



Immune Globulins

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS^{1,2,3,4,5,6,7,8,9,10,11,12,13}

Drug	Manufacturer	Indications
Intravenous		
Bivigam™	Biotest Pharmaceuticals Corporation	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency
Carimune NF, Nanofiltered®	CSL Behring LLC	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ Immune Thrombocytopenic Purpura
Flebogamma® DIF 5% and 10%	Instituto Grifols, SA	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency
Gammagard® S/D	Baxter Bioscience	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ B-cell Chronic Lymphocytic Leukemia ▪ Immune Thrombocytopenic Purpura ▪ Kawasaki Syndrome
Gammaplex®	Bio Products Laboratory	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ Immune Thrombocytopenic Purpura
Octagam®	OCTAPHARMA Pharmazeutika Produktionsges.m.B.H.	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency
Privigen®	CSL Behring AG	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ Immune Thrombocytopenic Purpura
Intravenous or Subcutaneous		
Gammagard® Liquid	Baxter Bioscience	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ Multifocal Motor Neuropathy
Gammaked™	Grifols Therapeutics, Inc. (distributed by Kedrion Biopharm)	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ Immune Thrombocytopenic Purpura ▪ Chronic Inflammatory Demyelinating Polyneuropathy
Gamunex,® Gamunex-C®	Grifols Therapeutics, Inc.	<ul style="list-style-type: none"> ▪ Primary Humoral Immunodeficiency ▪ Immune Thrombocytopenic Purpura ▪ Chronic Inflammatory Demyelinating Polyneuropathy
Subcutaneous		
Hizentra®	CSL Behring AG	<ul style="list-style-type: none"> ▪ Primary Immune Deficiency
Vivaglobin®	CSL Behring GmbH	<ul style="list-style-type: none"> ▪ Primary Immune Deficiency

OVERVIEW

Deficiency in the body's ability to fight infections through the humoral immune process predisposes an individual to significant morbidity and possible death from bacterial and viral insult. Under normal circumstances, the body produces a variety of immunoglobulin (e.g. antibody) isotypes – Immune globulin A (IgA), Immune globulin G (IgG), and Immune globulin M (IgM). Deficiency of one isotype may be observed with deficiencies of the other isotypes. IgG deficiencies in particular increases an individual's susceptibility to a host of infections. Primary antibody deficiencies, which accounts for nearly 50 percent of the 150 diseases falling under the primary immunodeficiency disease (PIDD) umbrella, has been characterized based on the presence or absence of B cells as well as the quantity and quality of an individual's IgG pool.¹⁴ B cells are integral to the body's humoral immune system by producing antibodies used to opsonize and neutralize foreign antigens, particularly bacterial and viral agents. If the B cell reservoir is impaired, the production of sufficient quantities of functional antibodies (Ab) is affected. Low numbers of immune globulin and/or antibodies of substandard quality require therapeutic intervention through the delivery of exogenous immune globulin preparations. Despite such varied phenotypic presentations, the continued hallmark of treatment for these diseases is the supplementation of immune globulin via either intravenous or subcutaneous means.

Table 1 outlines the various phenotypic categorizations of PIDD as offered by the American Academy of Allergy, Asthma, and Immunology (AAAAI).¹⁵

		IgG			
		Quantity/Quality			
		Absent/Absent	Low/Low	Normal/Low	Low/Normal
B cell	Absent	Category I <ul style="list-style-type: none"> ▪ Agamma-globulinemia ▪ SCID 			
	Present		Category II <ul style="list-style-type: none"> ▪ Hyper IgM ▪ CVID ▪ NEMO deficiency 	Category III <ul style="list-style-type: none"> ▪ Specific Ab Deficiency ▪ NEMO deficiency ▪ Subclass deficiency with specific antibody defect 	Category IV <ul style="list-style-type: none"> ▪ Transient hypogammaglobulinemia of infancy ▪ Primary hypogammaglobulinemia

Table 1. Phenotypic categories of primary immunodeficiency disease. Adapted from Stiehm, et al. 2010.¹⁶

In addition to its use in PIDD, exogenous immune globulin product has been FDA approved for use in certain neurologic disorders (multifocal motor neuropathy, MMN; chronic inflammatory demyelinating polyneuropathy, CIDP) and other diseases (immune thrombocytopenic purpura, ITP; Kawasaki syndrome; B-cell chronic lymphocytic leukemia).¹⁷

Therapeutic immune globulin is prepared from pooled plasma obtained from between 15,000 and 60,000 healthy donors (1,000 to 10,000 Source Plasma units) at plasma donation centers in the United States.^{18,19} The product provides exogenous immune globulin type G (IgG) antibodies. Pooling aids in offering broader coverage for a wide variety of antigens. Each FDA approved product is prepared using a slightly different

isolation and purification method. A frequently used method involves a cold alcohol (ethanol) fractionation process which subjects the plasma lysate to a series of sequential purification steps to isolate the immune globulin from the various other plasma factors, such as Factor VIII and Factor IX.

