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Abbreviated Class Review: Immunoglobulin G

Month/Year of Review: March 2014 **End date of literature search:** January 1, 2014
PDL Class: None

Research Questions:

- What is the comparative efficacy of immunoglobulin G products?
- What are the comparative safety differences between immunoglobulin G products?
- Are there certain subpopulations that benefit from a specific dosage form of immunoglobulin G?

Conclusions:

- There is robust evidence to support the use of intravenous immunoglobulin G (IVIG) for primary immunodeficiency. This route of administration allows a large volume per infusion, and is administered relatively infrequently (every three to four weeks), however it must be administered by a trained professional, venous access is required, and it is associated with greater fluctuations in IgG levels, potentially resulting in a greater incidence of adverse effects.[5]
- Currently, there is no evidence of efficacy differences among the different IVIG products. However, there are potential differences in adverse effects among the different products. Patients with renal dysfunction, diabetes, sepsis, or age >65 years are at increased risk of developing kidney problems if a sucrose-containing product is used. In general, products with higher IgA content are associated with increased adverse effects. There is a higher chance of adverse effects if the IVIG product is switched after establishing therapy with a particular product.
- There is robust evidence to support the use of subcutaneous IgG (SCIG) for primary immunodeficiency. This formulation may be appealing to patients due to a lack of requirement of venous access, a perceived sense of independence associated with self-administration, and more consistent serum IgG levels. Limitations of SCIG include increased dosing frequency, requirement of multiple dosing sites, and the need for competent and adherent patients.[5]
- There is no strong evidence that indicates a preferential route of administration of IgG. Systematic reviews and cross-trial comparisons indicate that there is no difference in efficacy between IVIG and SCIG products. Products with low IgA counts may be preferable to those who experience infusion reactions.
- There is no strong evidence that shows that the differences in the pharmacokinetic profiles of IVIG and SCIG translate to meaningful improvements in patient outcomes. While some studies showed a lower incidence of adverse events in SCIG versus IVIG, the 20% SCIG formulation has not been directly compared to IVIG.

Recommendations:

- IVIG products are similar in efficacy and should be prescribed based on the risk of adverse events with each formulation, cost, and history of IVIG use.
- The choice of IVIG or SCIG should account for the individual patient's ability to administer IgG at home, compliance, availability and ease of IV access, and comorbid conditions.
- Add class to PDL for Sub-Q, point of sale agents and designate Gamunex-C as preferred and all other Sub-Q agents as non-preferred. Do not create PDL class or require PA for physician administered products at this time.

Reason for Review:

The availability of a concentrated SCIG product has revived the question of the optimal administration of IgG therapy. This review will evaluate different IgG products and routes of infusion for products currently available in the United States.

Background:

Primary immunodeficiency (PI) is a group of more than 150 genetically determined conditions that leaves those affected susceptible to frequent infections.[1] PIs are distinct from secondary immunodeficiencies, which result from other causes including malnutrition, immunosuppressant drugs and infections.[2] The prevalence of PI in the United States is estimated to be 1/1,200 persons, which results in an estimated 250,000 cases.[3] Most PI disorders present early in childhood, but can present at any time throughout life.[4] Immunologists typically diagnose PI via a comprehensive immune evaluation that initially involves a complete blood count and blood smear.[2] PI can be fatal if patients contract infections that are not or cannot be treated.

Treatment for PI involves management of existing infections, IgG replacement therapy (often indefinitely), and antibiotic and antifungal prophylaxis to reduce frequency and severity of infections.[2] While IgA and IgM have been studied for immunodeficiencies, IgG is the only product approved for treating PI. Due to the long serum half-life, IgG infusion is typically administered every 2-4 weeks. A nationwide survey of patients showed that 83% of PI patients report receiving regular infusion of IgG.[3] IgG products are created by pooling IgG from 2,000 to 10,000 human donors and vary in their concentration, amount of IgA, pH, stabilizer, storage requirements, and sucrose content.[5] There is no general consensus on the appropriate dosing of IgG. Studies have shown that an individualized approach to IgG dosing should be done that factors in both serum levels and infections.[5]

IgG can be infused intravenously (IV), intramuscularly (IM), or subcutaneously (SC), however no IM formulations of IgG are available in the United States.[6] While immunoglobulin that is administered intravenously (IVIG) remains the most commonly used product, subcutaneous (SCIG) administration is gaining popularity due to availability of new SC products, which provide a lack of need for venous access and opportunity for in-home administration. Theoretically, the pharmacokinetic profile of SCIG results in fewer adverse events than IVIG formulations, because the peaks and nadirs are closer and more stabilized due to slow absorption and increased frequency of administration.

