

# Excellence and Innovation in Manufacturing

The leading Ig therapies of CSL Behring

  
**privigen**<sup>®</sup>  
Immune Globulin Intravenous  
(Human), 10% Liquid

  
**Hizentra**<sup>®</sup>  
Immune Globulin Subcutaneous  
(Human) 20% Liquid



Biotherapies for Life<sup>®</sup> **CSL Behring**

Please see full Important Safety Information for Hizentra and Privigen on pages 16–17 and full prescribing information for both products, including boxed warning, in pocket.

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## CSL Behring: A Leader in Ig Therapy

CSL Behring is a global leader in the plasma protein biotherapeutics industry. We have more than a century of experience in researching, developing, and manufacturing therapies, and are committed to saving and improving the lives of people with rare and serious diseases worldwide. Among the patients we help are those with immune globulin (Ig) therapy needs. Our Ig portfolio features both intravenous (IV) and subcutaneous (SC) biotherapeutics. Our flagship products include:

- **Privigen®**, Immune Globulin Intravenous (Human), 10% Liquid, the first and only proline-stabilized IVIg
- **Hizentra®**, Immune Globulin Subcutaneous (Human), 20% Liquid, the first 20% SCIg stabilized with proline

These Ig products are designed to offer healthcare professionals (HCPs) and their patients convenience, choice, and ease of administration.

Through leadership, innovation, and product efficiencies, we continually seek to anticipate and fulfill our Ig customers' needs. One example of our commitment to innovation is the use of **L-proline** (proline) in Privigen and Hizentra. This stabilizer promotes safety and quality, so that these products can:

- Meet the needs of a broad range of patients for whom Ig therapy is appropriate
- Be stored at room temperature for their entire shelf lives
- Provide ready-to-use convenience for HCPs and patients

We also use **advanced plasma collection and manufacturing processes** to maintain the quality and purity of our products. See page 10 of this brochure for more information.

### Important Safety Information for Hizentra and Privigen

Hizentra and Privigen are indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Hizentra is for use in patients 2 years of age or older; the safety and effectiveness of Privigen have not been established in patients with PI who are under 3 years of age.

### CSL Behring Ig therapies— timeline of FDA approval



\*Nucleic acid testing.



# Proline Stabilization

## Innovation in Ig therapy

Maintaining the stability of IgG is crucial for preserving an antibody's functionality and efficacy in IVIg and SCIg preparations.<sup>1</sup>

Privigen and Hizentra both use the amino acid stabilizer proline. Proline was specifically chosen as a stabilizer after extensive testing and analysis.<sup>2</sup>

Proline is a natural and critical component of human physiology and is a normal component of the human diet. Data from clinical trials of Privigen and Hizentra indicate that proline is rapidly cleared from the circulation and does not accumulate. Additionally, there were no confirmed adverse events attributed to proline.<sup>3</sup>

## The use of proline<sup>2</sup>:

- Enables room-temperature storage
- Reduces IgG aggregation, minimizes fragmentation, and prevents solution discoloration
- Preserves specific antibody function
- Helps reduce the formation of IgG dimers

The use of proline as a stabilizer in these **compatible IV and SC products** helps foster smooth transitions from one delivery method to the other as patients' needs change.

## Important Safety Information for Hizentra and Privigen

Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP). Safety and effectiveness for this use have not been established for patients under age 15.

### WARNING: THROMBOSIS

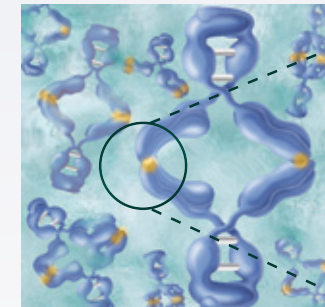
**Thrombosis may occur with immune globulin products, including Hizentra and Privigen. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**

**For patients at risk of thrombosis, administer Hizentra and Privigen 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. Thrombosis can occur even in absence of known risk factors.**

## How it works

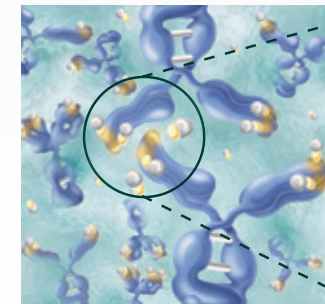
Proline reduces IgG dimer formation.<sup>2</sup>

### Dimer formation without proline



In solution, IgG molecules (shown in blue) reversibly bind to each other (circled), forming IgG dimers.<sup>2</sup>

### Proline reduce dimer formation



Proline (shown in yellow) may shield the IgG molecules from one another and thus interfere with dimer formation.<sup>2</sup>

## Why Choose CSL Ig Products

### IVIg and SCIg therapies for primary immunodeficiency (PI)—proven products from a leader in Ig

CSL Behring leads the industry with safe, high-quality, technically advanced Ig products designed to offer patients the convenience, choice, and ease of administration that they seek. The CSL Behring product portfolio includes both IVIg and SCIg products, both stabilized with proline.

#### CSL Behring's Ig Therapies



### Privigen



#1  
IVIg

Used in  
US Hospitals  
Since 2010<sup>4</sup>

#### Proven protection

Privigen is proven safe and effective for the treatment of PI

#### Proline stabilization

Proline has been proven to reduce dimer formation<sup>2</sup>

#### Ready to use

No reconstitution or refrigeration

### Hizentra



#1 Ig

Prescribed  
for PI<sup>5</sup>

#### Proven

Only SCIg that has provided safe and effective PI protection\* for over 6 years

#### Personalized

Can be dosed up to every 2 weeks

#### Leader

CSL Behring is a leading innovator in SCIg replacement therapy

\*Demonstrated in patients 2–65 years of age and older in the US phase 3 trial with Hizentra weekly dosing.

#### Important Safety Information for Hizentra and Privigen

##### **PRIVIGEN ADDITIONAL WARNING: RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of human immune globulin intravenous (IGIV) products in predisposed patients. For patients at risk of renal dysfunction or failure, administer Privigen at the minimum dose and infusion rate possible. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.

See full prescribing information for Hizentra and Privigen for complete boxed warnings.

Hizentra and Privigen are contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin preparations, as well as patients with immunoglobulin A deficiency who have antibodies against IgA and a history of hypersensitivity. Because Hizentra and Privigen contain the stabilizer L-proline, they are contraindicated in patients with hyperprolinemia. Hizentra is also contraindicated in patients with hypersensitivity to any of its components, such as polysorbate 80.

## Meeting High Standards for Quality

For more than 65 years, CSL Behring has been fractionating human plasma for use in our lifesaving biotherapies. During this time, we have developed and refined our Integrated Safety System of plasma collection, manufacturing, and distribution. The result is an efficient process designed to enhance our Ig products' ability to meet high quality and safety standards.

### Rigorous plasma testing

After plasma is collected, it is sent to state-of-the-art laboratories for pathology testing.

- 1 Each unit of plasma is screened for markers of infection, such as:
  - Anti-HIV-1 and anti-HIV-2 antibodies
  - Anti-HCV antibodies
  - Hepatitis B surface antigen (HBsAg)
- 2 Nucleic acid testing is utilized to test for HIV, HAV, HBV, HCV, and B19 genome
- 3 The final manufacturing plasma pool is screened and tested again for anti-HIV-1/2, HBsAg, and HIV, HCV, and HBV genome by nucleic acid testing

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus;  
HIV = human immunodeficiency virus.

### Purification through precipitation and chromatographic steps

Preparation of our Ig products, including Privigen®, Immune Globulin Intravenous (Human), 10% Liquid, and Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, includes a combination of:

#### Cold ethanol precipitation

Isolates and enriches the IgG fraction by removing albumin and  $\alpha$ - and  $\beta$ -globulins from plasma

#### Octanoic acid fractionation

Removes plasma lipids and the majority of remaining plasma proteins (other than IgG)

#### Anion exchange chromatography

A "polishing" process that depletes almost all IgA, remaining IgM, and other plasma constituents; this leads to an IgG purity of at least 98% for both Privigen and Hizentra

### Important Safety Information for Hizentra and Privigen

**Hizentra should be administered subcutaneously *only*. Do not administer intravenously.**

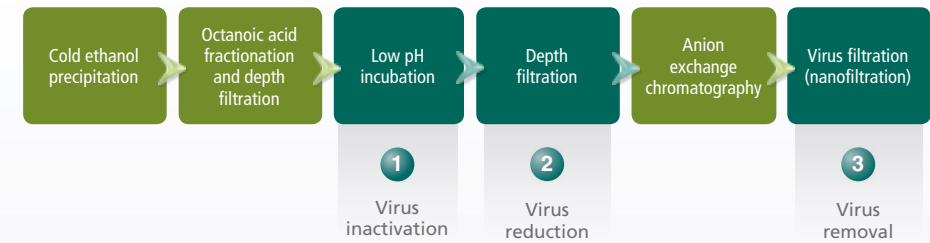
**Privigen should be administered intravenously *only*.**

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

## The 3-step Virus Inactivation/Elimination Process

- 1 **Virus inactivation by pH 4 incubation**
  - Some viruses, when exposed to a low pH, will break down spontaneously
  - This step destroys viruses by irreparably damaging their lipid layers and protein coats
  - Lipid-enveloped viruses, such as HIV-1, HIV-2, HBV, and HCV, are inactivated
  - Recent in vitro studies have shown that the non-enveloped B19 virus is also inactivated<sup>6,7</sup>
- 2 **Virus reduction through depth filtration**
  - Depth filtration, or partitioning, contributes to the overall virus reduction capacity
  - Some proteins, such as IgM, protein aggregates, and viruses that are potentially present, are removed
- 3 **Virus removal through filtration**
  - Virus filtration, also known as nanofiltration, removes both enveloped and non-enveloped viruses by size exclusion
    - Protein solutions are filtered through membranes with very small pore sizes that remove particles as small as ~20 nanometers
  - The main advantage of this process is that both enveloped and non-enveloped viruses can be removed without denaturing plasma proteins or affecting the quality of the derived products

### Ig purification and our 3-step process



### Validated TSE removal steps

Several of the production steps for Ig products have been shown to decrease transmissible spongiform encephalopathy (TSE) infectivity, a model for the CJD/variant Creutzfeldt-Jakob disease (vCJD) agent. These steps include:

- Octanoic acid fractionation
- Depth filtration
- Virus filtration

Studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed through these processes.

#### Important Safety Information for Hizentra and Privigen

Monitor patients for aseptic meningitis syndrome (AMS), which has been reported with SCIg, and in rare instances with IVIg—more frequently with high doses (2g/kg) and/or rapid IV infusion. In patients on either product at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output.

Discontinue treatment if renal function deteriorates. For both products, closely monitor patients for clinical signs of hemolysis and hemolytic anemia. Also monitor for pulmonary adverse reactions and transfusion-related acute lung injury (TRALI).

## Quality You Can Count On

### The foundation of our lifesaving Ig therapies

CSL Behring's US Ig products are prepared from plasma obtained from carefully selected US donors using rigorous donor screening procedures. All of our products are prepared from large donor pools, which may include up to 60,000 donations, providing a wide range of protective antibodies.<sup>2</sup>

### Passionate about quality and safety

At CSL Behring, we produce our Ig products in accordance with international safety and quality standards. From collection to infusion, we integrate our plasma collection efforts with newly discovered efficiencies in Ig manufacturing.

