Clinical Policy Title:	immune Globulins
Policy Number:	RxA.143
Drug(s) Applied:	Asceniv™, Bivigam™, Cutaquig®, Cuvitru™, Flebogamma® DIF, Gamastan® S/D, Gammagard® liquid, Gammagard® S/D, Gammaked™, Gammaplex®, Gamunex®-C, Hizentra®, Hyqvia®, Octagam®, Panzyga®, Privigen®, Xembify®
Original Policy Date:	02/07/2020
Last Review Date:	01/17/2022
Line of Business Policy Applies to:	All lines of business

Background

The following are immune globulins requiring prior authorization: Asceniv™, Bivigam™, Cutaquig®, Cuvitru™, Flebogamma® DIF, Gamastan® S/D, Gammagard® liquid, Gammagard® S/D, Gammaked™, Gammaplex®, Gamunex®-C, Hizentra®, Hyqvia®, Octagam®, Panzyga®, Privigen®, Xembify®.

Brand Name	ROA	PI	ITP	CIDP	KS	MMN	CLL	VPPX	DM
Asceniv™	Intravenous	x							
Bivigam™	Intravenous	x							
Cutaquig®	Subcutaneous	x							
Cuvitru™	Subcutaneous	x							
Flebogamma® DIF	Intravenous	x	x (10% only)						
Gamastan® S/D , Gamastan®	Intramuscular							x	
Gammagard® Liquid	Intravenous, Subcutaneous	x				x (Intravenous only)			

Brand Name	ROA	PI	ITP	CIDP	KS	MMN	CLL	VPPX	DM
Gammagard S/D Less IgA	Intravenous	x	x		x		x		
Gammaked™	Intravenous, Subcutaneous	x	x (Intravenous only)	x (intravenous only)					
Gammaplex®	Intravenous	x	x						
Gamunex®-C	Intravenous, Subcutaneous	x	x (Intravenous only)	x (Intravenous only)					
Hizentra®	Subcutaneous	x		x					
Hyqvia®	Subcutaneous	x							
Octagam®	Intravenous	x (5% only)	x (10% only)						x (10 % only)
Panzyga®	Intravenous	x	x	x					
Privigen	Intravenous	x	x	x					
Xembify	Subcutaneous	x							

ROA = route of administration; CIDP = chronic inflammatory demyelinating polyneuropathy; CLL = B-cell chronic lymphocytic leukemia; ITP = idiopathic thrombocytopenic purpura; KS = Kawasaki syndrome; MMN = multifocal motor neuropathy; PI = primary humoral immunodeficiency; VPPX = viral prophylaxis (for hepatitis A, measles, varicella, rubella); DM = Dermatomyositis

Refer to full prescribing information for specific dosage instructions. Dosage must be individualized and is highly variable depending on the nature and severity of the disease and on the individual patient response (e.g., serum IgG trough levels). There is no absolute maximum dosage of immune globulin or hyaluronidase.

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
Asceniv™	PI	300 to 800 mg/kg intravenously every 3 to 4 weeks	Not applicable
Bivigam™	PI	Initial: 300 to 800 mg/kg intravenously every 3 to 4 weeks Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response	Not applicable
Cutaquig®	PI	Switching from Intravenous immune globulin (IGIV) in patients treated regularly with IGIV for at least 3 months: Previous IGIV dose in gm divided by number of weeks between intravenously doses and multiplied by 1.3. Any dosage frequency (daily to weekly) may be used as long as total weekly dose is maintained. Begin 1 week after last IGIV dose. Switching from another formulation of subcutaneous immune globulin (IGSC) in patients treated regularly with IGSC for at least 3 months: Initial weekly subcutaneous infusion dose: Maintain the previous weekly IGSC dose (in gms). Begin 1 week after last IGSC dose.	Not applicable
Cuvitru®	PI	Initial: Previous IGIV/Hyqvia® dose in gms divided by number of weeks between IGIV or HyQvia® doses and multiplied by 1.30. Divide the calculated weekly dose by desired number of times per week or multiply the weekly dose by 2 and administer every 2 weeks. Give subcutaneous at regular intervals once daily to every 2 weeks beginning 1 week after last IGIV or Hyqvia dose. Switching from Immune Globulin Subcutaneous (Human) treatment (IGSC): Weekly dose (in gms) should be the same as the weekly dose of prior IGSC treatment (in gm). Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week. Biweekly dosing: Multiply the calculated weekly dose by 2. Infusion sites: up to 4 infusion sites simultaneously, with at least 4 inches between sites avoiding bony prominences. Rotate sites with each administration.	Not applicable

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
Flebogamma® 5%	PI	Initial: 300 to 600 mg/kg intravenous every 3 to 4 weeks	Not applicable
		Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response	
Flebogamma® 10%	ITP	1 g/kg intravenous once daily for 2 consecutive days	Not applicable
	PI	Initial: 300 to 600 mg/kg intravenous every 3 to 4 weeks	Not applicable
		Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response	
Gamastan® S/D	Hepatitis A prophylaxis	Household and institutional case contacts: 0.1 mL/kg intramuscular once	0.1 mL/kg as a single dose or 0.2 mL/kg every 2 months
		Travel to Hepatitis A- endemic areas: Up to 1 month stay: 0.1 mL/kg intramuscular once Up to 2 months stay: 0.2 mL/kg intramuscular once 2 months or longer intramuscular stay: 0.2 mL/kg intramuscular every 2 months	
	Measles postexposure prophylaxis	0.25 mL/kg intramuscular once 0.5 mL/kg intramuscular – Administer immediately to an immunocompromised child	0.5 mL/kg
	Rubella postexposure prophylaxis	0.55 mL/kg intramuscular once	0.55 mL/kg
	Varicella postexposure prophylaxis	0.6 to 1.2 mL/kg intramuscular once	1.2 mL/kg
Gammagard® Liquid	MMN	0.5 to 2.4 g/kg/month intravenous	Not applicable
	PI	Initial: Intravenous: 300 to 600 mg/kg every 3 to 4 weeks	Not applicable
		Subcutaneous: Previous IGIV dose in gms divided by number of weeks between intravenous doses and multiplied by 1.37	
		Maintenance: intravenous: given every 3 to 4 weeks with dose	

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		adjusted per serum IgG level and clinical response	
		Subcutaneous: Maintenance dose is based on clinical response and target IgG trough level	
Gammagard® S/D Less IgA	CLL	400 mg/kg intravenous every 3 to 4 weeks	Not applicable
	ITP	1 g/kg Intravenous, up to 3 doses on alternate days	Not applicable
	KS	1 gm/kg intravenous single dose or 400 mg/kg intravenous once daily for four consecutive days	Not applicable
	PI	Intravenous: 300 to 600 mg/kg every 3 to 4 weeks	Not applicable
Gammaked™	CIDP	Loading dose: 2 g/kg intravenous given in divided doses over 2 to 4 consecutive days Maintenance dose: 1 g/kg intravenous every 3 weeks	Not applicable
	ITP	2 g/kg intravenous	Not applicable
	PI	Initial: Intravenous: 300 to 600 mg/kg every 3 to 4 weeks Subcutaneous: Previous IGIV dose in gms divided by number of weeks between IGIV doses and multiplied by 1.37 Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response Subcutaneous: given once weekly with dose adjusted per PI	Not applicable
Gammaplex®	ITP	1 g/kg intravenous once daily for 2 consecutive days	Not applicable
	PI	Initial: 300 to 800 mg/kg intravenous every 3 to 4 weeks Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response	Not applicable
Gamunex®-C	CIDP	Total loading dose of 2 g/kg intravenous given in divided doses over 2 to 4 consecutive days. Maintenance infusion of 1 g/kg given over 1 day or divided into two doses of 0.5 g/kg given on two consecutive days, every 3 weeks.	Not applicable

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
	ITP	Total dose of 2g/kg given as 1 g/kg intravenous once daily on 2 consecutive days, or 0.4 g/kg intravenous once daily given on 5 consecutive days	Not applicable
	PI	Initial: Intravenous: 300 to 600 mg/kg every 3 to 4 weeks Subcutaneous: Previous IGIV dose in gms divided by number of weeks between IGIV doses and multiplied by 1.37 Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response Subcutaneous: given once weekly with dose adjusted per PI	Not applicable
Hizentra®	CIDP	0.2 to 0.4 g/kg subcutaneous per week given in 1 or 2 consecutive days	Not applicable
	PI	Initial weekly dose = Previous IGIV dose in gm divided by number of weeks between intravenous doses and multiplied by 1.37. Biweekly (every 2 weeks): Start Hizentra® 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly IGSC infusion. Administer twice the calculated weekly dose. Frequent dosing (2 to 7 times per week): Start Hizentra® 1 week after the last IGIV or IGSC infusion. Divide the calculated weekly dose by the desired number of times per week. Adjust the dose based on clinical response and serum IgG trough levels.	Not applicable
Hyqvia®	PI	If IG therapy naïve or switching from IGSC: 300 to 600 mg/kg every 3 to 4 weeks after initial ramp-up (see manufacturer labeling) If switching from IGIV therapy: Give subcutaneous at same dose and frequency as previous IV therapy after initial ramp-up (see manufacturer labeling)	Not applicable
Octagam® 5%	PI	Initial: 300 to 600 mg/kg intravenous every 3 to 4 weeks Maintenance: Intravenous: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical	Not applicable