Table 1. Indications and Dosing of IgG Products

Brand Name (Manufacturer)	INDICATIONS	STRENGTH/ROUTE	DOSE AND FREQUENCY:	INFUSION RATE

Gammunex-C[7] Gammaked[8] – distributed by Kedrion (Grifols)	PI ITP CIDP	10%/IV or SC 10%/IV 10%/IV	PI,IV: 300-600 mg/kg every 3-4 weeks PI,SC: (1.37xIV dose)/(IV interval) ITP: 2g/kg CIDP: 2g/kg (LD), 1g/kg (MD), every 3 weeks	PI,IV: 1-8mg/kg/min PI, SC: 20mL/hr/site ITP: 1-8mg/kg/min CIDP: 2-8mg/kg/min
Octagam[9] (Octapharma)	PI	5%/IV	300-600mg/kg every 3-4 weeks	0.5 – 3.33 mg/kg/min
Bivigam[10] (Biotest)	PI	10%/IV	300-800mg/kg every 3-4 weeks	0.5 - 6mg/kg/min
Gammaplex[11] (Bio Products Laboratory)	PI ITP	5%/IV	PI: 300-800mg/kg every 3-4 weeks ITP: 1g/kg x 2 days	0.5 - 4mg/kg/min (PI and ITP)
Gammagard Liquid[12] (Baxter)	PI MMN	10%IV 10% SC	PI,IV: 300-600mg/kg every 3-4 weeks PI,SC: (1.37xIV dose)/(IV interval) MMN,IV: 0.5-2.4g/kg/month	PI,IV: 0.5 -5mL/kg/hr PI,SC: ≥40kg: 30mL/site at 20-30 mL/hr/site <40kg: 20mL/site at 15-20mL/hr/site MMN: Up to 5.4mL/kg/hr
Carimune NF[13] (CSL Behring)	PI ITP	PI: 3%/IV ITP: 6%/IV	PI: 0.4-0.8 g/kg every 3-4 weeks ITP: 0.4 g/kg x 2-5 consecutive days	0.5 - 3 mg/kg/min (PI and ITP)
Privigen[14] (CSL Behring)	PI ITP	10%/IV	PI: 200-800 mg/kg every 3-4 weeks ITP: 1 g/kg x 2 consecutive days	PI: 0.5 - 8mg/kg/min ITP: 0.4 - 4mg/kg/min
Flebogamma Dif[15] (Grifols)	PI	10% /IV	300-600 mg/kg every 3-4 weeks	0.01 – 0.08 mL/kg/min
Hizentra[16] (CSL Behring)	PI	20%/SC	(1.53X IV dose)/(IV interval), weekly or biweekly	15-25 mL/hr/site

PI: Primary immunodeficiency; ITP: Idiopathic Thrombocytopenic Purpura; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; LD: Loading dose; MD: Maintenance dose; MMN: Multifocal Motor Neuropathy

Methods:

A Medline literature search ending January 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing IgG products for the treatment of primary immunodeficiency. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

1. Efficacy of IVIG and SCIG in Primary Immunodeficiency

There are no head to head studies comparing concentrated SCIG to IVIG in PI. Although immune globulin has been used since the 1950's to treat patients with PI, a 1997 shortage prompted the Food and Drug Administration (FDA) to review and adjust guidelines for the IVIG new drug approval process, which included standardizing the clinical trials used to establish efficacy and safety of new IVIG products. After difficulty recruiting patients with this rare disease, the FDA again revised their standards for IVIG clinical trials, and proposed single-arm, 12-month, open-label studies including about 50 patients as an acceptable trial design for studying IVIG products. The desired primary endpoint was determined to be the rate of acute serious bacterial infections (SBIs), which includes bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess. Using results from historical trials, the FDA established the target SBI rate at <1.0 per subject per year at the 0.01 level of significance.

