

# Immune Globulin Agents (Human) Drug Class Review

Bivigam  
Carimune NF  
Flebogamma DIF  
Gamastan S/D  
Gammagard  
Gammagard S/D Less IgA  
Gammaked  
Gammaplex  
Gamunex-C  
Hizentra  
Hyqvia  
Octagam  
Privigen

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## Executive Summary

**Introduction:** Thirteen immune globulin (IG) agents are currently available for use in the United States: Bivigam, Carimune NF, Flebogamma DIF, Gamastan S/D, Gammagard, Gammagard S/D Less IgA, Gammaked, Gammaplex, Gamunex-C, Hizentra, Hyqvia, Octagam and Privigen. The agents are available in intravenous, subcutaneous and intramuscular routes of administration and consist of a sterile solution of concentrated antibodies extracted from healthy donors which provide passive immunity for a number of different disorders.

Both subcutaneous (SCIG) and intravenous immunoglobulin (IVIG) therapy are indicated in the treatment of primary immunodeficiency syndromes. The agents may also be used in the treatment of idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Kawasaki syndrome and in the prevention of secondary infection in patients with chronic lymphocytic leukemia in addition to a number of off-label uses. The single intramuscular immunoglobulin agent is indicated as prophylaxis of Hepatitis A infection, Measles or Varicella. The Food and Drug Administration recommends IG therapy be prioritized to treat disease conditions known to respond to IGIV therapy and off-label use be strictly limited. Clinical guidelines for use of immunoglobulin recommend IG therapy in all patients with primary immunodeficiency and absent or deficient antibody production.

**Clinical Efficacy:** A literature search was conducted to identify systematic reviews and meta-analyses evaluating the immunoglobulin agents. A total of 13 systematic reviews were identified for evaluation of the IG agents, including reviews evaluating the agents in primary immunodeficiencies, idiopathic thrombocytopenia purpura, chronic inflammatory demyelinating polyradiculoneuropathy, Kawasaki disease, multifocal motor neuropathy, neurological disorders and in dose ranging and formulation specific (subcutaneous, intravenous) trials. Based on the available clinical evidence, different IG agents are equally efficacious in terms of improving clinical outcomes in patients with immunodeficiencies and neurologic disorders.

**Adverse Drug Reactions:** Adverse events reported with IG therapy tend to be mild and uncommon, occurring in less than 10% of patients. Injection site reactions (pain, swelling) are more common with subcutaneous IG therapy and systemic reactions (headache, flu-like symptoms) are more common with intravenous IG therapy. Rare but serious adverse events (anaphylaxis, thrombosis, renal failure) have been reported with IG therapy and treatment should be limited in patients with IgA deficiency, patients with elevated serum viscosity, patients with preexisting kidney disease or volume depletion and in geriatric and pediatric patient populations.

**Summary:** In general, the IG products have similar indications with similar rates of efficacy, are composed predominantly of IgG (>95%) and comply with the quality standards of regulatory agencies. However, the manufacturing process, excipients and adverse effect profiles vary between each of the individual products. Choice of therapeutic IG agent, administration type and dosing regimen requires assessment and periodic re-evaluation of the risks and benefits for each individual patient.

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## Introduction

Immune globulin (IG) is a sterile solution of concentrated antibodies extracted from healthy donors which provide passive immunity for a number of different disorders.<sup>1,2</sup> Currently, 13 immune globulin agents are available for use in the United States: Bivigam, Carimune NF, Flebogamma DIF, Gamastan S/D, Gammagard, Gammagard S/D Less IgA, Gammaked, Gammaplex, Gamunex-C, Hizentra, Hyqvia, Octagam and Privigen.<sup>3,4</sup> All but one of the agents (Gamastan S/D) are available in intravenous and subcutaneous formulations and are indicated in the treatment of primary immunodeficiency (PI). Gamastan S/D is the only intramuscular agent and is labeled only for use as prophylaxis of Hepatitis A infection, Measles or Varicella. Some of the intravenous and subcutaneous formulations are also labeled for use in the treatment of idiopathic thrombocytopenic purpura (ITP), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Kawasaki syndrome and in the prevention of secondary infection in patients with chronic lymphocytic leukemia (CLL).<sup>3,4</sup> Table 1 provides a summary of the immunoglobulin agents included in this report and Table 2 provides an overview of the labeled indications for the immunoglobulin agents.

Intravenous immune globulin (IVIG) has been used as a therapeutic agent since the 1950's. Due to a shortage and reduced availability of immune globulin in 1997, the Food and Drug Administration (FDA) published guidelines for appropriate use of IVIG.<sup>5</sup> In general, the FDA recommends IVIG use be prioritized to treat disease conditions known to respond to IGIV therapy and off-label use is strictly limited. The shortage resulted from reduced manufacturing capacity while the manufacturers improved their practices to meet new Good Manufacturing Practices (GMPs). Reduced manufacturing and availability of IVIG has since been resolved and, currently, shortage of the IG products is not a concern. The FDA recommendations remain in place to encourage appropriate use of the immunoglobulin agents.

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**Table 1. Immunoglobulin Agents<sup>3,4</sup>**

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<p><b>Bivigam (Biotest Pharmaceuticals Corporation)</b></p>	<p>Indicated for the treatment of primary humoral immunodeficiency (PI)</p>	<p>Immune Globulin Intravenous (Human), 10% Liquid; 5g in 50mL solution, 10g in 100mL solution</p>	<p>As there are significant differences in the half-life of IgG among patients with primary humoral immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.</p> <p>The recommended dose of BIVIGAM for replacement therapy in primary humoral immunodeficiency (PI) is 300 to 800 mg/kg body weight administered every 3 to 4 weeks.</p>	<p>Initial Infusion Rate (for first 10 minutes): 0.5 mg/kg/min (0.005 mL/kg/min)</p> <p>Maintenance Infusion Rate (if tolerated): Increase every 20 minutes (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min.</p>	<p>Initial U.S. Approval: 2012</p>
<p><b>Carimune NF (CSL Behring)</b></p>	<p>Indicated for the maintenance treatment of patients with primary immunodeficiencies (PID), e.g., common variable immunodeficiency, X-linked agammaglobulinemia, severe combined immunodeficiency.</p> <p>Indicated in the acute and chronic treatment of Immune Thrombocytopenic Purpura (ITP).</p>	<p>Immune Globulin Intravenous (Human), NF (nanofiltered) 6g single-use vial, 12g single-use vial</p>	<p>Primary Immunodeficiency is 0.4-0.8 g/kg of body weight administered once every 3-4 weeks</p> <p>Idiopathic Thrombocytopenic Purpura (ITP) 0.4 g/kg of body weight on 2–5 consecutive days</p>	<p>Initial Infusion Rate: 0.5 mg/kg/min Maintenance Rate: 1 mg/kg/min; 2 mg/kg/min* Maximum Infusion Rate: 3 mg/kg/min</p> <p>*Maximum infusion rate for patients at risk of renal dysfunction or thromboembolic events</p>	<p>Carimune NF may contain a significant amount of sodium and also contains sucrose.</p>

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<b>Flebogamma DIF (Grifols Biologicals Inc.)</b>	Indicated for treatment of Primary (inherited) Immunodeficiency (PI).	Immune Globulin Intravenous (Human), DIF (dual inactivation plus nanofiltration) 10% Liquid (100 mg/mL)	The recommended dose in primary humoral immunodeficiency is 300-600 mg/kg every 3-4 weeks	Initial Infusion Rate: 0.01 mL/kg/minute (1 mg/kg/min) Maintenance Infusion Rate (if tolerated): 0.08 mL/kg/minute (8 mg/kg/min)	Initial U.S. Approval: 2010
<b>Gamastan S/D (Grifols Therapeutics Inc.)</b>	Indicated to prevent or modify Hepatitis A infection, Measles, Varicella, Rubella.	Intramuscular Injectable, preservative free, solvent/detergent (S/D): 15% to 18% (150-180 mg/mL, 2-10 mL)	Hepatitis A household and institutional contacts: 0.01 mL/lb (0.02 mL/kg) travel: length of stay < 3 months 0.02 mL/kg; ≥ 3 months or longer 0.06 mL/kg (repeat every 4-6 months)  Measles adult: 0.11 mL/lb (0.25 mL/kg) child: 0.5 mL/kg (maximum dose, 15 mL)  Varicella 0.6 to 1.2 mL/kg  Rubella 0.55 mL/kg	Intramuscular Injection	Do not administer subcutaneously or intravenously due to potential for serious reactions (e.g., Renal dysfunction /Failure /Hemolysis. Do not inject into a blood vessel.