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		response	
Octagam® 10%	ITP	2 g/kg intravenous once daily for 2 consecutive days	Not applicable
	DM	2 g/kg divided in equal doses given over 2-5 consecutive days every 4 weeks	
Panzyga®	PI	300 to 600 mg/kg intravenous every 3 to 4 weeks	Not applicable
	ITP	2 g/kg, divided into two daily doses of 1 g/kg (10 mL/kg) given on two consecutive days	Not applicable
	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 dose: 1-2 g/kg (10-20 mL/kg) every 3 weeks divided in 2 doses given over 2 consecutive days	Not applicable
Privigen®	CIDP	Loading dose: 2 g/kg intravenous in divided doses over 2 to 5 consecutive days Maintenance dose: 1 g/kg intravenous every 3 weeks	Not applicable
	ITP	1 g/kg intravenous once daily for 2 consecutive days	Not applicable
	PI	200 to 800 mg/kg intravenous every 3 to 4 weeks	Not applicable
Xembify®	PI	Previous IGIV dose in gms divided by number of weeks between intravenous doses and multiplied by 1.37. Give subcutaneous at regular intervals once daily to every week beginning 1 week after last intravenous dose. Or Previous subcutaneous weekly dose administered in regular intervals once daily to every week. Switching from immune globulin subcutaneous (human) treatment (IGSC): Weekly dose (gm) should be the same as the weekly dose of prior IGSC treatment (gm).	Not applicable

Dosage Forms

- **Intravenous administration - ready to use**
  - Asceniv™ (10%)-Single-use vial: 5 gm in 50 ml solution
  - Bivigam™ (10%)-Single-use vial: 5 gm in 50 ml, 10 gm in 100mL solution
  - Flebogamma® DIF (5%)-Single-use vial: 5% IgG (50 mg per mL).
  - Flebogamma® DIF (10%)-Single-use vial: 10% IgG (100 mg per mL).
  - Gammaplex® (5%)-Single-use vial: 50 mg/mL

- Gammaplex® (10%)-Single-use vial: 100 mg/mL
- Octagam® (5%)-Single-use bottle: 1,2.5, 5, 10, 25 gm
- Octagam® (10%)-Single-use vial: 100 mg/mL
- Panzyga® (10%)-Single-use vial: 100 mg/mL
- Privigen (10%)-Single-use vial: 0.1 g/mL
  IV administration - lyophilized powder for reconstitution
- Gammagard S/D-Freeze-dried preparation containing 5 g or 10 g IgG

- **Intravenous or Subcutaneous administration - ready to use**
  - Gammagard® Liquid (10%)-Single-use bottle: 100 mg/mL
  - Gammaked™ is a sterile solution for injection supplied in 1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), or 20 g (200 mL) single use vials.
  - Gamunex®-C (10%)-Single-use vail: 1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL), or 40 g (400 mL)
- **Subcutaneous administration - ready to use**
  - Cutaquig® (16.5%)-Single-use vial: 165 mg/mL
  - Cuvitru (20%)-Single-use vial: 200 mg/mL
  - Hizentra® (20%)-Single-use prefilled syringe: 5 mL,10 mL, and 20 mL Tamper-evident vial: 5, 10, 20 and 50 mL .
  - Hyqvia® (10%) IgG and 160 U/mL recombinant human hyaluronidase*
    *Hyaluronidase increases permeability of the local SC tissue for approximately 24 to 48 hours.-Single-use dual vial set: 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL, 30 g/300 mL
  - Xembify® (20%)-Single-use vial: 0.2 g/mL (200 mg/mL; 20%) protein solution for subcutaneous infusion
- **IM administration - ready to use**
  - Gamastan® S/D (15-18%)-Single-use vial: 2 and 10 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. B-Cell Chronic Lymphocytic Leukemia Infection Prophylaxis (must meet all)**:**

1. Diagnosis of B-cell CLL;
2. Prescribed by or in consultation with a hematologist, oncologist, or immunologist;
3. Current (within the last 6 months) hypogammaglobulinemia as evidenced by two separate measurements of immunoglobulin G (IgG) level less than 500 mg/dL;
4. Member has had recurrent serious bacterial infections (e.g., requiring intravenous antibiotics, hospitalization, or consultation with an infectious disease specialist) within the past 12 months;
5. Dose does not exceed one of the following (a or b) (See Appendix D for weight-based dosing calculations):
   a. 400 mg per kg intravenous every 3 to 4 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

B. Dermatomyositis, Polymyositis (off-label) (must meet all)**:**

1. Diagnosis of dermatomyositis (DM) or polymyositis (PM);
2. Request for Octagam 10%;
3. Prescribed by or in consultation with a dermatologist, neurologist, or neuromuscular specialist;
4. Failure of a 4-month trial of a systemic corticosteroid (e.g., prednisone) in combination with one of the following immunosuppressive agents, both at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced: methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, tacrolimus, cyclosporine (see Appendix D);
5. Dose does not exceed one of the following (a or b)) (See Appendix D for weight-based dosing calculations):
   a. 2 gm per kg intravenous per month;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

C. Fetal/Neonatal Alloimmune Thrombocytopenia (off-label) (must meet all)**:**

1. Diagnosis of fetal/neonatal alloimmune thrombocytopenia (FNAIT);
2. Prescribed by or in consultation with a hematologist, immunologist, perinatologist, or neonatologist;
3. Meets one of the following (a, b, c, or d):
   a. Previous pregnancy affected by FNAIT;
   b. Serological confirmation of FNAIT as evidenced by maternal-fetal HPA incompatibility;
   c. Nadir platelet count < 100 x 10^9/L at birth or within 7 days after birth of the affected child;
   d. Fetal intracranial hemorrhage;
4. Dose does not exceed one of the following (a or b)) (See Appendix D for weight-based dosing calculations):
   a. 2 g per kg intravenous per week;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

D. Inflammatory Demyelinating Polyneuropathy (Acute/Guillain-Barre Syndrome or Chronic) (must meet all):

1. Diagnosis of acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain- Barre Syndrome (GBS) or CIDP;
2. Prescribed by or in consultation with a neurologist or neuromuscular specialist;
3. Member meets one of the following (a - h):
   a. Inability to stand or walk at least 30 feet without assistance;
   b. ICU admission required for aspiration or mechanical ventilation;
   c. Miller-Fisher syndrome;
   d. Inability to raise head against gravity;
   e. Severe bulbar palsy (e.g., impaired gag reflex, dysarthria and/or dysphagia);
   f. Bilateral facial weakness;
   g. Autonomic dysfunction (e.g., unexplained dysrhythmia, blood pressure fluctuations, significant bowel or bladder involvement);
   h. Disease is progressive or relapsing for more than 2 months;

4. Dose does not exceed one of the following (a, b, c, or d)) (See Appendix D for weight-based dosing calculations):
   a. For AIDP/GB: 0.4 g per kg per day intravenous for 5 days;
   b. For CIDP: Gammaked™, Gamunex®-C; Panzyga®, Privigen: Loading dose 2 g per kg Intravenous given in divided doses over two to four consecutive days, following by maintenance dose of 1 g per kg intravenous every 3 weeks;
   c. For CIDP: Hizentra 0.2 g per kg body weight subcutaneous per week, starting 1 week after last IVIG infusion or 0.4 g per kg body weight subcutaneous per week if evidence is submitted demonstrating worsening symptoms;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

E. Idiopathic Thrombocytopenic Purpura (Acute or Chronic) (must meet all)**:**
1. Diagnosis of ITP;
2. Member meets one of the following (a or b):
   a. Chronic ITP: If request is for Flebogamma® 10%, Gammagard S/D®, Gammaked™, Gammaplex®, Gamunex C®, Octagam 10%, Panzyga®, Privigen®
   b. Acute ITP: Gammaked™, Gamunex C®
3. Member meets one of the following (a or b or c):
   a. Octagam 10% , Gammaked®, Gammaplex®, Gammagard S/D®, Gamunex C®, Panzyga®: Age at least 18 years or older;
   b. Privigen®: Age at least 15 years or older;
   c. Flebogamma®: 10%: ≥ 2 years of age;
4. Prescribed by or in consultation with a hematologist;
5. Member meets one of the following (a or b):
   a. Failure of one of the following at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced (i or ii):
      i. Systemic corticosteroids (e.g., prednisone);
      ii. Rho(D) immune globulin (RhIG);
      *Prior authorization is required for RhIG
   b. Pregnant;
6. Member meets one of the following (a – e):
   a. Acute bleeding due to severe thrombocytopenia (platelet count less than 30,000/µL);
   b. In patients with severe thrombocytopenia (platelet counts less than 20,000/µL) considered to be at risk for intracerebral hemorrhage;
   c. Platelet counts persistently at or below 20,000/µl (For CITP) ;
   d. Splenectomy is scheduled;
   e. Pregnant;
7. Dose does not exceed one of the following (a or b) (See Appendix D for weight-based dosing calculations):
   a. Dose does not exceed FDA recommended maximum dose and frequency (refer to dosing information section for product specific dosing and frequency or manufacturer's prescribing information.
   b. Dose is supported by practice guidelines or peer-reviewed literatures for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

