Clinical Policy: Immune Globulins

Reference Number: PA.CP.PHAR.103
Effective Date: 01/2018
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Description

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

FDA Approved Indication(s)

Brand Name	ROA	PI	ITP	CIDP	KS	MMN	CLL	VPPX	DM
Alyglo	IV	x							
Asceniv	IV	x							
Bivigam	IV	x							
Cutaquig	SC	x							
Cuvitru	SC	x							
Flebogamma DIF	IV	x	x #						
GamaSTAN, GamaSTAN S/D	IM							x	
Gammagard Liquid	IV, SC	x		x*		x*			
Gammagard S/D	IV	x	x		x		x		
Gammaked	IV, SC	x	x*	x*					
Gammaplex	IV	x	x						
Gamunex-C	IV, SC	x	x*	x*					
Hizentra	SC	x		x					
HyQvia	SC	x		x					
Octagam	IV	X^	x #						x#
Panzyga	IV	x	x	x					
Privigen	IV	x	x	x					
Xembify	SC	x							

If available as IV and SC, then * = IV only; If available as 5% and 10%, then: # = 10% only, ^ = 5% only
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)

Limitation(s) of use:

- Safety and efficacy of chronic use of recombinant human hyaluronidase in Hyqiva have not been established in conditions other than PI.
- Privigen maintance therapy in CIDP has not been studied beyond 6 months

Policy/Criteria
Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of PA Health & Wellness® that the immune globulin products referenced above are **medically necessary** when the following criteria are met:

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 an hematology/oncology specialist or immunologist;
3. Current (within the last 6 months) hypogammaglobulinemia as evidenced by two separate measurements of immunoglobulin G (IgG) level <500 mg/dL;
4. Member has had recurrent serious bacterial infections (e.g., requiring IV antibiotics, hospitalization, or consultation with an infectious disease specialist) within the past 12 months;
5. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard, or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
6. Request meets one of the following (a or b) [Note: 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). *(See Appendix F for weight-based dosing calculations.)*]:
   a. 400 mg/kg IV every 3-4 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: 6 months

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

1. Diagnosis of dermatomyositis (DM) or polymyositis (PM);
2. Prescribed by or in consultation with a dermatologist, neurologist, or neuromuscular specialist;
3. 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*);

4. For dermatomyositis requests only: Failure of a trial of rituximab, unless contraindicated, clinically significant adverse effects are experienced, or the member is diagnosed with juvenile dermatomyositis plus calcinosis;
   **Prior authorization may be required for rituximab*
5. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard, or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
6. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. 2 g/kg IV 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: 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard, or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 2 g per kg IV 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: 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 or b):
    a. Diagnosis is AIDP/GBS and member meets one of the following (i-vii):
        i. Inability to stand or walk at least 30 feet without assistance;
        ii. ICU admission required for aspiration or mechanical ventilation;
        iii. Miller-Fisher syndrome;
        iv. Inability to raise head against gravity;
        v. Severe bulbar palsy (e.g., impaired gag reflex, dysarthria and/or dysphagia);
        vi. Bilateral facial weakness;
        vii. Autonomic dysfunction (e.g., unexplained dysrhythmia, blood pressure fluctuations, significant bowel or bladder involvement);
    b. Diagnosis is CIDP and member meets all of the following (i-v):
        i. Disease is progressive or relapsing for more than 2 months;
        ii. Member has either of the following (a or b):
            a. Both of the following, characterizing typical CIDP (i and ii):
                i. Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities;
                ii. Absent or reduced tendon reflexes in all extremities;
            b. One of the following, characterizing atypical CIDP (i-iii):
                i. Predominantly distal (distal acquired demyelinating symmetric, DADS) or asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb) disease;
                ii. Pure motor symptoms;
                iii. Pure sensory symptoms (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron);
        iii. Diagnosis has been confirmed via electrodiagnostic testing;
        iv. Member does not have any of the following (a-f):
            a. Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy;
            b. Hereditary demyelinating neuropathy;
            c. Prominent sphincter disturbance;
            d. Diagnosis of multifocal motor neuropathy;
            e. IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein;
            f. Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral radiculoplexus neuropathy;

v. For members who do not have pure motor symptoms, 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard:
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a, b or c) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. For AIDP/GB: Dose does not exceed 0.4 g per kg per day IV for 5 days;
   b. For CIDP (i, ii or iii):
      i. Dose does not exceed a loading dose of 2 g per kg IV given in divided doses over two to five consecutive days, followed by maintenance dose of 1 g per kg IV every 3 weeks;
      ii. For Hizentra: Dose does not exceed one of the following (1 or 2):
         1. 0.2 g per kg body weight SC per week, starting 1 week after last intravenous immune globulin (IVIG) infusion;
         2. If evidence is submitted demonstrating worsening symptoms on 0.2 g per kg dose, 0.4 g per kg body weight SC per week;
      iii. For HyQvia: Dose does not exceed previous IV dose (*refer to section V for poduct-specific dosing);*
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: – 6 months