Recent clinical trials evaluating the efficacy of IVIG include between 46 and 73 patients with PI. Common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) were the two most common types of PI studied. Gamunex and Gammimune N were evaluated in a prospective, randomized, double-blind, non-inferiority study. Octagam, Gammagard, Privigen, Flebogamma, Gammaplex, and Bivigam were all studied using the FDA recommended trial design of open-label, historically controlled, single-arm trials. The rate of SBIs was well below the target of <1.0 SBI/person/year, ranging from 0 to 0.08 SBI/person/year among the various products. The rate of non-serious infections varied from 1.96-3.55 infections/person/year. The rate of adverse events was variable between studies. Studies that reported out treatment-related adverse events as a percent of infusions showed rates from 5% -27.6% depending on the product. The most common adverse event reported in each study was headache.

Concentrated SCIG was studied in a prospective, open-label, multicenter, single-arm, phase 3 study. The study included patients who had previously been treated with IVIG and used an SCIG dose that was equivalent to the IVIG dose, as measured by the area under the concentration/time curve (AUC) of serum IgG. The study included a 12-week wash-in/wash-out period followed by a 12-month efficacy period. The primary efficacy end point of SBIs per patient was 0, exceeding the FDA's target. The safety profile of Hizentra 20% was similar to other IgG products in nature and in frequency. The overall rate of infusion-related AEs was 0.043 per infusion, and the most common adverse events were headache, fatigue, and nausea.[17] Results from this phase 3 trial aligned with that of another open-label, single-arm study (n=51), which found that 0 SBIs occurred after 40 weeks of treatment with Hizentra 20%. This study used a dose of Hizentra 20% that was equivalent to the subject's previous IVIG dose, measured by the trough IgG levels, in accordance with guidelines from the European Medicines Agency.[18]

A small comparative study (n=13) was completed in pediatric patients with PI in Argentina. In the observational, retrospective/prospective, open-label study, patients previously treated with IVIG for at least 12 months received SCIG (16%) for 26 weeks. The primary efficacy endpoints were the serum IgG trough level and the number of SBIs, which was defined using the FDA's criteria. There were no SBIs during the retrospective and prospective phases of the study. The rate of any infection was 0.4 infections/patient/year during the SCIG phase and 1.4 infections/patient/year during the IVIG phase. No serious adverse events were reported. During the IVIG phase, there were 0.08 events/infusion, most of which were headaches. During the SCIG phase, there were 0.14 events per infusion, however it should be noted that three subjects reported 88% of all adverse events. All adverse events were mild local infusion site reactions.[19]

Table 2. Summary of Pivotal Studies Completed in Patients with Primary Immunodeficiency

Treatment	Population	Outcome	Efficacy	Safety	Trough IgG

Gamunex 10% • 3 week: n=9 • 4 week: n=64 Gammimune N • 3 week: n=14 • 4 week: n=59	• Mean age: 35.1 • CVID: 53% • Hypogam: 45% • Mean age: 29.5 • CVID: 52% • Hypogam: 41%	Proportion of patients with at least one validated acute sinopulmonary infection	12.3% 23.3%	TRAEs: 5.7% of infusions TRAEs: 5.5% of infusions	Not reported
Octagam 5% • 3 week: n=19 • 4 week: n=27	• Mean age: 31 • CVID: 61% • XLA: 28%	Rate of serious infections per patient per year	0.1 serious infections/subject/year	TRAEs: 5% of infusions	• 3 week: 986 mg/dL • 4 week: 883 mg/dL
Gammagard 10% n=61	• Mean age: 34 • CVID or hypogam: 67.2%	Rate of serious infections per patient per year	No serious infections were reported	SAEs: 2 aseptic meningitis episodes in 1 patient	960-1,120 mg/dL
Privigen 10% • 3 week: n=16 • 4 week: n=64	• Mean age: 28 • CVID: 73.8% • XLA: 26.2%	Rate of serious infections per patient per year	0.08 serious infections/subject/year	TRAEs: 9% of infusions	884-1,027 mg/dL
Flebogamma DIF 10% • 3 week: n=16 • 4 week: n=30	• Mean age: 36.8 • CVID: 80.4% • XLA: 17.4%	Rate of serious infections per patient per year	0.025 serious infections/subject/year	TRAEs: 27.6% of infusions	Not reported
Gammaplex 5% • 3 week: n=22 • 4 week: n=38	• Mean age: 44 • CVID: 92% • XLA: 8%	Rate of serious infections per patient per year	0 serious infections/subject/year	TRAEs: 16.4% of infusions	• 3 week: 936-1,240 mg/dL • 4 week: 833-1,140 mg/dL
Bivigam 10% • 3 week: n=17 • 4 week: n=46	• Mean age: 41.2 • CVID: 81% • XLA: 9.5%	Rate of serious infections per patient per year	0.037 serious infections/subject/year	TRAEs: 63.5% of subjects	• 3 week: 1,076 mg/dL • 4 week: 943 mg/dL
Hizentra 20% n=49 (ITT) n=38 (MITT)	• Mean age: 36.3 • CVID: 95% • XLA: 5%	Rate of serious infections per patient per year	0 serious infections/subject/year (ITT and MITT)	TRAEs: 4.3% of infusions	12.53 g/dL