- Our Ig products are produced at facilities in Bern, Switzerland and Marburg, Germany
- We own and operate CSL Plasma, one of the world's largest plasma collection networks throughout the US and Germany, and use highly sensitive laboratory tests and purification processes
- We participate in the National Donor Deferral Registry (NDDR), using a computerized list to monitor deferred donors in the US




### Compliance with regulatory requirements

CSL Behring is dedicated to exceeding stringent international standards for plasma product safety in accordance with guidelines from worldwide regulatory agencies. CSL Behring is certified by:

 <p>Plasma Protein Therapeutics Association (PPTA) worldwide association of manufacturers of human plasma products</p>	 <p>International Quality Plasma Program (IQPP) certification for adherence to plasma collection standards</p>	 <p>Quality Standards of Excellence, Assurance and Leadership (QSEAL) certification</p>
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**For more information about CSL Behring and our Ig products, visit:**

	<p><b>CSLBehring-us.com</b> or call IgIQ at <b>1-877-355-IGIQ (4447)</b>. Monday–Friday, 8 AM to 8 PM ET</p>
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### Important Safety Information for Hizentra and Privigen

Consider the relative risks and benefits before prescribing high-dose regimen of Privigen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload. (Hizentra is not indicated for ITP.)

Hizentra and Privigen are 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.



## Important Safety Information for Hizentra and Privigen

Hizentra and Privigen are indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Hizentra is for use in patients 2 years of age or older; the safety and effectiveness of Privigen have not been established in patients with PI who are under 3 years of age.

Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP). Safety and effectiveness for this use have not been established for patients under age 15.

### WARNING: THROMBOSIS

**Thrombosis may occur with immune globulin products, including Hizentra and Privigen. 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 and Privigen 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. Thrombosis can occur even in absence of known risk factors.**

**PRIVIGEN ADDITIONAL WARNING: RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

**Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of human immune globulin intravenous (IGIV) products in predisposed patients. For patients at risk of renal dysfunction or failure, administer Privigen at the minimum dose and infusion rate possible. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.**

**See full prescribing information for Hizentra and Privigen for complete boxed warnings.**

Hizentra and Privigen are contraindicated in patients with a history of anaphylactic or severe systemic reaction to human immune globulin preparations, as well as patients with immunoglobulin A deficiency who have antibodies against IgA and a history of hypersensitivity. Because Hizentra and Privigen contain the stabilizer L-proline, they are contraindicated in patients with hyperprolinemia. Hizentra is also contraindicated in patients with hypersensitivity to any of its components, such as polysorbate 80.

**Hizentra should be administered subcutaneously only. Do not administer intravenously.**

**Privigen should be administered intravenously only.**

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

Monitor patients for aseptic meningitis syndrome (AMS), which has been reported with SCIG, and in rare instances with IVIg—more frequently with high doses (2g/kg) and/or rapid IV infusion. In patients on either product at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output. Discontinue treatment if renal function deteriorates. For both products, closely monitor patients for clinical signs of hemolysis and hemolytic anemia. Also monitor for pulmonary adverse reactions and transfusion-related acute lung injury (TRALI).

Consider the relative risks and benefits before prescribing high-dose regimen of Privigen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload. (Hizentra is not indicated for ITP.)

Hizentra and Privigen are 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.

For Hizentra, the most common adverse reactions (observed in 5% or more of study subjects receiving Hizentra) were local reactions (ie, swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, extremity pain, cough, rash, pruritus, vomiting, upper abdominal pain, migraine and pain.

In clinical studies of patients being treated with Privigen for PI, the most common adverse reactions observed in >5% of subjects were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature.

In clinical studies of patients being treated with Privigen for chronic ITP, the most common adverse reactions seen in >5% of subjects were headache, elevated body temperature, positive DAT, anemia, nausea, epistaxis, vomiting, increases in bilirubin, decreased hematocrit, and increased blood lactate dehydrogenase. A serious adverse reaction was aseptic meningitis syndrome (AMS).

Subcutaneous and intravenous Ig administration can transiently impair the efficacy of live attenuated virus vaccines, such as measles, mumps and rubella; and can lead to misinterpretation of serologic testing. Use in pregnant women only if clearly needed.

In patients over 65 or at risk of developing renal insufficiency, do not exceed recommended dose of Privigen or Hizentra, and infuse at the minimum rate practicable.

**Please see full prescribing information for Hizentra and Privigen, including boxed warning, in pocket.**



For more information about CSL Behring and our Ig products, visit:



[Privigen.com](http://Privigen.com)



[Hizentra.com](http://Hizentra.com)

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[CSLBehring-us.com](http://CSLBehring-us.com)

**References:** **1.** Cramer M, Frei R, Sebald A, Mazzoletti P, Maeder W. Stability over 36 months of a new liquid 10% polyclonal immunoglobulin product (IgPro10, Privigen®) stabilized with L-proline. *Vox Sang.* 2009;96(3):219-225. **2.** Bolli R, Woodtli K, Bärtschi M, Höffler L, Lerch P. L-Proline reduces IgG dimer content and enhances the stability of intravenous immunoglobulin (IVIg) solutions. *Biologicals.* 2010;38(1):150-157. **3.** Hagan JB, Wasserman RL, Baggish JS, et al. Safety of L-proline as a stabilizer for immunoglobulin products. *Expert Rev Clin Immunol.* 2012;8(2):169-178. **4.** Data on file. Available from CSL Behring as DOF PVG-002. **5.** Data on file. Available from CSL Behring as DOF HIZ-003. **6.** Boschetti N, Niederhauser I, Kempf C, Stühler A, Löwer J, Blümel J. Different susceptibility of B19 virus and mice minute virus to low pH treatment. *Transfusion.* 2004;44:1079-1086. **7.** Ros C, Baltzer C, Mani B, Kempf C. Parvovirus uncoating in vitro reveals a mechanism of DNA release without capsid disassembly and striking differences in encapsulated DNA stability. *Virology.* 2006;345:137-147.

Please see full Important Safety Information for Hizentra and Privigen on pages 16–17 and full prescribing information for both products, including boxed warning, in pocket.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRIVIGEN safely and effectively. See full prescribing information for PRIVIGEN .

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid  
Initial U.S. Approval: 2007

### WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including Privigen. 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.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Privigen does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

### RECENT MAJOR CHANGES

Boxed Warning	09/2013, 11/2013
Dosage and Administration (2)	09/2013
Warnings and Precautions (5.2, 5.3)	09/2013, 11/2013

### INDICATIONS AND USAGE

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

- Primary humoral immunodeficiency (PI) (1.1)
- Chronic immune thrombocytopenic purpura (ITP) (1.2)

### DOSAGE AND ADMINISTRATION

#### Intravenous Use Only

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (as tolerated)
PI	200-800 mg/kg (2-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

- Ensure that patients with pre-existing renal insufficiency are not volume depleted, and discontinue Privigen if renal function deteriorates (2.4, 5.2).
- For patients at risk of renal dysfunction or thrombosis, administer Privigen at the minimum dose and infusion rate practicable (2.4, 5.2, 5.3).

### DOSAGE FORMS AND STRENGTHS

Privigen is a liquid solution containing 10% IgG (0.1 g/mL) (3).

### CONTRAINDICATIONS

- History of anaphylactic or severe systemic reaction to human immune globulin (4)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

#### 1 INDICATIONS AND USAGE

- 1.1 Primary Humoral Immunodeficiency
- 1.2 Chronic Immune Thrombocytopenic Purpura

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage for Primary Humoral Immunodeficiency (PI)
- 2.2 Dosage for Chronic Immune Thrombocytopenic Purpura (ITP)
- 2.3 Preparation and Handling
- 2.4 Administration

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity
- 5.2 Renal Dysfunction and Acute Renal Failure
- 5.3 Thrombosis
- 5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia
- 5.5 Aseptic Meningitis Syndrome (AMS)
- 5.6 Hemolysis
- 5.7 Transfusion-Related Acute Lung Injury (TRALI)
- 5.8 Volume Overload
- 5.9 Transmissible Infectious Agents
- 5.10 Interference with Laboratory Tests

- Hyperprolinemia (Privigen contains the stabilizer L-proline) (4)
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (4)

### WARNINGS AND PRECAUTIONS

- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions (5.1).
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure (5.2).
- Thrombosis may occur with immune globulin products, including Privigen (5.3).
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur (5.4).
- Aseptic meningitis syndrome (AMS) may occur, especially with high doses or rapid infusion (5.5).
- Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to Privigen treatments. Risk factors for hemolysis include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia (5.6).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]) (5.7).
- Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload (5.8).
- Privigen is made from human blood and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.9).

### ADVERSE REACTIONS

- **PI** – The most common adverse reactions, observed in >5% of study subjects, were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature (6).
- **Chronic ITP** – The most common adverse reactions, observed in >5% of study subjects, were headache, elevated body temperature, positive direct antiglobulin test (DAT), anemia, nausea, epistaxis, vomiting, blood bilirubin unconjugated increased, blood bilirubin conjugated increased, blood total bilirubin increased, hematocrit decreased, and blood lactate dehydrogenase increased. A serious adverse reaction was aseptic meningitis (6).

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

### DRUG INTERACTIONS

The passive transfer of antibodies may:

- Lead to misinterpretation of the results of serological testing (5.10).
- Interfere with the response to live virus vaccines (7.1).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Geriatric: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Privigen at the minimum rate practicable (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November 2013

## 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

## 7 DRUG INTERACTIONS

- 7.1 Live Virus Vaccines

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- 16.2 Storage and Handling

## 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

# Privigen<sup>®</sup>, Immune Globulin Intravenous (Human), 10% Liquid

## WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- Thrombosis may occur with immune globulin products<sup>1-3</sup>, including Privigen. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors [see *Warnings and Precautions (5.3), Patient Counseling Information (17)*].
- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.<sup>4</sup> Privigen does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction or failure, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see *Dosage and Administration (2.3), Warnings and Precautions (5.2, 5.3)*].

## 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 immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked 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.

## 2 DOSAGE AND ADMINISTRATION

**Table 1: Recommended Dosage and Administration for Privigen**

Indication	Dose	Initial infusion rate	Maintenance infusion rate (as tolerated)
Primary Immunodeficiency	200-800 mg/kg (2-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
Chronic Immune Thrombocytopenic Purpura	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

### 2.1 Dosage for Primary Humoral Immunodeficiency (PI)

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

The recommended dose of Privigen for patients with PI is 200 to 800 mg/kg (2 to 8 mL/kg), administered every 3 to 4 weeks. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

Adjust the dosage over time to achieve the desired serum IgG trough levels and clinical responses. No randomized, controlled trial data are available to determine an optimal trough level in patients receiving immune globulin therapy.