Ig products are produced via such means that reduce the risk of viral exposure. Each product has validated their production methods to ensure the low risk of transmission of the viruses outlined in Table 2. The FDA issued guidance to assist manufacturers with ensuring the safety of their respective products.²⁰

	Fractionation						Exchange Chromatography					Filtration				
	Cohn-Oncley Conn-Oncrey cold ethanol	Kistler & Nitschman	Cold Alcohol	Octanoic Acid	Ethanol – fatty alcohol / pH precipitation	Ion	DEAE-Sephadex	Anion	Caprylate precipitation, filtration	Chromatography, unspecified	Nanofiltration	Cloth	Depth	Ultra-filtration	Solvent/detergent treatment	
Intravenous																
Bivigam	x										x ^b				x	
Carimune NF, Nanofiltered		x									x		x			
Flebogamma DIF 5% and 10%			x			x					x ^a					
Gammagard S/D	x															
Gammaplex		x					x									
Gamunex																
Octagam		x								x				x		
Privigen			x	x				x								
Intravenous or Subcutaneous																
Gammagard Liquid	x					x					x ^b					
Gammaked	x								x			x	x			
Gamunex-C			x					x	x	x		x	x			
Subcutaneous Only																
Hizentra			x	x				x			x		x			
Vivaglobin					x											

Table 2. Production methods.²¹ Adapted from Characteristics of Immune Globulin Products Used to Treat Primary Immunodeficiency Diseases, 2013 March. ^aSequential nanofiltration (35 and 20 nm); ^b35 nm.

Immune globulin product selection should be guided by patient specific characteristics. Renal insufficiency, insulin resistance, diabetes, congestive heart failure, and previous product tolerance should guide product selection. Table 3 outlines the variety of additives in each of the products and the relative comorbid conditions that may be impacted by the use of the product. The greatest number of adverse reactions from the use of Ig have been logged as a result of patients switching between products.²² AAAI and Clinical Immunology Society both support the use of individualized patient characteristic consideration and direct physician consultation in all situations of product selection.²³

Selection of product is largely a function of matching patient characteristics with product properties. With the availability of both intravenously- and subcutaneously-administered products, physicians have a broader repertoire from which to choose for their patients. A recently published study that looked at almost 3,200 patients receiving immune globulin in the home demonstrated that the subcutaneous route was preferentially chosen for individuals over the age of 65.²⁴ It is important to consider the appropriate utilization of donated plasma products due to the overall limited resource from which to harvest it. A recent article attempts to address this issue by proposing a preliminary framework for prioritizing the use of therapeutic immune globulin for various indications.²⁵ Managing demand with supply utilizing evidence-based means works to ensure prudent use of such a resource.

	Liquid	Lyophilized	Sugar Content	Sodium Content	Osmolarity/ Osmolality (mOsm/kg)	pH	IgA Content (mcg/mL)				
Intravenous											
Bivigam	x		no added sugars	0.100 – 0.140 M NaCl	< 510	4.0 – 4.6	≤ 200				
Carimune NF, Nanofiltered		x	1.67 gm sucrose ^α per gram of protein	< 20 mg NaCl per gram protein		6.4 – 6.8	720				
					NS			498	690	882	1074
					D5W			444	636	828	1020
					SW			192	384	576	768
Flebogamma DIF	5%	x	none	trace amounts	240 – 370	5.0 – 6.0	Average: < 3 Spec. value: < 50				
	10%						Average: < 3 Spec. value: < 10				
Gammagard S/D	5%		x	20 mg/mL glucose	8.5 mg/mL NaCl	6.8 ± 0.4	≤ 1				
	10%		x	40 mg/mL glucose	17 mg/mL NaCl		≤ 2.2				
Gammaplex	x		5% D-sorbitol (polyol)	30 – 50 mmol/L	460 – 500	4.6 – 5.1	Average: < 4 Spec. value: < 10				
Octagam	x		100 mg/mL maltose	≤ 30 mmol/L	310 – 380	5.1 – 6.0	< 100				
Privigen	5%	x	none	trace amounts	isotonic (320)	4.8	≤ 25				
	10%										
Intravenous or Subcutaneous											
Gammagard Liquid (IV, subQ)	x		no added sugars	no added sodium	240 – 300	4.6 – 5.1	37				
Gammaked (IV, subQ)	x		none	trace amounts	258	4.0 – 4.5	46				
Gamunex-C (IV, subQ)	x		none	trace amounts	258	4.0 – 4.5	46				
Subcutaneous Only											
Hizentra	x		none	trace amounts (≤10 mmol/L)	380	4.6 – 5.2	≤ 50				
Vivaglobin	x			0.3% NaCl	nr						

