Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Immunoglubulins	MP-RX-FP-40-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Description

This document addresses the use of intravenous (IVIG) and Subcutaneous (SCIG) Immunoglobulins (IG). This document does not address the use of GamaSTAN or GamaSTAN S/D. This document also does not address Rho (D) immune globulin and WinRho SD injections for the prevention or treatment of Rh incompatibility. Immunoglobulin products are prepared from pools of human plasma collected from healthy donors. It is a recognized treatment for a variety of medical conditions, not only for its use in fighting infections, but also for its anti-inflammatory and immunomodulating effects. Immunoglobulins are the cornerstone of therapy for primary immunodeficiencies, reflected in the FDA approval for this use. The FDA has also approved these products for other conditions, as shown in the table below. Carimune NF was discontinued by the manufacturer as of third quarter 2018. Utilization management clinical programs will remain active as claims can adjudicate up to 3 years after agent discontinuation.

Summary of FDA-Approved indications for Immunoglobulins:

Agent	Route	PI	ITP	MMN	CLL	KS	CIDP	DM
Asceniv	IV	x*						
Bivigam	IV	x*						
Carimune NF	IV	x	x* (acute and chronic)					
Cutaquig	SC	x*						
Cuvitru	SC	x*						
Flebogamma DIF 5%	IV	x*						
Flebogamma DIF 10%	IV	x	x* (chronic)					
Gammagard	IV, SC	x*		x				
Gammagard S-D/ Gammagard S-D less IgA	IV	x*	x (chronic)		x	x*		
Gammaked	IV, SC	x*	x* (acute and chronic)				x	
Gammaplex 5%	IV	x*	x* (chronic)					
Gammaplex 10%	IV	x*	x (chronic)					
Gamunex-C	IV, SC	x*	x* (acute and chronic)				x	
Hizentra	SC	x*					x	
Hyqvia	SC	x						
Octagam 5%	IV	x*						
Octagam 10%	IV		x (chronic)					x
Panzyga	IV	x*	x (chronic)				x	
Privigen	IV	x*	x*(chronic)				x	
Xembify	SC	x*						

*Includes pediatric indication

PI = Primary (Humoral) Immunodeficiency [including, but not limited to Common Variable Immunodeficiency (CVID), X-linked Agammaglobulinemia, Congenital Agammaglobulinemia, Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiencies]; **ITP** = Idiopathic Thrombocytopenic Purpura; **MMN** = Multifocal Motor Neuropathy; **CLL** = B-cell Chronic Lymphocytic Leukemia; **KS** = Kawasaki Syndrome; **CIDP** = Chronic Inflammatory Demyelinating Polyneuropathy; **IV** = Intravenous, **SC** = Subcutaneous; **DM** = Dermatomyositis

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Uses

A. Infection: Immunoglobulins play a role in the treatment and prevention of infection in a variety of clinical scenarios. NCCN recommends IG to prevent infections in certain individuals with chronic lymphocytic leukemia and multiple myeloma. The CDC continues to 2 recommend IG to some children with HIV as well as in the post-exposure prophylaxis of measles, tetanus, and varicella. IG remains first line therapy for Kawasaki disease, a syndrome affecting children which involves fever, rash, and systemic inflammation and vasculitis. The cause of the disease is unknown, but may have an infectious origin. IG is used in the acute phase of the disease to reduce the prevalence of coronary artery abnormalities. While it should ideally be administered within 10 days of onset, the American Heart Association recommends use beyond 10 days in the setting of persistent severe manifestations of the disease

B. Transplant: IG has also been used in individuals undergoing blood, bone marrow, or solid organ transplant. The consensus guidelines for infection complications in hematopoietic cell transplant suggest that, while IG should not be routinely used, it may be considered pre- and post- transplant when the patient is hypogammaglobulinemic. For solid organ transplant recipients, IG has been used routinely in desensitization prior to transplant. IG may also be considered in antibody-mediated rejection (AMR). AMR remains a significant problem with lack of standardized treatment and limited therapeutic options. Relevant specialists support this indication; and some transplant centers include IG in protocol for AMR. There is literature and guidelines recommending IG in the setting of AMR as well

