Plasma Therapies

Where Are We Now?

Several key variables play a role in the promising possibilities for lifesaving plasma protein therapies.

By Kris McFalls

As the market for plasma protein therapies continues to grow at a steady pace, the possibilities for these precious lifesaving proteins seem endless. Patients long for that one treatment to return them to the quality of health and life they once had. Scientists, in turn, are dedicated to providing the safest, most effective product possible. And the manufacturers' desire to make it all happen is indisputable.

However, the plasma protein market contains difficult-to-control variables that have a skewing effect on the laws of supply and demand. Limited natural resources, long processing time, increasing costs for expensive plasma testing, few manufacturers, costly but necessary government regulations and low reimbursement rates can make the plasma market particularly vulnerable to prolonged and painful market swings.

The Plasma Variable

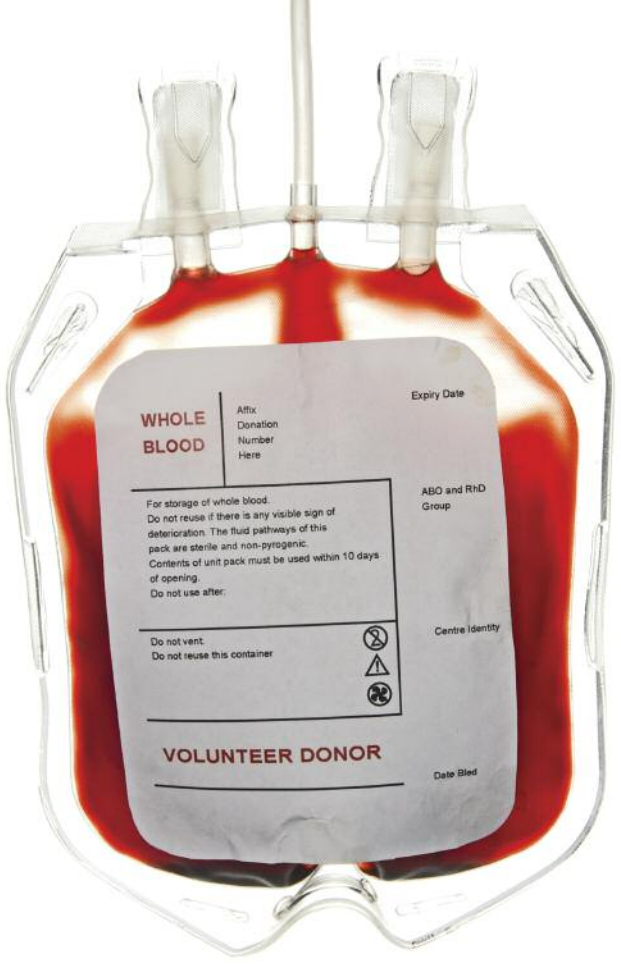
As the demand for plasma-based therapies continues to increase, several manufacturers are exploring new indications for these lifesaving therapies. But an increase in demand for these products first necessitates an increase in the raw product: plasma.

In the United States alone, there were roughly 22 million donations of plasma collected in 2009, according to the Plasma Protein Therapy Association (PPTA). This represents an approximate increase of 4.5 million donations over 2008. Most of the world's plasma was collected in about 400 plasma donation centers scattered throughout the U.S., the majority of which are owned by Baxter's BioLife Plasma Services, CSL Behring, Talecris Plasma Resources, Octapharma Plasma Inc. and Grifol's Biomat USA Inc.

Several industry and patient organizations continue to press Medicare for a change in the current reimbursement model.

Increasing the number of plasma donors to meet the increased product demand is challenging at best. And, regulations set forth by the U.S. Food and Drug Administration (FDA) to ensure the safety of the blood supply limits how much plasma can be collected. This raises the need for exploring safe and reliable ways to increase the donor pool.

This past year, the Health and Human Services' Advisory Committee on Blood Safety and Availability (ACBSA) considered relaxing the rules banning gay and bisexual men from donating blood or plasma. Current policy dictates that all men who have had sex with other men since 1977 be deferred as donors. Both patient and industry groups recognize that the HIV epidemic had disproportionally impacted both gay men and the plasma user community. The American Red Cross, America's Blood Centers and Advanced Transfusion and Cellular Therapies Worldwide were in favor of changing the ban to a temporary 12-month deferral after the last sexual encounter. But, several patient organizations, including the PPTA, released statements in favor of retaining the ban until further research into the matter could be attained because current data did not sufficiently support a change to the donor deferral policy. On June 10, 2010, the ACBSA found that data did not support changing the current policy and, therefore, did not recommend a change. The committee, however, did recommend researching the matter further.