### 2.2 Dosage for Chronic Immune Thrombocytopenic Purpura (ITP)

The recommended dose of Privigen for patients with chronic ITP is 1 g/kg (10 mL/kg) administered daily for 2 consecutive days, resulting in a total dosage of 2 g/kg.

Carefully consider the relative risks and benefits before prescribing the high dose regimen (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload [see *Warnings and Precautions (5.8)*].

### 2.3 Preparation and Handling

- Privigen is a clear or slightly opalescent, colorless to pale yellow solution. Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, turbid, or if it contains particulate matter.
- DO NOT SHAKE.
- Do not freeze. Do not use if Privigen has been frozen.
- Privigen should be at room temperature (up to 25°C [77°F]) at the time of administration.
- Do not use Privigen beyond the expiration date on the product label.

- The Privigen vial is for single-use only. Promptly use any vial that has been entered. Privigen contains no preservative. Discard partially used vials or unused product in accordance with local requirements.
- Infuse Privigen using a separate infusion line. Prior to use, the infusion line may be flushed with Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride for Injection, USP.
- Do not mix Privigen with other IGIV products or other intravenous medications. However, Privigen may be diluted with Dextrose Injection, USP (D5W).
- An infusion pump may be used to control the rate of administration.
- If large doses of Privigen are to be administered, several vials may be pooled using aseptic technique. Begin infusion within 8 hours of pooling.

## 2.4 Administration

### Privigen is for intravenous administration only.

Monitor the patient's vital signs throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients judged to be at risk for renal dysfunction or thrombosis, administer Privigen at the minimum dose and infusion rate practicable, and discontinue Privigen administration if renal function deteriorates [see *Boxed Warning, Warnings and Precautions (5.2, 5.3)*].

The following patients may be at risk of developing systemic reactions (mimicking symptoms of an inflammatory response or infection) on rapid infusion of Privigen (greater than 4 mg/kg/min [0.04 mL/kg/min]): 1) those who have never received Privigen or another IgG product or who have not received it within the past 8 weeks, and 2) those who are switching from another IgG product. These patients should be started at a slow rate of infusion (e.g., 0.5 mg/kg/min [0.005 mL/kg/min] or less) and gradually increase as tolerated.

## 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 a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline [see *Description (11)*].
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity [see *Warnings and Precautions (5.1)*].

## 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 ( $\leq 25$  mcg/mL) [see *Description (11)*]. 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 Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

### 5.2 Renal Dysfunction and Acute Renal Failure

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.<sup>4</sup> Privigen does not contain sucrose. 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 Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.<sup>4</sup> If renal function deteriorates, consider discontinuing Privigen. 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 obese, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable [see *Boxed Warning, Administration (2.4)*].

### 5.3 Thrombosis

Thrombosis may occur following treatment with immune globulin products<sup>1-3</sup>, including Privigen. 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 triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see *Boxed Warning, Dosage and Administration (2), Patient Counseling Information (17)*].

### 5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as 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 thromboembolic events.<sup>5</sup>

### 5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen [see *Adverse Reactions* (6)] and other human immune globulin products. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae.<sup>6</sup> 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. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytosis series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. 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 test (DAT) (Coombs' test) result and hemolysis.<sup>7-9</sup> Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.<sup>10</sup> Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen.

The following risk factors may be associated with the development of hemolysis: high doses (e.g.,  $\geq 2$  g/kg), given either as a single administration or divided over several days, and non-O blood group.<sup>11</sup> Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV,<sup>12</sup> but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI.<sup>9</sup>

Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform additional 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 following treatment with IGIV products, including Privigen.<sup>13</sup> 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. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) 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

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

### 5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, 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 Privigen.

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

### 5.10 Interference with Laboratory Tests

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

## 6 ADVERSE REACTIONS

Adverse reactions (ARs), as presented below and in Clinical Trials Experience (6.1), are defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion or treatment cycle (for ITP).

### Primary Humoral Immunodeficiency

The most serious adverse reaction observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject [see *Warnings and Precautions* (5.1)]. The most common adverse reactions observed in  $>5\%$  of clinical study subjects with PI were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness.

### Chronic Immune Thrombocytopenic Purpura

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 [see *Warnings and Precautions* (5.5, 5.6)]. A total of 8 subjects (14%) in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in  $>5\%$  of clinical study subjects with chronic ITP were headache, elevated body temperature, positive DAT, anemia, nausea, epistaxis, vomiting, blood bilirubin unconjugated increased, blood bilirubin conjugated increased, blood total bilirubin increased, hematocrit decreased, and blood lactate dehydrogenase increased.

## 6.1 Clinical Trials Experience

*Because different clinical trials 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 clinical practice.*

### Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen 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; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule.

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related ARs 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.

Table 2 summarizes the most frequent ARs (defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion) that occurred in  $>5\%$  of subjects.

**Table 2: PI Pivotal Study – ARs\* Occurring in  $>5\%$  of Subjects**

AR	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with AR [n=1038]
Headache	36 (45.0)	100 (0.096)
Fatigue	13 (16.3)	29 (0.028)
Nausea	11 (13.8)	23 (0.022)
Chills	9 (11.3)	15 (0.014)
Vomiting	9 (11.3)	15 (0.014)
Back pain	8 (10.0)	15 (0.014)
Pain	7 (8.8)	14 (0.013)
Elevated body temperature	7 (8.8)	12 (0.012)
Diarrhea	6 (7.5)	6 (0.006)
Cough	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

\* Excluding infections.

Of the 192 ARs reported (including 5 serious, severe ARs described below) 91 were mild (awareness of sign, symptom or event, but easily tolerated), 81 were moderate (discomfort enough to cause interference with usual activity and may have warranted intervention), 19 were severe (incapacitating with inability to do usual activities or significantly affected clinical status, and warranted intervention), and 1 was of unknown severity.

The five serious ARs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to ARs (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative 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).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min [see *Administration* (2.4)]. The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding

tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

Table 3 summarizes the ARs that occurred in >5% of subjects.

**Table 3: PI Extension Study – ARs\* Occurring in >5% of Subjects**

AR*	Number (%) of Subjects [n=55]	Number (Rate) of Infusions with AR [n=771]
Headache	18 (32.7)	76 (0.099)
Nausea	6 (10.9)	10 (0.013)
Elevated body temperature	4 (7.3)	12 (0.016)
Abdominal pain†	4 (7.3)	7 (0.009)
Chest pain	3 (5.5)	4 (0.005)
Chills	3 (5.5)	7 (0.009)
Joint swelling/effusion	3 (5.5)	7 (0.009)
Pain	3 (5.5)	6 (0.008)
Fatigue	3 (5.5)	5 (0.006)
Influenza-like illness	3 (5.5)	5 (0.006)
Pharyngolaryngeal pain	3 (5.5)	4 (0.005)
Urticaria	3 (5.5)	4 (0.005)
Dizziness	3 (5.5)	3 (0.004)

Note: The AR rates in this study cannot be compared directly to the rates in other IGIV studies, including the original pivotal study described earlier in this section, because (1) the extension study used an enriched population and (2) the selective use of higher infusion rates at the investigators' discretion in a subset of subjects may have introduced bias.

\* Excluding infections.

† Includes abdominal pain, abdominal pain upper, and abdominal pain lower.

Of the 125 reported ARs, 76 were mild (does not interfere with routine activities), 40 were moderate (interferes somewhat with routine activities), and 9 were severe (impossible to perform routine activities).

Three subjects experienced ARs that were considered to be at least possibly related to Priviligen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

#### 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 Priviligen administered as 1 g/kg infusions daily for 2 consecutive days [see *Clinical Studies (14.2)*]. Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

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 4 summarizes the most frequent ARs (adverse events at least possibly related or events occurring during or within 72 hours after the end of a treatment cycle [two consecutive infusions]) that occurred in >5% of subjects with chronic ITP.

**Table 4: Chronic ITP Study – ARs Occurring in >5% of Subjects**

AR	Number (%) of Subjects [n=57]	Number (Rate) of Infusions with AR [n=114]
Headache	37 (64.9)	52 (0.456)
Elevated body temperature	21 (36.8)	23 (0.202)
Positive DAT	7 (12.3)	8 (0.070)
Anemia	6 (10.5)	6 (0.053)
Nausea	6 (10.5)	8 (0.070)
Epistaxis	6 (10.5)	8 (0.070)
Vomiting	6 (10.5)	7 (0.061)
Blood bilirubin unconjugated increased	6 (10.5)	6 (0.053)
Blood bilirubin conjugated increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)

Of the 149 non-serious ARs, 103 were mild (awareness of sign, symptom or event, but easily tolerated), 37 were moderate (discomfort enough to cause interference with usual activity and may have warranted intervention), and 9 were severe (incapacitating with inability

to do usual activities or significantly affected clinical status, and warranted intervention).

One subject experienced a serious AR (aseptic meningitis).

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 Priviligen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

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 Priviligen 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 adverse reactions are reported voluntarily post-approval 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.

### Priviligen

The following adverse reactions have been identified during postmarketing use of Priviligen.

This list does not include reactions already reported in clinical studies with Priviligen [see *Adverse Reactions (6.1)*].

- **Infusion reactions:** Changes in blood pressure, dyspnea, tachycardia, flushing
- **Hematologic:** hemoglobinuria/hematuria/chromaturia, renal failure
- **Neurological:** photophobia
- **Integumentary:** pruritus, rash

### General

In addition, the following adverse reactions have been identified and reported during the post-approval use of immune globulin products.<sup>14</sup>

- **Infusion Reactions:** Tachycardia, malaise, flushing, rigors
- **Renal:** Acute renal dysfunction/failure, osmotic nephropathy
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, bronchospasm
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, tremor
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- **Hematologic:** Pancytopenia, leukopenia
- **Gastrointestinal:** Hepatic dysfunction

## 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)*].<sup>15</sup>

Inform the immunizing physician of recent therapy with Priviligen so that appropriate measures can be taken.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Priviligen. It is not known whether Priviligen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Priviligen should be given to pregnant women only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.<sup>16,17</sup>

### 8.3 Nursing Mothers

Use of Priviligen in nursing mothers has not been evaluated.

### 8.4 Pediatric Use

#### Treatment of Primary Humoral Immunodeficiency

Priviligen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI (pivotal study). 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 Priviligen have not been established in pediatric patients with PI who are under the age of 3.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

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

### 8.5 Geriatric Use

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

Use caution when administering Priviligen to patients age 65 and over who are judged to be at increased risk of developing acute renal insufficiency and thrombosis [see *Boxed Warning, Warnings and Precautions (5.2, 5.3)*]. Do not exceed recommended doses, and administer Priviligen at the minimum dose and infusion rate practicable.

## 10 OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with impaired renal function.

## 11 DESCRIPTION

Priviligen is a ready-to-use, sterile, 10% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous administration. Priviligen has a purity of at least 98% IgG, consisting primarily of monomers. The balance consists of IgG dimers ( $\leq 12\%$ ),

small amounts of fragments and polymers, and albumin. Privilgen contains  $\leq 25$  mcg/mL IgA. The IgG subclass distribution (approximate mean values) is IgG<sub>1</sub>, 67.8%; IgG<sub>2</sub>, 28.7%; IgG<sub>3</sub>, 2.3%; and IgG<sub>4</sub>, 1.2%. Privilgen has an osmolality of approximately 320 mOsmol/kg (range: 240 to 440) and a pH of 4.8 (range: 4.6 to 5.0).