F. Kawasaki Syndrome Aneurysm Prevention (must meet all)**:**
1. Diagnosis of Kawasaki Syndrome or Incomplete (Atypical) Kawasaki Disease;
2. Prescribed by or in consultation with a cardiologist, allergist, immunologist, infectious disease specialist, or rheumatologist;
3. Prescribed concurrently with aspirin therapy, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed one of the following (a or b) (See Appendix D for weight-based dosing calculations):
   a. Dose does not exceed FDA recommended maximum dose and frequency (refer to dosing information section for product specific dosing and frequency or manufacturer's prescribing information);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 1 month (one time approval)
Medicaid: 1 month (one time approval)

G. Kidney Transplant (off-label) (must meet all)**:**
1. Member meets one of the following (a or b):
   a. If prescribed prior to kidney transplant, member has high levels of "anti-donor" antibodies (i.e., member is highly sensitized to the tissue of the majority of living or cadaveric donors because of "non-self" human leukocyte antigen (HLA) or ABO incompatibility);
   b. If prescribed following kidney transplant, used for the treatment of antibody- mediated rejection;
2. Prescribed by or in consultation with a nephrologist, transplant specialist, or hematologist;
3. Dose does not exceed one of the following (a or b) (See Appendix D for weight-based dosing calculations):
   a. Dose does not exceed FDA recommended maximum dose and frequency (refer to dosing information section for product specific dosing and frequency or manufacturer's prescribing information);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

H. Multifocal Motor Neuropathy (must meet all)**:**
1. Diagnosis of MMN;
2. Prescribed by or in consultation with a neurologist or neuromuscular specialist;
3. Dose does not exceed one of the following (a or b):
   a. 2.4 g per kg intravenous per month;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration

Commercial: 6 months
Medicaid: 6 months

I. Multiple Myeloma Infection Prophylaxis (off-label) (must meet all)**:**
1. Diagnosis of multiple myeloma (MM) with stable plateau phase disease;
2. Prescribed by or in consultation with an hematologist, oncologist, or immunologist;
3. Current (within the last 6 months) hypogammaglobulinemia as evidenced by two separate measurements of immunoglobulin G (IgG) level less than 600 mg/dL;
4. Member has had recurrent serious bacterial infections (e.g., requiring intravenous antibiotics, hospitalization, or consultation with an infectious disease specialist) within the past 12 months;
5. Documented failure or inability to tolerate chemotherapy or radiation therapy;
6. Dose does not exceed one of the following (a or b):
   a. 400 mg per kg intravenous every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

J. Multiple Sclerosis (off-label) (must meet all)**:**
1. Diagnosis of relapsing-remitting multiple sclerosis (MS);
2. Prescribed by or in consultation with a neurologist;
3. Failure of three FDA-approved disease-modifying MS therapies (e.g., Avonex, Betaseron, Copaxone, Vumerity, Kesimpta) at up to maximally indicated doses unless contraindicated or clinically significant side effects are experienced;
   *Prior authorization is required for MS therapies
4. Dose does not exceed one of the following (a or b):
   a. Initial loading dose of 400 mg per kg intravenous for 5 days, followed by maintenance dose of 1 g per kg intravenous per month;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

K. Myasthenia Gravis (MG)/Lambert Eaton Myasthenic Syndrome (LEMS) (off-label) (must meet all)**:**
1. Diagnosis of myasthenia gravis (MG) or Lambert Eaton myasthenic syndrome (LEMS);
2. Prescribed by or in consultation with a neurologist or neuromuscular specialist;
3. Member meets one of the following (a, b, or c):
   a. Acute crisis (e.g., vital capacity less than 1 L/min, inability to walk 100 ft without assistance, intubation, dysphagia with aspiration, mechanical ventilation);
   b. Thymectomy surgery is scheduled;
   c. Failure of both of the following at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced (i and ii):
      i. Amifampridine or a cholinesterase inhibitor (e.g., pyridostigmine); for LEMS;
      ii. Systemic corticosteroid (e.g., prednisone) or immunosuppressant (e.g., azathioprine) for MG;
      *Prior authorization may be required for amifampridine

4. Dose does not exceed one of the following (a or b):
   a. 2 g per kg intravenous for 2 to 5 days per treatment course;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

L. Paraneoplastic Neurological Syndrome (off-label) (must meet all)**:**
1. Diagnosis of one of the following subtypes of paraneoplastic neurological syndrome (a or b):
   a. Opsoclonus-myoclonus syndrome;
   b. Anti-NMDA encephalitis;
2. Prescribed by or in consultation with a neurologist, neuromuscular specialist, or oncologist;
3. For opsoclonus-myoclonus syndrome: Failure of at least one systemic corticosteroid (e.g., prednisone) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed one of the following (a or b) (See Appendix D for weight-based dosing calculations):
   a. Dose does not exceed FDA recommended maximum dose and frequency (refer to dosing information section for product specific dosing and frequency or manufacturer's prescribing information);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

M. Parvovirus B19 Infection and Anemia (off-label) (must meet all)**:**
1. Diagnosis of anemia secondary to chronic parvovirus B19 infection;
2. Prescribed by or in consultation with a hematologist, infectious disease specialist, or immunologist;
3. Current (within the last 30 days) severe anemia (i.e., Hgb <10 or Hct < 30) due to bone marrow suppression;
4. Dose does not exceed one of the following (a or b):
   a. Initial dose of 2 g per kg per day for up to 5 days, followed by maintenance dose of 400 mg per kg intravenous every 4 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

N. Pediatric Human Immunodeficiency Virus (HIV) Infection Prophylaxis (off-label) (must meet all)**:**
1. Prescribed for prophylaxis of serious bacterial infection in a child who has human immunodeficiency virus (HIV);
2. Prescribed by or in consultation with an HIV or infectious disease specialist;
3. Current (within the last 6 months) hypogammaglobulinemia as evidenced by two separate measurements of serum IgG concentration less than 250 mg/dL;

4. Member meets one of the following (a - e):
   a. Recurrent serious bacterial infections (defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 12-month period);
   b. Inadequate antibody response to protein/polysaccharide antigens (e.g., measles, pneumococcal, and/or Haemophilus influenzae type b);
   c. Lives in an area where measles is highly prevalent and has not developed an antibody response after two doses of measles, mumps, and rubella virus live vaccine;
   d. Exposure to measles (requires a single dose);
   e. Chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy;
5. Dose does not exceed one of the following (a or b):
   a. 400 mg per kg intravenous every 2 to 4 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

O. Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid (a.k.a. Cicatricial Pemphigoid), Epidermolysis Bullosa Acquisita (off-label) (must meet all):

1. Diagnosis of one of the following (a, b, c, d, or e):
   a. Pemphigus vulgaris;
   b. Pemphigus foliaceus;
   c. Bullous pemphigoid;
   d. Mucous membrane pemphigoid (a.k.a. cicatricial pemphigoid);
   e. Epidermolysis bullosa acquisita;
2. Prescribed by or in consultation with a dermatologist;
3. Failure of at least one corticosteroid (e.g., prednisone) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of at least one immunosuppressive agent (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of Rituxan® unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is required for Rituxan
6. Dose does not exceed one of the following (a, b, c, or d):
   a. 2 gm per kg intravenous every 4 weeks;
   b. 400 mg per kg per day intravenous for 5 days (1 cycle only; may repeat up to three times in a 6-month period);
   c. 300 mg per kg perday intravenous for 5 days at monthly intervals (for up to 3 cycles);
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

P. Primary Immunodeficiencies (must meet all)**:**

1. Diagnosis of primary immunodeficiencies (PI), including any of the following (a - h):
   a. Agammaglobulinemia (e.g., X-linked, congenital);

b. Common variable immunodeficiency (CVID);
c. Congenital hypogammaglobulinemia;
d. Immunodeficiency with near/normal IgM (absent IgG, IgA) (also known as Hyper IgM syndrome);
e. Selective immunodeficiency (e.g., selective IgA, IgM, or IgG subclass);
f. Severe combined immunodeficiency disorders (SCID) (e.g., X-SCID, jak3, ZAP70, adenosine deaminase (ADA) deficiency, PNP, RAG defects, Ataxia Telangiectasia, Wiskott-Aldrich syndrome, DiGeorge syndrome);
g. Subclass deficiency (see Appendix D);
h. Functional/specific antibody deficiency (see Appendix D);

2. Prescribed by or in consultation with an immunologist or hematologist;
3. Meet one of the following (a, b or c)
   a. Asceniv™: Age atleast 12 years or older;
   b. Octagam®, Bivigam™: Age at least 6 years or older;
   c. Xembify®, Panzyga®, Hizentra®, Gamunex®-C, Gammaplex®, Gammaked™, Gammagard® S/D, Gammagard® liquid, Flebogamma® DIF, Cuvitru™ Cutaquig®: Age at least 2 years or older;
   d. Privigen: Age 3 years and older;
4. Member meets one of the following (a or b):
   a. For functional/specific antibody deficiency, meets all of the following (i, ii, and iii):
      i. Normal immune globulin levels;
      ii. Inadequate antibody response to polysaccharide antigens (e.g., pneumococcal);
      iii. Recurrent sinopulmomary infections within the past 12 months;
   b. Current (within the last 6 months) total or subclass immune globulin deficiency (below normal for age) as evidenced by two separate measurements of immunoglobulin level (see Appendix E) and one of the following (i, ii, iii, or iv):
      i. For ADA-SCID: failure (defined as experiencing continued recurrent serious bacterial infections) of Revcovi™, or hematopoietic stem cell transplant, unless contraindicated or clinically significant adverse effects are experienced;
      *Prior authorization is required for Adagen and Revcovi
      ii. SCID (not including ADA-SCID);
      iii. Recurrent serious bacterial infections (e.g., requiring intravenous antibiotics, hospitalization, or consultation with an infectious disease specialist) within the past 12 months;
      iv. Inadequate antibody response to protein/polysaccharide antigens (e.g., tetanus, diphtheria, pneumococcal);
5. Dose does not exceed one of the following (a or b) (See Appendix D for weight-based dosing calculations):
   a. Dose does not exceed FDA recommended maximum dose and frequency (refer to dosing information section for product specific dosing and frequency or manufacturer's prescribing information);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