E. Idiopathic Thrombocytopenic Purpura (Acute or Chronic) (must meet all)**:**
1. Diagnosis of acute or chronic ITP;
2. Prescribed by or in consultation with a hematologist;
3. Member meets one of the following (a or b):
   a. Failure of one of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated (i or ii):
      i. Systemic corticosteroids (e.g., prednisone);
      ii. Rh_o(D) immune globulin (RhIG);
      **Prior authorization is required for RhIG*
   b. Pregnant;
4. Member meets one of the following (a – e):
   a. Current (within the last 30 days) platelet count < 30,000/µL;
   b. Actively bleeding;
   c. High risk of life-threatening hemorrhage;

d. Splenectomy is scheduled;
e. Pregnant;

5. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
6. Request meets one of the following (a, b, c, or d) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 1 g per kg per day IV for 1 to 2 days;
   b. Dose does not exceed 400 mg per kg per day IV for up to 5 days;
   c. For Gammagard S/D: Dose does not exceed 1 g per kg for up to 3 total doses QOD;
   d. Dose is supported by practice guidelines or peer-reviewed literatures for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: – 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a, b, c, or d):
   a. Dose does not exceed 1 g per kg IV as a single infusion;
   b. Dose does not exceed 400 mg per kg IV daily for 4 consecutive days;
   c. Dose does not exceed 2 g per kg IV as a single infusion;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: One time approval (1 month)

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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
4. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 140 g IV per infusion;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
4. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 2.4 g per kg IV 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: 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 a hematologist, oncologist, or immunologist;
3. Current (within the last 6 months) hypogammaglobulinemia as evidenced by two separate measurements of immunoglobulin G (IgG) level < 400 mg/dL;
4. Member has had recurrent serious bacterial infections (e.g., requiring IV antibiotics, hospitalization, or consultation with an infectious disease specialist) within the past 12 months;
5. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
6. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 400 mg per kg IV 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: 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, Aubagio, Betaseron, Rebif, Copaxone, Tecfidera, Gilenya) at up to maximally indicated doses unless contraindicated or clinically significant side effects are experienced;
4. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed an initial loading dose of 400 mg per kg per day IV for 5 days, followed by maintenance dose of 1 g per kg IV 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: 6 months

K. Myasthenia Gravis (MG) Or 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 all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (i, ii, and iii):
      i. Amifampridine (for LEMS) or a cholinesterase inhibitor (e.g., pyridostigmine; for MG);
      ii. Systemic corticosteroid (e.g., prednisone);
      iii. Immunosuppressant (e.g., azathioprine) *(see Appendix B)*;
4. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 2 g per kg IV divided over 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: 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;

c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;

4. Request meets one of the following (a, b, c, or d) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 2 g per kg IV per month;
   b. Dose does not exceed 0.4 g per kg IV per day;
   c. Dose does not exceed 200 mg per kg SC per week;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed an initial dose of 2 g per kg per day for up to 5 days, followed by maintenance dose of 400 mg per kg IV 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: 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 400 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 vaccines (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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 400 mg per kg IV 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: 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 or immunologist;
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 rituximab unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for rituximab*

6. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
7. Request meets one of the following (a, b, c, or d) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 2 gm per kg IV every 4 weeks;
   b. Dose does not exceed 400 mg per kg per day IV for 5 days (1 cycle only; may repeat up to three times in a 6-month period);
   c. Dose does not exceed 300 mg per kg per day IV 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: 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, ADA, PNP, RAG defects, Ataxia Telangiectasia, Wiskott-Aldrich syndrome, DiGeorge syndrome);
   g. Subclass Deficiency or Functional Antibody Deficiency (*see Appendix D*);
   h. Functional/specific antibody deficiency (*see Appendix D*);
2. Prescribed by or in consultation with an immunologist or hematologist;
3. 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 serious bacterial infections (e.g., requiring IV antibiotics, hospitalization, or consultation with an infectious disease specialist) 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 IV 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);

4. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;
   d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;
5. Request meets one of the following (a, b, c, or d) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 800 mg per kg IV every 3 to 4 weeks;
   b. Dose does not exceed 600 mg per kg SC every 3 to 4 weeks;
   c. Dose does not exceed SC: initial dose of 1.37 x previous initial IV dose given 1 week after last IVIG infusion (*refer to section V. for product-specific dosing frequency*);
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 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. Member meets one of the following (a, b, c or d):
   a. Request is for Gammagard;
   b. Failure of Gammagard;
   c. Member has intolerance or contraindication to Gammagard or if Gammagard is unavailable due to shortage, member must use Gamunex®-C or Gammaked®, unless clinically significant adverse effects are experienced or both are contraindicated;

d. Gammagard, Gamunex-C, and Gammaked, are all unavailable due to shortage, and request is for an immune globulin product other than those listed;

