Immune Globulins
Therapeutic Class Review (TCR)

July 7, 2022

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
Intravenous		
Asceniv™[1]	ADMA	▪ Primary humoral immunodeficiency
Bivigam®[2]	ADMA	▪ Primary humoral immunodeficiency
Flebogamma® DIF 5% and 10%[3,4]	Grifols	▪ Primary (inherited) immunodeficiency ▪ Chronic primary immune thrombocytopenia (10% only)
Gammagard® S/D[5]	Baxalta	▪ Primary humoral immunodeficiency ▪ Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia ▪ Chronic idiopathic thrombocytopenic purpura ▪ Prevention of coronary artery aneurysms associated with Kawasaki syndrome
Gammaplex® 5% and 10%[6,7]	Bio Products Laboratory	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenic purpura
Octagam® 5% and 10%[8,9]	Octapharma	▪ Primary humoral immunodeficiency (5% only) ▪ Chronic immune thrombocytopenic purpura (10% only) ▪ Dermatomyositis (10% only)
Panzyga®[10]	Octapharma/ Pfizer	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenia ▪ Chronic inflammatory demyelinating polyneuropathy
Privigen®[11]	CSL Behring	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenic purpura ▪ Chronic inflammatory demyelinating polyneuropathy (Limitation of use: maintenance therapy has not been studied > 6 months)
Intravenous or Subcutaneous		
Gammagard® Liquid[12]	Baxalta	▪ Primary humoral immunodeficiency ▪ Multifocal motor neuropathy
Gammaked™[13]	Kedrion Biopharm*	▪ Primary humoral immunodeficiency ▪ Idiopathic thrombocytopenic purpura (IV use only) ▪ Chronic inflammatory demyelinating polyneuropathy (IV use only)
Gamunex®-C[14]	Grifols	▪ Primary humoral immunodeficiency ▪ Idiopathic thrombocytopenic purpura (IV use only) ▪ Chronic inflammatory demyelinating polyneuropathy (IV use only)
Subcutaneous		
Cutaquig®[15]	Octapharma/ Pfizer	▪ Primary humoral immunodeficiency
Cuvitru®[16]	Shire/Takeda	▪ Primary humoral immunodeficiency
Hizentra®[17]	CSL Behring	▪ Primary immune deficiency ▪ Maintenance therapy in patients with chronic inflammatory demyelinating polyneuropathy
immune globulin 10%/recombinant human hyaluronidase (Hyqvia®)[18]	Baxalta	▪ Primary immune deficiency†
Xembify®[19]	Grifols	▪ Primary humoral immunodeficiency

* Gammaked and Gamunex-C are manufactured by Grifols Therapeutics and are identical; Kedrion Biopharma has an agreement with Grifols to market the product under a private label name (Gammaked).

† Safety and efficacy of chronic use of recombinant human hyaluronidase in Hyqvia have not been established in conditions other than primary immune deficiency.

OVERVIEW

Primary immunodeficiencies are inherited disorders of the immune system that predispose an individual to an increased rate and severity of infections, as well as other possible sequelae such as autoimmune diseases and certain malignancies. Primary immune deficiencies are categorized as humoral (or antibody) deficiencies, cellular deficiencies, innate immune disorders, or a combination of deficiencies. The hallmark of humoral immunodeficiency is recurrent bacterial infections of the upper and lower respiratory tract.[20] 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 infections. 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 1 isotype may be observed with deficiencies of the other isotypes. IgG deficiencies, in particular, increase an individual's susceptibility to a host of infections. Primary antibody deficiencies, which account for approximately 50% of the diseases categorized under the primary immunodeficiency disease (PIDD) umbrella, have been characterized based on the presence or absence of B cells, as well as the quantity and quality of an individual's IgG pool.[21,22] The 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).[23,24]

		IgG			
		Quantity/Quality			
		Absent/Absent	**Low/Low**	**Normal/Low**	**Low/Normal**
B cell	**Absent**	**Category I** ▪ Agamma-globulinemia ▪ SCID			
	Present		**Category II** ▪ Hyper IgM ▪ CVID ▪ NEMO deficiency	**Category III** ▪ Specific Ab Deficiency ▪ NEMO deficiency ▪ Subclass deficiency with specific antibody defect	**Category IV** ▪ Transient hypogamma-globulinemia of infancy ▪ Primary hypogamma-globulinemia

Table 1. Phenotypic categories of primary immunodeficiency disease. Adapted from Stiehm, et al. 2010.[25]

Ab = antibody, CVID = common variable immunodeficiency, NEMO = NF-kappa B Essential Modulator, SCID = severe combined immunodeficiency

In addition to its use in PIDD, exogenous immune globulin product has been approved by the United States (US) Food and Drug Administration (FDA) for use in certain neurologic disorders (multifocal motor neuropathy [MMN], chronic inflammatory demyelinating polyneuropathy [CIDP]) and other diseases (idiopathic thrombocytopenic purpura [ITP]/immune thrombocytopenia, Kawasaki syndrome, B-cell chronic lymphocytic leukemia, and dermatomyositis).[26,27,28]

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 US.[29] The product

provides exogenous immune globulin type G (IgG) antibodies. Pooling aids in offering broader coverage for a wide variety of antigens.

Immune globulin 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.[30] Preparation for each product differs in purification, including production methods related to fractionation, exchange chromatography, and filtration. Detailed information on each is available in individual product labeling and the Immune Deficiency Foundation.[31]

Immune globulin product selection should be guided by patient-specific characteristics. The route of administration is an important consideration. The subcutaneous route is as efficacious as the intravenous route for the treatment of primary immunodeficiencies and may be useful in patients who have experienced or are at an increased risk for complications related to the intravenous immune globulin therapy.[32,33] Different immune globulin products also use different additives to stabilize their products. Some of these additives may be detrimental to patients with certain concurrent medical conditions. For example, products stabilized with sucrose may be inappropriate for diabetic patients while products stabilized with certain amino acids may need to be avoided in patients with certain metabolic conditions. The sodium content may also be a consideration in patients with heart failure. 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.[34,35,36,37] The AAAAI and the Immune Deficiency Foundation both support the use of individualized patient characteristic considerations and direct physician consultation in all situations of product selection.[38,39,40]

Product selection 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. It is important to consider the appropriate utilization of donated plasma products due to the overall limited resource from which to harvest the product. An article attempts to address this issue by proposing a preliminary framework for prioritizing the use of therapeutic immune globulin for various indications.[41] 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								
Asceniv		x		no added sugars	0.1–0.14 mol/L NaCl	not reported	4–4.6	≤ 200
Bivigam		x		no added sugars	0.1–0.14 mol/L NaCl	≤ 510	4–4.6	≤ 200
Flebogamma DIF	5%	x		none	trace amounts	240–370	5–6	Average: < 3
	10%							Average: < 3 Spec. value: < 100
Gammagard S/D	5%		x	20 mg/mL glucose	8.5 mg/mL NaCl	636	6.8 ± 0.4	≤ 1
	10%		x	40 mg/mL glucose	17 mg/mL NaCl	1,250		≤ 2.2
Gammaplex	5%	x		5% D-sorbitol (polyol)	30–50 mmol/L	460–500	4.6–5.1	Average: < 4
	10%	x		none	< 30 mmol/L	280 (typically)	4.9-5.2	Spec. value: < 20
Octagam	5%	x		100 mg/mL maltose	≤ 30 mmol/L	310–380	5.1–6	< 100
	10%	x		90 mg/mL maltose	≤ 30 mmol/L	310–380	4.5–5	Average: 106
Panzyga		x		no added sugars	trace amounts	240–310	4.5–5	Average: 100
Privigen	10%	x		none	trace amounts	320 (isotonic)	4.8	≤ 25
Intravenous or Subcutaneous								
Gammagard Liquid (IV, SC)		x		no added sugars	no added sodium	240–300	4.6–5.1	37
Gammaked (IV, SC)		x		none	trace amounts	258	4–4.5	46
Gamunex-C (IV, SC)		x		none	trace amounts	258	4–4.5	46
Subcutaneous Only								
Cutaquig		x		79 mg/mL maltose	≤ 30 mmol/L	310–380	5–5.5	≤ 600
Cuvitru		x		no added sugars	no added sodium	280–292	4.6–5.1	80
Hizentra		x		none	trace amounts (≤ 10 mmol/L)	380	4.6–5.2	≤ 50
Hyqvia*		x		no added sugars	no added sodium	240-300	4.6–5.1	37
Xembify		x		none	trace amounts	280-404	4.1-4.8	≤ 70