Q. Stiff Person Syndrome (off-label) (must meet all)**:**
1. Diagnosis of stiff person syndrome (also known as Moersch-Woltmann syndrome);
2. Prescribed by or in consultation with a neurologist or neuromuscular specialist;
3. Failure of a benzodiazepine (e.g., diazepam) or baclofen at up to maximally indicated doses, unless

contraindicated or clinically significant adverse effects are experienced;

4. Dose does not exceed one of the following (a or b):
   a. 2 g per kg given over two to three intravenous infusions, each separated by three to five days per treatment course;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

R. Viral Prophylaxis for Hepatitis A, Measles, Varicella, Rubella Viruses (must meet all):

1. Request is for intramuscular formulation;
2. Request is for one of the following indications (a, b, c, or d):
   a. Hepatitis A post-exposure/high-risk prophylaxis and meets both of the following (i and ii):
      i. Hepatitis A exposure or at high risk for exposure as evidenced by (a or b):
         a. Exposure to hepatitis A in the past 2 weeks (e.g., household contact, sexual contact, sharing illicit drugs with someone positive for hepatitis A, regular babysitters/caretakers, food handlers at the same establishment as one who is positive for hepatitis A) AND does not have clinical manifestations of hepatitis A;
         b. Traveling to or working in an area endemic for hepatitis A;
      ii. Meets at least one of the following (a, b, or c):
         a. Hepatitis A vaccine is locally unavailable;
         b. History of severe allergic reaction (anaphylaxis) to the hepatitis A vaccine;
         c. If either exposed to the virus or traveling in ≤ 2 weeks to an area endemic for hepatitis A, then (1, 2, or 3):
            1. Age < 1 year or > 40 years;
            2. Chronic liver disease or other chronic medical condition;
            3. Immunocompromised;
   b. Measles (rubella) post-exposure prophylaxis and meets all of the following (i, ii, iii, and iv):
      i. Exposure to measles within the past 6 days;
      ii. Member has not previously received a measles vaccine;
      iii. Member has not previously had measles;
      iv. Meets at least one of the following (a - f):
         a. Measles vaccine is locally unavailable;
         b. History of severe allergic reaction (anaphylaxis) to the measles vaccine;
         c. Pregnancy;
         d. Immunocompromised;
         e. Has been > 3 days since exposure
         f. Age < 12 months;
   c. Chickenpox (varicella) post-exposure prophylaxis and meets all of the following (i, ii, iii, and iv):
      i. Exposure to varicella within the past 10 days;
      ii. Member lacks immunity to varicella;
      iii. Varicella zoster immune globulin (VZIG) is currently unavailable;
      iv. Meets any of the following (a - e):
         a. Varicella vaccine is locally unavailable;
         b. History of a severe allergic reaction (anaphylaxis) to the varicella vaccine;
         c. Pregnancy;
         d. Immunocompromised;

e. Newborn of mother who had varicella from 5 days before to 2 days after delivery;

d. Rubella post-exposure prophylaxis (i and ii):
   i. Recent exposure to rubella;
   ii. Member is pregnant;

2. Dose does not exceed one of the following (a – e):
   a. Hepatitis A (i, ii, or iii):
      i. 0.1 mL/kg IM once;
      ii. For anticipated exposure up to 2 months: 0.2 mL/kg IM once;
      iii. For anticipated exposure 2 months or longer: 0.2 mL/kg IM every 2 months;
   b. Measles: 15 mL intramuscular once;
   c. Varicella: 1.2 mL/kg intramuscular once;
   d. Rubella: 0.55 mL/kg intramuscular once;
   e. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: Hepatitis A: Up to 6 months
Medicaid: Hepatitis A: Up to 6 months
All other indications: One-time approval (1 month)

S. Management of Immunotherapy-Related Toxicities (CAR T-Cell-Related Toxicities) (off-label) (must meet all):
1. Diagnosis of Immunotherapy-Related Toxicities (CAR T-Cell-Related Toxicities);
2. Prescribed by immunologist;
3. Member has serum IgG levels <400-600 mg/dL;
4. Serious or recurrent infections [particularly bacterial];
5. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: Not applicable
Medicaid: Not applicable

T. Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities) (off-label) (must meet all):
1. Diagnosis of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities);
2. Prescribed by immunologist;
3. Meet any one of the following:
   a. Additional therapy for suspected myocarditis if no improvement within 24 hours of starting pulse-dose methylprednisolone;
   b. Severe (G3) or life-threatening (G4) bullous dermatitis;
   c. Stevens-Johnson syndrome, or toxic epidermal necrolysis;
   d. Moderate, severe, or life-threatening steroid-refractory myalgias or myositis;
   e. Severe (G3-4) myasthenia gravis;
   f. Moderate (G2) or severe (G3-4) Guillain-Barré Syndrome or severe (G3-4) peripheral neuropathy in combination with pulse-dose methylprednisolone;
   g. Encephalitis in combination with pulse-dose methylprednisolone if severe or progressing symptoms, or if oligoclonal bands present;
   h. Transverse myelitis;
   i. severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone;

4. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: Not applicable
Medicaid: Not applicable

II. Continued Therapy Approval

A. Kawasaki Syndrome/Incomplete (Atypical) Kawasaki Disease, Viral Prophylaxis (Hep A, Measles, Varicella, Rubella), Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities), Management of Immunotherapy-Related Toxicities (CAR T-Cell-Related Toxicities)

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval Duration
Commercial: Not applicable
Medicaid: Not applicable

B. All Other Indications in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (see Appendix D for examples);
3. If request is for a dose increase, request meets one of the following (a or b):
   a. Dose titration or conversion is appropriate per package insert labeling;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

ACTH: Adrenocorticotropic hormone
ADA: Adenosine deaminase
AIDP: Acute inflammatory demyelinating polyneuropathy
CIDP: Chronic inflammatory demyelinating polyneuropathy
CLL: Chronic lymphocytic leukemia
CVID: Common variable immunodeficiency
DIF: Dual inactivation plus nanofiltration
FNAIT: Fetal/neonatal alloimmune thrombocytopenia
FDA: Food and Drug Administration
GBS: Guillain Barre Syndrome
HIV: Human immunodeficiency virus
HLA: Human leukocyte antigen
HPA: Human platelet antigen
IG: Immune globulin
IgA: Immune globulin A
IgG: Immune globulin G
IgM: Immune globulin M
IMIG: Intramuscular immune globulin
ITP: Immune thrombocytopenic purpura

NMDA: N-methyl D-aspartate
PI: Primary [humoral] Immunodeficiency
POEMS: polyneuropathy, organomegaly, endocrinopathy,monoclonal protein, skin changes
RhIG: Rho(D) immune globulin
SCID: Severe combined immunodeficiency disorders
SCIG: Subcutaneous immune globulin
S/D: Solvent/detergent treated
VZIG: Varicella zoster immune globulin
DM: Dermatomyositis