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<p><b>Gammagard (Baxter International Inc.)</b></p>	<p>Indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.</p> <p>Indicated as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy [MMN].</p>	<p>Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration</p>	<p>Primary immunodeficiency            Intravenous Administration: 300-600 mg/kg every 3-4 weeks based on clinical response            Subcutaneous Administration: Initial Dose is 1.37 x previous intravenous dose divided by # of weeks between intravenous doses. Maintenance dose is based on clinical response and target IgG trough level.</p> <p>Multifocal Motor Neuropathy            Intravenous Administration: 0.5-2.4 grams/kg/month based on clinical response</p>	<p>Primary immunodeficiency            Intravenous Administration: Initial 0.5 mL/kg/hr (0.8 mg/kg/min) for 30 minutes; Maintenance increase every 30 minutes (if tolerated) up to 5 mL/kg/hr (8 mg/kg/min)            Subcutaneous Administration: 40 kg BW and greater, 30 mL/site at 20 mL/hr/site; Under 40 kg BW: 20 mL/site at 15 mL/hr/site</p> <p>Multifocal Motor Neuropathy            Intravenous Administration: Initial 0.5 mL/kg/hr (0.8 mg/kg/min); increase if tolerated to 5.4 mL/kg/hr (9 mg/kg/min)</p>	<p>Initial U.S. Approval: 2005</p>

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<p>Gammagard S/D Less IgA (Baxter International Inc.)</p>	<p>Indicated in the treatment of Primary Immunodeficiency (PI) in adults and pediatric patients two years of age or older.</p> <p>Indicated in the prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL)</p> <p>Indicated in the prevention and/or control of bleeding in adult Chronic Idiopathic Thrombocytopenic Purpura (ITP) patients.</p> <p>Indicated in the prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients.</p>	<p>Immune Globulin Infusion (Human), 5% Solution, for intravenous administration</p>	<p>Primary immunodeficiency: 300-600 mg/kg, every 3-4 weeks</p> <p>Chronic Lymphocytic Leukemia: 400 mg/kg, every 3-4 weeks</p> <p>Idiopathic Thrombocytopenic Purpura: 1g/kg, max 3 doses on alternate days</p> <p>Kawasaki Syndrome: Single 1g/kg or 400 mg/kg for 4 consecutive days</p>	<p>0.5 mL/kg/hour, may be gradually increased to a maximum rate of 4 mL/kg/hour</p>	<p>Solvent Detergent Treated</p> <p>IgA less than or equal to 2.2 µg/mL in a 5% Solution</p> <p>Initial U.S. Approval: 1994</p>

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<b>Gammaked (Grifols Therapeutics Inc.)</b>	<p>Indicated in the treatment of primary humoral immunodeficiency (PI) disorder.</p> <p>Indicated in the treatment of idiopathic thrombocytopenic purpura (ITP).</p> <p>Indicated in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).</p>	Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration	PI: Intravenous: 300-600 mg/kg Subcutaneous: 1.37 x current IV dose in mg/kg/IV dose interval in weeks ITP: Intravenous only: 2g/kg CIDP: Intravenous only: loading dose 2g/kg, maintenance dose 1g/kg	PI: IV: 1mg/kg/min, maintenance 8mg/kg/min every 3-4 weeks; SC: 20mL/hr/site ITP: initial 1mg/kg/min, maintenance 8mg/kg/min CIDP: Initial 2mg/kg/min, maintenance 8mg/kg/min every 3 weeks	Initial US approval: 2003
<b>Gammaplex (Bio Products Laboratory Limited)</b>	<p>Indicated in the treatment of primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.</p> <p>Indicated in the treatment of chronic immune thrombocytopenic purpura (ITP).</p>	Immune Globulin Infusion (Human), 5% Solution, for intravenous administration	PI: 300-800 mg/kg (6-16 mL/kg) every 3-4 weeks  ITP: 1 g/kg (20 mL/kg) for 2 consecutive days	PI: Initial 0.5 mg/kg/min (0.01 mL/kg/min) for 15 min; Maintenance Increase gradually every 15 minutes to 4 mg/kg/min (0.08 mL/kg/min)  ITP: Initial 0.5 mg/kg/min (0.01 mL/kg/min) for 15 min; Maintenance Increase gradually every 15 minutes to 4 mg/kg/min (0.08 mL/kg/min)	Initial U.S. Approval: 2009

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<b>Gamunex-C</b> (Grifols Therapeutics Inc.)	<p>Indicated in the treatment of primary humoral immunodeficiency (PI) disorder.</p> <p>Indicated in the treatment of idiopathic thrombocytopenic purpura (ITP).</p> <p>Indicated in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).</p>	Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration	PI: Intravenous: 300-600 mg/kg Subcutaneous: 1.37 x current IV dose in mg/kg/IV dose interval in weeks ITP: Intravenous only: 2g/kg CIDP: Intravenous only: loading dose 2g/kg, maintenance dose 1g/kg	PI: IV: 1mg/kg/min, maintenance 8mg/kg/min every 3-4 weeks; SC: 20mL/hr/site ITP: initial 1mg/kg/min, maintenance 8mg/kg/min CIDP: Initial 2mg/kg/min, maintenance 8mg/kg/min every 3 weeks	Initial U.S. Approval: 2003  Caprylate/Chromatography purified
<b>Hizentra</b> (CSL Behring)	Indicated in the treatment of primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.	Immune Globulin Subcutaneous (Human), 20% Liquid	Weekly: Previous IGIV dose (in grams) x 1.37 Biweekly: Administer twice the calculated weekly dose. Frequent dosing (2 to 7 times per week): Divide the calculated weekly dose by the desired number of times per week.	15-25 mL/site at rate of 15-25 mL/hr/site	Initial U.S. Approval: 2010
<b>Hyqvia</b> (Baxter Healthcare Corporation)	Indicated in the treatment of primary humoral immunodeficiency (PI) in adult patients.	Immune Globulin Infusion 10% (Human) Solution for subcutaneous administration	30 g per 4 weeks	1-2 mL per minute	Initial U.S. Approval: 2014  With Recombinant Human Hyaluronidase