Privilgen contains approximately 250 mmol/L (range: 210 to 290) of L-proline (a nonessential amino acid) as a stabilizer and trace amounts of sodium. Privilgen contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative.

Privilgen is prepared from large pools of human plasma by a combination of cold ethanol 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). Privilgen does not activate the complement system or prekallikrein in an unspecific manner.

All plasma units used in the manufacture of Privilgen have been tested and approved for manufacture using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to HCV and HIV-1/2 as well as FDA-licensed Nucleic Acid Testing (NAT) for HBV, HCV and HIV-1 and found to be nonreactive (negative). In addition, the plasma has been tested for B19 virus (B19V) DNA by NAT. Only plasma that passed virus screening is used for production, and the limit for B19V in the fractionation pool is set not to exceed 10<sup>4</sup> IU of B19V DNA per mL.

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

These steps have been independently validated in a series of *in vitro* experiments for their capacity to inactivate and/or remove both enveloped and non-enveloped viruses.

Table 5 shows the virus clearance during the manufacturing process for Privilgen, expressed as the mean log<sub>10</sub> reduction factor (LRF).

**Table 5: Virus Inactivation/Removal in Privilgen\***

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
<b>Virus property</b>						
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
<b>Manufacturing step</b>		<b>Mean LRF</b>				
pH 4 incubation	$\geq 5.4$	$\geq 5.9$	4.6	$\geq 7.8$	nt	nt
Depth filtration	$\geq 5.3$	$\geq 6.3$	2.1	3.0	4.2	2.3
Virus filtration	$\geq 5.3$	$\geq 5.5$	$\geq 5.1$	$\geq 5.9$	$\geq 5.4$	$\geq 5.5$
<b>Overall reduction (log<sub>10</sub> units)</b>	<b><math>\geq 16.0</math></b>	<b><math>\geq 17.7</math></b>	<b><math>\geq 11.8</math></b>	<b><math>\geq 16.7</math></b>	<b><math>\geq 9.6</math></b>	<b><math>\geq 7.8</math></b>

HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MVM, minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF, log<sub>10</sub> reduction factor; nt, not tested.

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

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for CJD and its variant vCJD.<sup>18</sup> Several of the production steps have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include octanoic acid fractionation ( $\geq 6.4$  log<sub>10</sub>), depth filtration (2.6 log<sub>10</sub>), and virus filtration ( $\geq 5.8$  log<sub>10</sub>). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### Treatment of Primary Humoral Immunodeficiency

Privilgen is a replacement therapy for primary humoral immunodeficiency, and supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacterial, viral, parasitic and mycoplasma agents and their toxins. The mechanism of action in PI has not been fully elucidated.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

The mechanism of action of high doses of immunoglobulins in the treatment of chronic ITP has not been fully elucidated.

### 12.3 Pharmacokinetics

#### Treatment of Primary Humoral Immunodeficiency

In the clinical study (pivotal study) assessing the efficacy and safety of Privilgen in 80 subjects with PI [see *Clinical Studies* (14.1)], serum concentrations of total IgG and IgG subclasses were measured in 25 subjects (ages 13 to 69) following the 7<sup>th</sup> infusion for the 3 subjects on the 3-week dosing interval and following the 5<sup>th</sup> infusion for the 22 subjects on the 4-week dosing interval. The dose of Privilgen used in these subjects ranged from 200.0 mg/kg to 714.3 mg/kg. After the infusion, blood samples were taken until Day 21 and Day 28 for the 3-week and 4-week dosing intervals, respectively.

Table 6 summarizes the pharmacokinetic parameters of Privilgen, based on serum concentrations of total IgG.

**Table 6: PI Pivotal Study - Pharmacokinetic Parameters of Privilgen in Subjects**

Parameter	3-Week Dosing Interval (n=3)		4-Week Dosing Interval (n=22)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
C <sub>max</sub> (peak, mg/dL)	2,550 (400)	2,340 (2,290-3,010)	2,260 (530)	2,340 (1,040-3,460)
C <sub>min</sub> (trough, mg/dL)	1,230 (230)	1,200 (1,020-1,470)	1,000 (200)	1,000 (580-1,360)
t <sub>1/2</sub> (days)	27.6 (5.9)	27.8 (21.6-33.4)	45.4 (18.5)	37.3 (20.6-96.6)
AUC <sub>0-t</sub> (day × mg/dL)*	32,820 (6,260)	29,860 (28,580-40,010)	36,390 (5,950)	36,670 (19,680-44,340)
AUC <sub>0-∞</sub> (day × mg/dL)*	79,315 (20,170)	78,748 (59,435-99,762)	104,627 (33,581)	98,521 (64,803-178,600)
Clearance (mL/day/kg)*	1.3 (0.1)	1.3 (1.1-1.4)	1.3 (0.3)	1.3 (0.9-2.1)
Mean residence time (days)*	38.6 (8.1)	39.5 (30.1-46.2)	65.2 (24.7)	59.0 (33.2-129.6)
Volume of distribution at steady state (mL/kg)*	50 (13)	44 (40-65)	84 (35)	87 (40-207)

C<sub>max</sub>, maximum serum concentration; C<sub>min</sub>, trough (minimum level) serum concentration; t<sub>1/2</sub>, elimination half-life; AUC<sub>0-t</sub>, area under the curve from 0 hour to last sampling time; AUC<sub>0-∞</sub>, area under the curve from 0 hour to infinite time.

\* Calculated by log-linear trapezoidal rule.

The median half-life of Privilgen was 36.6 days for the 25 subjects in the pharmacokinetic subgroup.

Although no systematic study was conducted to evaluate the effect of gender and age on the pharmacokinetics of Privilgen, based on the small sample size (11 males and 14 females) it appears that clearance of Privilgen is comparable in males (1.27 ± 0.35 mL/day/kg) and females (1.34 ± 0.22 mL/day/kg). In six subjects between 13 and 15 years of age, the clearance of Privilgen (1.35 ± 0.44 mL/day/kg) is comparable to that observed in 19 adult subjects 19 years of age or older (1.29 ± 0.22 mL/day/kg).

The IgG subclass levels observed in the pharmacokinetic study were consistent with a physiologic distribution pattern (mean trough values): IgG<sub>1</sub>, 564.91 mg/dL; IgG<sub>2</sub>, 394.15 mg/dL; IgG<sub>3</sub>, 30.16 mg/dL; IgG<sub>4</sub>, 10.88 mg/dL.

#### Treatment of Chronic Immune Thrombocytopenic Purpura

Pharmacokinetic studies with Privilgen were not performed in subjects with chronic ITP.

## 14 CLINICAL STUDIES

### 14.1 Treatment of Primary Humoral Immunodeficiency

A prospective, open-label, single-arm, multicenter study (pivotal study) assessed the efficacy, safety, and pharmacokinetics of Privilgen in adult and pediatric subjects with PI, who were treated for 12 months at a 3-week or 4-week dosing interval. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female; 77.5% were Caucasian, 15% were Hispanic, and 7.5% were African-American. All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. The efficacy analysis included 80 subjects, 16 (20%) on the 3-week dosing interval and 64 (80%) on the 4-week dosing interval. Doses ranged from 200 mg/kg to 888 mg/kg per infusion. The median dose for the 3-week interval was 428.3 mg/kg per infusion; the median dose for the 4-week interval was 440.6 mg/kg per infusion. Subjects received a total of 1038 infusions of Privilgen, 272 for the 3-week dosing regimen and 766 for the 4-week dosing regimen. The maximum infusion rate allowed during this study was 8 mg/kg/min with 715 (69%) of the infusions administered at a rate of 7 mg/kg/min or greater. The primary analysis for efficacy was based on the annual rate of acute serious bacterial infections (aSBIs), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject per year. Secondary analyses were based on the annual rate of other infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization. During the 12-month study period, the aSBI rate was 0.08 (with an upper 1-sided 99% confidence interval of 0.203), which met the predefined success rate of less than one aSBI per subject per year. Six subjects experienced an aSBI, including three cases of pneumonia and one case each of septic arthritis, osteomyelitis, and visceral abscess. All six subjects completed the study.

The rate of other infections was 3.55 infections per subject per year. The infections that occurred most frequently were sinusitis (31.3%), nasopharyngitis (22.5%), upper respiratory tract infection (18.8%), bronchitis (13.8%), and rhinitis (13.8%). Among the 255 infections, 16 (6.3%) occurring in 10 subjects were considered severe.



Table 7 summarizes the efficacy results for all 80 subjects.

**Table 7: PI Pivotal Study – Summary of Efficacy Results in Subjects**

Number of Subjects	80
<b>Results from Case Report Forms</b>	
Total Number of Subject Days	26,198
Infections	
Annual rate of confirmed aSBIs*	0.08 aSBIs/subject year†
Annual rate of other infections	3.55 infections/subject year
Antibiotic use	
Number of subjects (%)	64 (80%)
Annual rate	87.4 days/subject year
<b>Results from Subject Diaries</b>	
Total Number of Diary Days	24,059
Out of work/school/day care or unable to perform normal activities due to illness	
Number of days (%)	570 (2.37%)
Annual rate	8.65 days/subject year
Hospitalization	
Number of days (%)	166 (0.69%)
Annual rate	2.52 days/subject year

\* Defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.  
† Upper 1-sided 99% confidence interval: 0.203.

#### 14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and tolerability of Privigen in 57 subjects with chronic ITP and a platelet count of  $20 \times 10^9/L$  or less. Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female; all were Caucasian.

Subjects received a 2 g/kg dosage of Privigen administered as 1 g/kg (10 mL/kg) intravenous infusion daily for 2 consecutive days, and were observed for 29 days. Fifty-three (93%) subjects received Privigen at the maximum infusion rate allowed (4 mg/kg/min [0.04 mL/kg/min]).

The primary analysis was based on the response rate defined as the percentage of subjects with an increase in platelet counts to at least  $50 \times 10^9/L$  within 7 days after the first infusion (responders). Secondary analyses were based on the increase in platelet counts and the time to reach a platelet count of at least  $50 \times 10^9/L$  at any point within the study period, the duration of that response, and the regression (decrease in the severity) of hemorrhage in subjects who had bleeding at baseline. Platelet counts were measured on Days 1, 2, 4, 6, 8, 15, 22, and 29. Additional measurements on Days 57 and 85 occurred in subjects with a platelet count of at least  $50 \times 10^9/L$  at the previous visit.

Of the 57 subjects in the efficacy analysis, 46 (80.7%) responded to Privigen with a rise in platelet counts to at least  $50 \times 10^9/L$  within 7 days after the first infusion. The lower bound of the 95% confidence interval for the response rate (69.2%) is above the predefined response rate of 50%.

The highest median increase in platelet counts was seen 7 days after the first infusion ( $123 \times 10^9/L$ ). The median maximum platelet count achieved was  $154 \times 10^9/L$ . The median time to reach a platelet response of more than  $50 \times 10^9/L$  was 2.5 days after the first infusion. Twenty-five (43%) of the 57 subjects reached this response by Day 2 prior to the second infusion and 43 (75%) subjects reached this response by Day 6.