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, April 2020 and Differentiating Characteristics and Evaluating Intravenous and Subcutaneous Immunoglobulin, June 2019.[42,43,44,45,46]

* In addition to the immune globulin 10% preparation, Hyqvia also contains a vial of recombinant human hyaluronidase genetically engineered utilizing Chinese Hamster Ovary (CHO) cells. The purified hyaluronidase has an approximate pH of 7.4 and an osmolality of 290 to 350 mOsm. Each vial contains 160 units (U)/mL of recombinant human hyaluronidase with 8.5 mg/mL sodium chloride, 1.78 mg/mL, sodium phosphate dibasic dihydrate, 1 mg/mL human albumin, 1 mg/mL edentate disodium dihydrate, 0.4 mg/mL calcium chloride dihydrate, and 0.17 mg/mL sodium hydroxide added for pH adjustment.

The AAAAI released a list of 8 guiding principles in December 2011 to support the safe and effective use of therapeutic immunoglobulin.[47] They have also published an evidence review on the use of immune globulin in human disease.[48]

Principles	Description
Indication	IVIG is FDA indicated for use in primary immunodeficiency where antibody production is absent or deficient
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
Frequency of Treatment	Once a diagnosis is confirmed, interruption of treatment places the patient at significant risk IVIG administration should occur at every 3 to 4 week intervals to ensure adequate coverage Due to patient-specific factors, shorter intervals may need to be considered
Dose	IVIG indicated for PI is supported by initial starting doses of 400 to 600 mg/kg every 3 to 4 weeks; alternate regimens are not supported by clinical literature
IgG Trough Levels	Interpretations 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
Site of Care	Clinical characteristics and stability of the patient within a particular regimen should guide the decision for where IVIG is administered
Route	The use of the subcutaneous (SC) versus intravenous (IV) route to administer immunoglobulin therapy relies on a variety of patient characteristics. Some benefit of SC administration may be afforded to patients with poor venous access, as well as those with difficult to control adverse reactions using the IV route
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 8 guiding principles for effective use of IVIG for patients with primary immunodeficiency.[49]
IVIG = intravenous immune globulin; PI = primary humoral immunodeficiency

PHARMACOLOGY[50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68]

Commercially available immune globulins supply IgG antibodies capable of opsonizing and neutralizing a wide variety of bacterial pathogens, 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[69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87]

Doses listed are those studied in pharmacokinetic analysis and may not reflect current dosing recommendations. Refer to the Dosages table for current dosage and administration.

Drug	Dose	Bioavailability (%)	Elimination Half-life (days)	Mean Trough (mg/dL)
Intravenous				
Asceniv	300–800 mg/kg/4 weeks	n/a	28.47–39.7	954–1,152
Bivigam	300–800 mg/kg/4 weeks	n/a	33.5	1,106
Flebogamma DIF 5% and 10%	496 mg/kg/4 weeks	n/a	37	87.7
Gammagard Liquid, IV	455 mg/kg/4 weeks (median)	n/a	35	1,030
Gammagard S/D	460 mg/kg	n/a	37.7	1,186
Gammaplex 5% and 10%	324–799 mg/kg/4 weeks	n/a	4.625–6.96	nr
Gamunex-C, IV Gammaked, IV	100–600 mg/kg	n/a	35.74	780
Octagam	300–600 mg/kg	n/a	40.7	763.5
Panzyga	300–600 mg/kg/4 weeks	n/a	6.2–8.7	nr
Privigen	200–714.3 mg/kg/4 weeks	n/a	45.4	1,000
Subcutaneous				
Cutaquig	Individualized by trough IgG	nr	nr	610–2,400
Cuvitru	Individualized by trough IgG	nr	nr	1,474
Gammagard, SC	183 mg/kg/week*	nr	nr	1,202
Gamunex-C, SC Gammaked, SC	total weekly IVIG dose multiplied by 1.37 and divided by previous dosing interval†	nr	nr	1,140
Hizentra, SC	228 mg/kg/week	nr	nr	1,448
Hyqvia	134–160 mg/kg/week	93.3‡	59.3	1,077
Xembify	total weekly IVIG dose multiplied by 1.37 and divided by previous dosing interval	nr	nr	1,245

IVIG = intravenous immune globulin; nr = not reported

* The subcutaneous dose of Gammagard liquid required to provide an area under the curve (AUC) exposure that is not inferior to IV Gammagard liquid is 137% of the intravenous dose for subjects 12 years of age and over.

† The subcutaneous doses of Gammaked and Gamunex-C required to provide an AUC exposure that is not inferior to their respective IV administrations is calculated by multiplying the total IV dose by 1.37 and then dividing by the weekly interval (3 or 4) of the previous IV administration frequency.

‡ Relative to IVIG.

CONTRAINDICATIONS/WARNINGS[88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106]

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).

Cutaquig and Hizentra are contraindicated in patients with known hypersensitivity to polysorbate 80. While polysorbate 80 is used in the manufacturing process for Asceniv, Bivigam, Cuvitru, Hyqvia, Gammagard Liquid, Gammagard S/D, and Gammaplex, the labeling for these products do not include hypersensitivity to polysorbate 80 as a contraindication for use.

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

Hyqvia is contraindicated in patients with known hypersensitivity to hyaluronidase, recombinant human hyaluronidase, human albumin within the hyaluronidase solution, or any excipients.

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

Warnings

Labels for all intravenous, subcutaneous, and intramuscular immune globulin products were updated in 2013 to include a boxed warning regarding the risk of thrombosis with these products. Risk factors for thrombosis include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in patients without identified risk factors. In patients with thrombosis risk factors, administration should occur at the minimum dose and infusion rate that is practical and adequate hydration should be ensured prior to administration. Patients should be monitored for hyperviscosity and signs or symptoms of thrombosis; patients should be instructed to immediately report symptoms of thrombosis. In patients at risk for hyperviscosity, an assessment of blood viscosity should be considered.

All intravenous immune globulin products contain a warning, including boxed warnings, of acute renal dysfunction and failure. Geriatric individuals over the age of 65 are at an increased risk, and this can occur more commonly in products containing sucrose. Administration should proceed at the minimum infusion rate practical and these products should be discontinued if renal function deteriorates. Assessment of renal function and volume status is prudent prior to initiation as well as periodically, as clinically appropriate. Labeling for Cuvitru, Cutaquig, Hizentra, and Xembify, which are administered subcutaneously, also carry a warning for renal dysfunction and/or renal failure.

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 1 product to another, or who have not received the immune globulin for at least 8 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.[107] Monitor patients, particularly those individuals at risk of hyperviscosity.

Acute intravascular hemolysis and hemolytic anemia are risks of immune globulin therapy. Risk factors include blood type (non-O serotypes) and high doses. Consider appropriate laboratory testing in higher risk individuals.