C. Autoimmune diseases: The anti-inflammatory and immunomodulating effects of IG have shown benefit in many autoimmune conditions such as ITP, autoimmune encephalitis, fetal alloimmune thrombocytopenia, autoimmune neutropenia, skin blistering disease, and dermatomyositis. Polymyositis is a very rare condition, but is thought to be similar to dermatomyositis. In autoimmune encephalitis, the autoimmune response may be triggered by tumors, and it is important to detect tumors promptly for appropriate overall management. Symptoms of AE may also precede the appearance of a tumor, so continued cancer screening is recommended, especially in individuals who have an incomplete response to medical therapy (Zuliani 2019).

D. Neurologic conditions: IG is also recommended in several neurologic conditions such as Lambert-Eaton myasthenic syndrome (LEMS), myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN). Several of these conditions require electrodiagnostic tests to confirm diagnosis. These tests include nerve conduction studies (NCS) measuring compound muscle action potential (CMAP), repetitive nerve stimulation (RNS), or single fiber electromyography (SFEMG) (see table below). Stiff person syndrome, a rare condition involving progressive muscle stiffness, is thought to have an autoimmune component. First line treatments are often benzodiazepines or baclofen, but IG is recommended in refractory cases. In some individuals with mild to moderate myasthenia gravis, symptoms may be well controlled on acetylcholinesterase inhibition alone (i.e., pyridostigmine), even though it does not treat the underlying cause. However, the cholinergic adverse effects of pyridostigmine are usually dose-limiting. Addition of steroidal and non-steroidal immunosuppressants is the typical clinical course for individuals whose symptoms are not well controlled

on pyridostigmine alone, with sufficient trial given to the non-steroidal immunosuppressants due to the lengthy onset of action. (Neurol Clin 2018, Neurology 2016/2020). CIDP is further discussed below.

Characteristic Electrodiagnostic Findings in Selected Neurologic Disorders:

Diagnosis	Typical Electrodiagnostic Findings
MG	• RNS shows progressive decline in CMAP amplitude greater than 10% • SFEMG shows abnormal jitter
LEMS	• NCS show reduced baseline CMAP • RNS or maximal isometric muscle activation show increase in compound muscle action potential (CMAP) amplitude of 60% to ≥100% compared with baseline • SFEMG shows significant jitter and transmission blocking that is improved at higher firing rates
MMN	• NCS show focal demyelination and conduction block

E. Chronic Inflammatory Demyelinating Polyneuropathy (or polyradiculoneuropathy) (CIDP): CIDP is an acquired, immunemediated neuropathy which currently lacks consensus on one gold standard for confirming diagnosis via electrophysiologic findings and for determining therapeutic improvement. Clinical trials for the FDA-approved CIDP products utilized the various diagnostic methods and objective measurements, including guidelines from the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS), cerebrospinal fluid analysis, Inflammatory Neuropathy Cause and Treatment (INCAT) scale, Medical Research Council (MRC) scale for muscle strength, and Jamar or Vigorimeter grip strength dynamometer. An American Academy of Neurology (AAN) ad hoc subcommittee also developed criteria for diagnosing CIDP in 1991, albeit originally intended for research purposes. The electrodiagnostic features of the EFNS/PNS (2021) and AAN criteria are below. Clinical trials for the FDA-approved CIDP products also differentiated acute inflammatory demyelinating polyneuropathy (AIDP) from chronic IDP by including only individuals with symptoms lasting greater than 2 months or 8 weeks.

