February 2018

IMPORTANT DRUG INFORMATION
Subject: Carimune® Immune Globulin Intravenous (Human), Nanofiltered
Product discontinuation notice

Dear Valued Customer:

For over a century, CSL Behring has earned a reputation as a passionate yet responsible organization driven to care for patients and successfully develop and dependably deliver innovations for patients and healthcare providers.

Carimune NF was introduced to the US market in 1984 and has played an important role in the maintenance treatment of primary immunodeficiency (PI) or acute and chronic immune thrombocytopenic purpura (ITP) for many patients. Given the preference among healthcare professionals and patients for newer, more advanced Immune Globulin options, such as Privigen®, Immune Globulin Intravenous (Human), 10% Liquid, and Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, CSL Behring has decided to discontinue the production of Carimune NF in 3Q 2018.

Consideration of yield is especially important when dealing with a resource as precious as human plasma. Discontinuation of Carimune NF will allow CSL Behring to dedicate more resources to Privigen and Hizentra, which yield higher rates of immunoglobulin (Ig). Over the long term, CSL Behring will be able to supply more immunoglobulin to the market due to greater yield and manufacturing efficiencies.

As you evaluate the alternatives to Carimune NF for your patients, we encourage you to consider Privigen and Hizentra.

If you have additional questions, we’re here to help. To find out more:
• Contact your CSL Behring representative
• Visit Privigen.com for more information about Privigen
• Visit Hizentra.com for more information about Hizentra
• Call IgIQSM at 1-877-355-IQiQ (4447), Monday to Friday, 8 am to 8 pm ET, and speak with our friendly and knowledgeable staff for more details about the support programs available to patients

Sincerely,

Debra Bensen-Kennedy, MD
Vice President, North America Medical Affairs

Please see next pages for Important Safety Information for Carimune NF, Privigen, and Hizentra, and see full prescribing information for Carimune NF, Privigen, and Hizentra, including boxed warning, enclosed.
**Important Safety Information for Immune Globulin Intravenous (Human), Carimune® NF, Nanofiltered**

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

- Thrombosis may occur with immune globulin products, including Carimune NF. 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 might occur in absence of known risk factors.

- Renal dysfunction, acute renal failure, osmotic nephrosis, and death can occur in predisposed patients with immune globulin intravenous (IGIV) products, including Carimune NF. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age over 65, volume depletion, sepsis, paraproteinemia, and those receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Carimune NF contains sucrose.

- For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Carimune NF 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 full prescribing information for full boxed warning.

Carimune NF is contraindicated in patients who have had anaphylactic or severe systemic reactions to the administration of human immune globulin. Individuals with selective IgA deficiency who possess antibody to IgA should only receive Carimune NF with utmost caution due to risk of severe, immediate hypersensitivity reactions, including anaphylaxis.

Increases in creatinine and blood urea nitrogen with progression to oliguria or anuria requiring dialysis have been observed as soon as one to two days following IGIV infusion. Severe renal adverse events have included acute renal failure, acute tubular nephropathy, proximal tubular nephropathy, and osmotic nephrosis.

Patients receiving Carimune NF should be monitored for clinical signs and symptoms of hemolysis, as well pulmonary adverse reactions, including TRALI. An aseptic meningitis syndrome (AMS) has been reported to occur infrequently with IVIG—more frequently in association with high dose (2 g/kg) treatment.

Inflammatory adverse reactions have been observed; they may become apparent within 30 minutes to an hour after beginning infusion. Slow or temporarily stop infusion if patient experiences facial flushing, tightness in chest, chills, fever, nausea, dizziness or other unusual response; stop infusion immediately if anaphylaxis or severe reaction occurs. Headache, usually mild, is the most common adverse reaction; mild hemolysis, arthralgia, myalgia, and transient skin reactions have also been reported.

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

Carimune NF should be given to a pregnant woman only if clearly needed.

**Indication**

Carimune NF is indicated for the maintenance treatment of patients with primary immunodeficiencies (PI), such as common variable immunodeficiency, X-linked agammaglobulinemia, and severe combined immunodeficiency, as well as for for acute and chronic immune thrombocytopenic purpura (ITP).

Please see enclosed full prescribing information, including boxed warning on thrombosis and renal dysfunction/failure.
Important Safety Information for Immune Globulin Intravenous (Human), Privigen®

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- 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 that contain 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.

See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

In patients at risk of developing acute renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine.

Hyperproteinemia, increased serum viscosity, or hyponatremia can occur with Privigen. Infrequently, aseptic meningitis syndrome (AMS) may occur—especially with high doses or rapid infusion.

Hemolysis, either intravascular or due to enhanced red blood cell sequestration, may occur. Risk factors include non-O blood group and high doses. Closely monitor patients for hemolysis and hemolytic anemia.

During and shortly following Privigen infusion, elevations of systolic and diastolic blood pressure (including cases of hypertensive urgency) have been observed. These elevations resolved or significantly improved within hours with oral anti-hypertensive therapy or observation alone. Check patients for a history of hypertension and monitor blood pressure during this period.

Consider relative risks and benefits before prescribing high-dose regimen for chronic ITP and CIDP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload. Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).

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

In clinical studies of patients with PI, the most common adverse reactions to Privigen, 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 for chronic ITP, the most common adverse reactions, seen in >5% of subjects, were laboratory findings consistent with hemolysis, headache, elevated body temperature, anemia, nausea, and vomiting. A serious adverse reaction was aseptic meningitis syndrome.

In clinical studies of patients being treated for CIDP, the most common reactions, observed in >5% of subjects, were headache, asthenia, hypertension, nausea, pain in extremity, hemolysis, influenza-like illness, leukopenia, and rash. Serious adverse reactions were hemolysis, exacerbation of CIDP, acute rash, increased diastolic blood pressure, hypersensitivity, pulmonary embolism, respiratory failure, and migraine.

Treatment with Privigen might interfere with a patient’s response to live virus vaccines and could lead to misinterpretation of serologic testing. In patients over 65 and those at risk of renal insufficiency, do not exceed recommended dose and infuse at the minimum rate practicable.

Indication

Privigen is indicated for the treatment of:
- Primary humoral immunodeficiency (PI)
- Chronic immune thrombocytopenic purpura (ITP) in patients age 15 years and older
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in adults
  - Limitation of use: maintenance therapy in CIDP has not been studied for periods longer than 6 months. Individualize duration of treatment beyond 6 months based on patient response.

Please see enclosed full prescribing information for Privigen.
**Important Safety Information for Immune Globulin Subcutaneous (Human), Hizentra®**

**WARNING: THROMBOSIS**

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. See full prescribing information for complete boxed warning.

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

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

IgA-deficient patients with anti-IgA antibodies may be at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Hizentra. 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. In patients at risk of acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine and urine output. Also monitor patients for clinical signs of hemolysis or transfusion-related acute lung injury (TRALI).

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

The most common 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.

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

**Indication**

Hizentra is indicated as replacement therapy for patients with primary humoral immunodeficiency (PI), age 2 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.

Please see enclosed full prescribing information for Hizentra.
Immune Globulin Intravenous (Human), Carimune® NF, Nanofiltered
Lyophilized Preparation

It only

CLINICAL PHARMACOLOGY
Carimune® NF contains a broad spectrum of antibody specificities against bacterial, viral, parasitic, and mycoplasma antigens, that are capable of both opsonization and neutralization of microbes and toxins. The 3 week half-life of Carimune® NF corresponds to that of immunoglobulin (Human) for intramuscular use, although individual variations in half-life have been observed.23,24

Appropriate doses of Carimune® NF restore abnormally low immunoglobulin G levels to the normal range. One hundred percent of the infused dose of IgG-products is available in the recipient’s circulation immediately after infusion. After approximately 6 days, equilibrium is reached between the intra- and extravascular compartments, with immunoglobulin G being present approximately 50% in the intravascular and 50% extravascular. In comparison, after the intravenous injection of immunoglobulin, the IgG requires 2–5 days to reach its maximum concentration in the intravascular compartment. This concentration corresponds to about 40% of the injected dose.23

While Carimune® NF has been shown to be effective in some cases of Immune Thrombocytopenic Purpura (ITP) (see INDICATIONS AND USAGE), the mechanism of action in ITP has not been fully elucidated. Toxicity from overdose has not been observed on regimes of 0.4 g/kg body weight each day for 5 days.20,21 Sucre is added to Carimune® NF for reasons of stability and solubility. Since sucrose is excreted unchanged in the urine when given intravenously, Carimune® NF may be given to diabetics without compensatory changes in insulin dosage regimen. Please see WARNINGS section.