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

Aseptic meningitis syndrome (AMS) has been reported with immune globulin products via both the intravenous and subcutaneous routes, particularly with female patients, rapid infusion, or high doses. Onset is typically within several hours to 2 days following administration.

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. This also applies to unknown or emerging viruses and other pathogens. There is a theoretical risk for the transmission of Creutzfeldt-Jakob disease (CJD) agent, although no cases of transmission due to immune globulin products have been identified. Production methods, as described above, are used to minimize this risk.

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

Transfusion-related acute lung injury (TRALI), characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever, may occur within 1 to 6 hours following transfusion. Evaluate patients with suspected lung injury for antineutrophil antibodies (ANA). Management consists of oxygen therapy with ventilatory support.

Subcutaneous infusion of immune globulins into or around an infected area can result in the spread of a localized infection.

Elevated systolic blood pressure (systolic ≥ 180 mmHg and/or diastolic > 120 mmHg) have occurred during or shortly following Panzyga or Privigen administration. Elevations were resolved or significantly improved within hours of observation alone or after oral antihypertensive therapy. This occurred more often in patients with a history of hypertension. Blood pressure should be monitored prior to, during, and following the infusion.

Patients receiving Hyqvia may develop non-neutralizing antibodies to the recombinant human hyaluronidase component. The potential exists for these antibodies to cross-react with endogenous PH20, which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may interfere with fertilization in humans; the clinical significance of these antibodies is not known.

False positive serological results may occur following an infusion due to the transitory rise of various passively-transferred antibodies. These products can lead to various abnormal laboratory results, including a false positive direct or indirect antiglobulin (Coombs') test or false positive beta-D-glucans (used for diagnosis of fungal infections).

Do not administer immune globulins subcutaneously in patients with ITP because of the risk of hematoma formation.

As Flebogamma 5% and 10% DIF contain sorbitol, both contain a warning regarding the risk of hereditary fructose intolerance (HFI). Neither product should be administered to a patient with HFI.

As Cutaquig contains maltose, certain blood glucose testing systems may incorrectly interpret the maltose as glucose, resulting in falsely increased glucose levels. As a result, a glucose-specific method should be utilized when assessing glucose levels in Cutaquig-treated patients.

Certain components used in the packaging Gammagard S/D contain latex; therefore, use with caution in patients with sensitivity to rubber latex.

DRUG INTERACTIONS[108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126]

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

Admixtures of Hyqvia with other drug solutions have not been evaluated. Hyqvia should not be mixed or administered with any other products.

ADVERSE EFFECTS[127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145]

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										
Asceniv	793 -- 59	nr	21 (2.6)	3 (0.4)	9 (1.1)	nr	nr	nr	5 (0.6)	nr
Bivigam	746 -- 63	5 (0.007)	115 (0.154)	nr	59 (0.079)	nr	nr	nr	8 (0.011)	nr
Flebogamma DIF 5%*	nr -- 46 (adults) 24 (pediatrics)	13	21.7 – 42	8 – 8.7	reported	6.5	reported	< 5	< 5 – 8	25
Flebogamma DIF 10%*	nr	6.5	52.2 – 60.3	5.2	< 5	reported	< 5	reported	8.7 – 20.7	5.2 – 23.9
Gammagard S/D	nr	nr	(0.051 – 0.109)	3 (0.014)	(0.01 – 0.052)	1 (0.003)	3 (0.014)	reported	(0.015 – 0.066)	reported
Gammagard liquid, IV	1,812 -- 61	nr	94 (0.052)	12 (0.007)	33 (0.018)	6 (0.003)	nr	5 (0.003)	17 (0.009)	nr
Gammaplex	703 (5%); nr (10%) -- 50 (5%); 32 – 35 (10%)	nr	53 (0.075) (5%); 4 – 10 (10%)	nr	9 (0.013) (5%); nr (10%)	reported	nr	2 (10%)	7 (0.01) (5%); 3 (10%)	nr

Adverse Effects (continued)

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 *(continued)*										
Gamunex-C, IV Gammaked, IV	825 -- 87	nr	57 (0.069)	nr	nr	5 (0.06)	nr	nr	31 (0.038)	nr
Octagam 5%	654 -- 46	11 (0.02)	62 (0.09)	22 (0.03)	9 (0.01)	8 (0.01)	(0.005 – 0.02)	15 (0.02)	8 (0.01)	reported
Octagam 10%	nr -- 54	nr	25	reported	reported	reported	reported	reported	reported	reported
Panzyga (PI)	700 -- 51	35	21 (0.03)	nr	reported	nr	reported	nr	reported	nr
Panzyga (ITP)	77 -- 40	33 (0.43)	reported	reported	nr	nr	nr	nr	reported	nr
Privigen (PI)	771 -- 55	reported	56 (0.073)	nr	nr	nr	4 (0.005)	nr	10 (0.013)	reported
Privigen (ITP)	114 -- 57		52 (0.456)	nr	nr	nr	nr	nr	8 (0.07)	
Privigen (CIDP)	259 -- 28		19 (0.073)	nr	nr	2 (0.008)	nr	nr	3 (0.012)	

Adverse Effects (continued)

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
Subcutaneous										
Cutaquig	3,956 -- 43	648 (16.4)	10 (0.002)	7 (0.002)	nr	6 (0.001)	nr	3(0.001)	nr	nr
Cuvitru	4,327 -- 74	96 (0.022)	50 (0.012)	5 (0.001)	9 (0.002)	nr	reported	reported†	16 (0.004)	reported
Gammagard liquid, SC	2,294 -- 47	55 (0.024)	31 (0.014)	5 (0.002)	11 (0.005)	nr	9 (0.004)	nr	7 (0.003)	11 (0.005)
Gamunex-C, SC Gammaked, SC	725 -- 32	24 (0.75)	4 (0.13)	nr	2 (0.063)	nr	nr	2 (0.063)	nr	nr
Hizentra (PI)	2,264 -- 49	1,322 (0.584)	32 (0.014)	6 (0.003)	4 (0.002)	nr	3 (0.001)	3 (0.001)	4 (0.002)	nr
Hizentra (CIDP)	4,225 -- 115	103 (0.024)	9 (0.002)	nr	5 (0.001)	nr	nr	5 (0.001)	nr	nr
Hyqvia†	1,129 -- 81	234 (0.21)	40 (0.04)	nr	16 (0.01)	nr	nr	nr	12 (0.01)	nr
Xembify	1,053 -- 49	nr (0.184 to 0.735)	nr	3 (0.003)	nr	nr	nr	nr	nr	reported

Adverse effects data are obtained from Prescribing Information and, therefore, should not be considered comparative or all inclusive. Rate is reported in parentheses. Nr = not reported

* Reported as percentage

† Adverse reaction data in 81 subjects included both adult and pediatric patients. A total of 15 out of 83 subjects who were treated with Hyqvia developed an antibody capable of binding to recombinant human hyaluronidase in the clinical trials. These antibodies were not capable of neutralizing recombinant human hyaluronidase. No temporal association between adverse reactions and the presence of antibodies capable of binding to the Recombinant Human Hyaluronidase could be demonstrated. There was no increase in incidence or severity of adverse reactions in subjects who developed antibodies to Recombinant Human Hyaluronidase and in all subjects, antibody titers decreased despite continued treatment.

SPECIAL POPULATIONS[146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164]

Pediatrics

Asceniv was evaluated in 11 pediatric subjects (6 children < 12 years and 5 adolescents age 12 to 16 years) with primary humoral immunodeficiency (PI). The pharmacokinetics, safety, and effectiveness in adolescent subjects were comparable to adults; however, the pharmacokinetics, safety, and effectiveness data from pediatric subjects younger than 12 years are insufficient. Safety and effectiveness have not been studied in pediatric patients < 3 years of age with PI.