CVID: Common variable immunodeficiency; XLA: X-linked agammaglobulinemia; TRAE: Treatment-related adverse events; SAE: serious adverse event; ITT: intention to treat; MITT: modified intention to treat RCT: randomized controlled trial, DB: double-blind, PG: parallel group

2. Systematic Reviews/Meta-analyses:

a. Primary Immunodeficiency

A systematic review/meta-analysis evaluated home-based SCIG versus hospital-based IVIG in the treatment of primary antibody deficiencies. The literature search used a Cochrane Collaboration tool for assessing risk of bias, including method of randomization, allocation concealment, incomplete data addressed blinding of involved participants, free of selective reporting, groups comparable at baseline, sample size calculation and withdrawals or loss to follow up reports. Data outcomes from the collected trials were organized into five subclasses: (1) trough level and pharmacokinetics, (2) side effects and pre-medication, (3) efficacy, infection rate and hospitalization, (4) health related quality of life, treatment satisfaction and convenience, (5) missed days of work/school, and cost. The data was then analyzed with random effect analysis model and Mantel-Haenszel statistical method using Review Manager software (version 5.0). For continuous data inverse variance method and fixed effect analysis model were used and the mean difference was considered as an effect measure.[20]

Table 3. Summary of a Meta-analysis Comparing IVIG to SCIG[20]

Outcome (# of articles; # of patients)	Odds Ratio (OR)	Mean Difference IV, Fixed, 95% CI	P-Value
IgG trough levels (31; 1,059)	1.00	(0.84-1.15)	<0.01
Serious infection rate in patients who received IVIG versus SCIG (9; 269)	0.59	(0.36-0.97)	0.04
Adverse events (15; 376)	0.09	(0.07-0.11)	<0.001

The initial data search found 156 titles, of which 79 met title review criteria. Of these, 47 (10 clinical trials, 17 prospective cohorts and 20 retrospective cohorts) met criteria and addressed at least one of the identified outcomes. These papers contained 1,484 of which 67.7% were adults, and 56.3% carried the diagnosis of common variable immunodeficiency. The results of the meta-analysis are summarized in table 3.[20]

One of the measured outcomes was IgG trough levels, and the data showed that serum IgG trough levels were comparable between IVIG and SCIG formulations. The two measured outcomes of serious infection rate in patients who received IgG, and adverse effects, showed significant preference for SCIG over IVIG. Most articles that evaluated IgG trough levels directly compared SCIG to IVIG.[20] Of the 31 trials included in the IgG trough level analysis, the range of study subjects was 3-262. One study found that the amount of IVIG (0.39 g/kg) or SCIG (0.37 g/kg) required to maintain adequate trough concentrations did not differ between routes.[21] The studies evaluating serious infection ranged from 11-65 subjects. The difference in infection rate is difficult to differentiate due to variation in dosing and infusion rates among the studies. One report found that the mean duration of recorded infections was 78 days among IVIG subjects (95% CI: 18-125 days) and 58 days for SCIG subjects (95% CI: 22-83 days), but the difference was not statistically significant (p=0.212).[22] Differences in antibiotic usage were inconsistent. One trial[23] showed a 24.4% decrease in antibiotic use when subjects were switched from IVIG to SCIG. A second trial[18] found a 28% increase in antibiotic use for subjects switched to SCIG. The trials that evaluated adverse effects enrolled 3-262 subjects.[20] Overall, there were fewer adverse reactions with the SCIG formulation, however patients using the SCIG formulation at home may have been less likely to report adverse events than those being treated with IVIG at the hospital.[20]