INDICATIONS AND USAGE
Immunodeficiency
Carimune® NF is indicated for the maintenance treatment of patients with primary immunodeficiencies (PID), e.g., common variable immunodeficiency, X-linked agammaglobulinemia, severe combined immunodeficiency.23,24 Carimune® NF is preferable to intramuscular Immune Globulin (Human) preparations in treating patients who require an immediate and large increase in the intravascular immunoglobulin level, in patients with limited muscle mass, and in patients with bleeding tendencies for whom intramuscular injections are contraindicated. The infusions must be repeated at regular intervals. Please see DOSAGE AND ADMINISTRATION section.

Immune Thrombocytopenic Purpura (ITP)

Acute
A controlled study was performed in children in which Carimune® was compared with steroids for the treatment of acute (defined as less than 6 months duration) ITP. In this study sequential platelet levels of 30,000, 100,000, and 150,000/μL were all achieved faster with Carimune® than with steroids and without any of the side effects associated with steroids.29,30 However, it should be noted that many cases of acute ITP in childhood resolves spontaneously within weeks to months. Carimune® has been used with good results in the treatment of acute ITP in adult patients.16–19 In a study involving 10 adults with ITP of less than 16 weeks duration, Carimune® therapy raised the platelet count to the normal range after a 5 day course. This effect lasted a mean of over 173 days, ranging from 30 to 372 days.23

Chronic
Children and adults with chronic (defined as greater than 6 months duration) ITP have
also shown an increase (sometimes temporary) in platelet counts upon administration of Carimune®.35,39-43 Therefore, in situations that require a rapid rise in platelet count, for example prior to surgery or to control excessive bleeding, use of Carimune® should be considered. In children with chronic ITP, Carimune® therapy resulted in a mean rise in platelet count of 312,000/µL with a duration of increase ranging from 2 to 6 months.41,43 Carimune® therapy may be considered as a means to defer or avoid splenectomy.42,44 In adults, Carimune® therapy has been shown to be effective in maintaining the platelet count in an acceptable range with or without periodic booster therapy. The mean rise in platelet count was 93,000/µL and the average duration of the increase was 20–24 days.39,40 However, it should be noted that not all patients will respond. Even in those patients who do respond, this treatment should not be considered to be curative.

CONTRAINDICATIONS
Carimune® NF is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. Individuals with IgA deficiency, especially those who have known antibody against IgA, or hypersensitivity to immunoglobulins should only receive Carimune® NF with utmost caution due to the risk of severe immediate hypersensitivity reactions including anaphylaxis.

WARNINGS
Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.1,14 Patients predisposed to acute renal failure include patients with:

1. any degree of pre-existing renal insufficiency
2. diabetes mellitus
3. age greater than 65
4. volume depletion
5. sepsis
6. paraproteinemias
7. patients receiving known nephrotoxic drugs

In such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Carimune® NF contains sucrose. See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

IgA deficient patients, especially those with known antibodies against IgA, are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Because Carimune® NF is made from human blood, it may carry a risk of transmitting certain viruses, by testing for the presence of certain current virus infections, and through the application of viral elimination/reduction steps such as alcohol fractionation in the presence of filter aids, nanofiltration and pH 4/pepsin treatment 19-21 (see Table 1). All infections thought by a physician possibly to have been transmitted by Carimune NF should be reported by lot number, by the physician, or other healthcare provider to CSL Behring Pharmacovigilance at 1-866-915-6598. The physician should discuss the risks and benefits of this product with the patient.

Patients with agamma- or extreme hypogammaglobulinemia who have never before received immunoglobulin substitution treatment or whose time from last treatment is greater than 8 weeks, may be at risk of developing inflammatory reactions on rapid infusion (greater than 2 mg/kg/min) of Carimune® NF. These reactions are manifested by a rise in temperature, chills, nausea, and vomiting. The patient’s vital signs should be monitored continuously. The patient should be carefully observed throughout the infusion, since these reactions on rare occasions may lead to shock. Epinephrine and other appropriate resuscitative drugs and equipment should be available for treatment of an acute anaphylactic reaction.

PRECAUTIONS
Please see DOSAGE AND ADMINISTRATION below, for important information on Carimune® NF compatibility with other medications or fluids. Patients should not be volume depleted prior to the initiation of the infusion of IGIV. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, should be assessed prior to the initial infusion of Carimune® NF and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, Carimune® NF should be infused at a rate less than 2 mg/kg/min.

Information for Patients
• Instruct patients to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.
• 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.

Laboratory Tests
IGIV recipients should be monitored for clinical signs and symptoms of hemolysis. IGIV recipients should be monitored for pulmonary adverse reactions. If Transfusion-Related Acute Lung Injury (TRALI) is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammapathies.

Pregnancy Category C
Animal reproduction studies have not been conducted with Carimune® NF. It is also not known whether Carimune® NF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Carimune® NF should be given to a pregnant woman only if clearly needed.38 Intact immune globulins such as those contained in Carimune® NF cross the placenta from maternal circulation approximately 30 weeks gestation.45,46 In cases of maternal ITP where Carimune® was administered to the mother prior to delivery, the platelet response and clinical effect were similar in the mother and neonate.47-49,55

Pediatric Use
High dose administration of Carimune® in pediatric patients with acute or chronic Immune Thrombocytoptenic Purpura did not reveal any pediatric-specific hazard.29 Antibodies in Immune Globulin Intravenous (Human) may impair the efficacy of live attenuated viral vaccines such as measles, rubella, and mumps.56-58 Immunizing physicians should be informed of recent therapy with Immune Globulin Intravenous (Human) so that appropriate precautions may be taken.

Geriatric Use
Carimune® NF should be used with caution in patients over 65 years of age and judged to be at increased risk of developing renal insufficiency (see DOSAGE AND ADMINISTRATION).

In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable. The product should be infused at a rate less than 2 mg/kg/min.

Aseptic Meningitis Syndrome
An aseptic meningitis syndrome (AMS) has been reported to occur frequently in association with Immune Globulin Intravenous (Human) (IGIV) treatment. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis
Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.39,41 Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration42 (see ADVERSE REACTIONS). IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (see PRECAUTIONS: Laboratory Tests).

Transfusion-Related Acute Lung Injury (TRALI)
There have been reports of noncardiogenic pulmonary edema Transfusion-Related Acute Lung Injury (TRALI) in patients administered IGIV.29 TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1–6 hours after transfusion. Patients with TRALI may be managed by using oxygen therapy with adequate ventilatory support. IVIG recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see PRECAUTIONS: Laboratory Tests).

Thrombosis
Thrombosis may occur following treatment with immune globulin products18, including Carimune NF. 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 Carimune® NF 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, PRECAUTIONS: Information for Patients).

ADVERSE REACTIONS
Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion. Progression to oliguria or anuria, requiring dialysis has been observed. Types of severe renal adverse events that have been seen following IGIV therapy include: acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis.6,10,12–15

Inflammatory adverse reactions have been described in agammaglobulinemic and hypogammaglobulinemic patients who have never received immunoglobulin substitution therapy before or in patients whose time from last treatment is greater than 8 weeks and whose initial infusion rate exceeds 2 mg/kg/min. This occurs in approximately 10% of such cases. Such reactions may also be observed in some patients during chronic substitution therapy. Reactions, which may become apparent only 30 minutes to 1 hour after the beginning of the infusion, are as follows: flushing of the face, feelings of tightness in the chest, chills, fever, dizziness, nausea, diaphoresis, and hypotension or hypertension. In such cases, the infusion should be slowed or temporarily stopped until the symptoms subside. The infusion may then be resumed at a lower rate that is comfortable for the patient. If anaphylaxis or other severe reactions occur, the infusion should be stopped immediately.