Available Agents (Manufacturer)	Indications	Strength & Route	Dosing Recommendations	Infusion Rate	Notes
<b>Octagam (Octapharma USA Inc.)</b>	<p>5%: Indicated in the treatment of primary humoral immunodeficiency (PI).</p> <p>10%: Indicated in the treatment of chronic immune thrombocytopenic purpura (ITP) in adult patients.</p>	Immune Globulin Intravenous Human 5-10% Liquid	<p>PI: 300-600 mg/kg every 3-4 weeks</p> <p>ITP: 1 g/kg daily for 2 consecutive days</p>	<p>PI: 0.5 mg/kg/min 3.33 mg/kg/min</p> <p>ITP: Initial 1.0 mg/kg/min (0.01 mL/kg/min), Maintenance Up to 12.0 mg/kg/min (Up to 0.12 mL/kg/min)</p>	Initial U.S. Approval: 2014
<b>Privigen (CSL Behring)</b>	<p>Indicated in the treatment of primary humoral immunodeficiency (PI).</p> <p>Indicated in the treatment of chronic immune thrombocytopenic purpura (ITP).</p>	Immune Globulin Intravenous (Human), 10% Liquid	<p>PI: 200-800 mg/kg (2-8 mL/kg) every 3-4 weeks</p> <p>ITP: 1 g/kg (10 mL/kg) for 2 consecutive days</p>	<p>PI: Initial 0.5 mg/kg/min (0.005 mL/kg/min), Maintenance Increase to 8 mg/kg/min (0.08 mL/kg/min)</p> <p>ITP: Initial 0.5 mg/kg/min (0.005 mL/kg/min), Maintenance Increase to 4 mg/kg/min (0.04 mL/kg/min)</p>	Initial U.S. Approval: 2007

**Table 2. Immunoglobulin FDA-Labeled Indications<sup>3,4</sup>**

	Primary Immunodeficiency	Idiopathic Thrombocytopenic Purpura	Chronic Inflammatory Demyelinating Polyneuropathy	Multifocal Motor Neuropathy	Kawasaki Syndrome	Chronic Lymphocytic Leukemia	Hepatitis A infection, Measles, Varicella, Rubella.
Bivigam	X						
Carimune NF	X	X					
Flebogamma DIF	X						
Gamastan S/D							X
Gammagard	X			X			
Gammagard S/D Less IgA	X	X			X	X	
Gammaked	X	X	X				
Gammaflex	X	X					
Gamunex-C	X	X	X				
Hizentra	X						
Hyqvia	X						
Octagam	X	X					
Privigen	X	X					

*Disease Overview*

Primary Immunodeficiency Diseases

Immunodeficiency is defined as abnormalities in the immune system which lead to reduced immunocompetence. Immunodeficiency is labeled as either primary immunodeficiency or secondary immunodeficiency. If the immunodeficiency is linked to a genetic defect, it is considered a primary immunodeficiency disorder.<sup>6</sup> Secondary immunodeficiency disorders are immunity defects resulting from external factors including viruses, pharmacological agents or cancer. The primary immunodeficiency (PI) disorders are a diverse group of immune system defects which result in the loss of quantity or quality of B cells, T cells, phagocytic cells and/or cytokines. More than 250 genetically based PI diseases have been identified including, but not limited to: chronic granulomatous disease (CGD), congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, severe combined immunodeficiency, etc. Table 3 summarizes the disorders associated with primary immunodeficiency. The number of PI disorders continues to grow and the prevalence of PI in the US is estimated at 1 in 1,200 individuals, though this is likely an underestimate.<sup>7</sup>

**Table 3. Primary Immunodeficiency Disorders<sup>1</sup>**

<b>System</b>	<b>Cells/Receptors</b>	<b>Disorder</b>
<b>Deficiencies of the Innate Immune System</b>	<i>Phagocytic cells</i>	<u>Impaired production</u> : severe congenital neutropenia (SCN), asplenia  <u>Impaired adhesion</u> : leukocyte adhesion deficiency (LAD)  <u>Impaired function</u> : chronic granulomatous disease (CGD)
	<i>Innate immunity receptors and signal transduction</i>	Defects in Toll-like receptor signaling  Mendelian susceptibility to mycobacterial disease
<b>Deficiencies of the Adaptive Immune System</b>	<i>T lymphocytes</i>	<u>Impaired development</u> : severe combined immune deficiencies (SCIDs), DiGeorge syndrome  <u>Impaired survival, migration, function</u> : combined immunodeficiencies, hyper-IgE syndrome (autosomal dominant), DOCK8 deficiency, CD40 ligand deficiency, Wiskott-Aldrich syndrome, ataxia-telangiectasia and other DNA repair deficiencies
	<i>B lymphocytes</i>	XL and AR agammaglobulinemia,

System	Cells/Receptors	Disorder
		Hyper-IgM syndrome, common variable immunodeficiency (CVID), IgA deficiency
Regulatory Defects	<i>Innate immunity</i>	Autoinflammatory syndromes, severe colitis
	<i>Adaptive immunity</i>	Hemophagocytic lymphohistiocytosis (HLH), autoimmune lymphoproliferation syndrome (ALPS), autoimmunity and inflammatory diseases (IPEX, APECED)

Adapted from: <http://accessmedicine.mhmedical.com/ViewLarge.aspx?figid=98729183>, accessed 9/29/2015

The loss of function of these foundational immune mediators results in an increased risk of infection.<sup>7</sup> Some primary immunodeficiencies are associated with multiple cell defects, resulting in more severe disease. Severe combined immunodeficiency (SCID), for example, results from multiple genetic defects (including abnormal thymic tissue and no lymphocytes present in the lymph nodes, spleen or other peripheral lymphoid tissues) which cause abnormalities in both B and T cell function. Patients with SCID are susceptible to almost any bacterial or viral infection and, without bone marrow transplantation for immune reconstitution, SCID frequently results in death within the first year of life. Chronic granulomatous disease (CGD), on the other hand, results from a deficiency in phagocyte function. Patients with CGD have normal levels and function of immunoglobulins, T cells and B cells. These patients also have normal levels of phagocytic cells but with reduced function due to a metabolic defect in the cell's ability to generate peroxide and superoxide resulting in the diminished ability to kill some bacteria or fungi (*Staphylococcus*, *E coli*, and *Aspergillus spp.*) Interferon therapy appears to restore phagocyte function in these patients. Without treatment, CGD results in death usually before the age of 10.<sup>7,8</sup>

Treatment of primary immunodeficiency varies by diagnosis.<sup>8</sup> In general, most patients with a PI disorder and antibody deficiencies are treated with IVIG. Adult-onset hypogammaglobulinemia is one of the most common PI disorders in adults and is associated with recurrent sinus and pulmonary infections and some noninfectious disorders, including gastrointestinal malabsorption, autoimmune disease and cancer. Regular immunoglobulin infusions are used to rebuild humoral immunity in these patients which results in decreased infections and improved quality of life.<sup>6</sup> IVIG therapy is also used frequently in patients with X-linked agammaglobulinemia, hyper IgM and SCID. IVIG therapy is used less frequently in DiGeorge syndrome, IgA deficiency and CGD.<sup>8</sup> According to the American Academy of Allergy, Asthma and Immunology Guiding Principles for Effective Use of IVIG (2015), all patients with a PI disorder with absent or deficient antibody production are candidates for IVIG therapy. In patients with PI, IVIG is administered at a starting dose of 400-600 mg/kg every 3-4 weeks.<sup>9</sup> Lower doses and/or frequencies have not demonstrated efficacy in patients with PI disorders.