The Manufacturer Variable

Even when the plasma supply is robust, there is a risk of a sudden shortage of plasma protein therapies due to a limited number of manufacturers. This is especially true in the immune globulin (IG) market, where current science is unable to develop a production method for manufacturing a recombinant product. And, because most of the manufacturers provide products for the worldwide market, a shortage creates a domino effect on the worldwide supply.

Those who have been in the IG business for a long time remember the mid- to late-1990s, when IG products were in very short supply. Some patients were forced to go without treatment or extend the intervals between treatments. Brand choice was limited, and many patients were forced to take whatever product was available due to shortages caused by plant shutdowns, viral contamination and discontinued products due to mergers. Since that time, manufacturing processes and safety continue to improve. Most products are now liquid, the result of a manufacturing process that produces a higher yield. Safety procedures are more stringent, and the blood supply is safer as evidenced by the significantly fewer number of recalls.

Yet, with so few manufacturers, recalls and withdrawals continue to pose a risk to the worldwide supply of IG. Recently, the market experienced a complete withdrawal of Octagam (immune globulin intravenous [human] 5% liquid preparation). Even though Octapharma is not one of the top-three producers of IG for the U.S., the voluntary withdrawal still affected the U.S. market since supplies from all markets were needed to fill the void of the loss of Octagam from the U.S., Australia and Europe. And, even with improved manufacturing efficiency, it still takes approximately nine months to transform a plasma donation into a vial of ready-to-infuse IG. Therefore, even a rapid increase of production by the other manufacturers may not be able to meet the demands caused by a sudden withdrawal of any one brand of IG.

While there is currently not a shortage of IG, history has shown that recalls and withdrawals can cause sudden and unexpected shortages at any time, and to be complacent and unprepared for such possibilities is to put patients' lives in danger. "The wonderful thing about IVIG [intravenous IG] is its unwavering path toward dozens of undiscovered areas of therapeutic promise for thousands of patients globally," says Chris Ground, FFF Enterprises' vice president of national accounts. "This is precisely why we must make every effort to be vigilant surrounding the global supply-and-demand ratio of IVIG and to work to try to keep those factors in balance. Being out of balance creates challenges either way. This, of course, is easier said than done, given the always present possibility of manufacturing issues. Yet, this is an inextricable fact of the plasma industry. We must strive to nurture demand, while delicately balancing this with managed increases in manufacturers' global capacity."

In the United States alone, there were roughly 22 million donations of plasma collected in 2009, according to the Plasma Protein Therapy Association (PPTA). This represents an approximate increase of 4.5 million donations over 2008.

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Reactions Reported to Occur With IGIV Treatment

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

Renal Dysfunction/Failure

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

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Hizentra. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Hizentra at the minimum rate practicable.

Thrombotic Events

Thrombotic events may occur with use of human immune globulin products[2-4]. Patients at increased risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Hizentra at the minimum rate practicable.

Aseptic Meningitis Syndrome (AMS)

AMS may occur with use of human immune globulin products.[5] The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Conduct a thorough neurological examination, including CSF studies, to rule out other causes of meningitis in patients exhibiting signs and symptoms of AMS. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis

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

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

Transfusion-Related Acute Lung Injury (TRALI)

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

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

5.3 Transmissible Infectious Agents

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

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

5.4 Laboratory Tests

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

Table 2: (Continued)

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

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

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

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

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

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

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

Table 4 summarizes injection-site reactions based on investigator assessments 15 to 45 minutes after the end of the 683 infusions administered during regularly scheduled visits (every 4 weeks).

Table 4: Investigator Assessments* of Injection-Site Reactions by Infusion

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

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

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

6.2 Postmarketing Experience

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

The following adverse reactions have been identified and reported during the postmarketing use of IGIV products[11]:

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

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

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

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

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

8.4 Pediatric Use

Hizentra was evaluated in 10 pediatric subjects (3 children and 7 adolescents) with PI. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Hizentra was not evaluated in neonates or infants.

