigen is manufactured by CSL Behring AG and distributed by CSL Behring LLC. Privigen is a registered trademark of CSL Behring AG.

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In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have been reported with Privigen and other IVIg treatments. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) has been reported infrequently with Privigen and other IVIg treatments; AMS may occur more frequently with high doses and/or rapid infusion of IVIg. Hemolysis, hemolytic anemia, and pulmonary adverse events have also been reported. There have been reports of noncardiogenic pulmonary edema in patients administered IVIg. If transfusion-related acute lung injury is suspected, test product and patient for antineutrophil antibodies.

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

In clinical studies, the most common adverse reactions with Privigen were headache, pain, nausea, pyrexia/hyperthermia, fatigue, and chills.

Please see brief summary of full Prescribing Information on following pages.

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.¹ Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (see **Warnings and Precautions [5.2]**). Privigen does not contain sucrose.

For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (see **Dosage and Administration [2.3]**, **Warnings and Precautions [5.2]**).

1 INDICATIONS AND USAGE

Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of the following conditions.

1.1 Primary Humoral Immunodeficiency

Privigen is indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

1.2 Chronic Immune Thrombocytopenic Purpura

Privigen is indicated for the treatment of patients with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

3 DOSAGE FORMS AND STRENGTHS

Privigen is a liquid solution containing 10% IgG (0.1 g/mL) for intravenous infusion.

4 CONTRAINDICATIONS

Privigen is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.

Because it contains the stabilizer L-proline, Privigen is contraindicated in patients with hyperprolinemia.

Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (see **Contraindications [4]**). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA (≤ 25 mcg/mL) (see **Description [11]**). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction (see **Contraindications [4]**).

5.2 Renal Failure

Ensure that patients are not volume depleted before administering Privigen. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction, administer Privigen at the minimum infusion rate practicable (see **Boxed Warning, Dosage and Administration [2.3]**).

5.3 Hyperproteinemia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Privigen and other IGIV product treatments. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.²

5.4 Thrombotic Events

Thrombotic events may occur following treatment with Privigen and other IGIV products.^{3,5} Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (see **Dosage and Administration [2.3]**). Weigh the potential risks and benefits of IGIV against those of alternative therapies in all patients for whom Privigen therapy is being considered.

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with Privigen (see **Adverse Reactions [6, 6.1]**) and other IGIV product treatments. Discontinuation of IGIV treatment has resulted in remission of AMS

within several days without sequelae.⁶ AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (see **Patient Counseling Information [17]**). Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.^{7,9} Hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration and/or intravascular RBC destruction.¹⁰

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (see **Adverse Reactions [6, 6.1]**). These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data. Monitor patients for clinical signs and symptoms of hemolysis (see **Patient Counseling Information [17]**). If these are present after Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment.¹¹ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions (see **Patient Counseling Information [17]**). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

The high-dose regimen (1 g/kg/day for 2 days) used to treat patients with chronic ITP is not recommended for individuals with expanded fluid volumes or where fluid volume may be of concern (see **Dosage and Administration [2.2]**).

5.9 Transmissible Infectious Agents

Privigen is made from human plasma. Based on effective donor screening and product manufacturing processes (see **Description [11]**), Privigen carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Privigen. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare professional to CSL Behring Pharmacovigilance at 1-866-915-6958. Before prescribing Privigen, the physician should discuss the risks and benefits of its use with the patient (see **Patient Counseling Information [17]**).

5.10 Monitoring: Laboratory Tests

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

If signs and/or symptoms of hemolysis are present after an infusion of Privigen, perform appropriate laboratory testing for confirmation.

If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.11 Interference With Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >10% of clinical study subjects with PI were headache, pain, nausea, fatigue, and chills.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data (see **Warnings and Precautions [5.5, 5.6]**). The most common adverse reactions observed in >10% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia.

6.1 Clinical Trials Experience

Because different clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in practice.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen intravenously every 3 or 4 weeks for up to 12 months (see **Clinical Studies [14.1]**). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 57.5% were male and 42.5% were female.