5. Request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
   a. Dose does not exceed 2 g per kg IV divided over 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: 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 follows (a or b):
         1) 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;
         2) 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 (rubeola) 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 (1 – 6):
         1) Measles vaccine is locally unavailable;
         2) History of severe allergic reaction (anaphylaxis) to the measles vaccine;
         3) Pregnancy;
         4) Immunocompromised;
         5) Has been >3 days since exposure;
         6) 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 (1 – 5):
1) Varicella vaccine is locally unavailable;
2) History of a severe allergic reaction (anaphylaxis) to the varicella vaccine;
3) Pregnancy;
4) Immunocompromised;
5) 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. Request meets one of the following (a – e) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less. For obese members, use adjBW. *(See Appendix F for weight-based dosing calculations.)*]:
a. Hepatitis A (i, ii, or iii): Dose does not exceed:
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: Dose does not exceed 15 mL IM once;
c. Varicella: Dose does not exceed 1.2 mL/kg IM once;
d. Rubella: Dose does not exceed 0.55 mL/kg IM 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:
Hepatitis A: Duration of request or 6 months, whichever is less
All other indications: One time approval (1 month)

S. Other diagnoses/indications
1. Refer to PA.CP.PMN.53

II. Continued Therapy

A. Kawasaki Syndrome/Incomplete (Atypical) Kawasaki Disease, Viral Prophylaxis (Hep A, Measles, Varicella, Rubella):
1. Re-authorization is not permitted. Members must meet the initial approval criteria.
Approval duration: Not applicable

B. All Other Indications in Section I (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase due to inadequate response to previous dose, request meets one of the following (a or b) [Note: for adults, calculate dosing based on TBW or IBW, whichever is less, and for obese members use adjBW, unless the newly

calculated dose is lower than the currently administered dose. *(See Appendix F for weight-based dosing calculations)*]:
   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*).
4. For adults with diagnoses other than primary immunodeficiency or cancer-related infection prophylaxis: the requested dose is calculated based on TBW or IBW, whichever is less, and for obese members adjBW is used for dose calculation, unless documentation supports the inability to adjust dosing in this manner (See Appendix F for weight-based dosing calculations).

Approval duration: 6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

B. The following conditions are considered not medically necessary:
1. Acquired factor VIII inhibitors;
2. Adrenoleukodystrophy;
3. Alzheimers Disease;
4. Amyotrophic lateral sclerosis;
5. Angioedema;
6. Antiphospholipid syndrome, not including catastrophic antiphospholipid syndrome (CAPS);
7. Aplastic anemia;
8. Asthma;
9. Autism;
10. Autoimmune chronic urticaria;
11. Behçet's syndrome;
12. Cardiomyopathy, acute;
13. Chronic fatigue syndrome;
14. Chronic sinusitis;
15. Complex pain regional syndrome (CPRS) ;
16. Congenital heart block;
17. Critical illness myopathy (necrotizing myopathy) (ICD10: G7281);
18. Cystic fibrosis;
19. Diabetes mellitus;
20. Diamond-Blackfan anemia;
21. Dysautonomia, acute idiopathic;

22. Eczema;
23. Encephalopathy, acute;
24. Endotoxemia;
25. Epilepsy;
26. Goodpasture's syndrome;
27. Hemolytic transfusion reaction;
28. Hemolytic-uremic syndrome;
29. Hemophagocytic syndrome;
30. Idiopathic lumbosacral flexopathy;
31. Idiopathic progressive neuropathy (ICD10: G603);
32. Immune-mediated neutropenia;
33. Inclusion body myositis;
34. Infection prevention and control in newborns;
35. Intractable seizures;
36. Iridocyclitis, unspecified (ICD10: H209);
37. Leukemia, acute lymphoblastic;
38. Lower motor neuron syndrome;
39. Multiple sclerosis - primary progressive or secondary types;
40. Myalgia, myositis, unspecified;
41. Myelopathy, HTLV-I associated;
42. Nephropathy, membranous;
43. Nephrotic syndrome;
44. Non-immune thrombocytopenia;
45. Ophthalmopathy, euthyroid;
46. Oral use;
47. Orbital myositis, bilateral (ICD10: H05123);
48. Otitis media, recurrent;
49. Other diseases of capillaries [Clarkson disease (systemic capillary leak syndrome)] (ICD10: I788);
50. Otitis media, recurrent;
51. Paraneoplastic cerebellar degeneration;
52. Paraproteinemic neuropathy;
53. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS);
54. POEMS syndrome (see General Information – Section III for definition);
55. Polyarteritis nodosa;
56. Progressive lumbosacral plexopathy;
57. Radiculoneuritis, Lyme;
58. Recurrent otitis media;
59. Recurrent spontaneous pregnancy loss;
60. Refractoriness to platelet transfusion;
61. Reiter's syndrome;
62. Renal failure, acute;
63. Rheumatoid arthritis (adult and juvenile);
64. Scleroderma;
65. Sensory neuropathy;