3. Guidelines

<u>The Immune Deficiency Foundation Guidelines</u>

In 2011, the Immune Deficiency Foundation (IDF) published guidelines on diagnosis and clinical care for primary immunodeficiency diseases. The guidelines help clinicians determine the possible type of PI and the screening diagnostic tests that should be ordered based on the site of infection. While there are several different types of PI, the types that result in antibody production defects are those that are eligible for IgG therapy.[5]

The IDF recommends regular IgG therapy for patients with identified antibody deficiency disorders. The guidelines state the IVIG product should be dosed every 2-4 weeks and SCIG should be given every 1-14 days. It is recommended that an immunologist should participate in the determination of the proper dose and interval for IgG therapy in each patient. Doses of IgG generally range from 400-600 mg/kg of body weight. A goal trough IgG level should be >500 mg/dl for most patients, however clinical considerations of the individual patient should be considered when determining dose changes. Patients with infections at standard levels or with pulmonary infectious complications may want to target a higher trough of>800 mg/dl. The guidelines note that IgG

therapy is considered a preventative therapy, and antibiotic should be used either prophylactically and/or for treatment of infections. Creatinine levels and liver function tests should be performed every 6-12 months while on IgG therapy. Should IgG treatment be required IV or SC administration are both recommended, and one product is not preferentially recommended over any other product.[5]

Canadian Blood Services and Canada's National Advisory Committee Guidelines

The Canadian Blood Services and Canada's National Advisory Committee on Blood and Blood Products led a joint initiative to create guidelines for treatment of PI with immunoglobulin therapy. While the guidelines are primarily intended for health care professionals in Canada, many of their recommendations may be applied in other parts of the world, including the United States.

The guidelines were constructed from an expert panel consisting of physicians from large pediatric and adult tertiary care centers who frequently cared for patients with primary immune deficiency, methodology experts, and members from the National Advisory Committee on Blood and Blood Products.[24] The levels of evidence and grades used for each recommendation were adapted from the Canadian Task Force on Preventative Health Care. The levels of evidence describe the methodological rigor of the study, and the grades of recommendation comprise the level of evidence and clinical expertise. Relevant recommendations include the following:

- Give immunoglobulin to patients with primary antibody deficiency to reduce infections. (Level of evidence: I, Grade of recommendation: A)
- Give immunoglobulin to reduce hospitalization and organ damage. (I, A)
- Give immunoglobulin to improve survival and quality of life. (III, A)
- With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one manufacturer of IG over another for currently available products. (I to II-2, I)
- With respect to clinical efficacy for reducing infections, IVIG and SCIG preparations should be considered equivalent. (I and II, B)
- When deciding on route of administration, patient preference should be taken into account. (III, A)
- Do not give IMIG for replacement therapy for primary immune deficiency. (I, D)
- Start IVIG at a dose of 400 to 600 mg/kg per 4 weeks or SCIG at a dose of 100 to 150 mg/kg per week in most patients. (III, B)
- Patient and practitioners should be aware that patients with primary immune deficiency may require immunoglobulin replacement therapy indefinitely. (II-3, A)

A systematic review and one randomized controlled trial were used to evaluate the comparative efficacy and safety of IVIG and SCIG, and no statistically significant differences were found for severity and duration of infections. One report found that the patients treated with SCIG had a lower rate of infections (IVIG: 2.8 ± 2.0 infections/6 months; SCIG: 1.9 ± 1.9 infections/6 months), and two studies showed that SCIG was associated with improved quality of life. Studies were prospective and had small sample sizes. There were no statistically significant differences in trough levels.[24]

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Appendix 1: Specific Drug Information