The safety analysis included all 80 subjects, 16 on the 3-week schedule and 64 on the 4-week schedule. The median doses of Privigen administered intravenously ranged from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg). A

total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule. Of the 1038 infusions, 435 were administered to females and 603 to males.

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint. The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects during a Privigen infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

Table 2: Adverse Events Occurring in >5% of Subjects With PI During a Privigen Infusion or Within 72 Hours After the End of an infusion, *Irrespective of Causality*

Adverse Event	Subjects (%) [n=80]	Infusions (%) [n=1038]
Headache	35 (43.8)	82 (7.9)
Pain	20 (25.0)	44 (4.2)
Fatigue	13 (16.3)	27 (2.6)
Nausea	10 (12.5)	19 (1.8)
Chills	9 (11.3)	15 (1.4)
Vomiting	7 (8.8)	13 (1.3)
Pyrexia	6 (7.5)	10 (1.0)
Cough	5 (6.3)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects).

Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that occurred in one subject and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative direct antiglobulin test (DAT) at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of $20 \times 10^9/L$ or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg intravenous infusions daily for 2 consecutive days (see *Clinical Studies* [14.2]). Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 3 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP during a Privigen infusion or within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen, *irrespective of causality*.

Table 3: Adverse Events Occurring in >5% Subjects With Chronic ITP During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle*, *Irrespective of Causality*

Adverse Event	Subjects (%) [n=57]	Infusions (%) [n=114]
Headache	37 (64.9)	41 (36.0)
Pyrexia/hyperthermia	21 (36.8)	22 (19.3)
Nausea	6 (10.5)	6 (5.3)
Epistaxis	6 (10.5)	6 (5.3)
Vomiting	6 (10.5)	6 (5.3)
Blood unconjugated bilirubin increased	6 (10.5)	6 (5.3)
Blood conjugated bilirubin increased	5 (8.8)	5 (4.4)
Blood total bilirubin increased	4 (7.0)	4 (3.5)
Hematocrit decreased	3 (5.3)	3 (2.6)

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding, which was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse events is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

Privigen Postmarketing Experience

Adverse reactions reported during worldwide postmarketing use of Privigen do not differ from what has been observed in clinical studies with Privigen and from what is known for IGIV products.

General

The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.¹²

Renal: Acute renal dysfunction/failure, osmotic nephropathy

Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm

Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension

Neurological: Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome

Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis

Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test

Musculoskeletal: Back pain

Gastrointestinal: Hepatic dysfunction, abdominal pain

General/Body as a Whole: Pyrexia, rigors

7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, and rubella.¹³ The immunizing physician should be informed of recent therapy with Privigen so that appropriate measures may be taken (see *Patient Counseling Information* [17]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Privigen. It is not known whether Privigen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Privigen should be given to pregnant women only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.^{14,15}

8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use

Treatment of Primary Humoral Immunodeficiency
Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI. There were no apparent differences in the safety and efficacy profiles as compared to those in adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen have not been established in pediatric patients with PI who are under the age of 3.

Treatment of Chronic Immune Thrombocytopenic Purpura

Safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of 15.

8.5 Geriatric Use

Clinical studies of Privigen did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Use caution when administering Privigen to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency (see *Boxed Warning, Warnings and Precautions* [5.2]). Do not exceed recommended doses, and administer Privigen at the minimum infusion rate practicable.

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Important Safety Information

Immune Globulin Subcutaneous (Human), Hizentra, is indicated as replacement therapy for patients with primary humoral immunodeficiency (PI). This includes but is not limited to the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Hizentra is contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin preparations or components of Hizentra, such as polysorbate 80. Because it contains the stabilizer L-proline, Hizentra is contraindicated in patients with hyperprolinemia. Hizentra is also contraindicated in patients with immunoglobulin A deficiency who have known antibody against IgA and a history of hypersensitivity.

All IgA-deficient patients with anti-IgA antibodies are at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. If hypersensitivity occurs or anaphylactic reactions are suspected, discontinue administration immediately and treat as medically appropriate.