The duration of platelet response was analyzed for the 48 subjects who achieved a response any time after the first infusion. The median duration of platelet response in these subjects was 15.4 days (range: 1 to >82 days). Thirty-six (75%) of the 48 subjects maintained the response for at least 8.8 days and 12 (25%) of them for at least 21.9 days. Five (9%) subjects maintained a response up to Day 29 and two (4%) up to Day 85.

A decrease in the severity of hemorrhage from baseline was observed in the following bleeding locations: skin (31 of 36 subjects), oral cavity (11 of 11 subjects), and genitourinary tract (7 of 9 subjects). This decrease was not sustained in all subjects up to the end of the 29-day study period.

#### 15 REFERENCES

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#### 16 HOW SUPPLIED/STORAGE AND HANDLING

##### 16.1 How Supplied

- Privigen is supplied in a single-use, tamper-evident vial containing the labeled amount of functionally active IgG.

Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
50 mL	44206-436-05	Vial containing 5 grams of protein (NDC 44206-436-90)
100 mL	44206-437-10	Vial containing 10 grams of protein (NDC 44206-437-91)
200 mL	44206-438-20	Vial containing 20 grams of protein (NDC 44206-438-92)
400 mL	44206-439-40	Vial containing 40 grams of protein (NDC 44206-439-93)

##### 16.2 Storage and Handling

- Keep Privigen in its original carton to protect it from light.
- Each vial has an integral suspension band and a label with two peel-off strips showing the product name, lot number, and expiration date.
- When stored at room temperature (up to 25°C [77°F]), Privigen is stable for up to 36 months, as indicated by the expiration date printed on the outer carton and vial label.
- Do not freeze.
- The Privigen packaging components are not made with natural rubber latex.

#### 17 PATIENT COUNSELING INFORMATION

Inform patients of the early signs of hypersensitivity reactions to Privigen (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis), and advise them to notify their physician if they experience any of these symptoms.

Inform patients to immediately report the following signs and symptoms to their physician:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath, which may suggest kidney problems
- Instruct patients to immediately report symptoms of thrombosis. These symptoms may include: 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, numbness or weakness on one side of the body.
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting, which may suggest aseptic meningitis syndrome
- Fatigue, increased heart rate, yellowing of skin or eyes, and dark-colored urine, which may suggest hemolysis
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever, which may suggest TRALI (a condition typically occurring within 1 to 6 hours following transfusion)

Inform patients that Privigen is made from human blood and may contain infectious agents that can cause disease (e.g., viruses and, theoretically the CJD agent). Explain that the risk that Privigen may transmit an infectious agent has been reduced by screening the plasma donors, by testing donated plasma for certain virus infections, and by inactivating or removing certain viruses during manufacturing, and counsel patients to report any symptoms that concern them.

Inform patients that administration of IgG may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella), and instruct them to notify their immunizing physician of recent therapy with Privigen.

Manufactured by:  
**CSL Behring AG**  
Bern, Switzerland  
US License No. 1766

Distributed by:  
**CSL Behring LLC**  
Kankakee, IL 60901 USA

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HIZENTRA safely and effectively. See full prescribing information for HIZENTRA.

HIZENTRA, Immune Globulin Subcutaneous (Human), 20% Liquid  
Initial U.S. Approval: 2010

### WARNING: THROMBOSIS

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

### RECENT MAJOR CHANGES

Dosage and Administration (2.2) 01/2015

### INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older (1).

### DOSAGE AND ADMINISTRATION

**For subcutaneous infusion only. Do not inject into a blood vessel.**

Administer at regular intervals from daily up to every two weeks (biweekly).

#### Dosage (2.2)

Before switching to Hizentra, obtain the patient's serum IgG trough level to guide subsequent dose adjustments.

- **Weekly:** Start Hizentra 1 week after last IGIV infusion  
Initial weekly dose =  $\frac{\text{Previous IGIV dose (in grams)}}{\text{No. of weeks between IGIV doses}} \times 1.37$
- **Biweekly:** Start Hizentra 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly Hizentra/IGSC infusion. Administer twice the calculated weekly dose.
- **Frequent dosing (2 to 7 times per week):** Start Hizentra 1 week after the last IGIV or Hizentra/IGSC infusion. Divide the calculated weekly dose by the desired number of times per week.
- **Adjust the dose** based on clinical response and serum IgG trough levels (see *Dose Adjustment*).

#### Administration (2.3)

- Infusion sites – 1 to 4 injection sites simultaneously, with at least 2 inches between sites.

Infusion Parameters*	Infusion Number			
	1 <sup>st</sup>	2 <sup>nd</sup> to 4 <sup>th</sup>	5 <sup>th</sup>	6 <sup>th</sup> and above
Volume (mL/site)	≤ 15		≤ 20	≤ 25
Rate (mL/hr/site)	15		≤ 25	

\* As tolerated

### DOSAGE FORMS AND STRENGTHS

0.2 g per mL (20%) protein solution for subcutaneous injection (3)

### CONTRAINDICATIONS

- Anaphylactic or severe systemic reaction to human immune globulin or components of Hizentra, such as polysorbate 80 (4)
- Hyperprolinemia (type I or II) (Hizentra contains the stabilizer L-proline) (4)
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (4)

### WARNINGS AND PRECAUTIONS

- IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions (5.1).
- Thrombosis may occur following treatment with immune globulin products, including Hizentra (5.2).
- Aseptic meningitis syndrome has been reported with IGIV or IGSC treatment (5.3).
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of acute renal failure (5.4).
- Monitor for clinical signs and symptoms of hemolysis (5.5).
- Monitor for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]) (5.6) Hizentra is made from human plasma and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.7).

### ADVERSE REACTIONS

The most common adverse reactions observed in ≥5% of study subjects were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain (6).

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

### DRUG INTERACTIONS

The passive transfer of antibodies may interfere with the response to live virus vaccines (7.1), and lead to misinterpretation of the results of serological testing (5.8, 7.2).

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** No human or animal data. Use only if clearly needed (8.1).
- **Pediatric:** No specific dose requirements are necessary to achieve the desired serum IgG levels (8.4).

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

Revised: January 2015

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\* Sections or subsections omitted from the full prescribing information are not listed.

# Hizentra®

## Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid

### FULL PRESCRIBING INFORMATION

#### WARNING: THROMBOSIS

- Thrombosis may occur with immune globulin products<sup>1,3</sup>, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors (see *Warnings and Precautions [5.2], Patient Counseling Information [17]*).
- For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity (see *Warnings and Precautions [5.2]*).

#### 1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

#### 2 DOSAGE AND ADMINISTRATION

For subcutaneous infusion only. Do not inject into a blood vessel.

##### 2.1 Preparation and Handling

Hizentra is a clear and pale yellow to light brown solution. Do not use if the solution is cloudy or contains particulates.

- Prior to administration, visually inspect each vial of Hizentra for particulate matter or discoloration, whenever the solution and container permit.
- Do not freeze. Do not use any solution that has been frozen.
- Check the product expiration date on the vial label. Do not use beyond the expiration date.
- Do not mix Hizentra with other products.
- Do not shake the Hizentra vial.
- Use aseptic technique when preparing and administering Hizentra.
- The Hizentra vial is for single-use only. Discard all used administration supplies and any unused product immediately after each infusion in accordance with local requirements.

##### 2.2 Dosage

- Hizentra can be administered at regular intervals from daily up to every two weeks (biweekly).
- Individualize the dose based on the patient's clinical response to Hizentra therapy and serum immunoglobulin G (IgG) trough levels.
- Before receiving treatment with Hizentra:
  - o Ensure that patients have received Immune Globulin Intravenous (Human) (IGIV) treatment at regular intervals for at least 3 months.
  - o Obtain the patient's serum IgG trough level to guide subsequent dose adjustments (see below under *Dose Adjustment*).

#### Dosage for patients switching to Hizentra from Immune Globulin Intravenous (Human) (IGIV)

- Establish the initial weekly dose of Hizentra by converting the monthly IGIV dose into a weekly equivalent and increasing it using a 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.
  - o To calculate the initial weekly dose of Hizentra, divide the previous IGIV dose in grams by the number of weeks between doses during the patient's IGIV treatment (e.g., 3 or 4); then multiply this by the dose adjustment factor of 1.37. [see *Pharmacokinetics (12.3, Table 8)*]
 
$$\text{Initial Hizentra dose} = \frac{\text{Previous IGIV dose (in grams)}}{\text{Number of weeks between IGIV doses}} \times 1.37$$
  - o To convert the Hizentra dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 5.
- Provided the total weekly dose is maintained, any dosing interval from daily up to biweekly can be used and will result in systemic serum IgG exposure that is comparable to the previous IGIV or weekly Hizentra treatment [see *Pharmacokinetics (12.3)*].
- For biweekly dosing, multiply the calculated Hizentra weekly dose by 2.
- For frequent dosing (2 to 7 times per week), divide the calculated weekly dose by the desired number of times per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

#### Dosage for patients switching to Hizentra from IGSC

- The previous weekly IGSC dose should be maintained.
- For biweekly dosing, multiply the previous weekly dose by 2.
- For frequent dosing (2 to 7 times per week), divide the previous weekly dose by the desired number of times per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

#### Start Hizentra treatment:

- For weekly or frequent dosing, start treatment with Hizentra 1 week after the patient's last IGIV infusion or Hizentra/IGSC infusion.
- For biweekly dosing, start treatment 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly Hizentra/IGSC infusion.

#### Dose Adjustment

Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level, irrespective of the frequency of administration. To determine if a dose adjustment should be considered, measure the patient's serum IgG trough level 2 to 3 months after switching to Hizentra.

**Weekly dosing:** When switching from IGIV to weekly Hizentra dosing, the target serum IgG trough level is projected to be approximately 16% higher than the last trough level during prior IGIV therapy [see *Pharmacokinetics (12.3)*].

**Biweekly dosing:** When switching from IGIV to biweekly Hizentra dosing, the target serum IgG trough level is projected to be approximately 10% higher than the last IGIV trough level. When switching from weekly to biweekly Hizentra dosing, the target trough is projected to be approximately 5% lower than the last trough level on weekly therapy [see *Pharmacokinetics (12.3)*].

**Frequent dosing:** When switching from weekly dosing to more frequent Hizentra dosing, the target serum IgG trough level is projected to be approximately 3 to 4% higher than the last trough level on weekly therapy [see *Pharmacokinetics (12.3)*].

To adjust the dose based on trough levels, calculate the difference (in mg/dL) between the patient's serum IgG trough level and the target IgG trough level for weekly or biweekly dosing. Then find this difference in Table 1 (Column 1) and, based on the Hizentra dosing frequency (for weekly or biweekly) and the patient's body weight, locate the corresponding adjustment amount (in mL) by which to increase (or decrease) the dose. For frequent dosing, add the weekly increment from Table 1 to the weekly-equivalent dose and then divide by the number of days of dosing.