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
baclofen (Lioresal®)	**Stiff Person Syndrome*** 20 mg by mouth twice daily or three times a day, or 50 to 1,600 mcg/day intrathecally	By mouth: 80 mg/day intrathecally (IT): 1600 mcg/day
diazepam (Valium®)	**Stiff Person Syndrome*** 2 to 10 mg orally 3 to 4 times daily	Daily doses needed to control the disease can be as high as 100 to 200 mg/day in some patients
Firdapse®	**Lambert-Eaton Myasthenic Syndrome** Adults: 15 mg to 30 mg by mouth in 3 to 4 divided doses daily. Dose can be increased by 5 mg daily every 3 to 4 days.	80 mg/day (20 mg/dose)
Ruzurgi®	**Lambert-Eaton Myasthenic Syndrome** Pediatric (age 6 to <17 years) and weight ≥ 45 kg: 15 to 30 mg by mouth in 2 to 3 divided doses. Dose can be increased by 5 mg to 10 mg increments daily, divided in up to 5 doses per day. Pediatric (age 6 to <17 years) and weight < 45 kg: 7.5 mg to 15 mg by mouth in 2 to 3 divided doses. Dose can be increased by 2.5 mg to 5 mg increments daily, divided in up to 5 doses per day.	100 mg/day (30 mg/dose) for weight ≥ 45 kg; 50 mg/day (15 mg/dose) for weight < 45 kg
pyridostigmine (Mestinon® ; Mestinon® Timespan extended release)	**Myasthenia Gravis** Immediate Release (IR) tablets and syrup Adults: 60 to 1,500 mg by mouth daily in divided doses (avg 600 mg by mouth daily) Pediatrics*: 0.5 to 1 mg/kg by mouth every 4 to 6 hrs	Immediate Release (IR): 1,500 mg/day (adults) or 7 mg/kg/day Pediatrics: Max: 60 mg/dose orally and 7 mg/kg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Extended Release 180 to 540 mg by mouth once daily or twice daily	Extended Release (ER): 1,080 mg/day
Revcovi™	**Adenosine deaminase-Severe combined immunodeficiency disorders (ADA-SCID)** Adagen-naïve: 0.2 mg/kg twice a week Intramuscular Transitioning from Adagen: 0.2 mg/kg weekly Intramuscular.	0.4 mg/kg/week
Rhophylac ®, WinRho ® SDF (Rho(D) immune globulin)	**Idiopathic Thrombocytopenic Purpura in non-splenectomized, Rho(D) antigen positive patients** Initial: 50 mcg/kg Intravenous Maintenance Therapy: 25 to 60 mcg/kg Intravenous	75 mcg/kg*
Rituxan®	**Pemphigus Vulgaris** Initial: Two-1000 mg Intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids Maintenance Therapy: 500 mg Intravenous at month 12 and every 6 months thereafter	500 mg/6 months
Immunosuppressive agents		
azathioprine (Imuran®)	**Dermatomyositis/Polymyositis*, Myasthenia Gravis*** 2 mg/kg by mouth once daily or 50 mg/day by mouth up to 2 to 3 mg/kg/day **Pemphigus vulgaris and associated conditions*** 2 to 3 mg/kg/day by mouth	3 mg/kg/day
cyclophosphamide	**Dermatomyositis/Polymyositis*** 1 to 3 mg/kg/day by mouth once daily or 500 mg Intravenous every 2 weeks for 6 doses **Pemphigus vulgaris and associated conditions*** 50 to 75 mg/day by mouth or pulsed regimen of 500 mg Intravenous on day, and then every 4 weeks thereafter in combination with oral cyclophosphamide and dexamethasone	Not applicable
cyclosporine (Gengraf® , Neoral®,	**Dermatomyositis/Polymyositis*** 5 to 10 mg/kg/day by mouth	Not applicable

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Sandimmune®)		
methotrexate	**Dermatomyositis/Polymyositis*** 10 to 25 mg/week by mouth / Intravenous	50 mg/week
mycophenolate mofetil (Cellcept®)	**Dermatomyositis/Polymyositis*** 250 to 500 mg by mouth twice daily, increasing to a target dose of 1,500-3,000 mg/day	3 g/day
tacrolimus (Prograf®)	**Dermatomyositis/Polymyositis*** 0.075mg/kg/day by mouth twice daily or begin at 1 mg by mouth twice daily, increase to reach trough of 6- 10 ng/ml	Not applicable
Systemic corticosteroids (e.g., prednisone, prednisolone, methylprednisolone)	An equivalent dose of prednisone 1 mg/kg/day (with or without tapering)	2 mg/kg/day
Disease-modifying therapies for relapsing remitting multiple sclerosis (MS)		
Aubagio®	7 or 14 mg by mouth once daily	14 mg/day
Avonex®, Rebif®	Avonex: 30 mcg intramascularly every week Rebif: 22 mcg or 44 mcg subcutaneous three times weekly	Avonex: 30 mcg/week Rebif: 44 mcg three times weekly
Betaseron®, Extavia®	250 mcg subcutaneous every other day	250 mg Every other day
glatiramer acetate (Copaxone®, Glatopa®)	Copaxone: 20 mg subcutaneous once daily or 40 mg subcutaneous three times in a Week Glatopa: 20 mg subcutaneous once daily	Copaxone: 20 mg/day or 40 mg three times weekly Glatopa: 20 mg/day
Gilenya™	0.5 mg by mouth once daily	0.5 mg/day
Lemtrada®	Intravenous infusion for 2 treatment courses: • First course: 12 mg/day on 5 consecutive days • Second course: 12 mg/day on 3 consecutive days 12 months after first course	See regimen
mitoxantrone	12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous every 3 months	Cumulative lifetime dose of ≥ 140 mg/ m^2
Ocrevus™	Initial: 300 mg intravenous, then 300 mg intravenous 2 weeks later Maintenance: 600 mg intravenously every 6 months	600 mg/6 months

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Plegridy®	125 mcg subcutaneous every 2 weeks	125 mcg/2 weeks
Tecfidera® (dimethyl fumarate)	120 mg by mouth twice daily for 7 days, followed by 240 mg by mouth twice daily	480 mg/day
Tysabri®	300 mg intravenous every 4 weeks	300 mg/4 weeks
Zinbryta® (daclizumab)	150 mg subcutaneously once monthly	150 mg/month

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.
*Off-label

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s)*:
  - History of anaphylactic or severe systemic reactions to human immune globulin;
  - IgA-deficient patients with antibodies against IgA and a history of hypersensitivity;
  - For Gammaplex® 5% only- Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established;
  - For Hyqvia® only- Known systemic hypersensitivity to hyaluronidase or recombinant human hyaluronidase and to human albumin (in the hyaluronidase solution);
    For Privigen® only- Hyperprolinemia (Privigen contains the stabilizer L-proline).

- Boxed Warning(s):
  - Thrombosis;
  - Renal dysfunction;
  - Acute renal failure.

*Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

APPENDIX D: General Information

- CLL:
  - These patients have a pattern of infection caused by encapsulated bacteria (Haemophilus influenzae, pneumococci, streptococci) which tends to be chronic and/or recurrent and does not demonstrate improvement with an adequate course of PO antibiotics and/or prophylactic antibiotics. Recurrent infections may include sinus infections, otitis media, bronchiectasis and pyogenic pneumonias.
- Dermatomyositis, Polymyositis:
  - IVIG may be medically necessary after less than 4 months trial of prednisone or prednisone combination therapies if the patient has profound, rapidly progressive and/or potentially life threatening muscular weakness (e.g., life-threatening aggressive disease with involvement of respiratory musculature, possibly requiring hospitalization, elective intubation and mechanical ventilatory support) and is refractory to or intolerant of previous therapy.
  - Failure or clinically significant adverse effects to continual high dose steroids in combination with other immunosuppressive agents is defined as the patient being unresponsive or poorly responsive to therapy (persistently elevated serum creatine kinase (CK) levels and/or lack of improvement on muscle strength improvement scales) or intolerant of therapy (i.e., steroid myopathy or severe

osteoporosis).
    - Inclusion body myositis (IBM) is classified as one of the idiopathic inflammatory myopathies. However, despite some histologic similarities, the clinical manifestations, treatment and prognosis are different from DM and PM. IBM is relatively resistant to standard immunosuppressive therapy. In two clinical studies, IVIG was unable demonstrate objective improvement in the treatment of IBM.
- ITP:
    - Definitions of acute vs. chronic ITP:
        - Per an International Working Group consensus panel of ITP experts, ITP is defined as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months). Although not formally validated, these definitions are supported and used by the American Society of Hematology (ASH).
        - In clinical trials evaluating the efficacy and safety of IVIG in ITP, acute ITP was defined as condition duration of up to 6 months while chronic ITP was defined as condition duration of greater than 12 months.
    - Per the 2011 ASH guidelines, response to treatment was defined by the following:
        - A response would be defined as a platelet count ≥ 30,000/µL and a greater than 2- fold increase in platelet count from baseline measured on 2 occasions > 7 days apart and the absence of bleeding.
        - A failure would be defined as a platelet count < 30,000/µL or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.
    - There have been reports of fatal intravascular hemolysis with Rho(D) immune globulin and specific monitoring is required. This therapy is not necessarily recommended over IVIG but can be used instead in patients who are Rh positive, have a negative direct antiglobulin test (DAT), and have not had a splenectomy.
    - For acute ITP, a single dose of IVIG is used as first line treatment. For adults, a second dose may be given if necessary.
- (Acute) Inflammatory Demyelinating Polyneuropathy or GBS:
    - GBS subtypes include the following: Acute inflammatory demyelinating polyneuropathy (AIDP), Acute motor axonal neuropathy (AMAN), Acute motor- sensory axonal neuropathy (AMSAN), and Miller Fisher Syndrome (MFS).
    - Miller Fisher syndrome is a rare, acute polyneuropathy characterized by ataxia (abnormal muscle coordination), ophthalmoplegia (paralysis of the eye muscles), and areflexia (absence of the reflexes).
    - Elevated CSF protein, with a normal CSF white blood cell count, is often present;
    - fifty to 66 percent the first week of symptoms and ≥75 percent the third week.
    - GBS and AIDP typically progresses over 2 weeks, and the majority of patients achieve nadir of the disease by four weeks.
    - Initiation of IVIG within 2 weeks of symptom onset appears to be as effective as plasma exchange (PE).
    - The combination of IVIG and plasmaphoresis used together is not better than either treatment used alone.
    - The combination of IVIG and IV methylprednisolone was not more effective than IVIG alone.
    - Immunoabsorption is an alternative technique to PE that removes immunoglobulins. There is insufficient evidence to recommend the use of immunoabsorption for GBS.
    - CSF filtration is as effective as PE for treatment of GBS.
    - Pulmonary function risk factors include one or more of the following:
        - Forced vital capacity < 20 mL/kg
        - Maximal inspiratory pressure < 30 cm H2O
        - Maximal inspiratory pressure < 40 cm H2O
        - 30% reduction in vital capacity from baseline