Bivigam has been studied in children with PI over 6 years of age. No differences in dosing requirements were determined. The safety and effectiveness of Bivigam have not been established in pediatric patients with PI who are under the age of 6.

Safety and efficacy of Cutaquig are established in patients 2 to < 17 years of age. In clinical trials, the overall safety and efficacy in pediatrics (n=38) were comparable to data in adults.

Cuvitru is approved for use in patients 2 years of age and older. It was evaluated in 21 patients (age range, 2 to 16 years) with PI and efficacy and safety findings were similar to those found in adults.

Flebogamma 5% DIF has been determined to be efficacious for the prevention of serious bacterial infections in children with PI aged 2 to 16 years. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and efficacy of Flebogamma 5% DIF in pediatric patients below the age of 2 years has not been established.

Only 3 pediatric patients with PI (2 children between the ages of 6 and 10, and 1 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. Flebogamma 10% DIF is approved for the treatment of chronic primary immune thrombocytopenia in patients 2 years of age and older.

Gammagard S/D is indicated as replacement therapy for PI in pediatric patients 2 years of age or older. Clinical studies of Gammagard S/D for the treatment of PI did not include sufficient numbers of subjects who were 16 or under to determine whether they respond differently from adults. Efficacy and safety of Gammagard S/D in pediatric patients with chronic ITP have not been established. Efficacy and safety of Gammagard S/D in pediatric patients with Kawasaki disease have been established with the majority of these patients being under 5 years of age and 20% of these patients under 1 year of age.

The safety and efficacy profiles for children ages 2 and older for Gammagard liquid (IV or SC administration) are similar to adult subjects. Safety and efficacy of Gammagard liquid in patients below the age of 2 have not been established.

Gammaplex 5% is indicated for replacement therapy in patients 2 years of age and older with PI. This is based on data in 31 patients aged 2 to 16 years. It is not indicated in pediatric patients with chronic ITP. While safety has been established in 31 pediatric patients, the number of patients with efficacy data (2 children aged 6 years; 1 aged 12 years) is too small to establish use in this population. Gammaplex 10% is approved for use in pediatric patients ≥ 2 years of age with PI. Data to support this expanded population were derived from a study in 13 pediatric patients with PI; no dose adjustments were necessary to achieve the desired serum IgG levels. Gammaplex 10% is not approved for use in pediatrics with chronic ITP.

Pharmacokinetics, safety, and efficacy of Gamunex-C in PI or SC were similar to those in adults with the exception that vomiting and fever were more frequently reported in pediatrics (3 of 18 subjects in PI IV study for vomiting; 6 of 12 subjects in ITP SC study). No pediatric-specific dose requirements were necessary to achieve serum IgG levels. Gamunex-C SC was evaluated in 14 pediatric subjects (age range, 2 to 16 years) with PI. Gamunex-C is approved for treatment of PI and ITP in pediatrics ages 2 years and older. It is not approved in pediatrics with chronic inflammatory demyelinating polyneuropathy.

Data with Gamunex-C have been extrapolated to Gammaked; it is indicated in pediatrics ages 2 years and older.

Hizentra in both the weekly-dosing schedule and the biweekly-dosing schedule have safety and effectiveness data for PI in the pediatric age groups 2 to 16 years, 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 for PI in children under the age of 2 years have not been established. Safety and effectiveness of Hizentra in pediatric patients with CIDP have not been established.

Safety of Hyqvia in children has not been established.

Panzyga has been found to be safe and effective in PI patients 2 years of age and older based on data in 25 pediatric patients between the ages of 2 and 15 years. Findings were comparable to those observed with adults and no specific dosage adjustments were needed to reach goal serum IgG levels. Use in pediatric patients with ITP and CIDP have 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 3. The safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of 15. The safety and effectiveness of Privigen have not been established in pediatric patients with CIDP.

Octagam 5% liquid was evaluated in 11 pediatric subjects (age range, 6 to 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. The safety and efficacy of Octagam 10% in pediatric patients with chronic ITP and dermatomyositis have not been established.

Xembify was assessed in 14 children ages 2 to 16 years and had efficacy and safety results similar to those seen in adults. Xembify is not approved in children < 2 years old.

Geriatrics

Insufficient numbers of geriatric patients (older than 65 years of age) were enrolled in most trials. While no differences in safety and efficacy were observed in any trial, there are insufficient data to determine whether geriatric patients respond differently than younger subjects. 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

Bivigam and Gammagard S/D are Pregnancy Category C. Asceniv, Cutaquig, Cuvitru, Panzyga, and Xembify have not been assigned a Pregnancy Category based on the Pregnancy and Lactation Labeling Rule (PLLR);

rather, the product labeling includes descriptive information. No human data on Asceniv, Cutaquig, Cuvitru, Panzyga, or Xembify are available to evaluate the drug-associated risk, but immune globulins can cross the placenta after 30 weeks of gestation. Previously assigned Pregnancy Category C, the package inserts for Flebogamma 5% and 10%, Privigen, Gammagard Liquid, Gammaked, Gammaplex 5% and 10%, Gamunex-C, Hizentra, Hyqvia, and Octagam were updated with similar descriptive information in compliance with the PLLR.

Hepatic/Renal Impairment

Individuals at risk for renal insufficiency are at increased risk for renal complications with the use of immune globulin. Renal function monitoring (e.g., serum creatinine, blood urea nitrogen) is recommended for such patients.

DOSAGES[165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183]

Please consult drug labeling for specific dosing adjustment recommendations.

Drug	Dose				Availability/Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
General Guidance, intravenous (IV)	▪ 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 (BW)				
Asceniv, *IV*	PI	300–800 mg/kg every 3–4 weeks	0.5 mg/kg/min for the first 15 minutes	Increase gradually every 15 minutes (if tolerated) up to 8 mg/kg/min	▪ 10% SUV, 50 mL ▪ Refrigerate
Bivigam, *IV*	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	▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ Refrigerate
Flebogamma DIF, *IV*	PI	300–600 mg/kg every 3–4 weeks	0.5 mg/kg/min (5%) or 1 mg/kg/min (10%)	Increase to (if tolerated) a max of 5 mg/kg/min (5%) or 8 mg/kg/min (10%)	▪ 5% SUV, 10 mL ▪ 5% SUV, 50 mL ▪ 5% SUV, 100 mL ▪ 5% SUV, 200 mL ▪ 5% SUV, 400 mL ▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ Room temperature
	ITP	1 gm/kg daily for 2 consecutive days	1 mg/kg/min (10% only)	If tolerated, increase to a max of 8 mg/kg/min (10%)	
Gammagard Liquid, *IV*	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	▪ 10% SUV, 10 mL ▪ 10% SUV, 25 mL ▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ 10% vial, 300 mL ▪ Room temperature or refrigerate
	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	