**Use the patient's clinical response as the primary consideration in dose adjustment. Additional dosage increments may be indicated based on the patient's clinical response (infection frequency and severity).**

**Table 1: Incremental Adjustment (mL)\* of the Hizentra Dose† Based on the Difference (±mg/dL) from the Target Serum IgG Trough Level**

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

n/a, not applicable.

\* 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.

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 1 also provides guidance for dose adjustment if their desired IGSC trough level is known.

#### Measles Exposure

Administer a minimum total weekly Hizentra dose of 200 mg/kg body weight for two consecutive weeks if a patient is at risk of measles exposure (i.e., due to an outbreak in the US or travel to endemic areas outside of the US. For biweekly dosing, one infusion of a

minimum of 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.


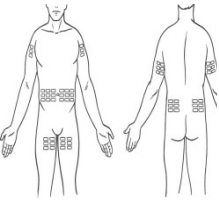
### 2.3 Administration

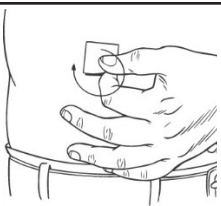
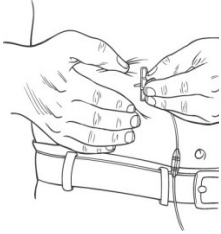
**Hizentra is for subcutaneous infusion only. Do not inject into a blood vessel.**

Hizentra is intended for subcutaneous administration using an infusion pump. Infuse Hizentra in the abdomen, thigh, upper arm, and/or lateral hip.

- Injection sites – A Hizentra dose may be infused into multiple injection sites. Use up to 4 sites simultaneously or up to 12 sites consecutively per infusion. Injection sites should be at least 2 inches apart. Change the actual site of injection with each administration.
- Volume – For the first infusion of Hizentra, do not exceed a volume of 15 mL per injection site. The volume may be increased to 20 mL per site for the fifth infusion and then to 25 mL per site as tolerated.
- Rate – For the first infusion of Hizentra, the recommended flow rate is 15 mL per hour per site. For subsequent infusions, the flow rate may be increased to 25 mL per hour per site as tolerated.

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

1.	<b>Assemble supplies</b> – Gather the Hizentra vial(s), disposable supplies (not provided with Hizentra), and other items (infusion pump, sharps or other container, patient’s treatment diary/log book) needed for the infusion.	
2.	<b>Clean surface</b> – Thoroughly clean a flat surface using an alcohol wipe.	
3.	<b>Wash hands</b> – Thoroughly wash and dry hands. The use of gloves when preparing and administering Hizentra is optional.	
4.	<b>Check vials</b> – Carefully inspect each vial of Hizentra. Do not use the vial if the liquid looks cloudy, contains particles, or has changed color, if the protective cap is missing, or if the expiration date on the label has passed.	
5.	<p><b>Transfer Hizentra from vial(s) to syringe</b></p> <ul style="list-style-type: none"> <li>• Remove the protective cap from the vial to expose the central portion of the rubber stopper of the Hizentra vial.</li> <li>• Clean the stopper with an alcohol wipe and allow it to dry.</li> <li>• If using a transfer device, follow the instructions provided by the device manufacturer.</li> <li>• If using a needle and a syringe to transfer Hizentra, follow the instructions below. <ul style="list-style-type: none"> <li>• Attach a sterile transfer needle to a sterile syringe. Pull back on the plunger of the syringe to draw air into the syringe that is equal to the amount of Hizentra to be withdrawn.</li> <li>• Insert the transfer needle into the center of the vial stopper and, to avoid foaming, inject the air into headspace of the vial (not into the liquid).</li> <li>• Withdraw the desired volume of Hizentra.</li> </ul> </li> </ul> <p>When using multiple vials to achieve the desired dose, repeat this step.</p>	
6.	<b>Prepare infusion pump and tubing</b> – Follow the manufacturer’s instructions for preparing the pump, using subcutaneous administration sets and tubing, as needed. Be sure to prime the tubing with Hizentra to ensure that no air is left in the tubing.	
7.	<p><b>Prepare injection site(s)</b></p> <ul style="list-style-type: none"> <li>• The number and location of injection sites depends on the volume of the total dose. Infuse Hizentra into a maximum of 4 sites simultaneously; or up to 12 consecutively per infusion. Injection sites should be at least 2 inches apart.</li> </ul>	

	<ul style="list-style-type: none"> <li>• Using an antiseptic skin preparation, clean each site beginning at the center and working outward in a circular motion. Allow each site to dry before proceeding.</li> </ul>	
8.	<p><b>Insert needle(s)</b></p> <ul style="list-style-type: none"> <li>• Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue.</li> <li>• If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.</li> <li>• Before starting the infusion, attach a sterile syringe to the end of the primed administration tubing and gently pull back on the plunger to make sure no blood is flowing back into the tubing. If blood is present, remove and discard the needle and tubing. Repeat the process beginning with step 6 (priming) using a new needle, new infusion tubing, and a different injection site.</li> </ul>	
9.	<b>Start infusion</b> – Follow the manufacturer’s instructions to turn on the infusion pump.	
10.	<b>Record treatment</b> – Remove the peel-off portion of the label from each vial used, and affix it to the patient’s treatment diary/log book or scan the vial if recording the infusion electronically.	
11.	<b>Clean up</b> – After administration is complete, turn off the infusion pump. Take off the tape or dressing and remove the needle set from the infusion site(s). Disconnect the tubing from the pump. Immediately discard any unused product and all used disposable supplies in accordance with local requirements. Clean and store the pump according to the manufacturer’s instructions.	

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

### 3 DOSAGE FORMS AND STRENGTHS

Hizentra is a 0.2 g/mL (20%) protein solution for subcutaneous injection.

### 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 (type I or II) 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. 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  $\leq 50$  mcg/mL IgA [see Description (11)].

#### 5.2 Thrombosis

Thrombosis may occur following treatment with immune globulin products<sup>1-3</sup>, 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 triacylglycerols (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 [see Boxed Warning, Patient Counseling Information (17)].

### 5.3 Aseptic Meningitis Syndrome (AMS)

AMS has been reported with use of IGIV<sup>4</sup> or IGSC. 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 ( $\geq 2$  g/kg) and/or rapid infusion of immune globulin product.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of immune globulin treatment has resulted in remission of AMS within several days without sequelae.

### 5.4 Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death may occur with use of human immune globulin products, especially those containing sucrose.<sup>5</sup> Hizentra does not contain sucrose. Ensure that patients are not volume depleted before administering Hizentra.

For patients judged to be at risk for developing renal dysfunction, including patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs, monitor renal function and consider lower, more frequent dosing [see Dosing and Administration (2.3)].

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.<sup>6</sup> Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Hizentra and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Hizentra.

### 5.5 Hemolysis

Hizentra can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.<sup>7-9</sup> 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.<sup>10</sup>

Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after Hizentra infusion, perform appropriate confirmatory laboratory testing.

### 5.6 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.<sup>11</sup> TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

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

### 5.7 Transmissible Infectious Agents

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

### 5.8 Laboratory Tests

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

## 6 ADVERSE REACTIONS

The most common adverse reactions (ARs), observed in  $\geq 5\%$  of study subjects receiving Hizentra, were local reactions (e.g., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain.

### 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.

#### US Study

The safety of Hizentra was evaluated in a clinical study in the US for 15 months (3-month wash-in/wash-out period followed by a 12-month efficacy period) in subjects with PI who

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

Subjects were treated with Hizentra at weekly median doses ranging from 66 to 331 mg/kg body weight (mean: 181.4 mg/kg) during the wash-in/wash-out period and from 72 to 379 mg/kg (mean: 213.2 mg/kg) during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

Table 2 summarizes the most frequent adverse reactions (ARs) (experienced by at least 2 subjects) occurring during or within 72 hours after the end of an infusion. Local reactions were assessed by the investigators 15 to 45 minutes post-infusion and by the subjects 24 hours post-infusion. The investigators then evaluated the ARs arising from the subject assessments. Local reactions were the most frequent ARs observed, with injection-site reactions (e.g., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

**Table 2: Incidence of Subjects with Adverse Reactions (ARs)\* (Experienced by 2 or More Subjects) and Rate per Infusion (ITT Population), US Study**

AR ( $\geq 2$ Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate <sup>†</sup> ) of ARs (n=2264 Infusions)
Local reactions <sup>‡</sup>	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.

<sup>†</sup> Rate of ARs per infusion.

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

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 3 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 3: Investigator Assessments\* of Injection-Site Reactions by Infusion, US Study**

Injection-Site Reaction	Number <sup>†</sup> (Rate <sup>‡</sup> ) of Reactions (n=683 Infusions <sup>§</sup> )
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 after the end of infusions administered at regularly scheduled visits (every 4 weeks).

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

<sup>‡</sup> Rate of injection-site reactions per infusion.

<sup>§</sup> Number of infusions administered during regularly scheduled visits.

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

### European Study

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

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

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

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

AR (≥2 Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=51)	Number (Rate <sup>†</sup> ) of ARs (n=1831 Infusions)
Local reactions <sup>‡</sup>	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.

<sup>†</sup> Rate of ARs per infusion.

<sup>‡</sup> 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.

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 injection-site pain and injection-site pruritus; the second subject experienced injection-site reaction, fatigue, and feeling cold; and the third subject experienced injection-site reaction and hypersensitivity. All reactions were judged by the investigator to be "at least possibly related" to the administration of Hizentra.

#### Biweekly (Every Two 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; however, it is unlikely that the safety profile is qualitatively different from that of weekly dosing.

#### 6.2 Postmarketing Experience

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

##### Hizentra

The following adverse reactions have been identified during postmarketing use of Hizentra. This list does not include reactions already reported in clinical studies with Hizentra [see *Adverse Reactions* (6.1)].

- **Infusion reactions:** Allergic-anaphylactic reactions such as swollen face or tongue and pharyngeal edema, pyrexia, chills, dizziness, hypertension/changes in blood pressure, malaise.
- **Cardiovascular:** Chest discomfort (including chest pain)
- **Respiratory:** Dyspnea
- **Neurological:** Tremor, burning sensation

The following adverse reactions have been reported during postmarketing use of immune globulin products<sup>5</sup>:

- **Infusion reactions:** Tachycardia, flushing, wheezing, rigors, myalgia
- **Renal:** Osmotic nephropathy
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), cyanosis, hypoxemia, pulmonary edema, bronchospasm
- **Cardiovascular:** Cardiac arrest, vascular collapse, hypotension
- **Neurological:** Coma, loss of consciousness, seizures, aseptic meningitis syndrome
- **Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- **Hematologic:** 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](http://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

#### Clinical Studies (Weekly Dosing)

The safety and effectiveness of weekly Hizentra have been established in the pediatric age groups 2 to 16. Hizentra was evaluated in 10 pediatric subjects with PI (3 children and 7 adolescents) in a study conducted in the US [see *Clinical Studies* (14)] and in 23 pediatric subjects with PI (18 children and 5 adolescents) in Europe. There were no differences in the pharmacokinetics, safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

#### Pharmacokinetic Modeling and Simulation (Biweekly or more Frequent Dosing)

The biweekly (every two weeks) or more frequent dosing (2 to 7 times per week) regimens, developed from population PK-based modeling and simulation, included 57 pediatric subjects (32 from Hizentra clinical studies) [see *Pharmacokinetics* (12.3)]. Hizentra dosing is adjusted to body weight. No pediatric-specific dose requirements are necessary for these regimens.