Table 4. Product Descriptions

MEDICATIONS	STORAGE	STABILIZER	IgA CONTENT	IgG PURITY	SODIUM CONTENT
Gammaked[8]	36-46°F (2-8°C) for up to 36 months or 77°F (25°C) up to 6 months	Glycine	Average 0.046 mg/mL	≥98%	Not listed
Octagam[9]	36-77°F (2-25°C) for up to 24 months	Maltose	≤0.2mg	≥96%	≤30mmol/l
Bivigam[10]	36-46°F (2-8°C)	Glycine	≤0.2mg/mL	≥96%	0.1-0.140M
Gammaplex[11]	36-77°F (2-25°C) for up to 24 months	Glycine	<10 mcg/mL	>95%	0.3g
Gammagard Liquid[12]	36-46°F (2-8°C) for up to 36 months or 77°F (25°C) up to 24 months	Glycine	Average 37mcg/mL	≥98%	No sodium
Carimune NF Nanofiltered[13]	Do not exceed 86°F (30°C)	Sucrose	Trace amounts	≥96%	20mg NaCl per gram of protein
Privigen[14]	77°F (25°C) for up to 36 months	Proline	≤25 mcg/mL mg	≥98%	Trace amounts
Flebogamma Dif[15]	36-77°F (2-25°C) for up to 24 months	Sorbitol	< 100 mcg/mL	≥97%	Trace amounts
Hizentra[16]	Room temperature (up to 77° F or 25°C) for up to 30 months.	Proline	≤50mcg/mL	≥98%	Trace amounts

USE IN SPECIFIC POPULATIONS

All IVIG and SCIG products are pregnancy category C. Efficacy and safety of all products has not been evaluated.

Table 5. Summary of FDA Guidance in Pediatric and Geriatric Populations

MEDICATIONS	PEDIATRIC USE	GERIATRIC USE
Gammaked[8]	PI, IV: Efficacy and safety similar to those in adults (n=18, age 0-16 years). PI,SC: Not established ITP: Efficacy and safety similar to those in adults (n=12) CIDP: Not established	Use with caution
Octagam[9]	No obvious differences in efficacy and safety compared to adults (n=11, age 6-16)	May be at increased risk for certain adverse reactions. Studied in 4 patients >65 years old
Bivigam[10]	Efficacy and safety not established	Use with caution
Gammaplex[11]	Population too small to evaluate efficacy and safety	Population too small to evaluate efficacy and safety
Gammagard Liquid[12]	MMN: Not studied PI,IV: Evaluated in 15 subjects ages 2-16 PI,SC: evaluated in 18 subject ages 2-16. Efficacy and safety were similar to those of adults	PI: studied in 8 subjects >65. No differences in efficacy or safety were observed. MMN: Population too small to evaluate efficacy and safety
Carimune NF Nanofiltered[13]	High dose administration in pediatric patients with acute or chronic ITP did not reveal any pediatric-specific hazard.	Use with caution
Privigen[14]	PI: Evaluated in 31 pediatric subjects. No apparent differences in efficacy and safety compared to adults	Population too small to evaluate efficacy and safety

	ITP: Not established in patients <15 years old	
Flebogamma Dif[15]	Population too small to evaluate efficacy and safety	Population too small to evaluate efficacy and safety
Hizentra[16]	Safety and efficacy established in patients 2-16 years old	Studied in 6 subjects ≥65 years old. No differences in efficacy or safety were observed

DRUG SAFETY[8,9,13–16]

Black Box Warnings

- Thrombosis may occur with immune globulin products. 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 the immune globulin 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.
- IVIG products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. For patients at risk of renal dysfunction or failure, administer immune globulin at the minimum concentration available and the minimum infusion rate practicable. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose. Cariumune NF contains sucrose, the other products included in this review do not. Hizentra does not carry this warning.

Contraindications

- Immune globulin products are contraindicated in patients with anaphylactic or severe ystemic reaction to human immune globulin or components of the product.
- Immune globulin product are contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity.
- Octagam is contraindicated in patients with acute hypersensitivity reaction to corn.
- Gammaplex and Flebogamma are contraindicated in those with intolerance to any component of the product (i.e. intolerance to fructose). Gammaplex is also contraindicated in infants and neonates for whom sucrose or fructose tolerance has not been established.
- If patients are known to be intolerant to any component of Flebogamma, such as sorbitol (i.e., intolerance to fructose), they should not receive the product.
- Privigen and Hizentra are contraindicated in patients with hyperprolinemia.