Arthralgia, myalgia, and transient skin reactions (such as rash, erythema, pruritus, urticaria, eczema or dermatitis) have also been reported. Immediate anaphylactoid and hypersensitivity reactions due to previous sensitization of the recipient to certain antigens, most commonly IgA, may be observed in exceptional cases, described under CONTRAINDICATIONS.24,71–73

In patients with ITP, who receive higher doses (0.4 g/kg/day or greater), 2.9% of infusions may result in adverse reactions.21

Headache, generally mild, is the most common symptom noted, occurring during or following 2% of infusions. A few cases of usually mild hemolysis have been reported after infusion of intravenous immunoglobulin products.59–61 These were attributed to transferal of blood group (e.g., anti-D) antibodies.

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

Respiratory
Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, 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
Pan cytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test

General/Body as a Whole
Pyrexia, rigors

Musculoskeletal
Back pain

Gastrointestinal
Hepatic dysfunction, abdominal pain

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.24

DOSAGE AND ADMINISTRATION
It is generally advisable not to dilute plasma derivatives with other infusible drugs. Carimune® NF should be given by a separate infusion line. No other medications or fluids should be mixed with Carimune® NF preparation.

Carimune® NF should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs). In these cases especially it is important to assure that patients are not volume depleted prior to Carimune® NF infusion. No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable. For patients judged to be at risk for developing renal dysfunction, Carimune® NF should be infused at a rate less than 2 mg/kg/min.

For patients judged to be at an increased risk for thrombosis, a maximum infusion rate of less than 2 mg/kg/min for patients is recommended (see PRECAUTIONS: Thrombosis). If side effects occur, the infusion should be stopped or slowed until the symptoms subside.

Adult and Child Substitution Therapy
The recommended dose of Carimune® NF in primary immunodeficiency is 0.4 to 0.8 g/kg of body weight administered once every three to four weeks by intravenous infusion. The first infusion of Carimune® NF in previously untreated agammaglobulinemic or hypogammaglobulinemic patients must be given as a 3% immunoglobulin solution (see Reconstitution). Subsequent infusions may be administered at a higher concentration if the patient shows good tolerance.

An initial infusion rate of 0.5 mg/kg/min is recommended. If tolerated, after 30 minutes, the rate may be increased to 1 mg/kg/min for the next 30 minutes. Thereafter, the rate may be gradually increased in a stepwise manner up to a maximum of 3 mg/kg/min as tolerated. Refer to Table 3 for the corresponding infusion rates in mg/kg/min or mL/kg/min for all product concentrations.

The first infusion of Carimune® NF in previously untreated agammaglobulinemic and hypogammaglobulinemic patients may lead to systemic side effects. The nature of these effects has not been fully elucidated. Some of them may be due to the release of proinflammatory cytokines by activated macrophages in immunodeficient recipients.57,68 Subsequent administration of Carimune® NF to immunodeficient patients as well as to normal individuals usually does not cause further untoward side effects.

Therapy of Idiopathic Thrombocytopenic Purpura (ITP)

Induction
The recommended dose of Carimune® NF for the treatment of ITP is 0.4 g/kg of body weight on 2–5 consecutive days. An immunoglobulin solution of 6% (see Reconstitution) is recommended for use in ITP.

The recommended initial infusion rate for the treatment of ITP is 0.5 mg/kg/min. If tolerated, after 30 minutes, the rate may be increased to 1 mg/kg/min for the next 30 minutes. Thereafter, the rate may be gradually increased in a stepwise manner up to a maximum of 3 mg/kg/min as tolerated. Refer to Table 3 for the corresponding infusion rates in mg/kg/min or mL/kg/min for all product concentrations.

Acute ITP – Childhood
In acute ITP of childhood, if an initial platelet count response to the first two doses is adequate (30–50,000/µL), therapy may be discontinued after the second day of the 5 day course.35

Maintenance – Chronic ITP
In adults and children, if after induction therapy the platelet count falls to less than 30,000/µL and/or the patient manifests clinically significant bleeding, 0.4 g/kg of body weight may be given as a single infusion. If an adequate response does not result, the dose can be increased to 0.8–1 g/kg of body weight given as a single infusion.36,39,70

Table 3: Infusion Rates for Carimune® NF Concentrations

<table>
<thead>
<tr>
<th>Concentration (%)</th>
<th>Initial Infusion Rate: 0.5 mg/kg/min</th>
<th>1 mg/kg/min</th>
<th>2 mg/kg/min</th>
<th>Maximum Infusion Rate: 3 mg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>0.0167 mL/kg/min</td>
<td>0.033 mL/kg/min</td>
<td>0.067 mL/kg/min</td>
<td>0.10 mL/kg/min</td>
</tr>
<tr>
<td>6%</td>
<td>0.009 mL/kg/min</td>
<td>0.0167 mL/kg/min</td>
<td>0.033 mL/kg/min</td>
<td>0.050 mL/kg/min</td>
</tr>
<tr>
<td>9%</td>
<td>0.006 mL/kg/min</td>
<td>0.011 mL/kg/min</td>
<td>0.022 mL/kg/min</td>
<td>0.033 mL/kg/min</td>
</tr>
<tr>
<td>12%</td>
<td>0.004 mL/kg/min</td>
<td>0.008 mL/kg/min</td>
<td>0.016 mL/kg/min</td>
<td>0.025 mL/kg/min</td>
</tr>
</tbody>
</table>

* Maximum infusion rate for patients at risk of renal dysfunction or thromboembolic events.
† For patients not at risk of renal dysfunction or thromboembolic events.

Reconstitution
(see also pictures next page)

1. Remove the protective plastic caps from the lyophilisate (LYO) and diluent bottle (see also pictures next page)

2. Remove the protective plastic caps from the lyophilisate (LYO) and diluent bottle (picture 2b).

3. Once the appropriate amount of diluent is transferred (see Table 4), lift the diluent bottle off the spike to release the vacuum (picture 3). This will reduce the risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable. For patients judged to be at risk for developing renal dysfunction, Carimune® NF should be infused at a rate less than 2 mg/kg/min.

4. Swirl vigorously but do not shake, otherwise a foam will form which is very slow to subside (picture 4). The lyophilisate dissolves within a few minutes.
To reconstitute Carimune® NF from the individual vial package, or when using other diluents or higher concentrations, Table 4 indicates the volume of sterile diluent required. Observing aseptic technique, this volume should be drawn into a sterile hypodermic syringe and needle. The diluent is then injected into the corresponding Carimune® NF vial size.

Table 4: Required Diluent Volume*

<table>
<thead>
<tr>
<th>Target Concentration</th>
<th>6 g Vial</th>
<th>12 g Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>200 mL</td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td>100 mL</td>
<td>200 mL</td>
</tr>
<tr>
<td>9%</td>
<td>66 mL</td>
<td>132 mL</td>
</tr>
<tr>
<td>12%</td>
<td>50 mL</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

* In patients judged to be at increased risk of developing renal insufficiency and thromboembolic events, the concentration and infusion rate of Carimune® NF should be the minimum practicable.

If large doses of Carimune® NF are to be administered, several reconstituted vials of identical concentration and diluent may be pooled in an empty sterile glass or plastic i.v. infusion container using aseptic technique.

Carimune® NF normally dissolves within a few minutes, though in exceptional cases it may take up to 20 minutes.

**DO NOT SHAKE!** Excessive shaking will cause foaming.

Any undissolved particles should respond to careful rotation of the bottle. Avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Filtering of Carimune® NF is acceptable but not required. Pore sizes of 15 microns or larger will be less effective in removing particulate matter.

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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 prednisosed 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 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.

REVISED: SEPTEMBER 2017

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

INDICATIONS AND USAGE

INTRAVENOUS USE ONLY

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) in patients age 15 years and older (1.2)

ADVERSE REACTIONS

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 hyperviscosity, chills, fatigue, dizziness, and increased body temperature. (6.1)

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.