Safety and effectiveness of Hizentra in pediatric patients below the age of 2 have not been established.

### 8.5 Geriatric Use

Of the 49 subjects evaluated in the US 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. The clinical study of Hizentra in Europe did not include subjects over the age of 65.

## 11 DESCRIPTION

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

Hizentra has a purity of ≥98% IgG and a pH of 4.6 to 5.2. Hizentra 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. Hizentra contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative.

Plasma units used in the manufacture of Hizentra are tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to human immunodeficiency virus (HIV)-1/2 and hepatitis C virus (HCV) as well as FDA-licensed Nucleic Acid Testing (NAT) for HBV, HCV and HIV-1. All plasma units have been found to be nonreactive (negative) in these tests. In addition, the plasma has been tested for B19 virus (B19V) DNA by NAT. Only plasma that passes virus screening is used for production, and the limit for B19V in the fractionation pool is set not to exceed 10<sup>4</sup> IU of B19V DNA per mL.

The manufacturing process for Hizentra includes three steps to reduce the risk of virus transmission. Two of these are dedicated virus clearance steps: pH 4 incubation to inactivate enveloped viruses; and virus filtration to remove, by size exclusion, both enveloped and non-enveloped viruses as small as approximately 20 nanometers. In addition, a depth filtration step contributes to the virus reduction capacity.<sup>12</sup>

These steps have been independently validated in a series of *in vitro* experiments for their capacity to inactivate and/or remove both enveloped and non-enveloped viruses. Table 5 shows the virus clearance during the manufacturing process for Hizentra, expressed as the mean log<sub>10</sub> reduction factor (LRF).

**Table 5: Virus Inactivation/Removal in Hizentra\***

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
<b>Virus Property</b>						
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
<b>Manufacturing Step</b>						
	Mean LRF					
pH 4 incubation	≥5.4	≥5.9	4.6	≥7.8	nt	nt
Depth filtration	≥5.3	≥6.3	2.1	3.0	4.2	2.3
Virus filtration	≥5.3	≥5.5	≥5.1	≥5.9	≥5.4	≥5.5
<b>Overall Reduction (Log<sub>10</sub> Units)</b>	<b>≥16.0</b>	<b>≥17.7</b>	<b>≥11.8</b>	<b>≥16.7</b>	<b>≥9.6</b>	<b>≥7.8</b>

HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a nonspecific model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhoea virus, a model for hepatitis C virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MVM, minute virus of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF, log<sub>10</sub> reduction factor; nt, not tested; na, not applicable.

\* The virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step.

† The estimated LRF obtained was ≥5.3.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for CJD and its variant (vCJD).<sup>12</sup> Several of the production steps have been shown to decrease infectivity of an experimental TSE model agent. TSE reduction steps include octanoic acid fractionation (≥6.4 log<sub>10</sub>), depth filtration (2.6 log<sub>10</sub>), and virus filtration (≥5.8 log<sub>10</sub>). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Hizentra supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action in PI has not been fully elucidated.

### 12.3 Pharmacokinetics

#### Clinical Studies

The pharmacokinetics (PK) of Hizentra was evaluated in a PK substudy of subjects (14 adults, 1 pediatric subject 6 to <12 years, and 3 adolescent subjects 12 to <16 years) with PI participating in the 15-month efficacy and safety study [see *Clinical Studies (14)*]. All PK subjects were treated previously with Privenge®, Immune Globulin Intravenous (Human), 10% Liquid and were switched to weekly subcutaneous treatment with Hizentra. After a 3-month wash-in/wash-out period, doses were adjusted individually with the goal of providing a systemic serum IgG exposure (area under the IgG serum concentration vs time curve; AUC) not inferior to that of the previous weekly-equivalent IGIV dose. Table 6 summarizes PK parameters for subjects in the substudy following treatment with Hizentra and IGIV.

**Table 6: Pharmacokinetics Parameters of Hizentra and IGIV, US Study**

	Hizentra	IGIV* (Privenge®)
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 <sup>†</sup> (day x mg/dL)		
Mean	10560	10320
Range	7210-18670	8051-15530
CL <sup>‡</sup> (mL/day/kg)		
Mean	2.2	1.3 <sup>§</sup>
Range	1.2-3.7	0.9-2.1

AUC, area under the curve; CL, clearance.

\* 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 Privenge PI study.

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.<sup>13,14</sup> 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 7 summarizes PK parameters at steady state for pediatric subjects (age groups: 6 to <12 and 12 to <16 years) and adults subjects (>16 years) in the European Hizentra study following weekly treatment [see *Clinical Studies (14.2)*]. Pediatric PK parameters are similar to those of adult subjects; thus no pediatric specific dose requirements are needed for Hizentra dosing.

**Table 7: Pediatric Pharmacokinetics Parameters of Hizentra, European Study**

	Age Group			Total (n=23)
	6 to <12 years (n=9)	12 to <16 years (n=3)	16 to <65 years (n=11)	
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 <sub>0-7d</sub> (day x mg/dL)				
Mean	5230	5491	5452	5370
Range	3890-6950	4480-6750	3860-6810	3860-6950
CL (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

AUC<sub>0-7d</sub>, area under the curve for the 7-day dosing interval; CL, apparent clearance (CL/F) (F = bioavailability).

### Pharmacokinetic Modeling and Simulation

#### Biweekly (Every Two Weeks) or more Frequent Dosing

Pharmacokinetic characterization of biweekly or more frequent dosing of Hizentra was undertaken using population PK-based modeling and simulation. Serum IgG concentration data consisted of 3837 samples from 151 unique pediatric and adult subjects with PI from four clinical studies of IGIV (Privenge®) 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<sub>max</sub>) and slightly lower trough (C<sub>min</sub>)]. 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<sub>max</sub>) and slightly higher trough (C<sub>min</sub>)]. Frequent dosing reduces the peak-to-trough variation in Hizentra exposure, thus resulting in more sustained IgG exposures. See Table 8 (columns for AUC, C<sub>max</sub> and C<sub>min</sub>).

#### Dose Adjustment Factor

Using data from four 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<sub>0-28days</sub> and C<sub>min</sub> ratios at ≥90% of values observed with 4-weekly IGIV dosing. See Table 8 (top two rows).

#### Prediction of Trough Levels Following Regimen Changes

PK modeling and simulation also predicted changes in trough levels after switching from (a) monthly IGIV to weekly or biweekly Hizentra dosing, (b) weekly to biweekly Hizentra dosing, or (c) weekly to more frequent dosing. Table 8 (last column) shows the predicted changes in steady-state IgG trough levels after switching between the various dosing regimens.

**Table 8: Predicted Ratios\* [Median (5<sup>th</sup>, 95<sup>th</sup> percentiles)] of AUC, C<sub>max</sub> and C<sub>min</sub> and Changes in IgG Trough Levels after Switching Between IGIV Dosing Regimens**

IGIV Dosing Regimen Switch		AUC	C <sub>max</sub>	C <sub>min</sub>	Predicted Change in Trough <sup>†</sup>
From:	To:				
IGIV	Weekly Hizentra <sup>‡</sup>	0.97 (0.90-1.04)	0.68 (0.60-0.76)	1.16 (1.07-1.26)	16% increase
IGIV	Biweekly Hizentra <sup>§</sup>	0.97 (0.91-1.04)	0.71 (0.63-0.78)	1.10 (1.02-1.18)	10% increase
Weekly Hizentra	Biweekly Hizentra <sup>§</sup>	1.00 (0.98-1.03)	1.06 (1.02-1.09)	0.95 (0.92-0.98)	5% decrease
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<sub>min</sub> 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<sub>0-28days</sub> for the IGIV to Hizentra switches, AUC<sub>0-14days</sub> for the weekly to biweekly Hizentra switch, and AUC<sub>0-7days</sub> for weekly to more frequent Hizentra switches; C<sub>max</sub>, maximum IgG concentration; C<sub>min</sub>, 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).

## Pediatric Pharmacokinetics

PK-based modeling and simulation results indicate that, similar to observations from the clinical study with weekly Hizentra dosing (Table 7), body weight-adjusted biweekly dosing accounted for age-related (>3 years) differences in clearance of Hizentra, thereby maintaining systemic IgG exposure (AUC values) in the therapeutic range.

## 13 NONCLINICAL TOXICOLOGY

### 13.2 Animal Toxicology and/or Pharmacology

Long- and short-term memory loss was seen in juvenile rats in a study modeling hyperprolinemia. In this study, rats received daily subcutaneous injections with L-proline from day 6 to day 28 of life.<sup>15</sup> The daily amounts of L-proline used in this study were more than 60 times higher than the L-proline dose that would result from the administration of 400 mg/kg body weight of Hizentra once weekly. In unpublished studies using the same animal model (i.e., rats) dosed with the same amount of L-proline with a dosing interval relevant to IGSC treatment (i.e., 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.

## 14 CLINICAL STUDIES

### 14.1 US Study

A prospective, open-label, multicenter, single-arm, clinical study conducted in the US 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 [see *Pharmacokinetics (12.3)*] and continued treatment for a 12-month efficacy period. The efficacy analyses included 38 subjects in the modified intention-to-treat (MITT) population. The MITT population consisted of subjects who completed the wash-in/wash-out period and received at least one infusion of Hizentra during the efficacy period.

Although 5% of the administered doses could not be verified, the weekly median doses of Hizentra ranged from 72 to 379 mg/kg body weight during the efficacy period. The mean dose was 213.2 mg/kg, which was 149% of the previous IGIV dose.

In the study, the number of injection sites per infusion ranged from 1 to 12. In 73% of infusions, the number of injection sites was 4 or fewer. Up to 4 simultaneous injection sites were permitted using 2 pumps; however, more than 4 sites could be used consecutively during one infusion. The infusion flow rate did not exceed 50 mL per hour for all injection 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 (SBI), defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess. The study also evaluated the annual rate of any infections, the use of antibiotics for infection (prophylaxis or treatment), the days out of work/school/kindergarten/day care or unable to perform normal activities due to infections, hospitalizations due to infections, and serum IgG trough levels.

Table 9 summarizes the efficacy results for subjects in the efficacy period (MITT population) of the study. No subjects experienced an SBI in this study.

**Table 9: Summary of Efficacy Results (MITT Population)**

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

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

<sup>†</sup> Upper 99% confidence limit: 0.132.

<sup>‡</sup> 95% confidence limits: 2.235; 3.370.

<sup>§</sup> 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.

## 14.2 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.

## 15 REFERENCES

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

- Hizentra is supplied in a single-use, tamper-evident vial containing 0.2 grams of protein per mL of preservative-free liquid.