### Idiopathic Thrombocytopenia Purpura

Thrombocytopenia resulting from pathogenic anti-platelet antibodies is referred to as autoimmune thrombocytopenia.<sup>10,11</sup> Autoimmune thrombocytopenia can be divided into four categories, including idiopathic thrombocytopenia purpura (ITP), secondary immune thrombocytopenia, viral infection-related thrombocytopenia and drug-induced thrombocytopenia.<sup>10</sup> Secondary autoimmune thrombocytopenia can result from systemic lupus erythematosus (SLE).<sup>10,12,13</sup> Viral related thrombocytopenia can result from infection with HIV or hepatitis C.<sup>13,14</sup> The exact mechanism underlying the immune dysfunction and platelet destruction in idiopathic thrombocytopenia purpura is unknown.<sup>13-16</sup>

Idiopathic thrombocytopenia purpura is an important and relatively common disorder. A broad range of incidence rates are reported in epidemiology studies largely due to use of varying platelet counts used to define the disease.<sup>13,17</sup> According to the 2011 American Society of Hematology guidelines on ITP, patients with platelet counts  $>50,000/\mu\text{L}$  generally do not require treatment, although no explicit cutoff level for diagnosis is defined.<sup>18</sup> In a recent study, incidence rates were reported as approximately five per 100,000 children and two per 100,000 adults with a platelet count ranging from  $<50,000/\mu\text{L}$  to  $<100,000/\mu\text{L}$ .<sup>17</sup> There was a slightly higher incidence among middle-aged women and the overall incidence of ITP doubled with age.<sup>17,19</sup> Life-threatening complications occur most frequently in patients over 60 years; however, overall mortality rates are low.<sup>13</sup> A low platelet count ( $<150,000/\mu\text{L}$ ) with an otherwise normal peripheral blood smear and mucocutaneous bleeding are the key characteristics of ITP.<sup>13-16</sup> Patients may present with ecchymoses and petechiae or thrombocytopenia found on a routine complete blood count (CBC).<sup>13,14,16</sup> Oral, gastrointestinal, or heavy menstrual bleeding may also present as signs and symptoms.<sup>14</sup> Rarely, life-threatening bleeding, wet purpura (blood blisters in the mouth), and retinal hemorrhages may be present.<sup>13,14</sup> Idiopathic thrombocytopenia purpura usually presents as a self-limited disorder resulting from an acute infection in children and it usually presents as a chronic disorder in adults.<sup>13-16</sup> Newborns of mothers with ITP can develop thrombocytopenia and close monitoring for 3-4 days after birth is recommended.<sup>20</sup> Diagnosis of ITP does not always necessitate treatment. Treatment is considered appropriate for patients with symptoms and for patients who are at high risk for bleeding.<sup>13-16</sup> Increased mortality risk is associated with patients who have platelet counts less than  $30,000/\mu\text{L}$ .<sup>13,14</sup>

Medications that reduce antibody production and/or macrophage uptake of the antibody-bound platelets are used to treat ITP.<sup>13,14,16</sup> Initial treatment consists of corticosteroids, typically prednisone 1 to 2 mg/kg daily in single or divided doses, initiated on an outpatient basis. Intravenous gamma globulin (IVIG) 2 gram/kg, given in divided doses over 2 to 5 days, is generally reserved for patients with critical bleeding or for patients who were unresponsive to corticosteroids. Rh0(D) immune globulin therapy (WinRho SDF), used only in Rh+ patients, at a dose of 50-75 mcg/kg, is also an option. Hospital admission, combination therapy, and platelet transfusions are recommended for patients with severe ITP and internal or profound bleeding. Splenectomy is indicated as second-line treatment for patients who relapse following glucocorticoid treatment. Rituximab, an anti-CD20 (B cell) antibody, may be effective for the treatment of refractory ITP and defer splenectomy.<sup>13,14,16</sup> Nearly 20% of patients are refractory to first-line treatments and an additional third will relapse after an initial response.<sup>21</sup> Patients who

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have not had an adequate response to corticosteroids, immunoglobulins, or a splenectomy, may respond to a TPO receptor agonist.<sup>14-16,22-24</sup>

### Kawasaki syndrome

Kawasaki syndrome, or mucocutaneous lymph node syndrome, is a vasculitis disorder first identified in 1967 in Japan.<sup>25</sup> The syndrome is defined as a chronic fever for 5+ days accompanied by at least four of the additional features: conjunctivitis, oral cavity inflammation, cervical lymphadenopathy, polymorphous exanthema, and/or redness and swelling of the extremities. Other clinical features associated with the disease include gastrointestinal upset, hematologic complications, respiratory disease, joint pain, proteinuria and, most concerning, cardiovascular disease. The underlying cause of Kawasaki syndrome is unknown, although it is thought to result from a viral infection. In the US, Kawasaki syndrome is relatively uncommon with an estimated 4,200 children diagnosed each year; despite this, Kawasaki syndrome is listed as a leading cause of pediatric acquired heart disease in the US. Most cases are diagnosed in patients before the age of 5 years (median age ~2 years) and the syndrome occurs more frequently in males (male-to-female ratio 1.5:1).<sup>26,27</sup>

During acute illness, Kawasaki syndrome is associated with coronary arteritis, myocarditis, pericarditis and valvular heart disease.<sup>25</sup> Severity of cardiovascular disease can range from mild, transient coronary artery dilation to large aneurysms. Patients at highest risk for aneurysm include young infants (< 6 months), males and those who have not received treatment. Within five years, coronary aneurysms tend to resolve but complications associated with the obstruction may persist and are associated with chronic coronary ischemia. Acute thrombosis and fatal myocardial infarction may occur in up to 20% of patients who experience an aneurysm. Immediate treatment of Kawasaki disease is recommended as soon as a diagnosis is made. According to the American Heart Association guidelines for management of Kawasaki disease (2004), IVIG and high-dose aspirin reduce the risk of coronary artery dilation and aneurysm formation and are the treatments of choice for acute illness.<sup>28</sup> IVIG 2 g/kg is administered over 10-12 hours and high-dose aspirin 80-100 mg/kg/d is given in four divided doses daily for up to 5 days after the last recorded fever. Low-dose aspirin (3–5 mg/kg/d) should be continued for up to 6-8 weeks or until the cardiovascular abnormalities resolve. A second dose of IVIG is recommended if fever recurs within 48–72 hours. Steroid therapy, plasma exchange and treatment with monoclonal antibodies are second-line treatment options in patients who did not respond to initial therapy.<sup>27</sup>

### Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP), or chronic relapsing polyneuropathy, is a neurological disorder resulting from peripheral nerve fiber myelin sheath damage.<sup>29,30</sup> There is evidence of autoimmune dysfunction in CIDP, although the exact cause of the myelin sheath damage is unknown. The disorder is progressive and characterized by gradual onset of impaired sensory function and weakness in the arms and legs. CIDP shares similar clinical characteristics with Guillain-Barré syndrome (GBS) except CIDP is chronic and progressive while Guillain-Barré syndrome is associated with acute, sometimes severe neuropathy. The incidence estimates for CIDP are lower than GBS (~1.5-3.6 per 1,000,000) but

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the prevalence of CIDP is higher than GBS (~8 per 100,000) due to the chronic nature of the disease.<sup>31</sup> CIDP occurs more frequently in older adults and males and is associated with both motor (tremor, loss of deep tendon reflexes) and sensory (numbness or tingling of the extremities) symptoms. CIDP can be chronic-progressive or relapsing-remitting, usually improves with treatment over time and is not usually associated with severe disease or death.<sup>32</sup>

Mild CIDP disease does not usually require treatment and careful observation for spontaneous remission is recommended.<sup>29-31</sup> Treatment of CIDP is appropriate in rapidly progressive disease or when walking is compromised.<sup>33</sup> According to the American Academy of Neurology, chronic corticosteroid therapy (prednisone 60-100 mg/d for 2-4 weeks, then taper) helps to improve weakness.<sup>34</sup> Intravenous immunoglobulin therapy (1 g/kg daily for 2 days and again at 3 weeks or 400 mg/kg/d for 5 consecutive days) is recommended as first-line or add-on therapy. Up to one-third of patients with CIDP are nonresponsive to corticosteroid or IVIG therapy; plasma exchange, methotrexate, cyclosporine, azathioprine or cyclophosphamide are considered effective second-line treatment options in patients who have failed initial therapies. Overall, choice of therapy requires assessment and periodic re-evaluation of the risks and benefits.<sup>33</sup>

### Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a rare neurological disorder characterized by motor weakness and atrophy occurring in a slow progression over years.<sup>30,32,35</sup> The sensory system is not generally affected. The upper extremities tend to be affected more frequently than the lower extremities and up to 75% of those diagnosed with MMN are male. Prevalence of MMN is reported anywhere from 0.3 up to 3 per 100,000 but is frequently under-recognized and mis-diagnosed.<sup>32</sup> Accurate diagnosis is based on electrophysiologic studies which demonstrate 1-2 motor deficits, usually asymmetric, linked to conduction block. The cause of MMN is unknown but related to demyelination, inflammation and alterations to motor unit potentials.<sup>36</sup> High-dose IVIG (2 g/kg daily) administered over 3-5 days every monthly is the treatment of choice for MMN. Azathioprine, cyclophosphamide, cyclosporine, infliximab, interferon, mycophenolate mofetil and rituximab may be considered second-line therapies, although insufficient evidence is available supporting their use in MMN.<sup>37,38</sup>

### Other

IVIG therapy is also indicated in the treatment of adverse events and secondary infections, particularly hypogammaglobulinemia, associated with chronic lymphocytic leukemia (CLL), bone marrow transplant (BMT) and pediatric human immunodeficiency virus (HIV).<sup>39,40</sup>

Chronic lymphocytic leukemia (CLL) is a blood and marrow disorder characterized by increased numbers of CD5-positive B cells.<sup>41</sup> The underlying cause of CLL is unknown, although it is thought to be genetically linked.<sup>42</sup> CLL is the most common lymphoid disorder in the Western hemisphere and is the cause of about 20% of all leukemias in the United States. The median age at diagnosis of CLL is ~67 years. The incidence of CLL increases with increasing age and males are twice as likely to have the disorder compared to females. CLL is often diagnosed after a routine complete blood count (CBC) panel demonstrating an elevated absolute

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lymphocyte count (ALC) ranging from  $5 \times 10^9/L$  to  $500 \times 10^9/L$ .<sup>41</sup> In some patients, symptoms of fatigue, frequent infections, fever and weight loss are presenting features. Clinical progression of CLL can vary widely and treatment can range from careful observation with as needed treatment of secondary infections and hemorrhagic complications to complicated combination therapies with steroids, chemotherapy, monoclonal antibodies and/or stem cell transplantation.<sup>43</sup> In general, treatment for CLL is not curative. Because CLL tends to occur in an older population and has a slow progression, there are a number of complications associated with the disease. Hypogammaglobulinemia is frequently linked to CLL and is associated with the development of various secondary infections including those caused by Herpes zoster, Pneumocystis carinii and Candida albicans.<sup>41</sup> According to the National Cancer Institute, early diagnosis and treatment of secondary infections greatly improves long-term survival. In patients with hypogammaglobulinemia, intravenous immunoglobulin (400 mg/kg every 3 weeks for 1 year) therapy demonstrated efficacy in reducing the number of bacterial infections.<sup>44</sup> However, no reduction in overall mortality was demonstrated and the long-term benefit (>1 year) of IVIG therapy is unknown.<sup>45,46</sup>

Bone marrow transplant (BMT) is a procedure indicated in the treatment of hematologic cancers. It is effective in curing many malignant and non-malignant disorders. In order for a BMT procedure to be successful, chemotherapy is first administered to ablate host immune function, rendering the patient immunodeficient. A BMT procedure is then administered to restore hematopoiesis.<sup>47</sup> Unfortunately, the lack of immune function puts the patient at high risk for serious opportunistic infections including cytomegalovirus (CMV). According to clinical evidence, IVIG is efficacious in preventing and treating CMV infection in patients who recently received a BMT and is recommended as prophylaxis in most patients. IVIG therapy has also demonstrated efficacy in modulating host immune responses and significantly reducing the rate of acute graft-versus-host disease (GVHD) with weekly doses (500-1000 mg/kg) for up to 90-120 days after the BMT procedure.<sup>48</sup>

The development of highly effective and potent combination active antiretroviral treatment (HAART) regimens has significantly decreased the rate of acquired immunodeficiency syndrome (AIDS), opportunistic infections and deaths in both children and adults with HIV. Pediatric patients who receive suboptimal care are at higher risk for developing protozoan, fungal and/or viral opportunistic infections. IVIG therapy has been used as a prophylaxis and treatment for opportunistic infections in pediatric patients with HIV. According to the CDC and NIH guidelines for opportunistic infections in pediatric patients with HIV, IVIG therapy (400 mg/kg every 2-4 weeks) is only appropriate for treatment of invasive bacterial infections in HIV-infected pediatric patients with concurrent hypogammaglobulinemia (i.e., IgG <400 mg/dL). IVIG therapy may also be used as a second-line treatment option in pediatric patients with Varicella-zoster virus who did not respond to Varicella-zoster immune globulin. According to the guidelines, clinical evidence does not support the use of IVIG in the prevention or treatment of other opportunistic infections associated with pediatric HIV infection.<sup>49</sup>

IVIG therapy is also administered in a number of off-label indications including: Guillain-Barré syndrome, solid organ transplant, multiple myeloma, hemolytic disease, mucocutaneous blistering disease, myasthenia gravis, Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), inflammatory myopathies, idiopathic progressive

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polyneuropathy, intractable epilepsy, acute cardiomyopathy, pure red cell aplasia, fatal autoimmune thrombocytopenia (FAIT), stiff person syndrome (SPS), etc. Some clinical data demonstrates efficacy for the IVIG agents in the treatment of off-label uses. This report focuses on the clinical safety and efficacy evidence available for IVIG therapy in FDA-approved indications.<sup>3,4</sup>

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## Mechanism of Action

IVIG is a sterile solution of concentrated polyvalent antibodies (~95% IgG) extracted from healthy donors.<sup>1,2</sup> The intravenous/subcutaneous immunoglobulin agents are a group of nonspecific immunoglobulins which provide passive immunity for a number of different disorders for up to 1-3 months after a single dose. Immunity to a specific disease occurs via disease-specific antibodies created through a process of active or passive immunity. Active immunity occurs after exposure to the disease organism either through infection with the actual disease, referred to as natural immunity, or exposure to a killed/weakened form of the organism via vaccination. Passive immunity occurs via the transfer of immunologic products, such as immunoglobulin, to an antibody-deficient individual. In general, active immunity is long-lasting while passive immunity is short-acting and requires repeat exposure. Passive immunity with immunoglobulin is indicated in patients with congenital or acquired immunodeficiency, in patients at high risk for drug or disease adverse effects or in patients with inadequate time to obtain active immunization (e.g., measles, rabies, diphtheria, tetanus). Passive immunization can occur after administration of nonspecific immunoglobulin agents or highly-specific agents (including antithymocyte globulin, botulism immune globulin, cytomegalovirus immune globulin, hepatitis B immune globulin, etc.) Specific immune globulin agents consist of a sterile solution of concentrated antibodies extracted from donors with high titers of the desired antibodies. The indications for IVIG therapy have expanded from replacement therapy for immunodeficiencies to treatment and prevention of bacterial/viral infections and various autoimmune and inflammatory diseases.<sup>50,51</sup> The exact mechanism of action of IVIG in immune modulation is unclear but may be linked to alterations in function of receptors on leukocytes and endothelial cells, complement activation and cytokine production.<sup>52</sup>

Immunoglobulin therapy is available in subcutaneous, intravenous and intramuscular formulations.<sup>2,53</sup> Intravenous immunoglobulin (IVIG) is the most commonly used formulation. Subcutaneous immunoglobulin (SCIG) products provide an option for immunoglobulin therapy without the need for venous access and hospital/clinic administration. One intramuscular immunoglobulin agent is currently available in the US (Gamastan); it is the only IG agent indicated for prophylaxis of hepatitis A infection, measles infection and passive immunization against varicella in immunosuppressed patients. Intramuscular administration is not recommended in the treatment of primary immunodeficiency as IM administration is associated with inadequate serum levels and increased rates of adverse effects.<sup>40</sup> Trough/steady state IgG levels may be considered surrogate markers for efficacy of immunoglobulin therapy. In a meta-analysis of 17 clinical studies published in 2010, Orange et al reported a reduced rate of secondary infections in patients with stable trough/steady state IgG levels receiving either intravenous or subcutaneous immunoglobulin.<sup>54</sup> Theoretically, SCIG therapy is associated with a more stabilized pharmacokinetic profile and fewer adverse events due to slow absorption and increased frequency of administration with subcutaneous therapy. However, clinical evidence reports no differences in efficacy between intravenous and subcutaneous immunoglobulin formulations despite differences in the pharmacokinetic profiles.<sup>55</sup> Table 4 provides a summary of the product properties for the agents.