DOSAGE AND ADMINISTRATION

Dosage for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults (1.3)

Privigen is a liquid solution containing 10% IgG (0.1 g/mL). (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 may occur. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia. (5.6)

Elevations of systolic and diastolic blood pressure (including cases of hypertensive urgency, hypertensive emergency, and malignant hypertension) have been observed during/shortly following Privigen infusion. These blood pressure elevations were resolved or significantly improved within hours with either observation alone or changes in oral anti-hypertensive therapy. Check patients for a history of hypertension and monitor blood pressure during and following Privigen infusion. (5.7)

Hyperprolinemia (Privigen contains the stabilizer L-proline) (4)

Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure. (5.2)

See full prescribing information for complete boxed warning.

Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

The passive transfer of antibodies may:

- Interfere with the response to live virus vaccines. (7.1)

USE IN SPECIFIC POPULATIONS

ADVERSE REACTIONS

The most common adverse reactions, observed in >5% of study subjects, were:

- Laboratory findings consistent with hemolysis (hemoglobin and hematocrit decrease without blood loss in conjunction with positive direct antiglobulin test (DAT) and elevated blood lactate dehydrogenase (LDH) and/or indirect bilirubin), headache, elevated body temperature, anemia, nausea, and vomiting. A serious adverse reaction was aseptic meningitis. (6.1)

- The most common adverse reactions observed in >5% of study subjects were:

- Headache, asthma, hypertension, nausea, pain in extremity, influenza-like illness, leukopenia, and rash. Serious adverse reactions were hemolysis, exacerbation of CIDP, acute rash, blood pressure diastolic increased, hyperviscosity, pulmonary embolism, respiratory failure, and migraine. (6.1)

- In patients over age 63 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: September 2017

FULL PRESCRIBING INFORMATION: CONTENTS*

ADVERSE REACTIONS

DRUG INTERACTIONS

USE IN SPECIFIC POPULATIONS

PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
CSL Behring
FULL PRESCRIBING INFORMATION
Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

WARNING: THROMBOSIS, RENAL DYSFUNCTION
AND ACUTE RENAL FAILURE

- 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 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. 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 age 15 years and older with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

1.3 Chronic Inflammatory Demyelinating Polyneuropathy

Privigen is indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.

Limitation of Use: Privigen maintenance therapy in CIDP has not been studied for periods longer than 6 months. After responding during an initial treatment period, not all patients require indefinite maintenance therapy with Privigen in order to remain free of CIDP symptoms. Individualize the duration of any treatment beyond 6 months based upon the patient’s response and demonstrated need for continued therapy.

2 DOSAGE AND ADMINISTRATION

Table 1. Recommended Dosage and Administration for Privigen

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial infusion rate</th>
<th>Maintenance infusion rate (as tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Immunodeficiency</td>
<td>200-800 mg/kg (2-8 mL/kg) every 3-4 weeks</td>
<td>0.5 mg/kg/min (0.005 mL/kg/min)</td>
<td>Increase to 8 mg/kg/min (0.08 mL/kg/min)</td>
</tr>
<tr>
<td>Chronic Immune Thrombocytopenic Purpura</td>
<td>1 g/kg (10 mL/kg) for 2 consecutive days</td>
<td>0.5 mg/kg/min (0.005 mL/kg/min)</td>
<td>Increase to 4 mg/kg/min (0.04 mL/kg/min)</td>
</tr>
<tr>
<td>Chronic Inflammatory Demyelinating Polyneuropathy</td>
<td>Loading dose: 2 g/kg (20 mL/kg) in divided doses over 2 to 5 consecutive days</td>
<td>0.5 mg/kg/min (0.005 mL/kg/min)</td>
<td>Increased to 8 mg/kg/min (0.08 mL/kg/min)</td>
</tr>
<tr>
<td>Maintenance dose: 1 g/kg (10 mL/kg) administrated in 1 to 2 infusions on consecutive days, every 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 (5.9)).

2.3 Dosage for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Privigen may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to five consecutive days. Privigen may be administered as a maintenance infusion of 1 g/kg (10 mL/kg) administered in a single infusion given in one day or divided into two doses given on two consecutive days, every 3 weeks. Maintenance therapy beyond 6 months has not been studied.

The recommended initial infusion rate is 0.5 mg/kg/min (0.005 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min) for patients judged to be at risk for thrombosis, renal dysfunction, or volume overload, administer Privigen at the minimum infusion rate practicable (see Warnings and Precautions (5.2, 5.3)).

2.4 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 (DSW) 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 (DSW).
- 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.

2.5 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 (≥25 mcg/mL) [see Description (1.1)]. 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, necrotic 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. Ê Privigen does not contain sucrose. Acute renal failure may also occur as a result of Privigen-induced hemolysis. 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. Ê 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 Ê and, 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 mononclonal gammapathies. 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 (2.2), 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 pseudo-hyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudo-hyponatremia, as treatment aimed at decreasing serum free water in patients with pseudo-hyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events. Ê

5.5 Aseptic Meningitis Syndrome (AMS)
AMS may occur infrequently following treatment with Privigen [see Adverse Reactions (6.2), and other human immune globulin products. Discontinuation of Treatment has resulted in remission of AMS within several days without sequelae. Ê 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, blurry or double vision, painful eye movements, nausea, vomiting, neck stiffness, Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, 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. Ê 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. Ê Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported. Ê 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., ≥2 g/kg), given either as a single administration or divided over several days, and non-O blood group. Ê 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. The role of these factors is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP, CIDP, and PI. Ê Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above and those with pre-existing anemia and/or cardiovascular or pulmonary compromise. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 hours and again 7 to 10 days 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 Hypertension
Elevations of systolic blood pressure to ≥180 mm Hg and/or of diastolic blood pressure to >120 mm Hg (hypertensive urgency) have been observed during and/or shortly following infusion of Privigen. These blood pressure elevations were resolved or significantly improved within hours with either observation alone or changes in oral anti-hypertensive therapy [see Adverse Reactions (6.1)]. Such elevations were reported more often among patients with a history of hypertension. Check patients for a history of hypertension and current antihypertensive medication use. Monitor blood pressure prior to, during, and following Privigen infusion.

5.8 Transfusion-Related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen. Ê 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.

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

5.10 Transmissible Infectious Agents
Because Privigen 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). 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.

5.11 Interference with Laboratory Tests
Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS
The following important adverse reactions are reported with IGIV: hypersensitivity, renal dysfunction and acute renal failure, thrombosis, hyperproteinemia, increased serum viscosity, hyponatremia, aseptic meningitis syndrome, hemolysis, hypertension, transfusion related acute lung injury, volume overload, and transmissible infectious agents [see Warnings and Precautions (5.1)].

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, 80 subjects with PI were treated with Privigen at the minimum dose and infusion rate practicable. 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 laboratory 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 reaction observed in the premarking 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 premarking ITP study experienced hemolysis as documented from clinical laboratory data. No serious adverse reactions were observed in the postmarketing chronic ITP study. A total of 12 subjects (21%) in the postmarketing ITP study were adjudicated to have mild hemolysis as documented from clinical laboratory data [see Warnings and Precautions (5.6)]. The most common adverse reactions observed in >5% of subjects in both clinical studies of subjects with chronic ITP were laboratory findings consistent with hemolysis (hemoglobin and hematocrit decrease without blood loss in conjunction with positive direct antiglobulin test (DAT) and elevated blood lactate dehydrogenase (LDH) and/or indirect bilirubin), headache, elevated body temperature, anemia, nausea, and vomiting.

Chronic Inflammatory Demyelinating Polyneuropathy
The most serious adverse reaction observed in clinical study subjects receiving Privigen for CIDP was hemolysis. The most common adverse reactions observed in >5% of subjects in both clinical studies of subjects with CIDP were headache, asthenia, hypertension, nausea, pain in extremity, hemolysis, influenza like illness, leukopenia, and rash.
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 IGV 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 mg/kg (3-week schedule) or 441 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 antiemetics. 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 that occurred in >5% of subjects.

### Table 2. PI Pivotal Study – ARs* Occurring in >5% of Subjects

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

* ARs are defined as adverse events at least possibly related or events occurring during or within 72 hours of a Privigen infusion. Infusions are excluded from this table.