Table 3. Physicochemical properties. NaCl, sodium chloride; nr, not reported; NS, normal saline; D5W, 5% dextrose in water; SW, sterile water. Adapted from Characteristics of Immune Globulin Products Used to Treat Primary Immunodeficiency Diseases; March, 2013.²⁶

^αSucrose does not require compensatory changes to insulin regimens; excreted unchanged in urine.²⁷

Treatment Guidelines

The AAAI released a list of eight guiding principles in December 2011 to support the safe and effective use of therapeutic immunoglobulin.²⁸

Principle	Description
1. Indication	IVIG is FDA indicated for use in primary immunodeficiency where antibody production is absent or deficient
2. Diagnoses	Primary immunodeficiency has varied phenotypic manifestations. IVIG is indicated and recommended for the following clinical situations: A. Primary immune defects with absent B cells. B. Primary immune defects with hypogammaglobulinemia and impaired specific antibody production. C. Primary immune defects with normogammaglobulinemia and impaired specific antibody production.
3. Frequency of Treatment	Once a diagnosis is confirmed, interruption of treatment places the patient at significant risk. IVIG administration should occur at every 3 – 4 week intervals to ensure adequate coverage. Due to patient specific factors, shorter intervals may need to be considered.
4. Dose	IVIG indicated for PI is supported by initial starting doses of 400 – 600 mg/kg every 3 – 4 weeks. Alternate regimens are not supported by clinical literature.
5. IgG Trough Levels	Interpretation of trough levels are only applicable in a subset of patients whose condition is characterized by low quantities of IgG levels. For patients with sufficient quantities of IgG but who have impaired quality, trough levels are not correlated to clinical benefit. Trough levels as a rule should be maintained above 500 mg/dL.
6. Site of Care	Clinical characteristics and stability of the patient within a particular regimen should guide the decision for where IVIG is administered.
7. Route	The use of the subcutaneous (subQ) versus intravenous (IV) route to administer immunoglobulin therapy relies on a variety of patient characteristics. Some benefit of subQ administration may be afforded to patients with poor venous access as well as those with difficult to control adverse reactions using the IV route.
8. Product	IVIG is not an interchangeable product. Product selection relies heavily on clinical discretion to match the appropriate product to the patient while considering various patient factors, including comorbidities.

Table 4. The AAAAI's Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency.²⁹

PHARMACOLOGY^{30,31,32,33,34,35,36,37,38,39,40,41,42}

Commercially available immune globulins supply IgG antibodies capable of opsonizing and neutralizing a wide host of bacterial and viral agents thus augmenting the patient's ability to fight foreign offenders. Additional immune globulin subtypes may be present in the formulations that may interact with erythrocytes and other immune cells thereby altering the activity of these cells. These secondary mechanisms of action have not been fully elucidated.

PHARMACOKINETICS^{43,44,45,46,47,48,49,50,51,52,53,54,55}

Drug	Dose	Bioavailability (%)	Elimination Half-life (days)	Mean Trough (mg/dL)
Intravenous				
Bivigam, IV	300 – 800 mg/kg/4 weeks	n/a	33.5	1106
Carimune NF, Nanofiltered	nr	n/a	nr	nr
Flebogamma DIF 5% and 10%	496 mg/kg/4 weeks	n/a	37	87.7
Gammagard, IV	455 mg/kg/4 weeks	n/a	35	1030
Gammagard Liquid				
Gammagard S/D	460 mg/kg	n/a	37.7	1186
Gammaked	n/a	n/a	n/a	n/a
Gammaplex	468 mg/kg/4 weeks	n/a	5.96	nr
Gamunex-C	100 – 600 mg/kg	n/a	35.74	958, IV 1140, subQ
Octagam	300 – 600 mg/kg	n/a	40.7	763.5
Privigen	200 – 714.3 mg/kg/4 weeks	n/a	45.4	1000
Subcutaneous				
Gammagard, subQ	183 mg/kg/week	nd	nd	1202
Hizentra, subQ	228 mg/kg/week	nd	nd	1448
Vivaglobin, subQ	165 mg/kg/week	73%	nd	1064

nd = no data

CONTRAINDICATIONS/WARNINGS^{56,57,58,59,60,61,62,63,64,65,66,67,68}

All intravenous immune globulin products contain a black box warning of acute renal dysfunction and failure. Geriatric individuals over the age of 65 are at an increased risk. Administration should proceed at the minimum infusion rate practical.