8.5 Geriatric Use

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

15 REFERENCES

1. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *J Am Soc Nephrol* 1997;8:1788-1793.
2. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994;44:223-226.
3. Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986;2:217-218.
4. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. *Am J Hematol* 2000;65:30-34.
5. Gabor EP, Meningitis and skin reaction after intravenous immune globulin therapy. *Ann Intern Med* 1997;127:1130.
6. Copelan EA, Strohm PL, Kennedy MS, Tutschka PJ. Hemolysis following intravenous immune globulin therapy. *Transfusion* 1986;26:410-412.
7. Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom-Davis J. Hemolysis after high-dose intravenous Ig. *Blood* 1993;15:3789.
8. Wilson JR, Bhoopalam N, Fisher M. Hemolytic anemia associated with intravenous immunoglobulin. *Muscle Nerve* 1997;20:1142-1145.
9. Kessary-Shoham H, Levy Y, Shoenfeld Y, Lorber M, Gershon H. *In vivo* administration of intravenous immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration. *J Autoimmun* 1999;13:129-135.
10. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001;41:264-268.
11. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Trans Med Rev* 2003;17:241-251.

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

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA
Based on March 2010 version

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Vivaglobin®

Immune Globulin Subcutaneous (Human) 16% Liquid

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

1 INDICATIONS AND USAGE

Vivaglobin is an Immune Globulin Subcutaneous (Human) (IGSC), 16% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the primary immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

4 CONTRAINDICATIONS

Vivaglobin is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of Immune Globulin (Human).

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Severe hypersensitivity reactions may occur (*see Patient Counseling Information [17.2]*). In case of hypersensitivity, discontinue the Vivaglobin infusion immediately and institute appropriate treatment. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions.

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. Vivaglobin contains ≤1.7 mg/mL IgA (*see Description [11]*). The minimum concentration of IgA that will provoke a hypersensitivity reaction is not known; therefore all IgG preparations carry the risk of inducing an anaphylactic reaction to IgA.

5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with IGIV treatment[5] and with Vivaglobin treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

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

5.3 Reactions Reported with IGIV Treatment

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

Renal Dysfunction/Failure

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

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Vivaglobin. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Vivaglobin at the minimum rate practicable.

Thrombotic Events

Thrombotic events may occur with use of human immune globulin products.[2-4] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Vivaglobin at the minimum rate practicable.

Hemolysis

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

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

Transfusion-Related Acute Lung Injury (TRALI)

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

Monitor recipients of Vivaglobin 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.

5.4 Transmissible Infectious Agents

Because Vivaglobin is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of Vivaglobin. Report all infections thought possibly to have been transmitted by Vivaglobin to the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient (*see Patient Counseling Information [17.2]*).

5.5 Laboratory Tests

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

6 ADVERSE REACTIONS

The most common adverse reactions (those AEs considered by the investigator to be at least possibly related to Vivaglobin administration) observed in ≥5% of study subjects receiving Vivaglobin were local injection-site reactions (swelling, redness, and itching), headache, nausea, rash, asthenia, and gastrointestinal disorder.

6.1 Clinical Studies Experience

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

US-Canada Study

The safety of Vivaglobin was evaluated in a clinical study in the US and Canada for 12 months in 65 subjects with PI who had been previously treated with IGIV every 3 or 4 weeks (*see Clinical Studies [14.1]*). After 3 months, subjects were switched from IGIV to weekly subcutaneous administration of Vivaglobin for 12 months. Subjects were treated weekly with Vivaglobin at a mean dose of 158 mg/kg body weight (range: 34 to 352 mg/kg). The 65 subjects received a total of 3,656 infusions of Vivaglobin.

Table 2 shows the number of subjects who withdrew from the US-Canada study due to adverse events (AEs) and the AEs leading to discontinuation.

Table 2: Subjects with Adverse Events (AEs) Leading to Discontinuation, US-Canada Study

AEs	Subjects with AEs *At Least Possibly Related*	Subjects with AEs *Irrespective of Causality*	Total Number (%) of Subjects
Subjects with at least 1 AE leading to discontinuation	4	1	5 (8%)
Injection-site reaction	3	–	3 (5%)
Intestinal obstruction	–	1	1 (2%)
Hyperventilation	1*	–	1 (2%)
Tachycardia	1*	–	1 (2%)

* One subject experienced hyperventilation and tachycardia.

Table 3 summarizes the most frequent AEs (experienced by more than 5% of subjects), *irrespective of causality*. It includes all AEs and those considered temporally associated with the Vivaglobin infusion, i.e., occurring during the infusion or within 72 hours after the end of the infusion.