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), 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 study described above 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 IGV 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%) 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 (42% of the 55 subjects in the extension study) received 265 (38%) 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

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

* ARs are defined as adverse events at least possibly related or events occurring during or within 72 hours after the end of a treatment cycle (two consecutive infusions).

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

Three subjects experienced ARs: 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 premarketing clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/L or less received a total of 2 g/kg dose of Privigen 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%) were male and 34 (60%) were female.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 4 summarizes the most frequent ARs that occurred in >5% of subjects with chronic ITP.

### Table 4. Chronic ITP Premarketing Clinical Study – ARs* Occurring in >5% of Subjects

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

* ARs are defined as adverse events at least possibly related or events occurring during or within 72 hours after the end of a treatment cycle (two consecutive infusions).

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 Privigen. 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 Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.
Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21%) developed a positive DAT during the 29-day study period.

Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter postmarketing clinical study whose primary objective was to evaluate mechanisms of hemolysis, 57 subjects with chronic ITP and a platelet count of <30 x 10^11 at screening were studied following treatment with Privigen. Twenty-one (21 subjects (37%) received 1 infusion of 1 g/kg on Day 1 and 36 subjects (63%) received 2 infusions each of 1 g/kg (Day 1 and Day 3). Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Subjects received premedication with acetaminophen and/or an antihistamine (see Clinical Studies (14.3)).

The most frequent ARs (adverse events at least possibly related or events occurring during or within 72 hours after the end of treatment) that occurred in >5% of subjects with chronic ITP were headache (16 subjects (28%)) and pyrexia (3 subjects (5%)). No subject experienced a serious adverse reaction.

Of the 23 non-serious ARs, 22 were mild (does not interfere with routine activities), 1 was moderate (interferes somewhat with routine activities), and none were severe (impossible to perform routine activities).

All 57 subjects had a negative DAT at baseline. Twenty-two (38%) developed a positive DAT by Day 4, 19 of these subjects were from blood group A. Fifteen subjects were adjudicated by an independent expert committee, for presumptive/possible hemolysis, all of whom received 2 g/kg IGIV during the study (see Clinical Studies (14.3).) Twelve subjects (21%) were judged to have mild hemolysis. In these 12 subjects there was a median hemoglobin drop from baseline at Day 9 (nadir) of -3.0 g/dL (range -0.9 to -5.8 g/dL) with Day 9 hemoglobin values ranging from 9.9 to 13.2 g/dL, and a median drop from baseline in hemoglobin of -1.2 g/dL (range -0.1 to -2.7 g/dL) at Day 29 (end of study) with hemoglobin values ranging from 11.8 to 15.8 g/dL. Ten subjects were blood group A and 2 subjects were blood group B. These hemoglobin drops were transient and were followed by recovery or partial recovery by Day 29. One subject experienced mild dyspnea between Day 9 and Day 16;

1 subject experienced mild dizziness on Day 4. No subject was judged as having experienced clinically significant intravascular hemolysis. Three of the 15 adjudicated subjects were judged not to have experienced hemolysis.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In a prospective, open-label, single-arm, multicenter clinical study (Privigen Impact on Mobility and Autonomy [PRIMA]), 28 subjects with CIDP received a Privigen loading dose of 2 g/kg followed by Privigen maintenance doses of 1 g/kg every 3 weeks for up to 21 weeks with 3 weeks follow up (see Clinical Studies (14.4)). Administration of the loading dose occurred over 2 days and the maintenance dose over 1 day in the majority of cases. Table 5 summarizes the most frequent ARs that occurred in ≥5% of subjects with CIDP.

<table>
<thead>
<tr>
<th>AR</th>
<th>Number (%) of Subjects</th>
<th>Number (Rate) of Infusions with AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8 (28.6)</td>
<td>19 (0.073)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (14.3)</td>
<td>4 (0.015)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (14.3)</td>
<td>6 (0.023)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (10.7)</td>
<td>3 (0.012)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (10.7)</td>
<td>3 (0.012)</td>
</tr>
<tr>
<td>Hemolyisis</td>
<td>2 (7.1)</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>2 (7.1)</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (7.1)</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (7.1)</td>
<td>2 (0.008)</td>
</tr>
</tbody>
</table>

*ARs were defined as adverse events at least possibly related or events occurring during or within 72 hours after IV infusion.

Two hemolysis serious adverse reactions occurred after the start of the Privigen induction dose in subjects with non-O blood groups (A and AB). The reactions resolved after discontinuation without the need for transfusion.

Four subjects, three of whom had a history of hypertension, had reversible increases in systolic blood pressure from 84 mm Hg to 160 mm Hg during or within 1 hour following Privigen infusion. One of these subjects who had a history of untreated hypertension had a reversible increase in diastolic blood pressure from 84 mm Hg pre-infusion to 135 mm Hg at 1 hour after the end of the infusion. All were resolved or significantly improved within 1 to 6 hours with either observation alone or changes in oral anti-hypertensive therapy.

A total of 71 ARs were reported: 46 were mild (does not interfere with routine activities), 23 were moderate (interferes somewhat with routine activities), and 2 were severe (impossible to perform routine activities) in intensity.

In a second prospective, open-label Privigen pre-randomization phase of a multicenter, randomized, double-blind, placebo-controlled clinical study (Polyneuropathy and Treatment with Hizentra [PATH]), 207 IGIV-pretreated subjects with CIDP received a Privigen loading dose of 2 g/kg followed by up to 4 Privigen maintenance doses of 1 g/kg every three weeks for up to 13 weeks. Additionally, 60 of these subjects received Privigen rescue treatment by the same dosing regimen following CIDP relapse during the double-blind post-randomization phase (see Clinical Studies (14.4)). Eight subjects experienced a serious adverse reaction (acute rash cutaneous, blood pressure diastolic increased, exacerbation of CIDP [2], hypersensitivity, pulmonary embolism, respiratory failure, and migraine). The serious adverse reactions of pulmonary embolism and respiratory failure occurred in subjects with preexisting risk factors. No serious adverse reactions resolved without sequelae.

Adverse reactions that occurred in ≥5% of subjects with CIDP were headache (33 subjects, 15.9% [rate per infusion 56/1894, 0.030]). A total of 225 ARs were reported: 160 were mild (transient, does not usually interfere with routine activities but minimal treatment or therapeutic intervention may be required), 59 were moderate (interferes somewhat with routine activities and usually associated with specific intervention but poses no significant or permanent risk of harm), and 6 were severe (interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention) in intensity.

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.

Privigen

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

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

General

In addition, the following adverse reactions have been identified and reported during the post-approval use of immune globulin products.†

- **Infection Reactions:** Tachycardia, malaise, flushing, rigors
- **Renal:** Acute renal dysfunction/failure, cosinophilic nephropathy
- **Respiratory:** Anemia, 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)).

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with Privigen. It is not known whether Privigen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. Privigen should be given to pregnant women only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Privigen and any potential adverse effects on the breastfed infant from Privigen or from the underlying maternal condition.

8.4 Pediatric Use

Treatment of Primary Humoral Immunodeficiency

Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI (prospective, open label, single arm, multicenter clinical 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 Privigen have not been studied in clinical trials in pediatric patients with PI who are under the age of 3.