Anaphylaxis and severe hypersensitivity are significant risks particularly for IgA deficient individuals who possess antibodies to IgA. Medications such as epinephrine should be immediately available. All patients receiving immune globulin for the first time, who are switching from one product to another, or who have not received the immune globulin for at least eight weeks should be monitored in a clinical setting for signs of fever, chills, nausea, vomiting, and shock.

Intravenous products may cause hyperproteinemia due to increased serum viscosity and may result in hyponatremia. Thromboembolic events have been reported.⁶⁹ Monitor patients, particularly those individuals at risk of hyperviscosity.

Transfusion-related acute lung injury may occur as a result of immune globulin therapy. Evaluate patients with suspected lung injury for antineutrophil antibodies (ANA).

Hemolytic anemia is a risk of immune globulin therapy. Risk factors include blood type (non-O serotypes) and high doses.

Subcutaneous products, unless specifically indicated, must not be injected directly into a blood vessel.

Aseptic meningitis syndrome has been reported with immune globulin products, particularly with rapid infusion or high doses.

Therapeutic immune globulin products are isolated from human plasma and may pose a risk to the patient of exposure to infectious agents such as viruses and, theoretically, prions.

Volume overload may be a risk when large volumes of lower concentration intravenous immune globulin solutions are administered.

Privigen is contraindicated in individuals with hyperprolinemia due to the presence of L-proline, a stabilizer.

CONTRAINDICATIONS

All immune globulin products are contraindicated in individuals with a history of severe anaphylaxis to such preparations and in individuals with known antibodies to IgA with selective immunoglobulin A deficiency (IgA < 0.05 gm/L).

Gammaplex is contraindicated in patients with a hereditary intolerance to fructose or infants and neonates with non-established sucrose or fructose tolerance.

DRUG INTERACTIONS

Immune globulin products should not be mixed or co-administered with any other products.

Lyophilized products should only be reconstituted with the solutions outlined in the package inserts.

Exogenous immune globulin may alter an individual's response to live virus vaccines such as measles, mumps, rubella, and varicella. Serological test results may be confounded.

Octagam contains maltose which may interfere with blood glucose test units that do not employ a glucose-specific method of testing.

ADVERSE EFFECTS^{70,71,72,73,74,75,76,77,78,79,80,81,82}**In Adults**

Drug	Number of Infusions -- Number of Subjects	Injection site/ Infusion reaction # (rate)	Number (Rate) of infusions with adverse event							
			Headache	GI Disorder, Diarrhea, etc.	Fatigue	Rash/ Urticaria	Abdominal Pain/ Discomfort	Arthralgia	Nausea	Tachycardia
Intravenous										
Bivigam	746 63	5 (0.007)	115 (0.154)	nr	59 (0.079)	nr	nr	nr	8 (0.011)	nr
Carimune NF	nr	nr	(0.02)	nr	nr	x	nr	x	nr	nr
Flebogamma DIF	nr	nr	x	nr	nr	nr	nr	x	x	x
Gammagard liquid	1812 61	nr	94 (0.052)	12 (0.007)	33 (0.018)	6 (0.003)	nr	5 (0.003)	17 (0.009)	nr
Gammaplex	703 50	nr	53 (0.075)	nr	9 (0.013)	nr	nr	nr	7 (0.01)	nr
Gamunex-C	825 nr	nr	57 (0.069)	nr	nr	5 (0.06)	nr	nr	31 (0.038)	nr
Privigen	771 55	nr	56 (0.073)	nr	nr	nr	4 (0.005)	nr	10 (0.013)	nr
Subcutaneous										
Gammagard liquid	2294 47	55 (0.024)	31 (0.014)	3 (0.001)	11 (0.005)	nr	nr	nr	7 (0.003)	11 (0.005)
Gamunex-C	725 nr	24 (0.75)	4 (0.13)	nr	2 (0.063)	nr	nr	2 (0.063)	nr	nr
Hizentra	2264 49	1322 (0.584)	32 (0.014)	6 (0.003)	4 (0.002)	nr	3 (0.001)	3 (0.001)	4 (0.002)	nr
Vivaglobin	3656	1787 (0.49)	59 (0.016)	3 (0.001)	nr	9 (0.002)	2 (0.001)	nr	9 (0.002)	2 (0.001)

Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Rate is reported in parentheses.

SPECIAL POPULATIONS

Pediatrics

Gammaplex is not recommended for use in children of any age due to lack of safety and efficacy data.

Only three pediatric patients with Primary humoral immunodeficiency (PHI) I (two children between the ages of six and 10, and one child 16 years old) were included in the clinical evaluation of Flebogamma 10% DIF. This number of subjects is too small to establish safety and efficacy in the pediatric population.

Bivigam has been studied in children with primary humoral immunodeficiency (PHI) over six years of age. No differences in dosing requirements were determined.