Each product presentation includes a package insert and the following components:

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)

### 16.2 Storage and Handling

- Keep Hizentra in its original carton to protect it from light.
- Each vial label contains a peel-off strip with the vial size and product lot number for use in recording doses in a patient treatment record.
- When stored at room temperature (up to 25°C [77°F]), Hizentra is stable for up to 30 months, as indicated by the expiration date printed on the outer carton and vial label.
- Do not shake.
- Do not freeze. Do not use product that has been frozen.
- The components used in the packaging for Hizentra contain no latex.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients to immediately report the following signs and symptoms to their healthcare provider:

- Hypersensitivity reactions to Hizentra (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) (see *Warnings and Precautions [5.1]*).
- Pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or



- discomfort that worsens on deep breathing, unexplained rapid pulse, or numbness or weakness on one side of the body (see *Warnings and Precautions [5.2]*).
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (see *Warnings and Precautions [5.3]*).
- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (see *Warnings and Precautions [5.4]*).
- Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine (see *Warnings and Precautions [5.5]*).
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever (see *Warnings and Precautions [5.6]*).

Inform patients that because Hizentra is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (see *Warnings and Precautions [5.7]* and *Description [11]*).

Inform patients that Hizentra may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella) and to notify their immunizing physician of recent therapy with Hizentra (see *Drug Interactions [7]*).

#### **Home Treatment for Primary Humoral Immunodeficiency 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.

## **Hizentra**

### **Immune Globulin Subcutaneous (Human), 20% Liquid**

#### **Information for Patients**

This patient package insert summarizes important information about Hizentra. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare professional, and it does not include all of the important information about Hizentra. If you have any questions after reading this, ask your healthcare professional.

#### **What is the most important information I should know about Hizentra?**

Hizentra is supposed to be infused under your skin only. DO NOT inject Hizentra into a blood vessel (vein or artery).

#### **What is Hizentra?**

Hizentra (Hi – ZEN – tra) is a prescription medicine used to treat primary immune deficiency (PI). Hizentra is made from human plasma. It contains antibodies, called immunoglobulin G (IgG), that healthy people have to fight germs (bacteria and viruses).

People with PI get a lot of infections. Hizentra helps lower the number of infections you will get.

#### **Who should NOT take Hizentra?**

Do not take Hizentra if you have too much proline in your blood (called “hyperprolinemia”) or if you have had reactions to polysorbate 80.

Tell your doctor if you have had a serious reaction to other immune globulin medicines or if you have been told that you also have a deficiency of the immunoglobulin called IgA.

Tell your doctor if you have a history of heart or blood vessel disease or blood clots, have thick blood, or have been immobile for some time. These things may increase your risk of having a blood clot after using Hizentra. Also tell your doctor what drugs you are using, as some drugs, such as those that contain the hormone estrogen (for example, birth control pills), may increase your risk of developing a blood clot.

#### **How should I take Hizentra?**

You will take Hizentra through an infusion, only under your skin. Make sure that the infusion is not into a blood vessel. You will place up to 4 needles into different areas of your body each time you use Hizentra. The needles are attached to a pump with an infusion tube. You can have infusions as often as every day up to every two weeks. For weekly infusions, it can take about 1 to 2 hours to complete an infusion; however,

- Ensure the patient understands the importance of adhering to their prescribed administration schedule to maintain appropriate steady IgG levels.
- Instruct patients to scan the 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 injection-site reactions (e.g., 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 patients of the importance of having an infusion needle long enough to reach the subcutaneous tissue and of changing the actual site of injection with each infusion. Explain that Hizentra is for subcutaneous infusion only, and must not be injected into a blood vessel. Make sure patients know how to avoid blood vessels and check if the needle has entered a blood vessel.
- Inform patients to consider adjusting the injection-site location, volume per site, and rate of infusion based on how infusions are tolerated.
- Inform patient to interrupt or terminate the Hizentra infusion if a hypersensitivity reaction occurs.
- Inform 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.

this time may be shorter or longer depending on the dose and frequency your doctor has prescribed for you.

Instructions for using Hizentra are at the end of this patient package insert (see “How do I use Hizentra?”). Do not use Hizentra by yourself until you have been taught how by your doctor or healthcare professional.

#### **What should I avoid while taking Hizentra?**

Vaccines may not work well for you while you are taking Hizentra. Tell your doctor or healthcare professional that you are taking Hizentra before you get a vaccine.

Tell your doctor or healthcare professional if you are pregnant or plan to become pregnant, or if you are nursing.

#### **What are possible side effects of Hizentra?**

The most common side effects with Hizentra are:

- Redness, swelling, itching, and/or bruising at the injection site
- Headache/migraine
- Nausea and/or vomiting
- Pain (including pain in the chest, back, joints, arms, legs)
- Fatigue
- Diarrhea
- Stomach ache/bloating
- Cough
- Rash (including hives)
- Itching
- Fever and/or chills
- Shortness of breath
- Dizziness

Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Tell your doctor right away if you have any of the following symptoms. They could be signs of a serious problem.

- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, or numbness or weakness on one side of the body. These could be signs of a blood clot.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity

- to light. These could be signs of a brain swelling called meningitis.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a blood problem.
  - Chest pains or trouble breathing.
  - Fever over 100°F. This could be a sign of an infection.

Tell your doctor about any side effects that concern you. You can ask your doctor to give you more information that is available to healthcare professionals.

### How do I use Hizentra?

Infuse Hizentra only after you have been trained by your doctor or healthcare professional. Below are step-by-step instructions to help you remember how to use Hizentra. Ask your doctor or healthcare professional about any instructions you do not understand.

### Instructions for use

Hizentra comes in single-use vials.

Keep Hizentra in the storage box at room temperature.

#### Step 1: Assemble supplies

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

- Infusion administration tubing
- Needle or catheter sets (for subcutaneous infusion)
- Y-site connectors (if needed)
- Alcohol wipes
- Antiseptic skin preps
- Syringes
- Transfer device or needle(s)
- Gauze and tape, or transparent dressing
- Gloves (if recommended by your doctor)

#### Step 2: Clean surface

Thoroughly clean a table or other flat surface using one of the alcohol wipes.

#### Step 3: Wash hands

- Thoroughly wash and dry your hands (Figure 1).
- If you have been told to wear gloves when preparing your infusion, put the gloves on.



Figure 1

#### Step 4: Check vials

Carefully look at the liquid in each vial of Hizentra (Figure 2). Hizentra is a pale yellow to light brown solution. Check for particles or color changes. **Do not use the vial if:**

- The liquid looks cloudy, contains particles, or has changed color.
- The protective cap is missing.
- The expiration date on the label has passed.



Figure 2

#### Step 5: Transfer Hizentra from vial(s) to syringe

- Take the protective cap off the vial (Figure 3).

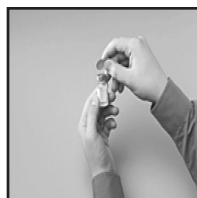


Figure 3

Clean the vial stopper with an alcohol wipe (Figure 4). Let the stopper dry.



Figure 4

- Attach a needle or transfer device to a syringe tip, using aseptic technique. If using a transfer device, follow the instructions provided by the device manufacturer. If using a needle and a syringe to transfer Hizentra, follow the instructions below.



Figure 5

- Attach a sterile transfer needle to a sterile syringe (Figure 5).
- Pull out the plunger of the syringe to fill the syringe with air. Make sure the amount of air is the same as the amount of Hizentra you will transfer from the vial.
- Put the Hizentra vial on a flat surface. Keeping the vial upright, insert the transfer needle into the center of the rubber stopper.
- Check that the tip of the needle is not in the liquid. Then, push the plunger of the syringe down. This will inject the air from the syringe into the airspace of the vial.
- Leaving the needle in the stopper, carefully turn the vial upside down (Figure 6).
- Slowly pull back on the plunger of the syringe to fill the syringe with Hizentra.
- Take the filled syringe and needle out of the stopper. Take off the needle and throw it away in the sharps container.



Figure 6

When using multiple vials to achieve the desired dose, repeat this step.

#### Step 6: Prepare infusion pump and tubing

Prepare the infusion pump (following the manufacturer's instructions) and prime (fill) the infusion tubing. To prime the tubing, connect the syringe filled with Hizentra to the infusion tubing and gently push on the syringe plunger to fill the tubing with Hizentra (Figure 7).



Figure 7

#### Step 7: Prepare injection site(s)

- Select an area on your abdomen, thigh, upper arm, or side of upper leg/hip for the infusion (Figure 8).
- Use a different site from the last time you infused Hizentra. New sites should be at least 1 inch from a previous site.

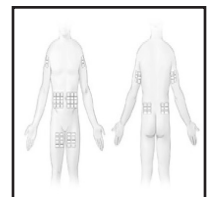


Figure 8

Never infuse into areas where the skin is tender, bruised, red, or hard. Avoid infusing into scars or stretch marks.

- If you are using more than one injection site, be sure the injection sites are at least 2 inches apart.

- During an infusion, do not use more than 4 injection sites at the same time.

Clean the skin at each site with an antiseptic skin prep (Figure 9). Let the skin dry.



Figure 9

### Step 8: Insert needle(s)

·With two fingers, pinch together the skin around the injection site. Insert the needle under the skin (Figure 10).

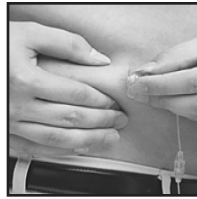


Figure 10

·Put sterile gauze and tape or a transparent dressing over the injection site (Figure 11). This will keep the needle from coming out.

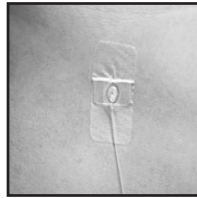


Figure 11

Make sure you are not injecting Hizentra into a blood vessel. To test for this, attach a sterile syringe to the end of the infusion tubing. Pull the plunger back gently (Figure 12). If you see any blood flowing back into the tubing, take the needle out of the injection site. Throw away the tubing and needle. Start the infusion over at a different site with new infusion tubing and a new needle.

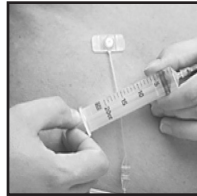


Figure 12

### Step 9: Start infusion

Follow the manufacturer's instructions to turn on the infusion pump (Figure 13).



Figure 13

### Step 10: Record treatment (Figure 14)

Peel off the removable part of the label of the Hizentra vial. Put this label in your treatment diary or log book with the date and time of the infusion. Also include the exact amount of Hizentra that you infused. Scan the vial if recording the infusion electronically.



Figure 14

### Step 11: Clean up

- When all the Hizentra has been infused, turn off the pump.
- Take off the dressing and take the needle out of the injection site. Disconnect the tubing from the pump.
- Throw away any Hizentra that is leftover in the single-use vial, along with the used disposable supplies, in the sharps or other container (Figure 15) as recommended by your healthcare professional.
- Clean and store the infusion pump, following the manufacturer's instructions.



Figure 15

Be sure to tell your doctor about any problems you have doing your infusions. Your doctor may ask to see your treatment diary or log book, so be sure to take it with you each time you visit the doctor's office.

Call your doctor for medical advice about side effects. You can also report side effects to FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

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