Dx = diagnosis; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Intravenous (*continued*)					
Gammagard S/D, *IV*	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 (patients who tolerate this rate can be infused with the 10% concentration starting at 0.5 mL/kg/hr) 10%: may increase gradually as tolerated to a maximum of 8 mL/kg/hr	▪ 5 gm SUV ▪ 10 gm SUV ▪ Room temperature or refrigerate
	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 a daily dose of 400 mg/kg on 4 consecutive days			
	▪ Kawasaki syndrome (KS); administer concomitant aspirin therapy of 80–100 mg/kg/day in 4 divided doses ▪ Begin therapy for KS 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				
Gammaplex, *IV*	PI	300–800 mg/kg every 3–4 weeks	0.5 mg/kg/min (0.01 mL/kg/min for 5%; 0.005 mL/kg/min for 10%) for 15 minutes	Increase up to max of 4 mg/kg/min (5%) or 8 mg/kg/min (10%) (0.08 mL/kg/min)	▪ 5% SUV, 100 mL ▪ 5% SUV, 200 mL ▪ 5% SUV, 400 mL ▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ Room temperature or refrigerate
	ITP	1 gm/kg for 2 consecutive days			
	▪ Insufficient data exist on the efficacy of Gammaplex using a low dose regimen (400 mg/kg per day for 5 consecutive days) in ITP				
Gammaked, *IV;* Gamunex-C, *IV*	PI	300–600 mg/kg every 3–4 weeks	1 mg/kg/min	8 mg/kg/min	▪ 1 gm/10 mL SUV ▪ 2.5 gm/25 mL SUV (Gamunex-C only) ▪ 5 gm/50 mL SUV ▪ 10 gm/100 mL SUV ▪ 20 gm/200 mL SUV ▪ 40 gm/400 mL SUV (Gamunex-C only) ▪ Room temperature or refrigerate
	ITP	2 gm/kg	1 mg/kg/min	8 mg/kg/min	
	CIDP	Loading dose: ▪ 2 gm/kg Maintenance: ▪ 1 gm/kg every 3 weeks	2 mg/kg/min	8 mg/kg/min	
	▪ Contains glycine to manage isotonicity				

Dx = diagnosis; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Intravenous (*continued*)					
Octagam, *IV*	PI	5%: 300–600 mg/kg every 3–4 weeks	0.5 mg/kg/min for the first 30 min	Increase to 1 mg/kg/min for 30 min; advance to 2 mg/kg/min for third 30 minutes; may increase up to max of 3.3 mg/kg/min	▪ 5% SUV, 20 mL ▪ 5% SUV, 50 mL ▪ 5% SUV, 100 mL ▪ 5% SUV, 200 mL ▪ 5% SUV, 500 mL ▪ Refrigerate
	chronic ITP	1 gm/kg for 2 consecutive days	1 mg/kg/min	May double infusion rate every 30 minutes up to 12 mg/kg/min	▪ 10% SUV, 20 mL ▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ 10% SUV, 300 mL ▪ Room temperature or refrigerate
	Derma-tomyo-sitis	2 g/kg divided in equal doses given over 2 to 5 consecutive days every 4 weeks	1 mg/kg/min	Up to 4 mg/kg/min	
Panzyga, *IV*	PI	300-600 mg/kg every 3-4 weeks	1 mg/kg/min	Increase up to a max of 14 mg/kg/min	▪ 10% SUV, 10 mL ▪ 10% SUV, 25 mL ▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ 10% SUV, 300 mL ▪ Room temperature or refrigerate
	chronic ITP	1 g/kg daily for 2 consecutive days	1 mg/kg/min	Increase up to a max of 8 mg/kg/min	
	CIDP	Loading dose: 2 g/kg (20 mL/kg), divided into 2 daily doses of 1 g/kg (10 mL/kg) given on 2 consecutive days Maintenance: 1 to 2 g/kg (10 to 20 mL/kg) every 3 weeks divided in 2 doses given over 2 consecutive days	1 mg/kg/min	12 mg/kg/min	
Privigen, *IV*	PI	200–800 mg/kg every 3 to 4 weeks	0.5 mg/kg/min	Increase up to max of 8 mg/kg/min	▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ 10% SUV, 400 mL ▪ Room temperature
	ITP	1 gm/kg for 2 consecutive days	0.5 mg/kg/min	Increase up to 4 mg/kg/min	
	CIDP	Loading dose: ▪ 2 gm/kg in divided doses over 2 to 5 consecutive days Maintenance: ▪ 1 gm/kg administered in 1 to 2 infusions on consecutive days every 3 weeks; use beyond 6 months has not been studied	0.5 mg/kg/min	Increase up to max of 8 mg/kg/min	

Dx = diagnosis; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/ Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Subcutaneous					
Cutaquig, *SC*	PI	Dose should be initially individualized based on pharmacokinetics and clinical response and subsequently by serum IgG trough levels (see Prescribing Information for details; administration frequency ranges from daily up to every 2 weeks) **If switching from IVIG: Multiply** Previous monthly IVIG dose (in grams) x 1.3; then divide by the number of weeks between intravenous doses; to convert the dose (in grams) to milliliters, multiply by 6; If needed, adjust dose based on serum IgG trough level 2 to 3 months after switching to Cutaquig or after the last change in dose **If switching from another SCIG,** maintain the same weekly dosing (in grams) of that was used for the previous SCIG product	First 6 infusions: 15-20 mL/hr/site; maximum is 30 mL/hr *for all sites combined* Maximum volume: 25 mL/site	For infusion 7 and above: 25 mL/hr/site as tolerated; gradual increase, *for all sites combined*, to 50 mL/hr, then to 80 mL/hr, and if tolerated, increase to 100 mL/hr Maximum volume: gradually increase to 40 mL/site Administered using infusion pump by a healthcare professional, caregiver or self-administered by the patient after appropriate training	▪ 16.5% SUV, 6 mL ▪ 16.5% SUV, 10 mL ▪ 16.5% SUV, 12 mL ▪ 16.5% SUV, 20 mL ▪ 16.5% SUV, 24 mL ▪ 16.5% SUV, 48 mL ▪ Room temperature

Dx = diagnosis; IVIG = intravenous immune globulin; SCIG = subcutaneous immune globulin; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/ Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Subcutaneous *(continued)*					
Cuvitru, *SC*	PI	Dose should be initially individualized based on pharmacokinetics and clinical response and subsequently by serum IgG trough levels (see Prescribing Information for details; administration frequency ranges from daily up to every 2 weeks) **If switching from IVIG:** **Multiply:** Previous IVIG dose (in grams) x 1.3; then divide by the number of weeks between intravenous doses; provides initial weekly dose, then adjust by desired frequency; initiate 1 week following prior IVIG dose **If switching from another SCIG,** maintain the same weekly dosing (in grams) of that was used for the previous SCIG product	First 2 infusions ≥ 40 kg BW: ▪ ≤ 60 mL/site; ▪ 10–20 mL/hr/site < 40 kg BW: ▪ ≤ 20 mL/site; ▪ 10–20 mL/hr/site	≥ 40 kg BW: ▪ ≤ 60 mL/site; ▪ ≤ 60 mL/hr/site < 40 kg BW: ▪ ≤ 60 mL/site; ≤ 60 mL/hr/site	▪ 20% SUV , 5 mL ▪ 20% SUV, 10 mL ▪ 20% SUV, 20 mL ▪ 20% SUV, 40 mL ▪ 20% SUV, 50 mL ▪ Room temperature or refrigerated

Dx = diagnosis; IVIG = intravenous immune globulin; SCIG = subcutaneous immune globulin; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Subcutaneous (*continued*)					
Gammagard Liquid, *SC*	PI	**Multiply:** Previous IVIG dose (in grams) x 1.37; then divide by the number of weeks between intravenous doses	≥ 40 kg BW: ▪ 30 mL/site; ▪ 20 mL/hr/site < 40 kg BW: ▪ 20 mL/site; 15 mL/hr/site	≥ 40 kg BW: ▪ 30 mL/site; ▪ 20–30 mL/hr/site < 40 kg BW: ▪ 20 mL/site; 15–20 mL/hr/site	▪ 10% SUV, 10 mL ▪ 10% SUV, 25 mL ▪ 10% SUV, 50 mL ▪ 10% SUV, 100 mL ▪ 10% SUV, 200 mL ▪ 10% SUV, 300 mL
Gammaked, *SC*; Gamunex-C, *SC*	PI	**Multiply:** Previous IVIG dose (in grams) x 1.37; then divide by the number of weeks between IV doses	20 mL/hr/site; multiple simultaneous infusion sites may be utilized; the maximum number of infusion sites is 8 in adults and 6 in children; children should start at a slower infusion rate (see Prescribing Information for weight-based details)	Not determined	▪ 1 gm/10 mL SUV ▪ 2.5 gm/25 mL SUV (Gamunex-C only) ▪ 5 gm/50 mL SUV ▪ 10 gm/100 mL SUV ▪ 20 gm/200 mL SUV ▪ 40 gm/400 mL SUV (Gamunex-C only)
	• May not be administered SC for ITP or CIDP				