Gammagard Liquid and Gammagard S/D are indicated as replacement therapy for primary humoral immunodeficiency (PI) in pediatric patients two years of age or older. Efficacy and safety of Gammagard S/D in pediatric patients with chronic immune thrombocytopenic purpura (ITP) has not been established

Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI (pivotal study). There were no apparent differences in the safety and efficacy profiles as compared to those in adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen have not been established in pediatric patients with PI who are under the age of three. The safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of fifteen.

Gammaked and Gamunex-C IV : Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that vomiting was more frequently reported in pediatrics (three of 18 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels.

Gammaked and Gamunex-C subcutaneous (SC): was evaluated in only three pediatric subjects (age range 13-15) with PI. This number of pediatric subjects was too small for separate evaluation of pharmacokinetics and safety to determine whether they respond differently from adults. Efficacy and safety in pediatric patients using the SC route of administration have not been established.

Hizentra in both the weekly dosing schedule and the biweekly dosing schedule have safety and effectiveness data in the pediatric age groups two to 16, as supported by evidence from adequate and well-controlled studies. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and effectiveness in children under the age of two has not been established.

Vivaglobin was evaluated in one study in six children (ages five through 11) and four adolescents (ages 13 through 16). In another study, Vivaglobin was evaluated in 16 children (ages three through 11) and six adolescents (ages 13 through 16). There were no differences in the safety and efficacy profiles as compared with adult subjects. No pediatric-specific dosing requirements were necessary to achieve the desired serum IgG levels. Divide doses greater than 15 mL and infuse into a maximum of three simultaneous sites for children weighing less than 45 kg (99 pounds). The safety and efficacy of Vivaglobin were not studied in pediatric subjects under two years of age.

Administration of Carimune® in pediatric patients with acute or chronic Immune Thrombocytopenic Purpura did not reveal any pediatric-specific hazard.

Octagam 5% liquid was evaluated in 11 pediatric subjects (age range six – 16 years). There were no obvious differences observed between adults and pediatric subjects with respect to pharmacokinetics, efficacy and safety. No pediatric specific dose requirements were necessary to achieve the desired serum IgG levels.

Geriatrics

For individuals over the age of 65, or for any patients at risk of developing renal insufficiency, it is advised that the recommended dose is not exceeded. The product should be infused at the minimum practical infusion rate.

Pregnancy

No human data is available. Immune globulin should be used only if benefit exceeds risk.

Hepatic/Renal Impairment

Individuals at risk for renal insufficiency are at increased risk for renal complications with the use of immune globulin.

DOSAGES ^{83,84,85,86,87,88,89,90,91,92,93,94,95}

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
General Guidance, intravenous					<ul style="list-style-type: none"> ▪ Refer to each product's package insert for special considerations for each product ▪ Use caution in pre-existing renal insufficiency; ensure patients are not volume depleted ▪ Administer at minimum infusion rate practical for patients at risk of renal dysfunction or thrombotic events ▪ Do not infuse or mix with other medications; administer via dedicated line ▪ Doses are in body weight
Bivigam, intravenous	PI	300 – 800 mg/kg every 3-4 weeks	0.5 mg/kg/min for first 10 minutes	Increase every 20 min (if tolerated) by 0.8 mg/kg/min up to 6 mg/kg/min	<ul style="list-style-type: none"> ▪ 10% vial, 50 mL ▪ 10% vial, 100 mL
Carimune NF, Nanofiltered, intravenous	PI	400 – 800 mg/kg every 3-4 weeks	0.5 mg/kg/min for first 10 minutes	Increase every 30 min (if tolerated) by 1 mg/kg/min up to max 3 mg/kg/min	<ul style="list-style-type: none"> ▪ 3 gm vial, lyophilized ▪ 6 gm vial, lyophilized ▪ 12 gm vial, lyophilized
	ITP	Induction therapy: 400 mg/kg on 2-5 consecutive days	0.5 mg/kg/min for first 10 minutes	Increase every 30 min (if tolerated) by 1 mg/kg/min up to max 3 mg/kg/min	
		<ul style="list-style-type: none"> ▪ Only two consecutive doses are required if the initial platelet count response to first two doses is adequate (30-50,000/μL) ▪ For chronic ITP, if platelet counts fall to < 30,000 L or there is significant bleeding, patient may be given a 400 mg/kg dose as a single infusion. Dose may be increased to 800 – 1,000 mg/kg if response is inadequate. 			
		<ul style="list-style-type: none"> ▪ In PI treatment naive patients, the first dose must be given as a 3% immunoglobulin solution; subsequent doses may be given at higher concentrations if tolerated ▪ Administer at minimum infusion rate practical for patients at risk of renal dysfunction or thrombotic events; do not infuse at a rate greater than 2 mg/kg/min ▪ Recommended concentration for ITP is 6% 			
Flebogamma DIF, intravenous	PI	300 – 600 mg/kg every 3-4 weeks	1 mg/kg/min	Increase to (if tolerated) a max of 8 mg/kg/min	<ul style="list-style-type: none"> ▪ 5% vial, 10 mL ▪ 5% vial, 50 mL ▪ 5% vial, 100 mL ▪ 5% vial, 200 mL ▪ 5% vial, 400 mL ▪ 10% vial, 50 mL ▪ 10% vial, 100 mL ▪ 10% vial, 200 mL