66. Thrombocytopenia (non-immune);
67. Vasculitis associated with other connective tissue diseases;
68. Vogt-Koyanagi-Harada syndrome;

IV. Appendices/General Information

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
DM: dermatomyositis
FAIT: fetal 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 MIMIG: immune globulin (IM route)
IGIV: immune globulin intravenous
ITP: immune thrombocytopenic purpura
IVIG: immune globulin (IV route)
LEMS: Lambert Eaton myasthenic syndrome
MG: myasthenia gravis
MM: multiple myeloma
MMN: multifocal motor neuropathy
NAIT: neonatal alloimmune thrombocytopenia
NF: nanofiltered
NMDA: N-methyl D-aspartate
OMS: opsoclonus-myoclonus syndrome
PI: primary [humoral] immunodeficiency
PM: polymyositis
POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes
RhIG: Rh_o(D) immune globulin
SCID: severe combined immunodeficiency disorders
SCIG: immune globulin (SC route)
S/D: solvent/detergent treated
VZIG: varicella zoster immune globulin

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
baclofen (Lioresal®)	**Stiff Person Syndrome*** 20 mg PO BID or TID, or 50 to 1,600 mcg/day intrathecally	PO: 80 mg/day IT: 1600 mcg/day
diazepam (Valium®)	**Stiff Person Syndrome*** 20 to 80 mg/day PO (given in divided doses)	Daily doses needed to control the disease can be as high as 100 to

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		200 mg/day in some patients
Firdapse® (amifampridine)	**Lambert-Eaton Myasthenic Syndrome** *Adults:* 15 mg to 30 mg PO 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® (amifampridine)	**Lambert-Eaton Myasthenic Syndrome** *Pediatric (age 6 to <17 years) and weight ≥ 45 kg:* 15 to 30 mg PO 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 PO 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 (pyridostigmine extended release)	**Myasthenia Gravis** Immediate Release (IR) tablets and syrup *Adults*: 60 to 1,500 mg PO daily in divided doses (avg 600 mg PO daily) *Pediatrics**: 1 mg/kg PO Q4 to 6 hrs Extended Release 180 to 540 mg PO QD or BID	IR: 1,500 mg/day (adults) or 7 mg/kg/day (pediatrics) ER: 1,080 mg/day
Revcovi™ (elapegademase-lvlr)	**ADA-SCID** Adagen-naïve: 0.2 mg/kg twice a week IM Transitioning from Adagen: 0.2 mg/kg weekly IM	0.4 mg/kg/week
Rhophylac, WinRho SDF (Rh_o(D) immune globulin)	**Idiopathic Thrombocytopenic Purpura in non-splenectomized, Rh_o(D) antigen positive patients** Initial: 50 mcg/kg IV Maintenance Therapy: 25 to 60 mcg/kg IV	75 mcg/kg*
Rituxan® (rituximab)	**Pemphigus Vulgaris** Initial: Two-1000 mg IV infusions separated by 2 weeks in combination with a tapering course of glucocorticoids Maintenance Therapy: 500 mg IV at month 12 and every 6 months thereafter **Dermatomyositis/Polymyositis*** 1,000 mg/m^2 IV weekly x 2 weeks	500 mg/6 months