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

The most common drug-related adverse reactions (observed in 5% or more of subjects in the clinical trial) were local reactions (ie, swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

Monitor patients for reactions reported to occur with IVIg treatment that might also occur with Hizentra, including renal dysfunction/failure, thrombotic events, aseptic meningitis syndrome (AMS), hemolysis, and transfusion-related acute lung injury (TRALI).

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

No overall differences in safety or efficacy were observed in patients over 65 or in pediatric patients. In the clinical study, desired serum IgG levels were achieved in pediatric patients without pediatric-specific dose requirements.

Please see brief summary of full Prescribing Information on next page.

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*Primary immunodeficiency disease.
†Subcutaneous immunoglobulin.

Hizentra™
Immune Globulin Subcutaneous
(Human) 20% Liquid

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

4 CONTRAINDICATIONS

Hizentra is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80.

Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (see Description [11]).

Hizentra is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (see Description [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur to human immune globulin or components of Hizentra, such as polysorbate 80. In case of hypersensitivity, discontinue the Hizentra infusion immediately and institute appropriate treatment.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Hizentra. Hizentra contains 50 mcg/mL IgA (see Description [11]).

5.2 Reactions Reported to Occur With IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

Renal Dysfunction/Failure

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter.

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.¹ If renal function deteriorates, consider discontinuing Hizentra. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Hizentra at the minimum rate practicable.

Thrombotic Events

Thrombotic events may occur with use of human immune globulin products²⁻⁴. Patients at increased risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Hizentra at the minimum rate practicable.

Aseptic Meningitis Syndrome (AMS)

AMS may occur with use of human immune globulin products.⁵ The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including 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, with 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 IGIV.

Conduct a thorough neurological examination, including CSF studies, to rule out other causes of meningitis in patients exhibiting signs and symptoms of AMS. Discontinuation

of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis

Hizentra can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.⁶⁻⁸ Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.⁹

Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If these are present after a Hizentra infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Hizentra, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.¹⁰ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

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

5.3 Transmissible Infectious Agents

Because Hizentra is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Hizentra.

Report all infections thought to be possibly transmitted by Hizentra to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.4 Laboratory Tests

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

6 ADVERSE REACTIONS

The most common adverse reactions (ARs), observed in 5% of study subjects receiving Hizentra, were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, AR rates observed in clinical studies of a product cannot be directly compared to rates in the clinical studies of another product and may not reflect the rates observed in clinical practice.

The safety of Hizentra was evaluated in a clinical study for 15 months in subjects with PI who had been treated previously with IGIV every 3 or 4 weeks. The safety analyses included 49 subjects in the intention-to-treat (ITT) population. The ITT population consisted of all subjects who received at least one dose of Hizentra (see Clinical Studies [14]).

Subjects were treated with Hizentra at weekly doses ranging from 66 to 331 mg/kg body weight during the wash-in/wash-out period and from 72 to 379 mg/kg during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

No deaths or serious ARs occurred during the study. Two subjects withdrew from the study due to ARs. One subject experienced a severe injection-site reaction one day after the third weekly infusion, and the other subject experienced moderate myositis. Both reactions were judged to be "at least possibly related" to the administration of Hizentra.

Table 2 summarizes the most frequent adverse events (AEs) (experienced by at least 4 subjects), *irrespective of causality*. Included are all AEs and those considered temporally associated with the Hizentra infusion, i.e., occurring during or within 72 hours after the end of an infusion. Local reactions were the most frequent AEs observed, with injection-site reactions (i.e., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

Table 2: Incidence of Subjects With Adverse Events (AEs)* (Experienced by 4 or More Subjects) and Rate per Infusion, *Irrespective of Causality* (ITT Population)

AE (4 Subjects)	All AEs*		AEs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate ¹) of AEs (n=2264 Infusions)	Number (%) of Subjects (n=49)	Number (Rate ¹) of AEs (n=2264 Infusions)
Local reactions [†]	49 (100)	1340 (0.592)	49 (100)	1322 (0.584)

Table 2: (Continued)