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Gammagard Liquid, <i>intravenous</i>	PI	300 – 600 mg/kg every 3 - 4 weeks based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min) for 30 min	Increase up to 5 mL/kg/hr (8 mg/kg/min) every 30 minutes if tolerated	<ul style="list-style-type: none"> ▪ 10% vial, 300 mL ▪ 10% vial, 200 mL ▪ 10% vial, 100 mL ▪ 10% vial, 50 mL ▪ 10% vial, 25 mL ▪ 10% vial, 10 mL
	MMN	0.5 – 2.4 gm/kg per month based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min)	Infusion rate may be advanced to 5.4 mL/kg/hr (9 mg/kg/min) if tolerated	
	<ul style="list-style-type: none"> ▪ Indicated for 2 years of age and older ▪ MMN, multifocal motor neuropathy 				
Gammagard S/D, <i>intravenous</i>	PI	300 – 600 mg/kg every 3-4 weeks	5%: 0.5 mL/kg/hr 10%: 0.5 mL/kg/hr	5%: may increase gradually as tolerated to a maximum of 4 mL/kg/hr 10%: may increase gradually as tolerated to a maximum of 8 mL/kg/hr	<ul style="list-style-type: none"> ▪ 2.5 gm ▪ 5 gm ▪ 10 gm ▪ 2.5 gm vial with set ▪ 5 gm vial with set ▪ 10 gm vial with set
	ITP	1 gm/kg for a maximum of 3 doses on alternate days			
	CLL	400 mg/kg every 3-4 weeks			
	KS	Single dose of 1 gm/kg, OR One daily dose of 400mg/kg on four consecutive days			
	<ul style="list-style-type: none"> ▪ KS, Kawasaki syndrome; administer concomitant aspirin therapy of 80-100 mg/kg/day in four divided doses ▪ Begin therapy for Kawasaki syndrome within 7 days of fever onset ▪ A maximum infusion rate of 3.3 mg/kg/min should be used in patients at risk for renal dysfunction or thrombotic complications. 				
Gammaked, <i>intravenous</i>					<ul style="list-style-type: none"> ▪ 1 gm / 10 mL vial ▪ 2.5 gm / 25 mL vial ▪ 5 gm / 50 mL vial ▪ 10 gm / 100 mL vial ▪ 20 gm / 200 mL vial

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Gammaplex, <i>intravenous</i>	PI	300 – 800 mg/kg every 3-4 weeks	0.5 mg/kg/min for (0.01 mL/kg/min) for 15 minutes	Increase up to max of 4 mg/kg/min (0.08 mL/kg/min)	<ul style="list-style-type: none"> ▪ 5% vial, 50 mL ▪ 5% vial, 100 mL ▪ 5% vial, 200 mL
	ITP	1 gm/kg for 2 consecutive days	0.5 mg/kg/min for (0.01 mL/kg/min) for 15 minutes	Increase up to max of 4 mg/kg/min (0.08 mL/kg/min)	
	<ul style="list-style-type: none"> ▪ Insufficient data exists on the efficacy of Gammaplex using a low dose regimen (400 mg/kg per day for five consecutive days) in ITP 				
Gamunex, <i>intravenous</i> Gamunex-C, <i>intravenous</i>	PI	300 – 600 mg/kg every 3-4 weeks	1 mg/kg/min	8 mg/kg/min	<ul style="list-style-type: none"> ▪ 10% vial, 10 mL ▪ 10% vial, 50 mL ▪ 10% vial, 100 mL ▪ 10% vial, 200 mL ▪ 1 gm / 10 mL vial ▪ 2.5 gm / 25 mL vial ▪ 5 gm / 50 mL vial ▪ 10 gm / 100 mL vial ▪ 20 gm / 200 mL vial
	ITP	2 gm/kg	1 mg/kg/min	8 mg/kg/min	
	CIDP	Loading dose: <ul style="list-style-type: none"> ▪ 2 gm/kg ▪ Maintenance: 1 gm/kg every 3 weeks 	2 mg/kg/min	8 mg/kg/min	
	<ul style="list-style-type: none"> ▪ Contains glycine to manage isotonicity 				
Octagam, <i>intravenous</i>	PI	200 – 800 mg/kg every 3-4 weeks	0.5 mg/kg/min for the first 30 min	Increase to 1 mg/kg/hr for 30 min; may increase by 0.5 mg/kg/hr up to max of 3.3 mg/kg/min	<ul style="list-style-type: none"> ▪ 5% vial, 20 mL ▪ 5% vial, 50 mL ▪ 5% vial, 100 mL ▪ 5% vial, 200 mL ▪ 5% vial, 500 mL
Privigen, <i>intravenous</i>	PI	200 – 800 mg/kg every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase up to max of 8 mg/kg/min (0.08 mL/kg/min)	<ul style="list-style-type: none"> ▪ 10% vial, 400 mL ▪ 10% vial, 200 mL ▪ 10% vial, 100 mL ▪ 10% vial, 50 mL
	ITP	1 gm/kg for two consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase up to max of 8 mg/kg/min (0.08 mL/kg/min)	