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Immunosuppressive agents		
azathioprine (Imuran®)	**Dermatomyositis/Polymyositis*, Myasthenia Gravis*** 2 mg/kg PO QD or 50 mg/day PO up to 2 to 3 mg/kg/day **Pemphigus vulgaris and associated conditions*** 2 to 3 mg/kg/day PO	3 mg/kg/day
cyclophosphamide (Cytoxan®)	**Dermatomyositis/Polymyositis*** 1 to 3 mg/kg/day PO QD or 500 mg IV every 2 weeks for 6 doses **Pemphigus vulgaris and associated conditions*** 50 to 75 mg/day PO or pulsed regimen of 500 mg IV on day, and then every 4 weeks thereafter in combination with oral cyclophosphamide and dexamethasone	Not applicable
cyclosporine (Gengraf®, Neoral®, Sandimmune®)	**Dermatomyositis/Polymyositis*, Myasthenia Gravis*** 5 to 10 mg/kg/day PO	Not applicable
methotrexate (Rheumatrex®)	**Dermatomyositis/Polymyositis*** 10 to 25 mg/week PO/IV	50 mg/week
mycophenolate mofetil (Cellcept®)	**Dermatomyositis/Polymyositis*** 250 to 500 mg PO BID, increasing to a target dose of 1,500-3,000 mg/day **Myasthenia Gravis*** 1 g PO BID **Pemphigus vulgaris and associated conditions*** 35 to 45 mg/kg/day PO or 1 g PO BID	DM/PM: 3 g/day PV, etc: 2 g/day
tacrolimus (Prograf®)	**Dermatomyositis/Polymyositis*** 0.075mg/kg/day PO BID OR begin at 1 mg PO BID, increase to reach trough of 5-10 ng/ml **Myasthenia Gravis*** 3 mg PO QD	Not applicable
Systemic corticosteroids (e.g., prednisone,	An equivalent dose of prednisone 1 mg/kg/day (with or without tapering)	2 mg/kg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
prednisolone, methylprednisolone)		
Disease-modifying therapies for relapsing remitting MS		
Aubagio® (teriflunomide)	7 or 14 mg PO QD	14 mg/day
Avonex®, Rebif® (interferon beta-1a)	*Avonex*: 30 mcg IM Q week *Rebif*: 22 mcg or 44 mcg SC TIW	*Avonex*: 30 mcg/week *Rebif*: 44 mcg TIW
Betaseron®, Extavia® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
glatiramer acetate (Copaxone®, Glatopa®)	*Copaxone*: 20 mg SC QD or 40 mg SC TIW *Glatopa*: 20 mg SC QD	*Copaxone*: 20 mg/day or 40 mg TIW *Glatopa*: 20 mg/day
Gilenya® (fingolimod)	0.5 mg PO QD	0.5 mg/day
Lemtrada® (alemtuzumab)	IV 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
Novantrone® (mitoxantrone)	12 mg/m^2 given as a short (approximately 5 to 15 minutes) IV every 3 months	Cumulative lifetime dose of ≥ 140 mg/m^2
Ocrevus® (ocreliuzmab)	Initial: 300 mg IV, then 300 mg IV 2 weeks later Maintenance: 600 mg IV every 6 months	600 mg/6 months
Plegridy® (peginterferon beta-1a)	125 mcg SC Q2 weeks	125 mcg/2 weeks
Tecfidera® (dimethyl fumarate)	120 mg PO BID for 7 days, followed by 240 mg PO BID	480 mg/day
Tysabri® (natalizumab)	300 mg IV every 4 weeks	300 mg/4 weeks
Zinbryta® (daclizumab)	150 mg SC once monthly	150 mg/month

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

**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
- Boxed warning(s): thrombosis, renal dysfunction, and acute renal failure

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:
  - Per the 2020 American Academy of Dermatology treatment guidelines for dermatomyositis, in cases where a combination of systemic corticosteroids and an oral immunosuppressant fail, rituximab is the appropriate next step in therapy. In individuals with vasculopathic or calcinotic lesions, adults with anti-MDA5 positivity, or children with NXP-2 positivity, rituximab plus systemic corticosteroids can be considered first-line treatment. Additionally, patients with juvenile dermatomyositis and calcinosis should be preferentially treated with IVIG because it has the best data supporting its use for calcinosis specifically.
  - 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 v. 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.
  - Response to treatment was defined by the following:
    - Per the 2019 ASH guidelines:
      - Early response is as a platelet count ≥ 30,000/µL and at least doubling baseline at 1 week
      - Initial response is defined as a platelet count ≥ 30,000/µL and at least doubling baseline at 1 month
      - Durable response is defined as a platelet count ≥ 30,000/µL and at least doubling baseline at 6 month
    - Per the 2009 International Working Group consensus panel of ITP excerpts:
      - Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define complete response [CR] or response [R]) or 1 day apart when used to define no response [NR] or loss of response
      - CR: platelet ≥ 100,000/µL and absence of bleeding
      - R: platelet count ≥ 30,000/µL and at least 2-fold increase the baseline count and absence of bleeding
      - NR: platelet < 30,000/µL or less than 2-fold increase of baseline platelet count or bleeding
      - Loss of CR or R: platelet count below 100,000/µL or bleeding (from CR) or below 30,000/µL or less than 2-fold increase of baseline platelet count or bleeding (from R)
  - 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 Disease:
  - The efficacy of intravenous immunoglobulin (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:
  - PA Health & Wellness considers the combination of intravenous immunoglobulin (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/m^2) 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 (OMS) 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, adrenocorticotropic hormone (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
- Pemphigus Vulgaris and related conditions:
    - IVIG therapy for Pemphigus Vulgaris must be used only for short-term therapy and not as a maintenance therapy.

- 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
  - Paraneoplastic Stiff-man 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.