- (Chronic) Inflammatory Demyelinating Polyneuropathy or CIDP:
  - The definition of CIDP includes multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) variant or when Sensory CIDP exists with other causes of neuropathy such as diabetes and Charcot-Marie-Tooth (CMT), as evidenced by superimposed features of CIDP.
  - IVIG, corticosteroids, and plasmapheresis are all considered first-line treatments for patients with moderate to severe disability. Patient-specific factors may determine the appropriate choice of therapy.
  - As evidence of progression is more significant than the level of disability, mild cases of CIDP may not need to be treated aggressively if they are stable, but any signs of progression warrants effective treatment with IVIG to begin immediately.
  - Plasmapheresis has not been shown to be more effective than IVIG, however, it may be used in patients who are unresponsive to both IVIG and corticosteroid therapy.
- Kawasaki:
  - The efficacy of IVIG administered in the acute phase of Kawasaki disease in reducing the prevalence of coronary artery abnormalities is well-established. The mechanism of action of IVIG in treating Kawasaki disease is unknown; however, IVIG appears to have a generalized anti-inflammatory effect.
  - For patients with persistent or recurrent fever after initial IVIG infusion, IVIG retreatment may be useful. Failure to respond usually is defined as persistent or recrudescent fever ≥36 hours after completion of the initial IVIG infusion. Most experts recommend retreatment with IVIG, 2 g/kg. The putative dose-response effect of IVIG forms the theoretical basis for this approach.
- Kidney Transplant:
  - RxAdvance considers the combination of IVIG and Rituxan (rituximab) for desensitization prior to renal transplantation, investigational at this time. Larger, prospective, randomized controlled trials are needed to evaluate the long-term efficacy and safety of this treatment and to compare this protocol with the current treatment of IVIG alone.
  - In a retrospective analysis of 50 kidney transplant patients at Johns Hopkins Hospital, all patients were live donor HLA incompatible recipients. Desensitization included plasmapheresis with low dose IVIG, mycophenolate and tacrolimus, and intraoperative induction therapy with anti-IL2 receptor antibodies. Twenty five of the higher risk patients also received rituximab (375 mg/m2) the day prior to transplant. There was no significant difference in the incidence of acute rejection within the first 3 months of transplant between the two groups. Further randomized, controlled trials are still needed.
- MMN:
  - Although not required for diagnosis, the presence of a high titer (>1:1000) of serum Immunoglobulin M (IgM) antibody directed against ganglioside-monodialic acid (IgM Anti-GM1 antibodies) provides independent support for MMN (> 80% of patients).
  - Although no reports exist of controlled trials of immunosuppressive drugs in patients with multifocal motor neuropathy, there are a series of anecdotal reports of patients who transiently responded to oral or pulsed doses of cyclophosphamide, however,this treatment was associated with significant side effects, related in part to the cumulative dose of cyclophosphamide.
- MM:
  - Plateau phase is defined as the time when other causative organisms that may be present due to dysfunction in other immunologic cells besides the B-cell lines of defense are less likely to be present. IVIG in any other phase is considered not medically necessary.
  - These patients have a pattern of infection caused by encapsulated bacteria (Haemophilus influenzae, pneumococci, streptococci) which tends to be chronic and/or recurrent and does not demonstrate improvement with an adequate course of PO antibiotics and/or prophylactic antibiotics. Recurrent infections may include sinus infections, otitis media, bronchiectasis and pyogenic pneumonias.
- MS:

  - The clinical course of MS usually falls within one of the following categories, with the potential for progression from one pattern to a more serious one:
    - Relapsing-remitting MS: This form of MS is characterized by clearly defined acute attacks with full recovery or with some remaining neurological signs/symptoms and residual deficit upon recovery. The periods between disease relapses are characterized by a lack of disease progression.
    - Secondary progressive MS: The disease begins with an initial relapsing-remitting course, followed by progression at a variable rate that may also include occasional relapses and minor remissions.
    - Progressive-relapsing MS: Persons with progressive-relapsing MS experience progressive disease from onset, with clear, acute relapses that may or may not resolve with full recovery. Unlike relapsing-remitting MS, the periods between relapses are characterized by continuing disease progression.
    - Primary progressive MS: The disease shows gradual progression of disability from its onset, without plateaus or remissions or with occasional plateaus and temporary minor improvements.
- MG:
  - Myasthenia gravis (MG) is a disorder of neuromuscular function that is characterized by fatigue and weakness of the muscular system without atrophy or sensory deficits.
  - Myasthenia “Crisis” refers to exacerbation sufficient to endanger life, and usually involves respiratory failure in MG, therefore would not include disabled patients who are able to walk with or without assistance.
  - Intravenous Immunoglobulin (IVIG) has not been shown to be superior to plasmapheresis in the treatment of life-threatening myasthenia gravis.
  - High-dose IVIG may temporarily modify the immune system and suppress autoantibody production to improve severe myasthenia gravis symptoms. The effect of IVIG is seen typically in less than a week, and the benefit can last for three to six weeks. IVIG is used to quickly reverse an exacerbation of myasthenia.
  - According to the European Federation of Neurological Studies (EFNS) guidelines on the use of intravenous immunoglobulin in treatment of neurological diseases, the efficacy of IVIG has been proven acute exacerbations of myasthenia gravis and short- term treatment of severe MG (level A recommendation).
  - A small clinical trial conducted by Wegner and Ahmed showed that long-term IVIG was effective. This trial included six patients who were anti-AChR-Ab-positive. These patients received IVIG at a dosage of 400 mg/kg/day for 5 days then a maintenance therapy of 400 mg/kg for 1 day every 3 to 4 months. After a 2 year follow up, all patients maintained a good functional status and side effects from IVIG did not increase.
- NAIT:
  - NAIT is caused by maternal alloantibodies directed against fetal (paternally inherited) platelet antigens as a result of feto-maternal transplacental passage of incompatible platelets during pregnancy.
  - HPA-1a is the platelet-specific antigen implicated in most cases of neonatal alloimmune thrombocytopenia.
  - Administering IVIG to the mother during pregnancy is the most successful strategy for increasing the fetal platelet count and has become the recommended standard treatment of known fetal alloimmune thrombocytopenia.
  - Studies have shown that weekly infusions (1 g/kg maternal body weight) beginning at 20 to 24 weeks' gestation stabilize or increase the fetal platelet count in fetuses with documented alloimmune thrombocytopenia.
  - In very high-risk pregnancies (intracranial hemorrhage in a previous sibling before 30 weeks' gestation), some investigators recommend starting IVIG therapy as early as 12 to 14 weeks' gestation.
  - Although the mechanism of action of IVIG in FAIT is not clearly defined, it is postulated that IVIG

decreases maternal alloantibodies and may also block transplacental transport of maternal antiplatelet antibodies.
    - There is still no consensus on the optimal protocol for managing IVIG after it is begun.
- Paraneoplastic Syndromes
    - Paraneoplastic syndromes are the remote effects of a cancer unrelated to the effects of the tumor or its metastasis. Sometimes they are associated with low immune globulin values and sometimes they are associated with autoantibodies.
    - The combination of IVIG, cyclophosphamide, and methylprednisolone in patients with paraneoplastic cerebellar degeneration and antineuronal antibodies in is not effective.
    - Anti-NMDA encephalitis
        - Although no standard of care for anti-NMDA encephalitis exists, on the basis of data from the reviews completed, concurrent IVIG (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) is preferred over plasma exchange.
        - If no response is seen after 10 days, a second-line therapy is started.
        - Although there is a paucity of randomized controlled and comparative trials regarding the use of IVIG for this disorder, because of the severity of anti-NMDA encephalitis and on the basis of data from the completed reviews and case series, it has been noted that individuals who received early tumor treatment (usually with immunotherapy) had better outcome and fewer neurological relapses than the rest of the patients,
        - IVIG given concurrently with corticosteroids has been determined to assist with full or substantial recovery in approximately 75% of the individuals with anti- NMDA encephalitis.
    - Opsoclonus-myoclonus-syndrome or "dancing eyes-dancing feet" syndrome is a rare neurological disorder that affects infants and young children and has been described in adult patients with cancer
        - The current therapeutic strategies for OMS provide a broad spectrum of nonselective immunotherapies, including noncytotoxic and cytotoxic drugs, intravenous immunoglobulins, ACTH and plasma exchange
        - Intravenous immunoglobulin G is occasionally used as an alternative to ACTH.
        - Altogether, the available evidence suggests that IVIG may be an effective treatment in parainfectious and idiopathic OMS.
        - Treatment with IVIG has been reported in a few idiopathic adult-onset OMS cases in literature and they have concluded that idiopathic OMS presents an age dependent prognosis and immunotherapy. IVIG seems to be associated with a faster recovery.
        - Trends in the standard of care of OMS report that ACTH, prednisone, and intravenous immunoglobulin were used with equal frequency, but ACTH was associated with the best early response
- Parvovirus B19 Infection
    - Human parvovirus B19 infection can give rise to the loss of mature red blood cells, severe anemia and the formation of immune complexes.
    - A robust antibody response is necessary for virus clearance and control of the infection.
    - IVIG has been shown to be effective in recurrent infection in augmenting the inadequate humoral immune response. Based on the evidence available, IVIG therapy has become the standard of care if the aplastic crisis becomes prolonged, even though there are no definitive clinical trials demonstrating the efficacy of HPV B19-induced anemia.
    - Use of IVIG for treatment in parvovirus B19 infection is a category 2A NCCN recommendation
    - IVIG dose adjustments:
        - Adjustment of the IVIG dose and time interval between doses should be based on trough levels measured every month for the first three months of therapy and again at six months
        - Adjustments to infusion rates and measuring of serum IgG levels may be needed during