Treatment of Chronic Immune Thrombocytopenic Purpura

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

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

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

8.5 Geriatric Use

Clinical studies of Privigen in PID and ITP did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.
The safety and effectiveness of Privigen in CIDP subjects age 65 and over was similar to those under age 65. Use caution when administering Privigen 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 Privigen 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

Privigen is a ready-to-use, sterile, 10% protein liquid preparation of polyclonal human immunoglobulin G (IgG) for intravenous administration. Privigen has a purity of at least 98% IgG, consisting primarily of monomers. The balance consists of IgG dimers (≥5 mcg/mL). IgA. The IgG subclass distribution (approximate mean values) is IgG1, 67.8%; IgG2, 28.7%; IgG3, 98%; IgG4, consisting primarily of monomers. The balance consists of IgG dimers (≥5 mcg/mL). Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

The IgG subclass distribution (approximate mean values) is IgG1, 67.8%; IgG2, 28.7%; IgG3, 98%; IgG4, consisting primarily of monomers. The balance consists of IgG dimers (≥5 mcg/mL). Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

The IgG subclass distribution (approximate mean values) is IgG1, 67.8%; IgG2, 28.7%; IgG3, 98%; IgG4, consisting primarily of monomers. The balance consists of IgG dimers (≥5 mcg/mL). Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

The IgG subclass distribution (approximate mean values) is IgG1, 67.8%; IgG2, 28.7%; IgG3, 98%; IgG4, consisting primarily of monomers. The balance consists of IgG dimers (≥5 mcg/mL). Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

Doses, and administer Privigen at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

The IgG subclass distribution (approximate mean values) is IgG1, 67.8%; IgG2, 28.7%; IgG3, 98%; IgG4, consisting primarily of monomers. The balance consists of IgG dimers (≥5 mcg/mL). Doses, and administer Privigen at the minimum dose and infusion rate practicable.
14 CLINICAL STUDIES

14.1 Treatment of Primary Humoral Immunodeficiency

A prospective, open-label, single-arm, multicenter study assessed the efficacy, safety, and pharmacokinetics of Privigen 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 Privigen, 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.

Subjects maintained a response up to Day 29 and two (4%) up to Day 85. The median time to reach a platelet response of more than 50 x 10^9/L was 25 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.

14.3 Postmarketing Commitment Study in Chronic Immune Thrombocytopenic Purpura

Table 8 summarizes the efficacy results for all 80 subjects.

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results from Case Report Forms</strong></td>
<td></td>
</tr>
<tr>
<td>Total Number of Subject Days</td>
<td>26,198</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Annual rate of confirmed aSBLs*</td>
<td>0.08 aSBLs/subject year*</td>
</tr>
<tr>
<td>Annual rate of other infections</td>
<td>3.55 infections/subject year</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td></td>
</tr>
<tr>
<td>Number of subjects (%)</td>
<td>64 (80%)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>84.7 days/subject year</td>
</tr>
<tr>
<td><strong>Results from Subject Diaries</strong></td>
<td></td>
</tr>
<tr>
<td>Total Number of Diary Days</td>
<td>24,059</td>
</tr>
<tr>
<td>Out of work/school/day care or unable to perform normal activities due to illness</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>570 (2.37%)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>8.65 days/subject year</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>Number of days (%)</td>
<td>166 (0.69%)</td>
</tr>
<tr>
<td>Annual rate</td>
<td>2.52 days/subject year</td>
</tr>
</tbody>
</table>

* Defined as pneumonia, bacterial meningitis, bacteremia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, 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.

Of the 57 subjects in the efficacy analysis, 46 (80.7%) responded to Privigen with a rise in platelet counts to at least 50 x 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 x 10^9/L). The median maximum platelet count achieved was 154 x 10^9/L. The median time to reach a platelet response of more than 50 x 10^9/L was 25 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.

14.4 Treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In a post-hoc analysis, the efficacy endpoint platelet response (increase in platelet count at least once to at least 50 x 10^9/L within 6 days after the first infusion) was achieved in 42 subjects (74%; 95% confidence interval [CI]: 61% to 83%). Fifteen subjects with a suspicion of hemolysis based on laboratory data were referred for independent expert adjudication during the study. The adjudication committee selected from treatment options for their determination: no hemolysis, hemolysis, or clinically significant intravascular hemolysis. The set of antibodies most frequently bound to erythrocytes in subjects with clinically significant intravascular hemolysis could not be analyzed, because no subject experienced clinically significant intravascular hemolysis. No irregular antibodies were detected in any subject; therefore, no association between such antibodies and hemolytic laboratory changes could be established. Hemolytic laboratory changes were most often found in non-O blood group (especially the A blood group) subjects and those receiving 2 infusions. These laboratory parameters improved or normalized by the end of the study in the majority of subjects. Seven subjects (12% of the study population) with a normal hemoglobin at baseline had an abnormal hemoglobin at Day 29 (end of study) with a hemoglobin range from 11.2 to 13.6 g/dL. Post-hoc analyses were performed using a set of defined criteria for hemolysis. The hemoglobin group (18 subjects, 32%) met the criterion for greater than 1 g/dL drop in hemoglobin within a 21-day interval since the last IGIV administration not explained by weight loss or repeated phlebotomy, were treatment-emergent DAT positive, and met at least one other minor criterion (eg, fall in serum haptoglobin level to below the lower limit of normal, rise in lactate dehydrogenase level above the upper limit of normal, rise in indirect or total bilirubin to above the upper limit of normal, or rise in plasma-free hemoglobin above the upper limit of normal). Fourteen of 15 previously adjudicated presumptive hemolysis cases during the study were included in this post-hoc hemolysis group.
(90.7%) responded during the Privigen "restabilization" period with an increase of one or more adjusted INCAT score points. The overall median time to first adjusted INCAT response in PRIMA was 7.5 weeks (18 weeks in IGIV-untreated and 3 weeks in IGIV-pretreated). The median time to first adjusted INCAT response in PATH (all IGIV-pretreated) was 3.7 weeks (95% CI: 3.4 to 5.9 weeks). Mean INCAT score in PRIMA showed a clinically meaningful improvement by 1.4 points (1.1 points for IGIV-untreated, and 1.8 points for IGIV-pretreated) (PATH).

Figure 1. Percentage of Responders (Adjusted INCAT Score)

Medical Research Council (MRC) sum score in PRIMA improved by a mean of 6.9 points (7.7 points for IGIV-untreated and 6.1 points for IGIV-pretreated). MRC sum score in PATH improved by a mean of 3.6 points. Grip strength of the dominant hand improved in PRIMA by a mean of 14.1 kPa (17.0 kPa for IGIV-untreated and 10.8 kPa for IGIV-pretreated subgroups). Grip strength of the dominant hand improved in PATH by a mean of 12.2 kPa. Similar results were observed for the non-dominant hand in both studies.

15 REFERENCES

8. Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom-Davis J. Hemolytic transfusion reactions after administration of intravenous immunoglobulin (IVlg) (5.2)

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- Privigen is supplied in a single-use, tamper-evident vial containing the labeled amount of functionally active IgGs. The Privigen packaging components are not made with natural rubber latex.

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

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton</th>
<th>NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>44206-436-05</td>
<td>Vial containing 5 grams of protein</td>
<td>(NDC 44206-436-90)</td>
</tr>
<tr>
<td>100 mL</td>
<td>44206-437-10</td>
<td>Vial containing 10 grams of protein</td>
<td>(NDC 44206-437-91)</td>
</tr>
<tr>
<td>200 mL</td>
<td>44206-438-20</td>
<td>Vial containing 20 grams of protein</td>
<td>(NDC 44206-438-92)</td>
</tr>
<tr>
<td>400 mL</td>
<td>44206-439-40</td>
<td>Vial containing 40 grams of protein</td>
<td>(NDC 44206-439-93)</td>
</tr>
</tbody>
</table>

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.

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 [see Warnings and Precautions (5.1)].

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 [see Warnings and Precautions (5.2)].
- 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, disoloration 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 [see Warnings and Precautions (5.3)].
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting, which may suggest aseptic meningitis syndrome [see Warnings and Precautions (5.5)].
- Fatigue, increased heart rate, yellowing of skin or eyes, and dark-colored urine, which may suggest hemolysis [see Warnings and Precautions (5.6)].
- 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) [see Warnings and Precautions (5.8)].

Inform patients that Privigen is made from human blood and may contain infectious agents that can cause disease (eg, viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent 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 [see Warnings and Precautions (5.10)].

Inform patients that administration of IgG may interfere with the response to live virus vaccines (eg, measles, mumps, rubella, and varicella), and instruct them to notify their immunizing physician of recent therapy with Privigen [see Warnings and Precautions (5.11)].
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HIZENTRA safely and effectively. See full prescribing information for HIZENTRA.

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

WARNING: THROMBOSIS
See full prescribing information for complete boxed warning.