AE (4 Subjects)	All AEs*		AEs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate [†]) of AEs (n=2264 Infusions)	Number (%) of Subjects (n=49)	Number (Rate [†]) of AEs (n=2264 Infusions)
Other AEs:				
Headache	13 (26.5)	40 (0.018)	12 (24.5)	32 (0.014)
Cough	8 (16.3)	9 (0.004)	5 (10.2)	6 (0.003)
Diarrhea	7 (14.3)	8 (0.004)	5 (10.2)	6 (0.003)
Fatigue	6 (12.2)	6 (0.003)	4 (8.2)	4 (0.002)
Back pain	5 (10.2)	11 (0.005)	4 (8.2)	5 (0.002)
Nausea	5 (10.2)	5 (0.002)	4 (8.2)	4 (0.002)
Abdominal pain, upper	5 (10.2)	5 (0.002)	3 (6.1)	3 (0.001)
Rash	5 (10.2)	7 (0.003)	2 (4.1)	3 (0.001)
Pain in extremity	4 (8.2)	7 (0.003)	4 (8.2)	6 (0.003)
Migraine	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Pain	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Epistaxis	4 (8.2)	6 (0.003)	2 (4.1)	3 (0.001)
Pharyngolaryngeal pain	4 (8.2)	6 (0.003)	2 (4.1)	2 (<0.001)
Arthralgia	4 (8.2)	5 (0.002)	2 (4.1)	3 (0.001)

* Excluding infections.

† Rate of AEs per infusion.

‡ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

The ratio of infusions with temporally associated AEs, including local reactions, to all infusions was 1338 to 2264 (59.1%; upper 95% confidence limit of 62.4%). Excluding local reactions, the corresponding ratio was 173 to 2264 (7.6%; upper 95% confidence limit of 8.9%).

Table 3 summarizes the most frequent ARs (i.e., those AEs considered by the investigators to be “at least possibly related” to Hizentra administration) experienced by at least 2 subjects.

Table 3: Incidence of Subjects With Adverse Reactions (Experienced by 2 or More Subjects) to Hizentra and Rate per Infusion (ITT Population)

Adverse Reaction (2 Subjects)	Number (%) of Subjects (n=49)	Number (Rate*) of Adverse Reactions (n=2264 Infusions)
Local reactions [†]	49 (100)	1338 (0.591)
Other ARs:		
Headache	12 (24.5)	36 (0.016)
Vomiting	3 (6.1)	3 (0.001)
Pain	3 (6.1)	4 (0.002)
Fatigue	3 (6.1)	3 (0.001)
Contusion	2 (4.1)	3 (0.001)
Back pain	2 (4.1)	3 (0.001)
Migraine	2 (4.1)	3 (0.001)
Diarrhea	2 (4.1)	2 (<0.001)
Abdominal pain, upper	2 (4.1)	2 (<0.001)
Nausea	2 (4.1)	2 (<0.001)
Rash	2 (4.1)	2 (<0.001)
Arthralgia	2 (4.1)	2 (<0.001)

* Rate of ARs per infusion.

† Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

Table 4 summarizes injection-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 Assessments* of Injection-Site Reactions by Infusion

Injection-Site Reaction	Number [†] (Rate [‡]) of Reactions (n=683 Infusions [§])
Edema/induration	467 (0.68)
Erythema	346 (0.50)
Local heat	108 (0.16)
Local pain	88 (0.13)
Itching	64 (0.09)

* 15 to 45 minutes after the end of infusions administered at regularly scheduled visits (every 4 weeks).

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

‡ Rate of injection-site reactions per infusion.

§ Number of infusions administered during regularly scheduled visits.

Most local reactions were either mild (93.4%) or moderate (6.3%) in intensity.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during the postmarketing use of IGIV products¹¹:

- **Infusion reactions:** Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- **Renal:** Acute renal dysfunction/failure, osmotic nephropathy
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- **Hematologic:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain
- **General/Body as a Whole:** Pyrexia, rigors

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

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

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

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

8.4 Pediatric Use

Hizentra was evaluated in 10 pediatric subjects (3 children and 7 adolescents) with PI. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Hizentra was not evaluated in neonates or infants.

8.5 Geriatric Use

Of the 49 subjects evaluated in the clinical study of Hizentra, 6 subjects were 65 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger subjects.