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**Table 4. Product properties of the IG agents<sup>3,4</sup>**

Agent	Stabilizing Agent	IgG Content	IgA Content	Sodium Content
<b>Bivigam</b>	Glycine	>96%	<0.2 mg/mL	0.1-0.140M
<b>Carimune NF</b>	Sucrose	>96%	Trace amounts	20 mg/g of protein
<b>Flebogamma DIF</b>	Sorbitol	>97%	<100 mcg/mL	Trace amounts
<b>Gamastan S/D</b>	Glycine	NR	NR	Present
<b>Gammagard</b>	Glycine	>98%	~37 mcg/mL	None
<b>Gammagard S/D</b>	Glycine, Glucose	>90%	<2.2 mcg/mL	8.5 mg/mL
<b>Gammaked</b>	Glycine	>98%	~0.046 mg/mL	NR
<b>Gammaplex</b>	Glycine	>95%	<10 mcg/mL	0.3g
<b>Gamunex-C</b>	Glycine	>98%	46 mcg/mL	NR
<b>Hizentra</b>	Proline	>98%	<50 mcg/mL	Trace amounts
<b>Hyqvia</b>	Glycine		37 mcg/mL	None
<b>Octagam</b>	Maltose	>96%	<0.2 mg	<=30mm/L
<b>Privigen</b>	Proline	>98%	<25 mcg/mL	Trace amounts

Key: NR = not reported

## Clinical Efficacy

### *Methods*

A literature search was conducted to identify systematic reviews searching the MEDLINE database (1950 – 2015), the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only systematic reviews published in English, evaluating efficacy of the IVIG agents are included. Reviews evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Non-comparative evidence and evidence comparing monotherapy with combination regimens are excluded.<sup>54,56-60</sup> Evidence evaluating the IVIG preparations in the treatment of off-label uses were also excluded.<sup>54,61-92</sup>

### *Systematic Reviews*

A total of 13 systematic reviews were identified for evaluation of the immunoglobulin agents. Two reviews evaluated the efficacy of the agents in patients with primary immunodeficiencies, one review evaluated the efficacy of the agents in patients with idiopathic thrombocytopenia purpura, one review evaluated the efficacy of the agents in patients with chronic inflammatory demyelinating polyradiculoneuropathy, one review evaluated the efficacy of the agents in pediatric patients with Kawasaki disease, one review evaluated the efficacy of the agents in patients with multifocal motor neuropathy, four reviews evaluated the efficacy of the agents in patients with neurological disorders and three reviews evaluated the efficacy of the agents in dose ranging and formulation specific (subcutaneous, intravenous) trials.

Primary Immunodeficiency: Two systematic reviews evaluating the efficacy of the IG agents in patients with primary immunodeficiency were identified for evaluation. In 2010, Shehata et al<sup>93</sup> published evidence-based guidelines for the use of IG therapy in patients with PI. The recommendations are based on evidence from a systematic search of the clinical evidence available for IG therapy, including a summary of the two available systematic reviews. In total, 1,087 citations were reviewed and 101 were included in the analysis. Sixteen citations compared the efficacy of IG agents from different manufacturers. According to the evidence, no significant differences in efficacy were reported between IG agents. Of note, most of the studies were small and only conducted for licensing purposes rather than to compare the efficacy of the agents. One study reported differences in antibody levels between manufactured products but no differences in overall efficacy were reported. One systematic review and 2 clinical trials compared the efficacy of intravenous IG to subcutaneous IG. According to the evidence, no statistically significant differences in efficacy were reported between intravenous and subcutaneous IG therapy. Seven clinical trials evaluated the efficacy of IG therapy with differing doses. According to the evidence, improved efficacy and sustained effects are seen with high-dose IG therapy compared to low-dose therapy. Overall, the guidelines recommend IG therapy in the treatment of primary immunodeficiency disorders based on evidence that suggests IG therapy reduces secondary infection rates, hospitalizations and mortality and improves quality of life. The guidelines do not recommend one product or formulation over another.<sup>93</sup> An additional

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clinical review not included in the evidence-based guideline is available for evaluation. According to the review, the efficacy and safety of intravenous and subcutaneous IG therapy are well-documented with similar rates of efficacy, adverse events and IgG steady-state levels and both therapies have similar costs. According to the review, selection of an IG agent should be based on individual clinical response.<sup>94</sup>

Idiopathic Thrombocytopenia Purpura: One systematic review evaluated the efficacy of different doses of IVIG therapy in patients with acute idiopathic thrombocytopenic purpura (ITP). A total of 13 randomized controlled trials (n = 646 patients) comparing high-dose IVIG with low-dose IVIG were identified for evaluation. According to the evidence, no differences in efficacy (defined as differences in effective rate, time to effects, peak effects and rate of chronic ITP) were reported between the treatment groups. A statistically significant reduced rate of adverse events was reported in the low-dose treatment groups compared to high-dose treatment groups (p = 0.01). This evidence suggests low-dose IVIG therapy is as effective and safer than high-dose IVIG therapy in patients with acute ITP.<sup>95</sup>

Chronic Inflammatory Demyelinating Polyradiculoneuropathy: No comparative systematic reviews evaluating the efficacy of the IG agents in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are available for evaluation. One systematic review of eight randomized controlled trials comparing IG therapy to other treatments in patients with CIDP was identified. Eftimov et al (2013) evaluated the efficacy of IVIG therapy compared to placebo (5 trials, n = 235), plasma exchange (1 trial, n = 20) or corticosteroids (2 trials, n = 78) in patients diagnosed with definite or probable CIDP. According to the evidence, IVIG therapy improves patient outcomes (defined as improvements in disability scores) for at least 2-6 weeks compared to placebo (RR 2.40; CI 1.72-3.36). No differences in efficacy were reported between IVIG treatment groups and plasma exchange or corticosteroid treatment groups. No differences in rate of adverse events were reported between treatment groups but further research is recommended to evaluate the safety and efficacy of long-term IVIG therapy in the treatment of CIDP.<sup>96</sup>

Kawasaki Disease: One systematic review evaluated the efficacy of IVIG therapy in the treatment and prevention of cardiovascular complications in pediatric patients with Kawasaki disease. A total of 59 randomized controlled trials were identified for evaluation and 16 were included in the analysis. Three citations compared the efficacy of IG agents from different manufacturers. According to the evidence, no significant differences in efficacy (defined as rate of new coronary artery abnormalities (CAAs)) were reported between IG agents. Statistically significant decreases in CAAs were reported with IVIG therapy when compared to placebo (p < 0.05). Fifteen clinical trials evaluated the efficacy of IG therapy with differing doses. According to the evidence, reduced rate of new CAAs, reduction in fever duration and sustained clinical effects are seen with high-dose IG therapy compared to low-dose therapy. No statistically significant differences in adverse effects were reported in any of the treatment groups.<sup>97</sup>