- Coverage is excluded for the following indications. The use of immune globulins for these indications is considered investigational due to lack of conclusive, evidence-based data with randomized controlled trials. As such, alternative therapies for these indications include:
  - Critical illness myopathy (necrotizing myopathy): corticosteroids (e.g., prednisone, methylprednisolone), immunosuppressive agents (e.g., cyclophosphamide, methotrexate, azathioprine)
  - Idiopathic progressive neuropathy: corticosteroids
  - Iridocyclitis, unspecified: corticosteroids
  - Orbital myositis, bilateral: corticosteroids
  - Other diseases of capillaries [Clarkson disease (systemic capillary leak syndrome)]: corticosteroids
- On February 2018, CSL Behring announced product discontinuation of Carimune NF given the preference among healthcare professionals and patients for newer, more advanced immune globulin options.
  https://www.fffenterprises.com/assets/downloads/PR-carimune-nf-letter-of-discontinuation.pdf

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/d

- 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

Age	IgG1	IgG2	IgG3	IgG4
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

Appendix F: Weight-based Dose Calculations

- 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/m^2 or TBW is > 20-30% over IBW), adjusted 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-weight-adjusted-body-weight
- Online BMI calculator: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

V. Dosage and Administration

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.

Drug Name	Indication	Dosing Regimen	Maximum Dose
Alyglo	PI	300 to 800 mg/kg IV every 21 or 28 days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable

Asceniv	PI	300 to 800 mg/kg IV every 3 to 4 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Bivigam	PI	Initial: 300 to 800 mg/kg IV every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Cutaquig	PI	Previous IGIV dose in grams divided by number of weeks between IV doses and multiplied by 1.40. Provided the total weekly dose is maintained, any dosing interval from daily up to weekly can be used. [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Cuvitru	PI	Initial: Previous IGIV/HyQvia dose in grams divided by number of weeks between IV doses and multiplied by 1.30. Prorate the weekly dose and give SC at regular intervals QD to every 2 weeks beginning 1 week after last IV or HyQvia dose. [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Flebogamma 5%	PI	Initial: 300 to 600 mg/kg IV every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response	Not applicable

		[Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	
Flebogamma 10%	ITP	1 g/kg IV QD for 2 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: 300 to 600 mg/kg IV every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Gamastan, Gamastan S/D	Hepatitis A prophylaxis	Household and institutional case contacts: 0.1 mL/kg IM once Travel to Hepatitis A-endemic areas: Up to 1 month stay: 0.1 mL/kg IM once Up to 2 months stay: 0.2 mL/kg IM once 2 months or longer stay: 0.2 mL/kg IM every 2 months [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	0.1 mL/kg as a single dose or 0.2 mL/kg every 2 months
	Measles postexposure prophylaxis	0.25 mL/kg IM once [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	0.25 mL/kg
	Rubella postexposure prophylaxis	0.55 mL/kg IM once [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	0.55 mL/kg

	Varicella postexposure prophylaxis	0.6 to 1.2 mL/kg IM once [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	1.2 mL/kg
Gammagard Liquid	MMN	0.5 to 2.4 g/kg/month IV [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: IV: 300 to 600 mg/kg every 3 to 4 weeks SC: Previous IGIV dose in grams divided by number of weeks between IV doses and multiplied by 1.37 Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response SC: given once weekly with dose adjusted per PI [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	CIDP	Loading dose: 2 g/kg IV given in divided doses over 2 to 5 consecutive days Maintenance dose: 1 g/kg IV given in divided doses over 1 to 4 consecutive days, every 3 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Gammagard S/D	CLL	400 mg/kg IV every 3 to 4 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	ITP	1 g/kg IV, up to 3 doses on alternate days	Not applicable

		[Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	
	KS	1 g/kg IV single dose or 400 mg/kg IV QD for four consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: IV: 300 to 600 mg/kg every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Gammaked	CIDP	Loading dose: 2 g/kg IV given in divided doses over 2 to 4 consecutive days Maintenance dose: 1 g/kg IV every 3 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	ITP	1 g/kg IV QD given on 2 consecutive days or 0.4 g/kg IV QD given on 5 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: IV: 300 to 600 mg/kg every 3 to 4 weeks SC: Previous IGIV dose in grams divided by number of weeks between IV doses and multiplied by 1.37 Maintenance:	Not applicable

		IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response SC: given once weekly with dose adjusted per PI [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	
Gammaplex	ITP	1 g/kg IV QD for 2 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: 300 to 800 mg/kg IV every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Gamunex-C	CIDP	Initial: 2 g/kg IV given in divided doses over 2 to 4 consecutive days Maintenance: 1 g/kg IV on one day or 0.5 g/kg IV on two consecutive days, every 3 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	ITP	1 g/kg IV QD on 2 consecutive days, or 0.4 g/kg IV QD given on 5 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: IV: 300 to 600 mg/kg every 3 to 4 weeks	Not applicable

		SC: Previous IGIV dose in grams divided by number of weeks between IV doses and multiplied by 1.37 <u>Maintenance:</u> IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response SC: given once weekly with dose adjusted per PI [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	
Hizentra	CIDP	0.2 to 0.4 g/kg SC per week, administered in 1 or 2 sessions over 1 or 2 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial weekly dose: previous IGIV dose in grams divided by number of weeks between IV doses and multiplied by 1.37. Prorate the weekly dose to 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. [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	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 SC at same dose and frequency as previous IV therapy after initial ramp-up (see manufacturer labeling)	Not applicable