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

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

DOSAGE AND ADMINISTRATION
For subcutaneous infusion only.
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 = Previous IGIV dose (in grams) x 1.37
  No. of weeks between IGIV doses
- 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 3 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.

<table>
<thead>
<tr>
<th>Infusion Number</th>
<th>1st</th>
<th>2nd to 4th</th>
<th>5th</th>
<th>6th and above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL/site)</td>
<td>± 15</td>
<td>± 20</td>
<td>± 25</td>
<td></td>
</tr>
<tr>
<td>Rate (mL/hr/site)</td>
<td>± 15</td>
<td>± 25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As tolerated

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.

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
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: 10/2016

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2 DOSAGE AND ADMINISTRATION
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3 DOSAGE FORMS AND STRENGTHS
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DOSAGE FORMS AND STRENGTHS
0.2 g per mL (20%) protein solution for subcutaneous injection (3)

CONTRAINDICATIONS
- IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions (5.1).

WARNINGS AND PRECAUTIONS
- 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).

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

FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS
• Thrombosis may occur with immune globulin products1,2, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors [see Warnings and Precautions (5.2), and Patient Counseling Information (17)].
• For patients at risk of thrombosis, administer Hizentra at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE
Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated 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.

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 unused 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)]
  
  Initial Hizentra dose = Previous IGIV dose (in grams) x 1.37
  Number of weeks between IGIV doses
  o To convert the Hizentra dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 5.
  o 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 serum 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 (weekly or biweekly) and the patient’s body weight, locate the corresponding adjustment amount (in mL) by which to increase (or decrease) the dose. For frequent dosing, add the weekly increment from Table 1 to the weekly-equivalent dose and then divide by the number of days of dosing.

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

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

<table>
<thead>
<tr>
<th>Difference From Target Serum IgG Trough Level (mg/dL)</th>
<th>Dosing Frequency</th>
<th>Weight Adjusted Dose Increment (mL)*</th>
<th>Weight Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weekly*</td>
<td>&gt;10 to 30 kg</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Biweekly</td>
<td>&gt;30 to 50 kg</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 to 70 kg</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;70 to 90 kg</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;90 kg</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>**</td>
<td>40</td>
</tr>
</tbody>
</table>

* 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
minimize 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.

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. Assemble supplies – 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. Clean surface – Thoroughly clean a flat surface using an alcohol wipe.
3. Wash hands – Thoroughly wash and dry hands. The use of gloves when preparing and administering Hizentra is optional.
4. Check vials – 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. Transfer Hizentra from vial(s) to syringe
   - Remove the protective cap from the vial to expose the central portion of the rubber stopper of the Hizentra vial.
   - Clean the stopper with an alcohol wipe and allow it to dry.
   - If using a transfer device, follow the instructions provided by the device manufacturer.
   - If using a needle and a syringe to transfer Hizentra, follow the instructions below.
   - Attach a sterile transfer needle to a sterile syringe. Pull back on the plunger of the syringe to draw air into the syringe that is equal to the amount of Hizentra to be withdrawn.
   - 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).
   - Withdraw the desired volume of Hizentra. When using multiple vials to achieve the desired dose, repeat this step.
6. Prepare infusion pump and tubing – 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. Prepare injection site(s)
   - 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.
8. Insert needle(s)
   - 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.
   - Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue.
   - If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.
9. Start infusion – Follow the manufacturer’s instructions to turn on the infusion pump.
10. Record treatment – 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. Clean up – 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 hyperprolinaemia (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 ≤50 mcg/mL IgA [see Description (11)].

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

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triglycerides (triglycerides), or monoclonal gammapathies. For patients at risk for 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 and Patient Counseling Information (17)].
5.3 Aseptic Meningitis Syndrome (AMS)
AMS has been reported with use of IGIV 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 (≥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. 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. 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. 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.

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. 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 ≥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

<table>
<thead>
<tr>
<th>AR (≥2 Subjects)</th>
<th>Number (%) of Subjects (n=49)</th>
<th>Number (Rate) of ARs (n=2264 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions*</td>
<td>49 (100)</td>
<td>132.2 (0.584)</td>
</tr>
<tr>
<td><strong>Other ARs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 (24.5)</td>
<td>32 (0.014)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (10.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (8.2)</td>
<td>5 (0.002)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4 (8.2)</td>
<td>6 (0.003)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (8.2)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>3 (6.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Migraine</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (6.1)</td>
<td>4 (0.002)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Contusion</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4.1)</td>
<td>3 (0.001)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (4.1)</td>
<td>2 (&lt; 0.001)</td>
</tr>
</tbody>
</table>

- * Including infections.
- † Rate of ARs per infusion.
- ‡ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.
- The ratio of infusions with 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 Assessment of Injection-Site Reactions by Infusion, US Study

<table>
<thead>
<tr>
<th>Injection-Site Reaction</th>
<th>Number (Rate) of Reactions (n=683 Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/induration</td>
<td>467 (0.68)</td>
</tr>
<tr>
<td>Enanthema</td>
<td>346 (0.51)</td>
</tr>
<tr>
<td>Local heat</td>
<td>108 (0.16)</td>
</tr>
<tr>
<td>Local pain</td>
<td>88 (0.13)</td>
</tr>
<tr>
<td>Itching</td>
<td>64 (0.09)</td>
</tr>
</tbody>
</table>

- 15 to 45 minutes following infusions administered at regularly scheduled visits (every 4 weeks).
- For multiple injection sites, every site was judged, but only the site with the strongest reaction was recorded.
- Rate of injection-site reactions per infusion.
- Number of infusions administered during regularly scheduled visits.

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

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 myostitis. 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 51 to 243 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.
The following adverse reactions have been reported during postmarketing use of immune globulin in subcutaneous infusion (Hizentra) [see Clinical Studies (14)].

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, perioral, chills, dizziness, hypertension/changes in blood pressure, malaise.

**Cardiovascular:** Chest discomfort (including chest pain)

**Respiratory:** Dyspnea

**Neurological:** Tremor, burning sensation

**General disorders and administration site conditions:** infusion site ulcer

The following adverse reactions have been reported during postmarketing use of immune globulin products:

- **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:** Panocytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
- **Gastrointestinal:** Hepatic dysfunction

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

### 7 DRUG INTERACTIONS

#### 7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella (see Patient Counseling Information (17)).
Table 5. Virus Inactivation/Removal in Hizentra*

<table>
<thead>
<tr>
<th>Step</th>
<th>Mean LRF</th>
<th>pH 4 incubation</th>
<th>≥5.4</th>
<th>≥5.9</th>
<th>4.6</th>
<th>≥7.8</th>
<th>nt</th>
<th>nt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth filtration</td>
<td>≥5.3</td>
<td>≥6.3</td>
<td>2.1</td>
<td>3.0</td>
<td>4.2</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus filtration</td>
<td>≥5.3</td>
<td>≥5.5</td>
<td>≥5.1</td>
<td>≥5.9</td>
<td>≥5.4</td>
<td>≥5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Reduction (Log10 Units)</td>
<td>≥16.0</td>
<td>≥17.7</td>
<td>≥11.8</td>
<td>≥16.7</td>
<td>≥9.6</td>
<td>≥7.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Pharmacokinetics Parameters of Hizentra and IGIV, US Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hizentra</th>
<th>IGIV* (Privigen®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Dose (mg/kg) Mean</td>
<td>228</td>
<td>141-281</td>
</tr>
<tr>
<td>Mean</td>
<td>152</td>
<td>86-254</td>
</tr>
<tr>
<td>IgG peak levels (mg/dL) Mean</td>
<td>1616</td>
<td>1090-2825</td>
</tr>
<tr>
<td>Mean</td>
<td>2564</td>
<td>2046-3456</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL) Mean</td>
<td>1448</td>
<td>952-2623</td>
</tr>
<tr>
<td>Mean</td>
<td>1127</td>
<td>702-1810</td>
</tr>
<tr>
<td>AUC (day x mg/dL) Mean</td>
<td>10560</td>
<td>7210-18670</td>
</tr>
<tr>
<td>Mean</td>
<td>10320</td>
<td>8051-15530</td>
</tr>
<tr>
<td>CL (ml/day/kg) Mean</td>
<td>2.2</td>
<td>1.3^*</td>
</tr>
<tr>
<td>Mean</td>
<td>2.3</td>
<td>0.9-2.1</td>
</tr>
</tbody>
</table>