Table 6. Summary of Warnings and Precautions for IgG Products

Warning	Gammaked/ Gamunex-C[7,8]	Octagam[9]	Bivigam[10]	Gammaplex[11]	Gammagard[12]	Carimune[13]	Privigen[14]	Flebogamma-DIF[15]	Hizentra[16]
Hypersensitive/anaphylaxis in IgA deficiency	✔	✔	✔	✔	✔	✔	✔	✔	✔
Monitor those at risk of acute renal function	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hyperproteinemia, change in serum viscosity and electrolyte imbalances	✔	✔	✔	✔	✔		✔	✔	
Thrombosis	✔	✔	✔	✔	✔	✔	✔	✔	✔
Aseptic meningitis syndrome	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hemolytic anemia	✔	✔	✔	✔	✔	✔	✔	✔	✔
Pulmonary adverse reactions (TRALI)	✔	✔	✔	✔	✔	✔	✔	✔	✔
Volume overload	✔			✔					
Contain infectious agents (e.g., viruses)	✔	✔	✔	✔	✔	✔	✔	✔	✔
Do not administer SC	✔								
Passive transfer of antibodies confounds serologic testing	✔			✔			✔	✔	

TRALI: transfusion-related acute lung injury

- Falsely elevated blood glucose readings may occur during and after the infusion of Octagam 5% liquid with some glucometer and test strip systems
- Patients receiving Flebogamma-DIF for the first time or being retarted on the product after a treatment hiatus of more than 8 weeks may be at a hiher risk for development of fever, chill, nausea and vomiting.

Table 7. Clinical Pharmacology

Pharmacokinetics	Cmax	Mean AUC	Mean Half-life	Trough IgG level
Gammaked[8]	19 ± 3.1 mg/mL Not reported	7640 mg*hr/mL 1947 mg*h/mL	35.7 days	9.6 mg/mL 11.4 mg/mL
Gamunex-C IV[7] Gamunex-C SC	19 ± 3.1 mg/mL Not reported	7640 mg*hr/mL 1947 mg*h/mL	35.7 days	9.6 mg/mL 11.4 mg/mL
Octagam[9]	16.7 ± 3.2 mg/mL	7022 ± 1179 mg*hr/mL	40.7 ± 17 days	Q3W: 881.6 ± 151.5 mg/dL Q4W: 763.5 ± 156.8 mg/dL
Bivigam Q3W[10] Bivigam Q4W	2184 ± 293 mg/dL 2122 ± 425 mg/dL	27841 ± 4925 day*mg/dL 35509 ± 6472 day*mg/dL	19.6 ± 4.1 days 33.5 ± 10.7 days	996 ± 17.6 mg/dL 1106 ± 396 mg/dL
Gammaplex Q3W[11]	1060 mg/dL	6292 days*mg/dL	6.3 days	Not reported

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Gammaplex Q4W Gammaplex for ITP	1190 mg/dL 3165 mg/dL	8792 day*mg/dL 20375 day*mg/dL	6 days 8.5 days	
Gammagard IV[12] Gammagard SQ Gammagard for MMN	2050 mg/dL 1939 mg/dL Not studied	29139 days*mg/dL 9176 days*mg/dL Not studied	35 days Not reported Not studied	1030 mg/dL 1202 mg/dL 16.4 g/L
Carimune NF [13]Nanofiltered	Not reported			
Privigen Q3W[14] Privigen Q4W Privigen for ITP	2550 ± 400 mg/dL 2260 ± 530 mg/dL Not studied	32820 ± 6260 day*mg/dL 36390 ± 5950 day*mg/dL Not studied	27.6 ± 5.9 days 45.4 ± 18.5 days Not studied	1230 ± 230 mg/dL 1000 ± 200 mg/dL Not studied
Flebogamma Dif[15]	195 ± 28.3 mg/mL 209.2 ± 36.6 mg/dL	3395 ± 452.7 day*mg/dL 3423.7 ± 397.2 day*mg/dL	34 ± 10 days 37 ± 13 days	97.6 ± 16.5 mg/mL 87.7 ± 12.6 mg/mL
Hizentra[16]	Not reported	10560 day*mg/dL	Not reported	1448 mg/dL