		[Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	
	CIDP	Switching from IGIV therapy: Give SC at same dose and frequency as previous IV therapy after initial ramp-up (see manufacturer labeling) [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Octagam 5%	PI	Initial: 300 to 600 mg/kg IV every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Octagam 10%	ITP	1 g/kg IV QD for 2 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	DM	2 g/kg divided in equal doses given over 2-5 consecutive days every 4 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Panzyga	PI	300 to 600 mg/kg IV every 3 to 4 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	ITP	1g/kg IV QD for 2 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	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 IV in divided doses over 2 to 5 consecutive days Maintenance dose: 1 g/kg IV every 3 weeks [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	ITP	1 g/kg IV QD for 2 consecutive days [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
	PI	Initial: 200 to 800 mg/kg IV every 3 to 4 weeks Maintenance: IV: given every 3 to 4 weeks with dose adjusted per serum IgG level and clinical response [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable
Xembify	PI	Previous IGIV dose in grams divided by number of weeks between IV doses and multiplied by 1.37. Prorate the weekly dose and give SC at regular intervals QD to every week beginning 1 week after last IV dose. Or Previous SC weekly dose administered in regular intervals with prorated doses QD to every week. [Use TBW or IBW, whichever is *less*; if member is obese, use adjBW – see *Appendix F*.]	Not applicable

VI. Product Availability

Drug	Availability
IV administration - ready to use	
Alyglo (10%)	Single-use vials: 5, 10, 20 gram
Asceniv (10%)	Single-use vial: 5 gram
Bivigam (10%)	Single-use vial: 5, 10 gram
Flebogamma DIF (5%)	Single-use vial: 0.5, 2.5, 5, 10, 20 gram
Flebogamma DIF (10%)	Single-use vial: 5, 10, 20 gram
Gammaplex (5%)	Single-use bottle: 5, 10, 20 gram
Gammaplex (10%)	Single-use bottle: 5, 10, 20 gram
Octagam (5%)	Single-use bottle: 1, 2.5, 5, 10, 25 gram
Octagam (10%)	Single-use bottle: 2, 5, 10, 20, 30 gram
Panzyga (10%)	Single-use bottle: 1, 2.5, 5, 10, 20, 30 gram
Privigen (10%)	Single-use vial: 5, 10, 20, 40 gram
IV administration - freeze dried for reconstitution	
Gammagard S/D	5% single-use bottle: 5 gram 10% single-use bottle: 10 gram
IV or SC administration - ready to use	
Gammagard Liquid (10%)	Single-use bottle: 1, 2.5, 5, 10, 20, 30 gram
Gammaked (10%)	Single-use bottle: 1, 2.5, 5, 10, 20 gram
Gamunex-C (10%)	Single-use vial: 1, 2.5, 5, 10, 20, 40 gram
SC administration - ready to use	
Cutaquig (16.5%)	Single-use vials: 1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g (165 mg/mL)
Cuvitru (20%)	Single-use vial: 1, 2, 4, 8, 10 gram
Hizentra (20%)	Single-use vial: 1, 2, 4, 10 gram Single-use prefilled syringe: 1, 2, 4, 10 gram
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 and 200 U/1.25 mL, 5 g/50 mL and 400 U/2.5 mL, 10 g/100 mL and 800 U/5 mL, 20 g/200 mL and 1,600 U/10 mL, 30 g/300 mL and 2,400 U/15 mL
Xembify (20%)	Single-use vial: 1, 2, 4, 10 gram
IM administration – ready to use	
GamaSTAN (16.5%)	Single-use vial: 2 mL and 10 mL
GamaSTAN S/D (15-18%)	Single-use vial: 2 mL and 10 mL

VII. References

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Weight-based Dosing

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Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1460	Injection, gamma globulin, intramuscular, 1 cc
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1554	Injection, immune globulin (Asceniv), 500
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (Xembify), 100 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1560	Injection, gamma globulin, intramuscular, over 10 cc
J1561	Injection, immune globulin (Gamunex-C/Gammaked), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin (Gammagard liquid), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1572	Injection, immune globulin (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase (Hyqvia), 100 mg immunoglobulin
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg
J1577	Injection, immune globulin (panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg

Reviews, Revisions, and Approvals	Date
3Q 2018 annual review: separated CytoGam into an individual policy, added criteria for off-label uses for DM/PM, AIDP/GBS, acute ITP, kidney transplant, MM, MS, MG, NAIT/FAIT, paraneoplastic neurologic syndrome, parvovirus, peds HIV, pemphigus vulgaris, and stiff person syndrome; for CLL: added documentation of recurrent bacterial infection; for ITP: added criteria for pregnancy or trial and failure of first line agents, added criteria for high risk ITP requiring rapid increase in platelet count	09/2018