Dosages (continued)

Drug	Dose			Availability	
	Dx	Dose	Initial		Maintenance
SUBCUTANEOUSLY ADMINISTERED PRODUCTS					
Hizentra, <i>subcutaneous</i>		Initial Weekly Dose: $\frac{\text{Previous IGIV dose (in grams)}}{\text{No. of weeks between IGIV doses}} \times 1.53$			<ul style="list-style-type: none"> ▪ Vial sizes: <ul style="list-style-type: none"> – 1 gm / 5 mL vial – 2 gm / 10 mL vial – 4 gm / 20 mL vial ▪ Single-use, tamper-evident vial ▪ Preservative-free ▪ Latex-free ▪ Room temperature
		<p><i>Additional notes:</i></p> <ul style="list-style-type: none"> ▪ Administer first dose one week after receiving a regularly scheduled IVIG infusion ▪ Hizentra may be administered after the patient has received IVIG infusions at regular intervals for at least 3 months ▪ Adjust the dose to achieve a serum IgG trough level that is approximately 290 mg/dL higher than the last trough level during prior IGIV therapy. ▪ Divide doses over 15 mL into multiple administration sites ▪ Infuse via CADD pump ▪ Rotate administration sites weekly (abdomen, thighs, upper arms, and/or lateral hip). May use up to 4 injection sites simultaneously; minimum 2 inches between sites. ▪ Infusion volume – For the first infusion, up to 15 mL per injection site. This may be increased to 20 mL per site after the fourth infusion and to a maximum of 25 mL per site as tolerated. ▪ Infusion rate – For the first infusion, up to 15 mL/hr per site. This may be increased, to a maximum of 25 mL/hr per site as tolerated. The maximum flow rate may not exceed a total of 50 mL/hr for all sites combined ▪ Must NOT be administered intravenously 			
Vivaglobin, <i>subcutaneous</i>		100 – 200 mg/kg body weight weekly			<ul style="list-style-type: none"> ▪ Vial sizes: <ul style="list-style-type: none"> – 3 mL (box of 10) – 10 mL – 10 mL (box of 10) – 20 mL – 20 mL (box of 10) ▪ Preservative-free ▪ Refrigerated
		<p><i>Additional notes:</i></p> <ul style="list-style-type: none"> ▪ Allow to reach ambient room temp prior to administration ▪ If previously receiving IVIG: <ul style="list-style-type: none"> ▪ administer first dose one week after receiving a regularly scheduled IVIG infusion ▪ multiply previous IVIG dose by 1.37 then divide by previous administration interval to get weekly subQ dose ▪ Adjust dose to achieve target serum IgG trough level (≥ 500 mg/dL) ▪ Divide doses over 15 mL into multiple administration sites ▪ Infuse via CADD pump ▪ Rotate administration sites weekly (abdomen, thighs, upper arms, and/or lateral hip) ▪ Must NOT be administered intravenously 			

Dosages (continued)

Drug	Dose				Availability
	Dx	Dose	Initial	Maintenance	
Gammagard Liquid, <i>subcutaneous</i>	PI	<p><u>Multiply:</u> Previous IGIV dose (in grams) x 1.53 Then divide by the number of weeks between intravenous doses</p>	<p>≥ 40 kg BW:</p> <ul style="list-style-type: none"> ▪ 30mL/site; ▪ 20 mL/hr/site <p>< 40 kg BW:</p> <ul style="list-style-type: none"> ▪ 20 mL/site; ▪ 15 mL/hr/site 	<p>≥ 40 kg BW:</p> <ul style="list-style-type: none"> ▪ 30mL/site; ▪ 20 - 30 mL/hr/site <p>< 40 kg BW:</p> <ul style="list-style-type: none"> ▪ 15 - 20 mL/site; ▪ 20 mL/hr/site 	<ul style="list-style-type: none"> ▪ 10% vial, 300 mL ▪ 10% vial, 200 mL ▪ 10% vial, 100 mL ▪ 10% vial, 50 mL ▪ 10% vial, 25 mL ▪ 10% vial, 10 mL
Gamunex-C, <i>subcutaneous</i>	PI	<p><u>Multiply:</u> Previous IGIV dose (in mg/kg) x 1.37 Then divide by the number of weeks between intravenous doses</p>	20 mL/hr/site	Not determined	<ul style="list-style-type: none"> ▪ 1 gm / 10 mL vial ▪ 2.5 gm / 25 mL vial ▪ 5 gm / 50 mL vial ▪ 10 gm / 100 mL vial ▪ 20 gm / 200 mL vial
<ul style="list-style-type: none"> ▪ May not be administered subcutaneously for ITP 					