infections or in persons who have a high catabolism of infused IgG
    - To reduce infection frequency in immunodeficient patients, serum trough levels should be maintained at 670-730 mg/dl, a value close to the lower limit of normal. All IgG trough levels outside of the low normal range of 6.7-7.3 mg/dl require dosage adjustment.
- Pemphigus Vulgaris and related conditions:
    - IVIG therapy for Pemphigus Vulgaris must be used only for short-term therapy and not as a maintenance therapy.
    - IVIG dose adjustments:
        - Adjustment of the IVIG dose and time interval between doses should be based on trough levels measured every month for the first three months of therapy and again at six months
        - Adjustments to infusion rates and measuring of serum (immunoglobulin G) IgG levels may be needed during infections or in persons who have a high catabolism of infused IgG
        - To reduce infection frequency in immunodeficient patients, serum trough levels should be maintained at 670-730 mg/dl, a value close to the lower limit of normal. All IgG trough levels outside of the low normal range of 6.7-7.3 mg/dl require dosage adjustment.
    - For Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid (a.k.a. Cicatricial Pemphigoid), Epidermolysis Bullosa Acquisita: the treatment is considered complete when the patient is free of disease after a 16-week interval between the last two infusion cycles;
    - Examples of clinically significant adverse effects to corticosteroids, immunosuppressive agents (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil) are diabetes or fractures from chronic steroid use.
- PI:
    - Common variable immunodeficiency (CVID), the most frequently diagnosed primary immunodeficiency, is characterized by a low serum IgG level antibody deficiency at least 2 SDs below the mean for age, with most patients having concurrent deficiencies of IgA and IgM. Many Patients with CVID have IgG levels below 639 that require IVIG. However, there are rare instances when a patient will have normal IgG levels. The serum immunoglobulin measurement alone does not establish a diagnosis of CVID. A definitive diagnosis of CVID is established when a patient does not demonstrate a prolonged antibody response to immunization with protein antigens (e.g., tetanus) or carbohydrate antigens (e.g., pneumococcal capsular polysaccharides such as pneumovax).
    - Subclass deficiency or IgG subclass deficiency (IGGSD) is diagnosed in patients with recurrent infections, deficiency in one or more IgG subclass levels (less than the 5th percentile or 2 standard deviations below), and normal total concentrations of IgG, IgM, and IgA.
    - Specific antigen deficiency or functional antibody deficiency is diagnosed in patients 2 years and older who present with recurrent respiratory tract infections, normal immunoglobulin and IgG subclass levels, and impaired IgG response to pneumococcal capsular polysaccharide.
    - The gamma globulin band consists of 5 immunoglobulins: about 80% immunoglobulin G (IgG), 15% immunoglobulin A (IgA), 5% immunoglobulin M (IgM), 0.2% immunoglobulin D (IgD), and a trace of immunoglobulin E (IgE).
    - The use of intravenous immune globulin should be reserved for patients with serious defects of antibody function. All immune deficiency conditions require ongoing monitoring of the patient's clinical condition with measurement of pre-infusion (trough) serum IgG levels.
    - For lifelong treatment serum trough IgG levels should be measured before the infusion, and then monitored every 3 months to maintain low normal level (usually 400 – 600 mg/dl).
    - See Appendix E: Reference Ranges for Immune Globulin Levels
- Stiff person syndrome
    - Stiff person syndrome (also known as Moersch-Woltmann syndrome) is a rare progressive neurological disorder characterized by progressive rigidity and stiffness of the axial musculature, associated with

painful spasms, primarily in the lower limbs, neck and trunk.
  - Symptoms are related to autoantibodies directed against glutamic acid decarboxylase in the nervous system called anti-GAD antibodies. This antibody marker, which is an antibody to an enzyme found both in the pancreas and in nerve tissue, is found in high concentrations in classical Stiff-man syndrome.
  - In most cases, improvement in symptoms occurs with combinations of diazepam and baclofen, often in reasonably high dosage. Where all drug treatments fail to give sufficient relief from spasms and pain, treatment is directed against the underlying immunologic condition with drug choices consisting of steroids (either intravenous or orally), plasma exchange or pooled IVIG.
  - Current treatments do not offer or lead to a cure. However, they are able to control symptoms in the majority of patients.
- Weight based dosing calculations: For adults, calculate dosing based on total body weight (TBW) or ideal body weight (IBW), whichever is less. For obese members, use adjusted body weight (adjBW)
  - Cost-effective dosing of immune globulins is achieved by dosing based on the lesser of either total body weight (TBW; i.e., actual body weight) or ideal body weight (IBW).
    - IBW for males: 50 kg + (2.3 x inches over 5 feet)
    - IBW for females: 45.5 kg + (2.3 x inches over 5 feet)
  - For obese members (e.g., BMI is ≥ 30 kg/m2 or TBW is > 20-30% over IBW), adjustes body weight (adjBW) should be used for dose calculations.
    - AdjBW = IBW + [0.4 x (TBW-IBW)]
  - Online adult IBW and adjBW calculator: https://www.mdcalc.com/ideal-body-weightadjusted-body-weight
  - Online BMI calculator: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

APPENDIX E: Reference Ranges for Immune Globulin Levels

- The Mayo Clinic suggests the following reference ranges of immune globulins:

Age	Total IgG	Total IgA	Total IgM
0 to < 5 months	100-334 mg/dL	7-37 mg/dL	26-122 mg/dL
5 to < 9 months	164-588 mg/dL	16-50 mg/dL	32-132 mg/dL
9 to < 15 months	246-904 mg/dL	27-66 mg/dL	40-143 mg/dL
15 to < 24 months	313-1,170 mg/dL	36-79 mg/dL	46-152 mg/dL
2 to < 4 years	295-1,156 mg/dL	27-246 mg/dL	37-184 mg/dL
4 to < 7 years	386-1,470 mg/dL	29-256 mg/dL	37-224 mg/dL
7 to < 10 years	462-1,682 mg/dL	34-274 mg/dL	38-251 mg/dL
10 to < 13 years	503-1,719 mg/dL	42-295 mg/dL	41-255 mg/dL
13 to < 16 years	509-1,580 mg/dL	52-319 mg/dL	45-244 mg/dL
16 to < 18 years	487-1,327 mg/dL	60-337 mg/dL	49-201 mg/dL
≥ 18 years	767-1,590 mg/dL	61-356 mg/dL	37-286 mg/dL

- Some primary immunodeficiency disorders, such as functional antibody deficiency or specific antibody deficiency exhibit normal total IgG concentration but deficiencies in one or more IgG subclasses. The Mayo Clinic suggests the following references ranges:

Age	IgG1	IgG2	IgG3	IgG4
0 to < 5 months	56-215 mg/dL	≤ 82 mg/dL	7.6-82.3 mg/dL	≤ 19.8 mg/dL
5 to < 9 months	102-369 mg/dL	≤ 89 mg/dL	11.9-74.0 mg/dL	≤ 20.8 mg/dL
9 to < 15 months	160-562 mg/dL	24-98 mg/dL	17.3-63.7 mg/dL	≤ 22.0 mg/dL
15 to < 24 months	209-724 mg/dL	35-105 mg/dL	21.9-55.0 mg/dL	≤ 23.0 mg/dL
2 to < 4 years	158-721 mg/dL	39-176 mg/dL	17.0-84.7 mg/dL	0.4-49.1 mg/dL
4 to < 7 years	209-902 mg/dL	44-316 mg/dL	10.8-102.6 mg/dL	0.8-81.9 mg/dL
7 to < 10 years	253-1,019 mg/dL	54-435 mg/dL	8.5-102.6 mg/dL	1.0-108.7 mg/dL
10 to < 13 years	280-1,030 mg/dL	66-502 mg/dL	11.5-105.3 mg/dL	1.0-121.9 mg/dL
13 to < 16 years	289-934 mg/dL	82-516 mg/dL	20.0-103.2 mg/dL	0.7-121.7 mg/dL
16 to < 18 years	283-772 mg/dL	98-486 mg/dL	31.3-97.6 mg/dL	0.3-111.0 mg/dL
≥ 18 years	341-894 mg/dL	171-632 mg/dL	18.4-106.0 mg/dL	2.4-121.0 mg/dL