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 AUC ratios, 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, which is administered every 3 to 4 weeks, weekly subcutaneous administration results in relatively stable steady-state IgG levels.\textsuperscript{11,14} 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 years 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 of Hizentra, European Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 to &lt;12 years (n=9)</th>
<th>12 to &lt;16 years (n=3)</th>
<th>≥16 years (n=1)</th>
<th>Total (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>120</td>
<td>115</td>
<td>117</td>
<td>118</td>
</tr>
<tr>
<td>Range</td>
<td>71-170</td>
<td>72-150</td>
<td>87-156</td>
<td>71-170</td>
</tr>
<tr>
<td>IgG trough levels (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>731</td>
<td>764</td>
<td>754</td>
<td>746</td>
</tr>
<tr>
<td>Range</td>
<td>531-915</td>
<td>615-957</td>
<td>505-898</td>
<td>505-957</td>
</tr>
<tr>
<td>AUC (day x mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5230</td>
<td>5491</td>
<td>5452</td>
<td>5370</td>
</tr>
<tr>
<td>Range</td>
<td>3805-6950</td>
<td>4480-6750</td>
<td>3800-6810</td>
<td>3800-6950</td>
</tr>
<tr>
<td>CL (ml/day/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.19</td>
<td>2.17</td>
<td>2.30</td>
<td>2.23</td>
</tr>
<tr>
<td>Range</td>
<td>1.57-3.05</td>
<td>1.38-3.34</td>
<td>1.82-3.34</td>
<td></td>
</tr>
</tbody>
</table>

Table 7 summarizes PK parameters at steady state for pediatric subjects (age groups: 6 to <12 years 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.

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 (Privigen®) and/or Hizentra. Of the 151 subjects, 94 were adult subjects (63 from Hizentra clinical studies) and 57 were pediatric subjects (32 from Hizentra clinical studies). Compared with weekly administration, PK modeling and simulation predicted that administration of Hizentra on a biweekly basis at double the weekly dose results in comparable IgG exposure (equivalent AUCs, with a slightly higher IgG peak (Cmax) and slightly lower trough (Cmin)). In addition, PK modeling and simulation predicted that for the same total weekly dose, Hizentra infusions given 2, 3, or 7 times per week (frequent dosing) produce IgG exposures comparable to weekly dosing (equivalent AUCs, with a slightly lower IgG peak (Cmax) and slightly higher trough (Cmin)). Frequent dosing reduces the peak-to-trough variation in Hizentra exposure, thus resulting in more sustained IgG dosing. See Table 8 (columns for AUC, Cmax, and Cmin).

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:IGGSC dose adjustment factor of 1:1.37 adequately maintain median AUC(0-28d) and Cmin 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 5th, 95th percentiles) of AUC, Cmax, and Cmin Changes in IgG Trough Levels after Switching Between IgG Dosing Regimens

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>AUC</th>
<th>Cmax</th>
<th>Cmin</th>
<th>Predicted Change in Trough †</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGIV</td>
<td>Weekly Hizentra</td>
<td>0.97</td>
<td>0.68</td>
<td>1.16</td>
<td>16% increase</td>
</tr>
<tr>
<td>IGIV</td>
<td>Biweekly Hizentra</td>
<td>0.97</td>
<td>0.71</td>
<td>1.00</td>
<td>10% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>Biweekly Hizentra</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>5% decrease</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>2 times per week Hizentra</td>
<td>1.01</td>
<td>0.99</td>
<td>1.00</td>
<td>3% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>3 times per week Hizentra</td>
<td>1.01</td>
<td>0.99</td>
<td>1.00</td>
<td>4% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>5 times per week Hizentra (daily for 5 days)</td>
<td>1.01</td>
<td>1.00</td>
<td>1.01</td>
<td>4% increase</td>
</tr>
<tr>
<td>Weekly Hizentra</td>
<td>Daily Hizentra (3 times per week)</td>
<td>1.01</td>
<td>0.99</td>
<td>1.00</td>
<td>4% increase</td>
</tr>
</tbody>
</table>

† Ratios are based on comparison of second regimen vs first regimen. 1 Approximate change in trough based on predicted median Cmin ratio. 2 Weekly dose based on dose adjustment factor of 1.37 when switching from IGIV. 3 Biweekly dose = 2x weekly dose, based on dose adjustment factor of 1.37 when switching from IGIV. 4 AUC, area under the curve, calculated as AUC(0-28d) for the IGIV to Hizentra switches, and AUC(0-7d) for the weekly to biweekly Hizentra switch, and AUC(0-14d) for weekly to more frequent Hizentra switches; Cmax, maximum IgG concentration; Cmin, 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).
PK-based modeling and simulation results indicate that, similar to observations from the clinical study with weekly Hizentra dosing (Table 7), body weight-adjusted bisweekly 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 hyperprolinaemia. In this study, rats received daily subcutaneous injections with L-proline from day 6 to day 28 of life.3,4 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 (SBIs), defined as bacterial pneumonia, bacteremia/septicaemia, 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/range from 1.6 to 2.0 hours.

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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>
<thead>
<tr>
<th>Table 9. Summary of Efficacy Results (MITT Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (efficacy period)</td>
</tr>
<tr>
<td>Total number of subject days</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Annual rate of any infections</td>
</tr>
<tr>
<td>Number of subjects (%)</td>
</tr>
<tr>
<td>Antibiotic use for infection (prophylaxis or treatment)</td>
</tr>
<tr>
<td>Total number of subject days</td>
</tr>
<tr>
<td>Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections</td>
</tr>
<tr>
<td>Number of days (%)</td>
</tr>
<tr>
<td>Annual rate</td>
</tr>
<tr>
<td>Hospitalizations due to infections</td>
</tr>
</tbody>
</table>

* Defined as bacterial pneumonia, bacteremia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess.
† Upper 99% confidence limit: 0.132.
‡ 95% confidence limits: 2.235, 3.370.
§ Based on 1 subject.

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

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

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:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mL</td>
<td>44206-451-01</td>
<td>Vial containing 1 gram of protein (NDC 44206-451-90)</td>
</tr>
<tr>
<td>10 mL</td>
<td>44206-452-02</td>
<td>Vial containing 2 grams of protein (NDC 44206-452-91)</td>
</tr>
<tr>
<td>20 mL</td>
<td>44206-454-04</td>
<td>Vial containing 4 grams of protein (NDC 44206-454-92)</td>
</tr>
<tr>
<td>50 mL</td>
<td>44206-455-10</td>
<td>Vial containing 10 grams of protein (NDC 44206-455-93)</td>
</tr>
</tbody>
</table>

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 [5.7]).
- Pain and/or swelling of an arm or leg due to 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. 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, this time may be shorter or longer depending on the dose and frequency your doctor has prescribed for you.

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.

Inform patients to consider adjusting the injection-site location, volume per site, and rate of infusion based on how infusions are tolerated.

Inform patients 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.

• Ensure the patient understands the importance of adhering to their prescribed administration schedule to maintain appropriate steady IgG levels.

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.

**Step 4: Check vials**

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

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

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

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

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

- Attach a needle to 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.

  - 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.

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).

**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.

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.
Step 8: Insert needle(s)
- With two fingers, pinch together the skin around the injection site. Insert the needle under the skin (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.

Step 9: Start infusion
Follow the manufacturer’s instructions to turn on the infusion pump (Figure 12).

Step 10: Record treatment (Figure 13)
Peel off the removable part of the label of the Hizentra vial. Put this label in your treatment diary or log book with the date and time of the infusion. Also include the exact amount of Hizentra that you infused. Scan the vial if recording the infusion electronically.

Step 11: Clean up
- When all the Hizentra has been infused, turn off the pump.
- Take off the dressing and take the needle out of the 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 14) as recommended by your healthcare professional.
- Clean and store the infusion pump, following the manufacturer’s instructions.

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

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

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