Multifocal Motor Neuropathy: No comparative systematic reviews evaluating the efficacy of the IG agents in the treatment of multifocal motor neuropathy are available for evaluation. One systematic review comparing IG therapy to placebo in patients with multifocal motor neuropathy was identified. Van Schaik et al (2006) evaluated four randomized controlled

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trials (n = 34) for improvements in disability, strength or conduction block with IG therapy. According to the evidence, statistically significant improvements in strength were reported in patients receiving IVIG therapy compared to those receiving placebo (78% vs 4%,  $p < 0.05$ ). No differences in disability or conduction block were reported between treatment groups.<sup>98</sup>

Neurologic Conditions: A summary of clinical evidence and treatment recommendations in patients with neurological autoimmune diseases is available in several review studies. A clinical review (Dalakas, 2004) of the evidence-based indications for the IG agents reports IVIG therapy is an effective first-line treatment option in patients with neurologic disorders, including CIDP and multifocal MMN.<sup>99</sup> A second review by Latov et al (2000) provides recommendations for IVIG as first-line therapy in patients with CIDP or MMN based on rigorously controlled, double-blind clinical trials.<sup>100</sup> Stangel et al (1998) provides evidence in favor of IVIG as an immunomodulatory therapy based on clinical data demonstrating efficacy for IVIG in the treatment of neurological autoimmune diseases including CIDP and MMN.<sup>101</sup> The National Advisory Committee on Blood and Blood Products (NAC) and Canadian Blood Service published evidence-based guidelines for use of IVIG therapy in neurologic conditions in 2007.<sup>102</sup> According to the review of clinical evidence, the treatment guidelines recommend IVIG therapy in 14 neurologic conditions, including CIDP and MMN. None of the published reviews report differences in efficacy between the agents and do not recommend a specific IVIG agent over another.

Pharmacokinetic Clinical Evidence: One systematic review evaluated the pharmacokinetic (PK) profiles of different IVIG agents.<sup>103</sup> A total of 1200 clinical trials were identified for evaluation and 50 were included in the analysis. Trials included in the analysis ranged from randomized controlled (12 trials), nonrandomized controlled (3 trials), cohort (30 trials) and case reports or descriptive studies (5 trials). Study populations included patients with primary immunodeficiency disease (PID), bone marrow transplant, chronic lymphocytic leukemia or multiple myeloma, women with pregnancy complications and high-risk neonates/infants. It appears IVIG therapy produces serum IgG levels which decline rapidly after initial infusion and continue to gradually decline over the following weeks with a half-life ~20-30 days in patients with normal or near-normal baseline immunoglobulin levels. Variation in IVIG PK profiles is highest in patients with abnormal baseline IgG levels. Across the majority of included clinical trials, initial IGIV dose was 0.4 g/kg every 3-4 weeks with steady state reached within 4-6 months. Based on the data, pharmacokinetic profiles can also vary widely between different patient populations.

Two systematic reviews evaluated the efficacy of different formulations of IG therapy. Abolhassani et al<sup>104</sup> identified a total of 156 clinical trials for evaluation and 47 of those trials (10 controlled trials and 37 cohort studies; n = 1,484) were included in the analysis. The majority of the evidence (31 studies, n = 1,059) suggests subcutaneous and intravenous administration of IG produces similar serum IgG trough levels ( $p < 0.01$ ) with no differences in dosing patterns. Clinical trials reporting outcomes for infection and hospitalization rates are mixed. Some trials report improved outcomes with subcutaneous therapy, some report improved outcomes with intravenous therapy and some report no differences in efficacy between the different routes of administration. The authors conclude that the available clinical efficacy data are difficult to interpret. Clinical trials evaluating safety outcomes associated with IG therapy report

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significantly greater patient preference for subcutaneous IG therapy based on reduced rates of systemic adverse events (such as severe headache, fever and anaphylactoid reactions) reported with subcutaneous administration ( $p < 0.01$ ). Lingman-Framme et al<sup>105</sup> identified a total of 508 clinical trials for evaluation and 25 of those trials were included in the analysis. Eleven studies evaluated the difference in IgG trough levels between the different routes of administration and reported an increase in IgG levels with subcutaneous IG administration. No difference in clinical efficacy or adverse event rates were reported between treatment groups. The authors concluded both routes of administration are efficacious in reducing the rate of serious bacterial infections and have good safety profiles in patients with immunodeficiency.

Based on the available clinical evidence, different IG agents are equally efficacious in terms of improving clinical outcomes in patients with immunodeficiencies and neurologic disorders. In addition, the available IG agents are labeled for use in a common group of indications. As the list of therapeutic uses for immunoglobulin continues to increase, some clinical evidence suggests the agents should be considered generic and substitutable. According to a recent review of the topic<sup>106</sup>, “the manufacturing process and associated excipients for individual products varies, all currently licensed IVIG products are composed predominantly of IgG (>95%) and comply with the quality standards of regulatory agencies.” However, other evidence suggests the differences in risk of adverse effects between agents and difficulty in tracking a specific agent associated with an IVIG-associated viral transmission or contaminant limits the likelihood of generic IVIG formulations.<sup>106</sup>

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## Adverse Drug Reactions

Adverse events reported with IG therapy tend to be mild and uncommon, occurring in less than 10% of patients.<sup>34,107,108</sup> Systemic reactions usually reported with intravenous therapy include mild to moderate headache (treated with nonsteroidal anti-inflammatory therapy), chills/myalgia and pruritus within the first hour of infusion (treated by stopping the infusion and restarting at a reduced rate) and post-infusion fatigue, fever or nausea. Mild chest discomfort and hypotension may also occur while receiving the infusion. Local reactions usually reported with subcutaneous therapy include swelling, erythema and itching at the site of injection. Rare but serious adverse events reported with IG therapy include anaphylaxis, thrombosis and acute renal tubular necrosis. Individuals with IgA deficiency (prevalence about 1:1000) may have anti-IgA antibodies and can develop hypersensitivity reactions to immune globulin therapy, resulting in severe anaphylaxis. Patients with high-normal or slightly elevated serum viscosity, as seen with hypercholesterolemia or hypergammaglobulinemia, are at increased risk for experiencing thrombosis with IG therapy. Patients with preexisting kidney disease and/or volume depletion, especially in patients with advancing age or a diagnosis of diabetes, are at increased risk of developing acute renal tubular necrosis with IG therapy. Renal insufficiency reported with IG therapy is frequently linked to high sucrose concentration of some IG agents. Overall, differences in presence of IgA, sugar and sodium content and osmolarity between the IG agents has little effect on efficacy but may have significant impact on safety, especially in different patient populations.<sup>109</sup> Table 5 provides a summary of the safety information available for the IG agents, according to package labeling.