Table 3: Incidence of Subjects With Adverse Events (AEs)* (Experienced by >5% of Subjects) and Rate† per Infusion, *Irrespective of Causality*, in the US-Canada Study

AEs* (>5% of Subjects)	All AEs		AEs Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=65)	Number (Rate†) of AEs per Infusion (n=3656)	Number (%) of Subjects (n=65)	Number (Rate†) of AEs Per Infusion (n=3656)
AEs at the injection site‡	60 (92%)	1789 (0.49)	60 (92%)	1767 (0.4848)
Other AEs				
Headache	31 (48%)	159 (0.04)	30 (46%)	104 (0.033)
Gastrointestinal disorder	24 (37%)	35 (0.01)	18 (28%)	24 (0.007)
Fever	16 (25%)	28 (0.008)	12 (8%)	20 (0.005)
Nausea	12 (18%)	18 (0.005)	11 (17%)	15 (0.004)
Rash	11 (17%)	22 (0.006)	10 (15%)	16 (0.004)
Sore throat	10 (15%)	17 (0.005)	8 (12%)	11 (0.003)
Allergic reaction	7 (11%)	8 (0.002)	5 (8%)	5 (0.001)
Pain	6 (9%)	8 (0.002)	4 (6%)	4 (0.001)
Diarrhea	6 (9%)	6 (0.002)	5 (8%)	5 (0.001)
Cough increased	6 (9%)	6 (0.002)	5 (8%)	5 (0.001)
Gastrointestinal pain	5 (8%)	6 (0.002)	4 (6%)	5 (0.001)
Migraine	5 (8%)	5 (0.001)	2 (3%)	2 (0.001)
Skin disorder	5 (8%)	7 (0.002)	3 (5%)	5 (0.001)
Asthma	5 (8%)	8 (0.002)	3 (5%)	4 (0.001)
Arthralgia	4 (6%)	4 (0.001)	3 (5%)	3 (0.001)
Asthenia	4 (6%)	4 (0.001)	2 (3%)	2 (0.001)
Malaise	4 (6%)	5 (0.001)	2 (3%)	2 (0.001)

* Excluding infections. † Rate, number of AEs per infusion. ‡ Includes injection-site inflammation.

The total number of AEs, *irrespective of causality,* including injection-site reactions, that began during or within 72 hours after the end of an infusion was 2262 (a rate of 0.62 AEs per infusion); excluding injection-site reactions, the rate of AEs per infusion was 0.14.

Table 4 summarizes the severity of local AEs by infusion, *irrespective of causality*.

Table 4: Severity of Local Adverse Events (AEs) by Infusion, *Irrespective of Causality*, in the US-Canada Study

AEs (Number of infusions: 3656)	Number (Rate*) of AEs	Number (Rate*) of AEs Occurring During or Within 72 Hours of Infusion
AEs at the injection site	1789 (0.49)	1767 (0.48)
Mild†	1112 (0.30)	1100 (0.30)
Moderate‡	601 (0.16)	593 (0.16)
Severe§	65 (0.02)	64 (0.02)
Unknown severity	11 (<0.01)	10 (<0.01)
Discontinuations due to AEs at the injection site	3 subjects	

* Rate, number of AEs per infusion.
† Defined as those reactions that did not interfere with routine activities.
‡ Defined as those reactions that interfered with routine activities.
§ Defined as those reactions that made it impossible to perform routine activities.

Of the three subjects who discontinued the study due to injection-site reactions, one withdrew on Day 1 (Infusion 1) of the wash-in/wash-out period after a moderate injection-site reaction and a mild headache; one withdrew on Day 22 (Infusion 4) of the wash-in/wash-out period following severe injection-site reactions for two weeks; and one withdrew on Day 78 following a mild injection-site reaction.

Local reactions decreased substantially after repeated use.

Table 5 summarizes the most frequent adverse reactions (experienced by at least 3% of subjects) and considered by the investigator to be *at least possibly related* to Vivaglobin administration.

Table 5: Incidence of Subjects With Adverse Reactions (Experienced in ≥3% of Subjects) and Rate* Per Infusion in the US-Canada Study

Related Adverse Reactions (≥3% Subjects)	Number (%) of Subjects (n=65)	Number (Rate*) of Adverse Reactions per Infusion (n=3656)
Adverse reactions at the injection site†	60 (92%)	1787 (0.49)
Other Adverse reactions		
Headache	21 (32%)	59 (0.016)
Nausea	7 (11%)	9 (0.002)
Rash	4 (6%)	9 (0.002)
Asthenia	3 (5%)	3 (0.001)
Gastrointestinal disorder	3 (5%)	3 (0.001)
Fever	2 (3%)	2 (0.001)
Skin disorder	2 (3%)	3 (0.001)
Tachycardia	2 (3%)	2 (0.001)
Urine abnormality	2 (3%)	3 (0.001)

***** Rate, number of adverse reactions per infusion. † Includes injection-site inflammation.

Europe-Brazil Study

In a clinical study conducted in Europe and Brazil, the efficacy and safety of Vivaglobin were evaluated for 10 months in 60 subjects with PI. Subjects were treated weekly with Vivaglobin at a mean dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% of their previous weekly IGIV or IGSC dose (*see Clinical Studies [14.2]*). Study subjects received a total of 2,297 infusions of Vivaglobin.