Dx = diagnosis; IVIG = intravenous immune globulin; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Subcutaneous (*continued*)					
Hizentra, *SC*	PI	Initial weekly dose: ▪ (Previous IVIG dose [in grams]/ Number of weeks between IVIG doses) x 1.37 ▪ Maintain the same dose if converting from SC immunoglobulin Biweekly (every 2 weeks): ▪ Initiate 1 to 2 weeks after the last infusion or 1 week after last SC dose; administer twice the calculated dose Frequent dosing (2 to 7 times/week): ▪ Initiate 1 week after the last IVIG or SC infusion; divide calculated dose	Up to 15 mL per hour per infusion site in patients; do not exceed a volume of 15 mL per infusion site	Up to 25 mL per hour per infusion site in patients; do not exceed a volume of 25 mL per infusion site	▪ 1 gm/5 mL SUV ▪ 2 gm/10 mL SUV ▪ 4 gm/20 mL SUV ▪ 10 gm/50 mL SUV ▪ 1 gm/5 mL syringe ▪ 2 gm/10 mL syringe ▪ 4 gm/20 mL syringe ▪ Room temperature
	CIDP	▪ Initiate 1 week after the last IVIG infusion ▪ 0.2 gm/kg (1 mL/kg) body weight per week, ▪ A dose of 0.4 gm/kg (2 mL/kg) body weight per week was also safe and effective in the clinical study to prevent CIDP relapse. If worsens, consider increasing to 0.4 g/kg body weight per week. If worsens, consider re-initiating IVIG and discontinue SCIG	Up to 20 mL per hour per site; do not exceed a volume of 20 mL per infusion site	Up to 50 mL per hour per infusion site in patients; do not exceed a volume of 50 mL per infusion site	
	Additional notes: ▪ Must **NOT** be administered intravenously ▪ Hizentra may be administered after the patient has received IVIG infusions at regular intervals for at least 3 months ▪ Infuse via an infusion pump and rotate administration sites weekly (abdomen, thighs, upper arms, and/or lateral hip); may use up to 8 sites simultaneously, minimum 2 inches between sites ▪ Individualize dose based on clinical response and IgG trough levels (detailed recommendations based on serum IgG are available in product labeling)				

Dx = diagnosis; IVIG = intravenous immune globulin; SCIG = subcutaneous immune globulin; SUV = single-use vial

Dosages (continued)

<table>
<tr><th>Drug</th><th>Dose</th><th>Availability/Storage</th></tr>
<tr><td colspan="3">Subcutaneous (continued)</td></tr>
<tr><td>Hyqvia, SC</td><td>
Dosing:
For patients previously treated with another IgG treatment, administer the first dose approximately 1 week after the last infusion of their previous treatment.
Initial Treatment Interval/Ramp-up Schedule:
<table>
<tr><th>Week</th><th>Infusion</th><th>Dose/Interval</th><th>Example:
30 grams/4 weeks</th></tr>
<tr><td>1</td><td>1st infusion</td><td>1-week-dose</td><td>7.5 grams</td></tr>
<tr><td>2</td><td>2nd infusion</td><td>2-week-dose</td><td>15 grams</td></tr>
<tr><td>3</td><td colspan="3">No Infusion</td></tr>
<tr><td>4</td><td>3rd infusion</td><td>3-week-dose</td><td>22.5 grams</td></tr>
<tr><td>5</td><td colspan="3">No Infusion</td></tr>
<tr><td>6</td><td colspan="3">No Infusion</td></tr>
<tr><td>7</td><td>4th infusion
(if required)</td><td>4-week-dose</td><td>30 grams</td></tr>
</table>
For patients switching from IVIG:
▪ Administer Hyqvia at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up
For patients naïve to IgG treatment or switching from another SCIG:
▪ Administer Hyqvia at 300 to 600 mg/kg at 3 to 4 week intervals, after initial ramp up
Administration:
▪ Hyqvia should be administered by a healthcare professional, caregiver or self-administered by the patient after appropriate training
▪ Infusion requires an infusion pump meeting flow rate specifications and a subcutaneous 24-gauge needle set labeled for high flow rates
▪ Suggested sites for infusion are the abdomen and thighs; if 2 infusion sites are used, the 2 infusion sites should be on opposite sides of the body
▪ The 2 components must be infused sequentially, beginning with the Recombinant Human Hyaluronidase, followed by the full dose of Immune Globulin 10% through the same subcutaneous needle set within ~10 minutes of the Recombinant Human Hyaluronidase infusion
▪ Administer the Recombinant Human Hyaluronidase at an initial rate of approximately 1 to 2 mL per minute, or as tolerated
Immune Globulin Infusion Rate:
<table>
<tr><th></th><th colspan="2">First Two Infusions</th><th colspan="2">Subsequent 2 or 3 Infusions</th></tr>
<tr><th></th><th>< 40 kg</th><th>≥ 40 kg</th><th>< 40 kg</th><th>≥ 40 kg</th></tr>
<tr><td>Intervals (minutes)</td><td>Rate per site (mL/ hour)</td><td>Rate per site (mL/hour)</td><td>Rate per site (mL/hour)</td><td>Rate per site (mL/hour)</td></tr>
<tr><td>5-15</td><td>5</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>5-15</td><td>10</td><td>30</td><td>20</td><td>30</td></tr>
<tr><td>5-15</td><td>20</td><td>60</td><td>40</td><td>120</td></tr>
<tr><td>5-15</td><td>40</td><td>120</td><td>80</td><td>240</td></tr>
<tr><td>Remainder of infusion</td><td>80</td><td>240</td><td>160</td><td>300</td></tr>
<tr><td>Remainder of infusion</td><td>80</td><td>240</td><td>160</td><td>300</td></tr>
</table>
</td><td>
▪ Dual-vial unit of 2 SUVs; 1 vial containing immune globulin 10% and 1 vial containing recombinant human hyaluronidase
▪ 2.5 gm (25 mL) IG/200 units (1.25 mL) hyaluronidase
▪ 5 gm (50 mL) IG/400 units (2.5 mL) hyaluronidase
▪ 10 gm (100 mL) IG/800 units (5 mL) hyaluronidase
▪ 20 gm (200 mL) IG/ 1,600 units (10 mL) hyaluronidase
▪ 30 gm (300 mL) IG/ 2,400 units (15 mL) hyaluronidase
▪ Room temperature or refrigerate
</td></tr>
</table>

Dx = diagnosis; IVIG = intravenous immune globulin; SCIG = subcutaneous immune globulin; SUV = single-use vial

Dosages (continued)

Drug	Dose				Availability/Storage
	Dx	Dose	Initial Infusion Rate	Maintenance Infusion Rate	
Subcutaneous (*continued*)					
Xembify, *SC*	PI	When switching from IVIG, multiply the previous IVIG dose (in grams) x 1.37; then divide by the number of weeks between IV doses When switching from another SC formulation, dose should be the same weekly dose For frequent dosing (2 to 7 times per week), divide calculated weekly dose by desired number of times per week	Initial rate not specified; up to 25 mL per hour per infusion site	Up to 25 mL per hour per infusion site (up to 6 sites, most commonly 4 sites)	▪ 20% (1 gm) SUV, 5 mL ▪ 20% (2 gm) SUV, 10 mL ▪ 20% (4 gm) SUV, 20 mL ▪ 20% (10 g) SUV, 50 mL ▪ Room temperature (up to 6 months) or refrigerate

Dx=diagnosis; IVIG = intravenous immune globulin; SUV = single-use vial

Additional dosing details regarding potential measles exposure are outlined in the product labeling.