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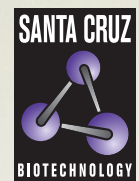
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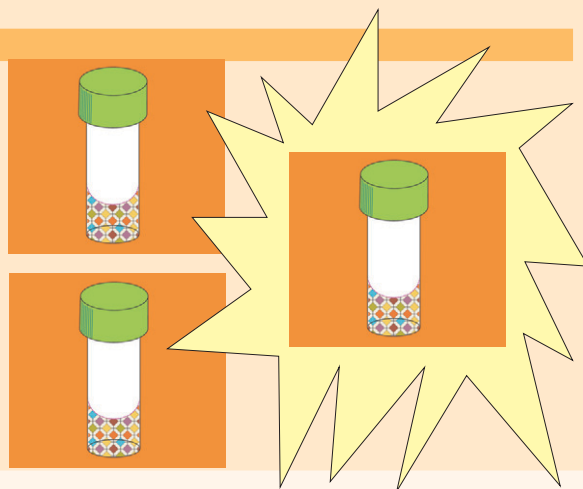
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SF20
TNF alpha
VEGF

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SDF-1b/CXCL12

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BD Biosciences flow cytometry systems

2003

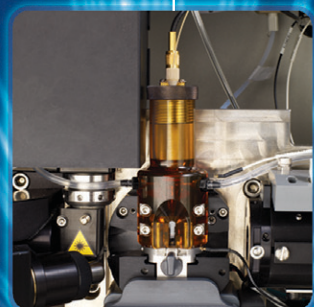
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2007

2009



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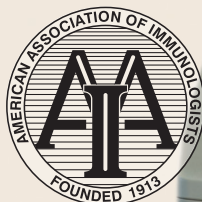
GRIP

Grant Review for Immunologists Program

Get a GRIP: An AAI program designed to help new investigators prepare their NIH grant proposals

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BD Biosciences flow cytometry systems

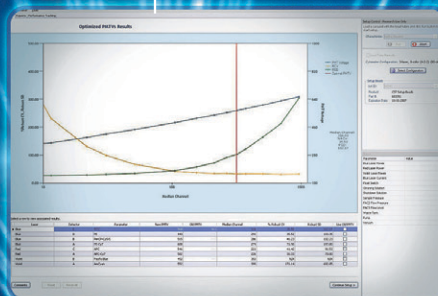
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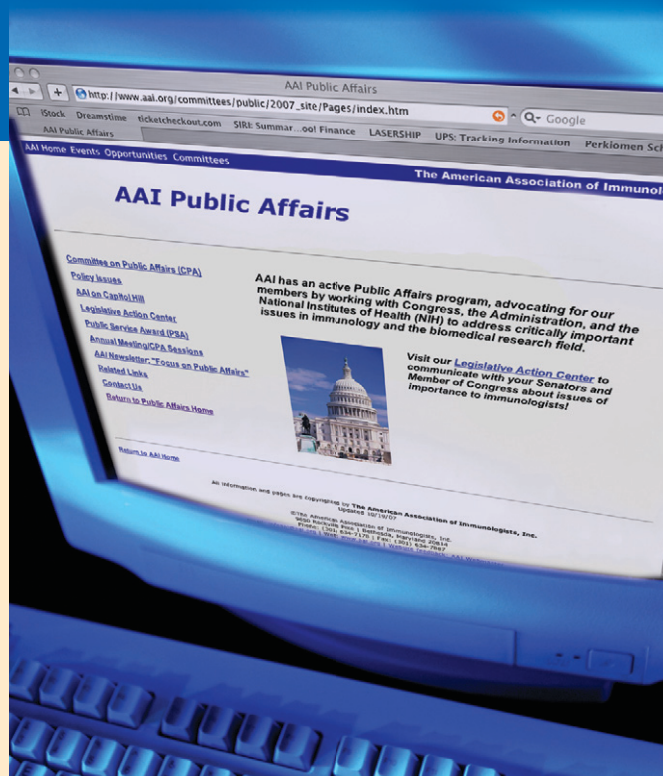
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