Reviews, Revisions, and Approvals	Date
(e.g., active bleeding, current platelet count < 30,000/µL, etc.); for CIDP: added criteria for high risk (e.g., inability to stand/walk for 30 ft without assistance, ICU admission for aspiration or mechanical ventilation, muscle weakness (various), chronic disease); for PI: added hypogammaglobulinemia levels, documentation of recurrent bacterial infection or inadequate antibody response; for viral prophylaxis: defined recent varicella exposure, removed requirement that request is for IM GamaSTAN S/D to allow for off-label IV use for measles, modified duration of therapy to up to 6 months for hep A and one time approval for other postexposure prophylaxis; for continued therapy, added requirement that member be re-evaluated using initial approval criteria for KS and viral prophylaxis; added specialist requirement for all diagnoses; references reviewed and updated.	
3Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	07/2019
Added products Asceniv, Cutaquig, Gammaplex 10%, Panzyga, and Xembify; for B-cell CLL, MM, and PI: revised classification of high risk patients to require history of recent (within past 12 months) recurrent serious bacterial infections; for FNAIT: removed oncologist and added perinatologist and neonatologist as specialist requirement options, removed requirement that father is homozygous for HPA genotype if previous pregnancy was affected by FNAIT, removed requirement of cordocentesis, removed requirement for symptomatic neonates to have both platelet count and high risk of developing intracranial hemorrhage, added option for nadir platelet count less than 100,000/microliter, added option for fetal intracranial hemorrhage; for kidney transplant: removed oncologist as a prescriber option; for MM infection prophylaxis: removed option for one infection requiring consultation by an ID specialist and consolidated it with the requirement for two or more infections requiring IV antibiotics; for MG/LEMS: added option for trial and failure of amifampridine for LEMS; for parvovirus, removed oncologist and HIV specialist as prescriber options; for pediatric HIV infection prophylaxis: revised to require all members to exhibit hypogammaglobulinemia, expanded dosing requirement to every 4 weeks; for pemphigus: removed immunologist as a specialist requirement, added requirement for trial and failure of Rituxan; for PI: added additional criteria for functional antibody deficiency diagnosis, clarified immune globulin deficiency could refer to total or subclass deficiency, added requirement for ADA-SCID for trial and failure of first line agents, added option for member to have SCID (non-ADA type), removed option for one infection requiring consultation by an ID specialist and consolidated it with the requirement for two or more infections requiring IV antibiotics; added additional specific dosing requirements for B-cell CLL, IDP, ITP, MG/LEMS, Stiff Person Syndrome, PI; revised preferencing of IVIG products Gammagard; Added	01/2020

Reviews, Revisions, and Approvals	Date
hematologist as a prescriber option for primary immunodeficiencies; references reviewed and updated.	
3Q 2020 annual review: for dermatomyositis added a requirement for a prior trial of rituximab; added new Hizentra prefilled syringe dosage form; references reviewed and updated.	08/2020
3Q 2021 annual review: Added guidance language re: optimal dose calculations for adults based on ideal or total body weight, whichever is less, and re: using adjusted body weight for dosing for obese members; For AIDP/GBS/CIDP: separated existing criteria to clearly delineate which apply to AIDP/GBS and which apply to CIDP; added criteria for confirmation of CIDP diagnosis, per 2010 EFNS/PNS guidelines; added requirement for a prior trial of corticosteroid therapy. RT4 update: added newly approved indication for Panzyga for CIDP; For myasthenia gravis/LEMS, revised requirement for steroid or alternative immunosuppressant to a requirement for both; for multiple myeloma infection prevention, updated IgG level to < 400 mg/dL per NCCN guidelines; references reviewed and updated.	07/2021
Revised requirement for trial of corticosteroid before IG to apply only to CIDP and to only apply when the member does not have CIDP with pure motor symptoms; removed "Dermatomyositis, autoimmune blistering" from Section III, since coverage for this indication is included in the criteria for Sections I.B. (dermatomyositis) and I.O. (pemphigus disorders); removed "Systemic vasculitides" and "Wegener's granulomatosis" from Section III, based on 2021 ACR guidelines and 2016 EULAR guidelines providing some support use of IG products for patients with refractory GPA/MPA	01/2022
3Q 2022 annual review: per May SDC and prior clinical guidance added requirement for use of Gammunex-C or Gammaked if is unavailable due to shortage; references reviewed and updated.	07/2022
2Q 2023 annual review: added limitation of use for HyQvia and Privigen; removed HCPCS code C9270; added HCPCS Codes J1460, J1554, J1558, J1560; removed references to Carimune NF due to product discontinuation; references reviewed and updated.	04/2023
RT4: added Alyglo to policy.	01/2024
2Q 2024 annual review: removed Rasmussen's syndrome from Section III; references reviewed and updated. RT4: for HyQvia, Gammagard Liquid and Panzyga, added CIDP indication per updated PI.	04/2024