All products in this review are preservative-free. All products are latex-free, with the exception of Gammagard S/D for IV administration.

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% 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Only clinical trials involving subcutaneous administration of immune globulin for the treatment of primary immunodeficiency are included in this review.

The limitation of all these 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.

Subcutaneous – therapeutic switch

A 40-week prospective, open-label, multicenter, single-arm, phase 3 study, enrolled 51 patients with PI.[184] Participants were switched from their current IV or SC regimens to weekly SC 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, 1.57] and 8.1 [SD, 1.34], respectively). Secondary efficacy was determined by the rate of serious bacterial infections (SBIs). No SBIs were identified during the efficacy period. For non-SBI infections, participants experienced a rate of 5.18 infections/patient/year (95% confidence interval [CI], 4.305 to 6.171). 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 5 adolescents was performed using Hizentra.[185] Again, no SBIs 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); 2 other recipients withdrew from the study due to other AEs.

Forty-nine participants ages 3 to 77 years of age with a diagnosis of PI were enrolled in a multicenter, prospective, open-label study.[186] The initial study period consisted of IV treatment with Gammagard liquid followed by a transition to SC administration with the same product at 137% of the IV dose. All SC 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, 3 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.

A multicenter, prospective, open-label, single-arm study conducted in the US and Canada compared Xembify to Gammunex-C 10% (IVIG, human) in 53 patients ≥ 2 years of age who were receiving IgG replacement infusion (IV or SC) for ≥ 3 months.[187] Following a run-in phase of 3 or 4 months with Gammunex-C 10% IV (depending on prior treatment and including an assessment of this IV phase), the patients entered a SC phase of 24 weeks with Xembify (with a dose adjustment factor of 1.37). No further dose adjustments were made. The primary efficacy endpoint for approval was the rate of SBI, which was 0.05 events per subject-year (upper 99% confidence limit, 0.11), and met the 1 SBI per subject-year rate threshold for efficacy (n=49). The annualized rate of infections of any kind was 2.4 (95% CI, 1.6 to 3.3) and the hospitalization rate due to infections was 0.05 (95% CI, 0.02 to 0.1).

A prospective, open-label, multicenter trial was conducted in the US with 83 patients diagnosed with PIDD. The median age was 35 years (range, 4 to 78 years).[188] All patients had received previous IV immune globulin therapy and 31 of the patients had received prior SC therapy. Planned outcome measures included the rate of infections, adverse reactions, tolerability of the Hyqvia infusions, number of infusion sites per month, and infusion rate. All patients received hyaluronidase subcutaneous infusion. This was followed within 10 minutes by the immune globulin infusion. All patients followed a ramp-up schedule over 3 to 4 weeks to become familiar with the large volumes required for a full 3- or 4-week treatment. Subsequently, all patients continued the 3- or 4-week dosing for the remainder of the trial. After 3 doses at the full volume, a serum IgG trough level was obtained and used to adjust the Hyqvia dose if needed. All subjects who completed the trial received a minimum of 12 infusions at this individually adapted dose. The assessment period for efficacy and safety began after completion of the ramp-up initiation schedule and the length of therapy in the trial ranged from 42 to 507 days. None of the subjects withdrew due to a severe or serious local or systemic

adverse reaction. There were 2 acute SBIs; both were episodes of pneumonia. The annualized rate of acute serious bacterial infections while treated with Hyqvia was 0.025. A total of 78 of the 83 patients receiving Hyqvia (94%) attained the same 3- or 4-week dosing interval as compared to their previous IV immune globulin regimen and the monthly median infusion time was 3.2 hours for the intravenous immune globulin group and 2.64 hours for the Hyqvia group.

SUMMARY

Immune globulin products are derived from the pooled human plasma of thousands of donors. These products are purified to contain 95% to 99% IgG (the major antibody produced by B lymphocytes) with trace amounts of IgA and IgM. While all the products in the class have similar efficacy and safety profiles, they are not considered therapeutically equivalent due to differences in purification methods, the use of different chemical stabilizers, different physiochemical properties, and differences in the recommended route of administration. The primary use for immune globulin therapy is the management of primary immunodeficiency disease (PIDD). Pooled IgG provides patients with passive immunity thereby decreasing the PIDD patient's risk of severe bacterial and viral infections. Immune globulin therapy for the treatment of PIDD is generally considered to be chronic therapy although some patients may be able to stop therapy at some point, according to physician discretion. Other FDA-approved indications for immune globulin therapy are dermatomyositis, idiopathic thrombocytopenic purpura (ITP), multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP), B-cell chronic lymphocytic leukemia, and the treatment of Kawasaki disease. Multiple IgG products, administered intravenously or subcutaneously, are available for selection. The final product selection for a given patient should consider diagnosis, past product usage/tolerability, time since last dose, route of administration, individual risk factors for adverse events, comorbid conditions, and the product's physicochemical properties. Reserving the use of immune globulin products for approved indications or conditions where the benefit has been clearly established and is consistent with clinical guidelines ensures that the most vulnerable patients have access to a limited resource.

REFERENCES

1 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
2 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
3 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
4 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
5 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
6 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
7 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
8 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
9 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
10 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
11 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
12 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
13 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
14 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
15 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
16 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
17 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
18 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
19 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
20 Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015; 136(5): 1186-1205. DOI: 10.1016/j.jaci.2015.04.049. Available at: http://www.aaaai.org/practice-resources/statements-and-practice-parameters. Accessed July 19, 2022.
21 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14: 1-12. Immune Deficiency Foundation. https://primaryimmune.org/publication/healthcare-professionals/idf-clinical-focus-clinical-update-immunoglobulin-therapy. Accessed July 19, 2022.
22 Buckley RH. Immune Deficiency Foundation diagnostic and clinical care guidelines for primary immunodeficiency diseases. 3rd ed. 2015. Available at: https://primaryimmune.org/publication/healthcare-professionals/idf-diagnostic-clinical-care-guidelines-primary. Accessed July 19, 2022.