The AEs and their rates reported in this study were similar to those reported in the US-Canada study, with two exceptions: no episodes of headache were reported; and 18 (a rate of 0.008 per infusion) episodes of fever were judged to be related to the administration of Vivaglobin. One subject discontinued due to repeated local reactions of moderate severity.

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.

Vivaglobin

Adverse reactions identified during worldwide postmarketing use of Vivaglobin for treatment of PI are allergic-anaphylactic reactions (including dyspnea, pruritus, urticaria, rash, edema and other cutaneous reactions, wheezing, syncope, hypotension, and throat swelling), generalized reactions (including flu-like symptoms, myalgia, chills, fever, tachycardia, arthralgia, nausea and vomiting, diarrhea, gastrointestinal cramping, stomach pain, back pain, headache, headache possibly caused by increased blood pressure, and chest tightness), migraine, and injection-site reactions.

General

The following adverse reactions have been identified and reported during the postmarketing use of IGIV products[11]:

- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *General/Body as a Whole:* Pyrexia, rigors
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain

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 [17.2]*).

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Vivaglobin has not been evaluated in nursing mothers.

8.4 Pediatric Use

- In the US-Canada study, Vivaglobin was evaluated in 6 children (ages 5 through 11) and 4 adolescents (ages 13 through 16). In the Europe-Brazil study, Vivaglobin was evaluated in 16 children (ages 3 through 11) and 6 adolescents (ages 13 through 16).
- The safety and efficacy of Vivaglobin were not studied in pediatric subjects under 2 years of age.
- There were no differences in the safety and efficacy profiles as compared with adult subjects.
- No pediatric-specific dosing requirements were necessary to achieve the desired serum IgG levels.
- For recommendations on the number of simultaneous injection sites for pediatric patients who weigh less than 45 kg (99 pounds), *see Administration (2.4)*.

8.5 Geriatric Use

The clinical studies of Vivaglobin did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. For recommendations on the number of simultaneous injection sites for geriatric patients, see *Administration (2.4)*.

Manufactured by:
CSL Behring GmbH
Marburg, Germany
US License No. 1765

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA
Based on April 2010 Revision.

The Reimbursement Variable

Even in stable markets, reimbursement rates continue to pose a risk to plasma-derived therapies. Several industry and patient organizations continue to press Medicare for a change in the current reimbursement model. In its public comments to the Centers for Medicare and Medicaid Services (CMS), the PPTA supported the "CMS proposal to set the payment level of separately payable non-pass-through drugs and biologicals, which include most plasma protein therapies, at average sales price (ASP) plus 6 percent. [However, the PPTA raised objections to] the policy of using hospital claims data that includes drugs and biologicals sold as part of the heavily discounted 340B Drug Pricing Program when setting Outpatient Prospective Payment System (OPPS) payment rates." Additionally, several patient organizations continue to press hard for changes in the Medicare payment system to allow patients equal access to care both in a home and clinical setting.

Some states are trying to ensure patient access to care by targeting private insurers' policies. A few states have either passed or are considering legislation to disallow private insurers from moving plasma therapies into a high tier-level program with copayments as high as 50 percent of the cost of the medication. Included in the same legislation is a proposal that also would limit the yearly out-of-pocket maximum patients must pay. With decreasing reimbursement rates and increased patient liability, legislation will continue to play a key role in patient access to care.

Possibilities and Responsibilities

As the plasma therapy market continues to evolve and grow, so will the possibilities and responsibilities. It is clear that the industry is excited about the promises these lifesaving products bring to patients worldwide. Yet, while focused on fulfilling this potential, all participants also are working very hard to not lose sight of their responsibilities for doing it right. ❖

KRIS MCFALLS *is a staff writer for* BioSupply Trends Quarterly *and the patient advocate for* IG Living *magazine, distributed to patients who rely on immune globulin and to their healthcare providers.*