CLINICAL TRIALS**Search Strategy**

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

subcutaneous – treatment naïve

In a six-month prospective, open-label, multicenter study, a total of 18 patients diagnosed with PI who were immune globulin therapy naïve were evaluated for safety and efficacy of initiating subcutaneous IgG (SCIG) with Vivaglobin.⁹⁶ All patients were required to have baseline IgG levels less than 500 mg/dL (average, 356 mg/dL; standard deviation [SD], 128). The patients were subjected to a loading phase of five consecutive days of 100 mg/kg/day. Subsequent maintenance doses were self-infused subcutaneously at

home utilizing a 100mg/kg/week regimen (24 weeks). Efficacy was assessed by the achievement of IgG trough levels greater than 500 mg/dL on day 12. Ninety-four percent of participants achieved this endpoint [0.727 – 0.999; 95% Confidence Interval (CI)]. Clinical significance is unable to be determined as it is unknown the nature of the participants underlying condition (i.e. impaired Ab quality or isolated low quantity). An annualized infection rate was determined to be 3.946 infections/patient/year using the intent-to-treat (ITT) population. Since the study was single-armed, a generalization of the results to the broader population are difficult. Secondary outcomes evaluating health quality of life utilized the SF-36 (ages 14 years and older) and CHQ-PF50. Mean improvement in these scores was observed in the domains of general health, vitality, and social functioning in the younger group; similar domains improved with the older group – global health, physical functioning, and role/social limitations.

subcutaneous – therapeutic switch

A 40-week prospective, open-label, multicenter, single-arm, Phase III study, enrolled 51 patients with PI.⁹⁷ Participants were switched from their current IV or subQ regimens to weekly subcutaneous infusions of Hizentra at equivalent doses. Primary efficacy was measured as IgG levels prior to next infusion. IgG trough levels maintained similar concentrations between both the pre-study and efficacy portion of the study [7.49 (SD, 1.570) and 8.10 (SD, 1.340), respectively]. Secondary efficacy was determined by the rate of serious bacterial infections (SBI). No SBI were identified during the efficacy period. For non-SBI infections, participants experienced a rate of 5.18 infections/patient/year (4.305-6.171; 95% CI). No serious adverse events were reported. Given the study design, extrapolation cannot be done to determine superiority.

A similarly structured study with 18 children and five adolescents was performed using Hizentra.⁹⁸ Again, no SBI were reported during the efficacy period and the overall infection rate was similar to the previous study with a rate of 4.77 infections/patient/year for the children and 5.18 infections/patient/year for the adolescent group. Three participants experienced serious adverse events (AE); two other recipients disenrolled from the study due to two other AEs.

Forty-nine participants ages three to 77 years of age with a diagnosis of PI were enrolled in a multi-center, prospective, open-label study. The initial study period consisted of IV treatment with Gammagard liquid followed by a transition to subcutaneous administration with the same product at 137% of the IV dose. All subcutaneous doses were administered weekly. At the end of the assessment period, the mean trough IgG level was 1,202 mg/dL which is above the generally accepted level of 500 mg/dL. The overall infection rate was similar to other studies at 4.1 infections/patient/year however three serious acute bacterial infections did occur resulting in a rate of 0.067 SBI/patient/year. Minor localized infusion site reactions were observed, but in general, the product was reasonably well tolerated.

The limitation of all three studies continues to be the unknown subclassification of the participants' primary immunodeficiency. Given the overall low incidence of this umbrella of disease, it would be difficult to account for and study all subclassifications to minimize confounding elements inherent to the variability of the phenotypes.

SUMMARY

Therapeutic immune globulin products are integral in the management of primary immunodeficiency disease (PID). Pooled IgG affords patients humoral immune support via exogenous means thereby decreasing patient risk of severe bacterial and viral infections. Multiple IgG products are available for selection. The final product selection for a given patient should consider diagnosis, past product usage/tolerability, time since last dose, individual risk factors for adverse events, comorbid conditions and the product's physicochemical properties. Ensuring the use of the product for approved indications ensures that the most vulnerable patients have access to a limited resource.

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