**Table 5. Safety of the IG Agents<sup>39,110</sup>**

<b>Contraindications</b>	History of anaphylactic or severe systemic reactions to human immunoglobulin. IgA deficient patients with antibodies to IgA and a history of hypersensitivity.
<b>Black Box Warnings</b>	<p>Thrombosis may occur with immune globulin intravenous (IGIV) products. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors.</p> <p>Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.</p>
<b>Warnings &amp; Precautions</b>	<ul style="list-style-type: none"> <li>• Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.</li> <li>• IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have medications such as epinephrine available immediately to treat any acute severe hypersensitivity reactions.</li> <li>• Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure.</li> <li>• Hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia can occur in patients receiving IGIV therapy.</li> </ul>

	<ul style="list-style-type: none"> <li>• Aseptic meningitis syndrome (AMS) has been reported with IGIV treatments, especially with high doses or rapid infusion.</li> <li>• Hemolytic anemia can develop subsequent to treatment with IGIV products. Monitor patients for hemolysis and hemolytic anemia.</li> <li>• Monitor patients for pulmonary adverse reactions (Transfusion-related acute lung injury [TRALI]). If transfusion-related acute lung injury is suspected, test the product and patient for antineutrophil antibodies.</li> <li>• Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.</li> </ul>
<b>Drug Interactions</b>	<ul style="list-style-type: none"> <li>• Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, rubella, and varicella.</li> <li>• Passive transfer of antibodies may confound the results of serological testing.</li> </ul>
<b>Special Populations</b>	<ul style="list-style-type: none"> <li>• <b>Pregnancy:</b> Use in pregnant women has not been evaluated. Use in pregnant women only if clearly needed.</li> <li>• <b>Geriatric Use:</b> In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse at the minimum infusion rate practicable.</li> <li>• <b>Pediatric Use:</b> Safety and effectiveness in the pediatric population have not been established</li> </ul>
<b>Adverse Events</b>	
<b>Bivigam</b>	The most common adverse reactions to BIVIGAM (reported in $\geq 5\%$ of clinical study subjects) were headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, and lethargy.
<b>Carimune NF</b>	<p>Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as 1-2 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. 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.</p> <p>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. Arthralgia, myalgia, and transient skin reactions (such as rash, erythema, pruritus, urticaria, eczema or dermatitis) have also been reported.</p>
<b>Flebogamma DIF</b>	The most common adverse reactions (reported in $\geq 5\%$ of clinical trial subjects) were headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion site reactions and pain in extremities.
<b>Gamastan S/D</b>	Local pain and tenderness at the injection site, urticaria, and angioedema may occur. Anaphylactic reactions, although rare, have been reported following the injection of human immune globulin preparations. Anaphylaxis is more likely to occur if GamaSTAN S/D is given intravenously; therefore, GamaSTAN S/D must be administered only intramuscularly.
<b>Gammagard</b>	<p>The most common adverse reactions observed in <math>\geq 5\%</math> of patients were:</p> <p>PI:</p> <p>Intravenous Administration: Headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur.</p> <p>Subcutaneous Administration: Infusion site (local) event, headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.</p> <p>MMN:</p> <p>Headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain,</p>

	<p>and pain in extremity.</p> <p>Serious adverse reactions which occurred in the clinical trials were aseptic meningitis, pulmonary embolism, and blurred vision.</p>
<b>Gammaagard S/D</b>	<p>The most common adverse reactions observed in <math>\geq 5\%</math> of patients during the clinical trials were headache, nausea, chills, fatigue, pyrexia, upper abdominal pain, diarrhea, back pain, infusion site pain, hyperhidrosis and flushing.</p> <p>Severe adverse reactions reported postmarketing include renal failure, thrombotic events (myocardial infarction, cerebrovascular accidents, and pulmonary embolism), anaphylactic shock, aseptic meningitis and hemolysis.</p>
<b>Gammaked</b>	<p>The most common adverse reactions observed in <math>\geq 5\%</math> of patients were:</p> <p>PI:</p> <p>Intravenous Administration: Headache, cough, injection site reaction, nausea, pharyngitis, urticarial</p> <p>Subcutaneous Administration: Infusion site reaction, headache, fatigue, arthralgia, pyrexia</p> <p>ITP: Headache, vomiting, fever, nausea, back pain, rash</p> <p>CIDO: Headache, fever, chills, hypertension, rash, nausea, asthenia</p> <p>Serious adverse reactions which occurred in the clinical trials were an exacerbation of autoimmune pure red cell aplasia in one subject and pulmonary embolism in one subject with a history of pulmonary embolism.</p>
<b>Gammaplex</b>	<p>PI: The most common adverse reactions reported in <math>&gt;5\%</math> of clinical trial subjects were headache, pyrexia, nasal congestion/edema, fatigue, nausea, hypertension, rash, hypotension, infusion site reaction, vomiting, myalgia, chills, tachycardia, chest pain/discomfort, pain, dizziness, malaise, dysuria, and dry skin.</p> <p>Chronic ITP: The most common adverse reactions reported in <math>&gt;5\%</math> of clinical trial subjects were headache, vomiting, nausea, pyrexia, pruritus, dehydration, and arthralgia</p>
<b>Gamunex-C</b>	<p>The most common adverse reactions observed in <math>\geq 5\%</math> of patients were:</p> <p>PI:</p> <p>Intravenous Administration: Headache, cough, injection site reaction, nausea, pharyngitis, urticarial</p> <p>Subcutaneous Administration: Infusion site reaction, headache, fatigue, arthralgia, pyrexia</p> <p>ITP: Headache, vomiting, fever, nausea, back pain, rash</p> <p>CIDO: Headache, fever, chills, hypertension, rash, nausea, asthenia</p> <p>Serious adverse reactions which occurred in the clinical trials were an exacerbation of autoimmune pure red cell aplasia in one subject and pulmonary embolism in one subject with a history of pulmonary embolism.</p>
<b>Hizentra</b>	<p>The most common adverse reactions observed in <math>\geq 5\%</math> 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</p>
<b>Hyqvia</b>	<p>The most common adverse reactions observed in clinical trials in <math>&gt;5\%</math> of subjects were: local reactions, headache, antibody formation against recombinant human hyaluronidase (rHuPH20), fatigue, nausea, pyrexia, and vomiting.</p>
<b>Octagam</b>	<p>5%: Most common adverse reactions with an incidence of <math>&gt; 5\%</math> during a clinical trial were headache and nausea.</p> <p>10%: The most common adverse reactions reported in greater than 5% of subjects during a clinical trial were headache, fever and increased heart rate</p>
<b>Privigen</b>	<p>PI: The most common adverse reactions, observed in <math>&gt;5\%</math> 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.</p> <p>Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature</p>

Chronic ITP: The most common adverse reactions, observed in >5% of study subjects, were headache, elevated body temperature, positive direct antiglobulin test (DAT), anemia, nausea, epistaxis, vomiting, blood bilirubin unconjugated increased, blood bilirubin conjugated increased, blood total bilirubin increased, hematocrit decreased, and blood lactate dehydrogenase increased. A serious adverse reaction was aseptic meningitis

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## Summary

Both subcutaneous and intravenous immunoglobulin therapy are indicated in the treatment of primary immunodeficiency syndromes. The agents may also be used in the treatment of idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Kawasaki syndrome and in the prevention of secondary infection in patients with chronic lymphocytic leukemia in addition to a number of off-label bacterial/viral infections and various auto-immune and inflammatory diseases. The single intramuscular immunoglobulin agent is indicated as prophylaxis of Hepatitis A infection, Measles or Varicella. The FDA recommends IG therapy be prioritized to treat disease conditions known to respond to IGIV therapy and off-label use be strictly limited. Clinical guidelines for use of immunoglobulin recommend IG therapy in all patients with absent or deficient antibody production.

Based on the available clinical evidence, different IG agents are equally efficacious in terms of improving clinical outcomes in patients with immunodeficiencies and neurologic disorders. Adverse events reported with IG therapy tend to be mild and uncommon, occurring in less than 10% of patients. Injection site reactions (pain, swelling) are more common with subcutaneous IG therapy and systemic reactions (headache, flu-like symptoms) are more common with intravenous IG therapy. Rare but serious adverse events (anaphylaxis, thrombosis, renal failure) have been reported with IG therapy and treatment should be limited in patients with IgA deficiency, patients with elevated serum viscosity, patients with preexisting kidney disease or volume depletion and in geriatric and pediatric patient populations. Overall, choice of therapeutic IG agent, administration type and dosing regimen requires assessment and periodic re-evaluation of the risks and benefits for each individual patient.

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