23 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117: S525–553. DOI: 10.1016/j.jaci.2006.01.015. Available at: https://www.aaaai.org/Practice-Management/Practice-Tools/IVIG-Toolkit. Accessed July 19, 2022.
24 Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017; 139(3S): S1-S46. DOI: 10.1016/j.jaci.2016.09.023. Available at: https://primaryimmune.org/resource/update-use-immunoglobulin-human-disease-review-evidence. Accessed July 19, 2022.
25 Stiehm ER, Orange JS, Ballow M, et al. Therapeutic use of immunoglobulins. Adv Pediatr. 2010; 57: 185–218. DOI: 10.1016/j.yapd.2010.08.005.
26 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117: S525–553. DOI: 10.1016/j.jaci.2006.01.015.
27 Buckley RH. Immune Deficiency Foundation diagnostic and clinical care guidelines for primary immunodeficiency diseases. 3rd ed. 2015. Available at: https://primaryimmune.org/publication/healthcare-professionals/idf-diagnostic-clinical-care-guidelines-primary. Accessed July 19, 2022.
28 Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017; 139(3S): S1-S46. DOI: 10.1016/j.jaci.2016.09.023. Available at: https://primaryimmune.org/resource/update-use-immunoglobulin-human-disease-review-evidence. Accessed July 19, 2022.
29 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14: 1-12. Immune Deficiency Foundation. https://primaryimmune.org/publication/healthcare-professionals/idf-clinical-focus-clinical-update-immunoglobulin-therapy.. Accessed July 19. 2022.
30 FDA. Guidance for industry: safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. 2008 June. Rockville, MD. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf. Accessed July 19, 2022.
31 Immune Deficiency Foundation. Characteristics of immune globulin products used to treat primary immunodeficiency diseases licensed for use in the United States. Towson, MD; Immune Deficiency Foundation; April 2020. Available at: https://primaryimmune.org/publication/characteristics-ig-products-used-treat-pi-licensed-use-us. Accessed July 19, 2022.
32 Immune Deficiency Foundation. Clinical focus on primary immunodeficiencies: subcutaneous immunoglobulin replacement. June 2015. Available at: https://primaryimmune.org/sites/default/files/publications/ClinicalFocus_SCIG_2015_1.pdf. Accessed July 20, 2022.
33 Buckley RH. Immune Deficiency Foundation diagnostic and clinical care guidelines for primary immunodeficiency diseases. 3rd ed. 2015. Available at: https://primaryimmune.org/publication/healthcare-professionals/idf-diagnostic-clinical-care-guidelines-primary. Accessed July 20, 2022.
34 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117: S525–553. DOI: 10.1016/j.jaci.2006.01.015.
35 Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017; 139(3S): S1-S46. DOI: 10.1016/j.jaci.2016.09.023. Available at: https://primaryimmune.org/resource/update-use-immunoglobulin-human-disease-review-evidence. Accessed July 19, 2022.
36 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14:1–12. Immune Deficiency Foundation. Available at: https://primaryimmune.org/publication/healthcare-professionals/idf-clinical-focus-clinical-update-immunoglobulin-therapy. Accessed July 19, 2022.
37 Buckley RH. Immune Deficiency Foundation diagnostic and clinical care guidelines for primary immunodeficiency diseases. 3rd ed. 2015. Available at: https://primaryimmune.org/publication/healthcare-professionals/idf-diagnostic-clinical-care-guidelines-primary. Accessed July 20, 2022.
38 Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006; 117: S525–553. DOI: 10.1016/j.jaci.2006.01.015.
39 Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017; 139(3S): S1-S46. DOI: 10.1016/j.jaci.2016.09.023. Available at: https://primaryimmune.org/resource/update-use-immunoglobulin-human-disease-review-evidence. Accessed July 19, 2022.
40 Orange JS. Clinical update in immunoglobulin therapy for primary immunodeficiency diseases. 2011; 14: 1–12. Immune Deficiency Foundation. https://primaryimmune.org/publication/healthcare-professionals/idf-clinical-focus-clinical-update-immunoglobulin-therapy. Accessed July 19, 2022.
41 Orange JS, Ochs HD, Cunningham-Rundles C. Prioritization of evidenced-based indications for intravenous immunoglobulin. J Clin Immunol. 2013; 33: 1033–1036. DOI: 10.1007/s10875-013-9912-3.
42 Immune Deficiency Foundation. Characteristics of immune globulin products used to treat primary immunodeficiency diseases licensed for use in the United States. Towson, MD; Immune Deficiency Foundation; April 2020. Available at: https://primaryimmune.org/publication/characteristics-ig-products-used-treat-pi-licensed-use-us. Accessed July 19, 2022.
43 Flebogamma 10% DIF [package insert]. Los Angeles, CA; Grifols; Barcelona, Spain; Grifols; September 2019.
44 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
45 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
46 Ness S. Differentiating characteristics and evaluating intravenous and subcutaneous immunoglobulin. Am J Manag Care. 2019; 25: S98-S104.
47 American Academy of Allergy Asthma and Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. December 2011. Available at: https://www.aaaai.org/Practice-Management/Practice-Tools/IVIG-Toolkit. Accessed July 20, 2022.
48 Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017; 139(3S): S1-S46. DOI: 10.1016/j.jaci.2016.09.023. Available at: https://primaryimmune.org/resource/update-use-immunoglobulin-human-disease-review-evidence. Accessed July 19, 2022.
49 American Academy of Allergy Asthma and Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. December 2011. Available at: https://www.aaaai.org/Practice-Management/Practice-Tools/IVIG-Toolkit. Accessed July 20, 2022.
50 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
51 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
52 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
53 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
54 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
55 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
56 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.

57 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
58 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
59 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
60 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
61 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
62 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
63 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
64 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
65 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
66 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
67 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
68 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
69 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
70 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
71 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
72 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
73 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
74 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
75 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
76 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
77 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
78 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
79 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
80 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
81 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
82 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
83 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
84 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
85 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
86 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
87 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
88 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
89 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
90 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
91 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
92 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
93 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
94 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
95 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
96 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
97 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
98 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
99 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
100 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
101 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
102 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
103 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
104 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
105 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
106 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
107 FDA safety communication: new boxed warning for thrombosis related to human immune globulin products. June 10, 2013. Available at: http://primaryimmune.org/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products/. Accessed July 20, 2022.
108 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
109 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
110 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
111 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
112 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
113 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
114 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
115 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
116 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
117 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
118 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
119 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
120 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
121 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
122 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
123 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.

124 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
125 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
126 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
127 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
128 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
129 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
130 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
131 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
132 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
133 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
134 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
135 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
136 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
137 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
138 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
139 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
140 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
141 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
142 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
143 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
144 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
145 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
146 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
147 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
148 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
149 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
150 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
151 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
152 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
153 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
154 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
155 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
156 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
157 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
158 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
159 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
160 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
161 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
162 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
163 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
164 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
165 Asceniv [package insert]. Boca Raton, FL; ADMA; April 2019.
166 Bivigam [package insert]. Boca Raton, FL; ADMA; July 2019.
167 Flebogamma 10% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
168 Flebogamma 5% DIF [package insert]. Barcelona, Spain; Grifols; September 2019.
169 Gammagard S/D [package insert]. Lexington, MA; Baxalta; March 2021.
170 Gammaplex 10% [package insert]. Durham, NC; BPL; September 2019.
171 Gammaplex 5% [package insert]. Durham, NC; BPL; September 2019.
172 Octagam 10% [package insert]. Paramus, NJ; Octapharma; March 2022.
173 Octagam 5% [package insert]. Paramus, NJ; Octapharma; March 2022.
174 Privigen [package insert]. Kankakee, IL; CSL Behring; March 2022.
175 Gammagard Liquid [package insert]. Lexington, MA; Baxalta; March 2021.
176 Gammaked [package insert]. Fort Lee, NJ; Kedrion; June 2018.
177 Gamunex-C [package insert]. Research Triangle Park, NC; Grifols; January 2020.
178 Cuvitru [package insert]. Lexington, MA; Baxalta; September 2021.
179 Hizentra [package insert]. Kankakee, IL; CSL Behring; April 2022.
180 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.
181 Cutaquig [package insert]. New York, NY; Pfizer; November 2021.
182 Panzyga [package insert]. Vienna, Austria; Octapharma USA; January 2021.
183 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
184 Jolles S, Bernatowska E, de Gracia J, et al. Efficacy and safety of Hizentra in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol. 2011; 141(1): 90-102. DOI:10.1016/j.clim.2011.06.002.
185 Borte M, Pac, M, Serban M, et al. Efficacy and safety of Hizentra, a new 20% immunoglobulin preparation for subcutaneous administration, in pediatric patients with primary immunodeficiency. J Clin Immunol. 2011; 31(5): 752-761. DOI: 10.1007/s10875-011-9557-z.
186 Wasserman RL, Melamed I, Kobrynski L, et al. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (Gaammagard Liquid, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. J Clin Immunol. 2011; 31(3): 323-31. DOI: 10.1007/s10875-011-9512-z.
187 Xembify [package insert]. Research Triangle Park, NC; Grifols; August 2020.
188 Hyqvia [package insert]. Lexington, MA; Baxalta; March 2021.