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Reviewed criteria and updated dosing information	04/2020	
Policy was reviewed: 1) Dosing information Abbreviated forms changed to full forms-QD,BID,TID 2) Dosing info, for drug-Cutaquig regimen updated 3) Dosage form updated for drugs-Flebogamma DIF (5%),Flebogamma DIF (10%),Octagam (10%),Privigen (10%),Gammagard Liquid (10%),Cuvitru (20%) ,Hizentra® (20%) 4) Initial Approval Criteria-Approval duration updated for commercial 5) APPENDIX B: Therapeutic Alternatives verbiage changed 6) APPENDIX C: Contraindications/Boxed Warnings added for Gammaplex 5%,Hyqvia, Privigen 7) Continuation therapy criteria II.A.1. rephrased to “Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy 8) References were updated	02/10/2021	03/09/2021
Policy was reviewed: 1. Background: Updated to include new indication Dermatomyositis. 2. Policy updated to remove drug Carimune NF as it is no longer available. 3. Dosing Information, a. Dosing Regimen, Gammagard® Liquid: Updated maintenance dosing information from Subcutaneous: given once weekly with dose adjusted per PI to Subcutaneous: Maintenance dose is based on clinical response and target IgG trough level	12/15/2021	01/17/2022

b. Dosing Regimen, Hizentra®: updated dosing information from Previous IGIV dose in gm divided by number of weeks between intravenous doses and multiplied by 1.37. Give SC at regular intervals QD to every 2 weeks beginning 1 to 2 weeks after last IV or SC dose depending on dosing regimen. to Initial weekly dose = Previous IGIV dose in gm divided by number of weeks between intravenous doses and multiplied by 1.37. Biweekly (every 2 weeks): Start Hizentra® 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly IGSC infusion. Administer twice the calculated weekly dose. Frequent dosing (2 to 7 times per week): Start Hizentra® 1 week after the last IGIV or IGSC infusion. Divide the calculated weekly dose by the desired number of times per week. Adjust the dose based on clinical response and serum IgG trough levels. c. Dosing Regimen, Cuvitru®: updated dosing information from Previous IGIV/HyQvia dose in grams divided by number of weeks between IGIV or HyQvia doses and multiplied by 1.30. Divide the calculated weekly dose by desired number of times per week or multiply the weekly dose by 2 and administer every 2 weeks. Give subcutaneous at regular intervals once daily to every 2 weeks beginning 1 week after last IGIV or HyQvia dose to Initial: Previous IGIV/HyQvia dose in grams divided by number of weeks between IGIV or HyQvia doses and multiplied by 1.30. Divide the calculated weekly dose by desired number of times per week or multiply the weekly dose by 2 and administer every 2 weeks. Give subcutaneous at regular intervals once daily to every 2 weeks beginning 1 week after last IGIV or HyQvia dose. Switching from Immune Globulin Subcutaneous (Human) treatment (IGSC): Weekly dose (in grams) should be the same as the weekly dose of prior IGSC treatment (in gm). Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week. Biweekly dosing: Multiply the calculated weekly dose by 2. Infusion sites: up to 4 infusion sites simultaneously, with at least 4 inches between sites avoiding bony prominences. Rotate sites with each administration. d. Dosing Regimen, Xembify®: updated dosing information from Previous IGIV dose in grams divided by number of weeks between intravenous doses and		

multiplied by 1.37. Give subcutaneous at regular intervals once daily to every week beginning 1 week after last intravenous dose. Or Previous subcutaneous weekly dose administered in regular intervals once daily to every week. To Previous IGIV dose in grams divided by number of weeks between intravenous doses and multiplied by 1.37. Give subcutaneous at regular intervals once daily to every week beginning 1 week after last intravenous dose. Or Previous subcutaneous weekly dose administered in regular intervals once daily to every week. Switching from immune globulin subcutaneous (human) treatment (IGSC): Weekly dose (grams) should be the same as the weekly dose of prior IGSC treatment (grams). e. Dosing Regimen, Octagam® 10%: Updated to include dosing information for indication Dermatomyositis. f. Gammagard S/D: Updated to remove dosing information for Subcutaneous dosage. g. Panzyga®: Updated to include dosing information for indication CIDP h. Dosing Regimen, Gammaked® Liquid: Updated dosing information from 1 g/kg IV once daily given on 2 consecutive days or 0.4 g/kg IV once daily given on 5 consecutive days to 2 g/kg for indication ITP. 4. Dosage Forms, a. Gammagard S/D: Updated dosage form from IV administration - freeze dried for reconstitution Gammagard S/D-5% single-use bottle: 5 gm 10% single-use bottle: 10 gram to Gammagard S/D-Freeze-dried preparation containing 5 gm or 10 gm IgG b. Gammaked™ : Updated dosage form from Gammaked™ (10%)-Single-use bottle: 1, 2.5, 5, 10, 20 gram to Gammaked™ is a sterile solution for injection supplied in 1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), or 20 g (200 mL) single use vials. c. Asceniv™: Updated dosage form from (10%)-Single-use vial: 5 gm to (10%)-Single-use vial: 5 gm in 50 ml solution. d. Bivigam™: Updated dosage form from (10%)-Single-use vial: 5, 10 gm to (10%)-Single-use vial: 5 gm in 50 ml, 10 gm in 100mL solution 5. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy.		

6. Initial Approval Criteria,
   a. I.E.1: Updated indication from Diagnosis of acute or chronic ITP to Diagnosis of ITP.
   b. I.A.E.2: Updated to include new indication criteria Member meets one of the following (a-b):
      a. Chronic ITP: If request is for Flebogamma® 10%, Gammagard S/D®, Gammaked™, Gammaplex®, Gamunex C®, Octagam 10%, Panzyga®, Privigen
      b. Acute ITP: Gammaked™, Gamunex C®
   c. I.D.5.b: Updated Dose criteria from For CIDP: Loading dose 2 g per kg Intravenous given in divided doses over two to four consecutive days, following by maintenance dose of 1 g per kg IV every 3 weeks;to For CIDP: Gammaked™, Gamunex®-C; Loading dose 2 g per kg Intravenous given in divided doses over two to four consecutive days, following by maintenance dose of 1 g per kg IV every 3 weeks.
   d. I.B.2: Updated to include Request for Octagam 10%;
   e. Initial Approval Criteria, I.E.3: Updated to include new age criteria Member meets one of the following (a or b or c):
      a. Octagam 10% , Gammaked®, Gammagard S/D®, Gamunex C®: Age at least 18 years or older
      b. Privigen®: Age at least 15 years or older
      c. Flebogamma®, Gammaplex®: 10%: 2 years of age and older
   f. I.P.3: Updated to include new age criteria Meet one of the following (a, b or c)
      a. Asceniv™: Age 12 to 17 years
      b. Octagam®, Bivigam™: Age at least 6 years or older
      c. Xembify®, Panzyga®, Hizentra®, Gamunex®-C, Gammaplex®, Gammaked™, Gammagard® S/D, Gammagard® liquid, Flebogamma® DIF, Cuvitru™ Cutaquig®: Age at least 2 years or older
   g. I.S: Updated to include approval criteria for indication, Management of Immunotherapy-Related Toxicities (CAR T-Cell-Related Toxicities)
   h. I.T: Updated to include approval criteria for indication, Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities)
   i. E.6: Updated to add a.Acute bleeding due to severe thrombocytopenia (platelet count less than 30,000/ µL), b. In patients with severe thrombocytopenia(platelet counts less than 20,000/ µL) considered to be

at risk for intracerebral hemorrhage; c. Platelets counts persistently at or below 20,000/ µL(for CITP);

j. I.5:Updated to add ,"documented failure or inability to tolerate chemotherapy or radiation therapy".
k. K.3.C.i and K.3.C.ii updated to add for LEMS and for MG respectively.
l. N.3 updated serum IgG concentration to less than 250 mg/dl from 400 mg/dl.

7. All Initial Approval Criteria were updated to remove requirement: Member meets one of the following (a or b): a.Request is for Gammagard unless there is a specific health plan-preferred* immune globulin product; b. Failure of Gammagard (or health plan-preferred* immune globulin product) unless contraindicated or clinically significant adverse effects are experienced; *Immune globulin products are generally interchangeable, and it is at the health plan's discretion to prefer a clinically appropriate alternative product based on the time of request.
8. Continued Therapy Approval Crtieria, IIA updated from Kawasaki Syndrome/Incomplete (Atypical) Kawasaki Disease, Viral Prophylaxis (Hep A, Measles, Varicella, Rubella) to Kawasaki Syndrome/Incomplete (Atypical) Kawasaki Disease, Viral Prophylaxis (Hep A, Measles, Varicella, Rubella), Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities), Management of Immunotherapy-Related Toxicities (CAR T-Cell-Related Toxicities).
9. Appendix A: Updated to include abbreviations DM.
10. Appendix B, Dosing Regimen, for
    a. diazepam (Valium®): Updated dosing information from 20 to 80 mg/day by mouth (given in divided doses) to 2 to 10 mg orally 3 to 4 times daily for indication stiff person syndrome.
    b. pyridostigmine (Mestinon®; Mestinon® Timespan extended release): Updated dosing information from Pediatrics*: 1 mg/kg by mouth Q4 to 6 hrs to Pediatrics*: 0.5 to 1 mg/kg by mouth every 4 to 6 hrs for indication Myasthenia Gravis.
    c. tacrolimus (Prograf®): Updated dosing information from 0.075mg/kg/day by mouth PO OR begin at 1 mg by mouth BID, increase to reach trough of 5- 10 ng/ml to 0.075mg/kg/day by mouth twice daily or begin at 1 mg by mouth twice daily, increase to reach trough of 6- 10 ng/ml for indication Dermatomyositis/Polymyositis

11. Appendix B, Dosing Regimen, pyridostigmine (Mestinon®; Mestinon® Timespan extended release): Updated to include dosing information for Pediatrics for indication Myasthenia Gravis. 12. Appendix B, Drug Name: Updated to remove unavailable generic therapeutic alternative a. amifampridine b. elapegademase-lvlr c. rituximab d. rheumatrex e. teriflunomide f. interferon beta-1a g. interferon beta-1b h. fingolimod i. alemtuzumab j. ocreliuzmab k. peginterferon beta-1a l. natalizumab 13. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 14. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 15. References were reviewed and updated.		