CIDP Typical Electrodiagnostic Findings	
EFNS/PNS	At least one (1) of the following demyelinating parameters are necessary: • ≥50% prolongation of motor distal latency above ULN in 2 nerves • ≥30% reduction of motor conduction velocity below LLN in 2 nerves • ≥20% prolongation of F-wave latency above ULN in 2 nerves, or ≥50% if amplitude of distal negative peak CMAP is <80% of LLN • Absence of F-waves in 2 nerves, if nerves have amplitudes of distal negative peak CMAPs ≥20% of LLN, plus ≥1 other demyelinating parameter in ≥1 other nerve • Motor conduction block: ≥30% amplitude reduction of proximal relative to distal negative peak CMAP, excluding tibial nerve, relative to distal, and distal negative peak CMAP ≥20% of LLN in 2 nerves, or in 1 nerve plus ≥1 other demyelinating parameter except absence of F-waves in ≥1 other nerve

	• Abnormal temporal dispersion: >30% duration ↑ between proximal and distal negative peak CMAP (at least 100% in the tibial nerve) in ≥2 nerves • Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) ↑ in ≥1 nerve plus ≥1 other demyelinating parameter in ≥1 other nerve
AAN	At least three (3) of the four demyelinating parameters are necessary: • Reduction in conduction velocity in 2 or more nerves: ○ <80% of LLN if CMAP amplitude >80% of LLN ○ <70% of LLN if CMAP amplitude <80% of LLN • Partial conduction block in 1 or more nerves: ○ Proximal:distal amplitude ratio <0.8 with <15% increase in CMAP negative peak duration, or abnormal temporal dispersion with proximal:distal amplitude or area ratio <0.8 with >15% increase in CMAP negative peak duration dispersion • Prolonged distal latency in 2 or more nerves: ○ >125% of ULN if CMAP amplitude >80% of LLN ○ >150% of ULN if amplitude <80% • Absent or F-wave latencies in 2 or more nerves: ○ >120% of ULN if amplitude >80% of LLN ○ >150% of ULN if CMAP amplitude <80% of LLN

Contraindications:
Due to the various immunoglobulin preparations, agents have different contraindications. All immunoglobulins are contraindicated in IgA deficient patients who have antibodies against IgA. Gammagard S/D less IgA contains

Black Box Warnings:
Immunoglobulins (SC and IV) have a black box warning for thrombosis. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, IG should be administered at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity Intravenous Immunoglobulins (IVIG) have a black box warning for renal dysfunction and acute renal failure. Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. For patients at risk of renal dysfunction or acute renal failure, administer IG at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. Carimune NF is the only IVIG that contains sucrose.

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Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

B vs D Criteria: Gammagard SD, Privigen, Gammagard, Gamunex drugs included in this PA are subject to B vs D evaluation. Medication must be furnished "incident to" physician service provided and usually not self-administered to be covered by Medicare and to be eligible to be evaluated through part B. If not, medication must be evaluated through part D.

Immunoglobulins

Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

All requests require documentation provided for diagnosis.

Requests for Immunoglobulin therapy may be approved if the following criteria are met:

I. **Individual is using for treatment of one of the following primary immunodeficiencies (AAAAI/ACAAI 2015):**

A. Primary humoral immunodeficiency including congenital agammaglobulinemia, X-linked immunodeficiency, severe combined immunodeficiency [SCID], or Wiskott-Aldrich syndrome [WAS]) when:

1. The initial, pre-treatment total serum IgG is below the lower limit of the age adjusted laboratory reference range, or more than two standard deviations below the age adjusted mean; **AND**
2. There is no evidence of renal (nephrotic syndrome) and gastrointestinal (for example, protein losing enteropathy) as causes of hypogammaglobulinemia

OR

B. Primary humoral immunodeficiency common variable immunodeficiency (CVID) when:

1. There is a history of recurrent sinopulmonary infections requiring antibiotic therapy; **AND**
2. There is a lack of, or inadequate response to immunization (for example, but not limited to tetanus or pneumococcal antigen); **AND**
3. The initial, pre-treatment total serum IgG is below the lower limit of the age adjusted laboratory reference range, or more than two standard deviations below the age adjusted mean; **AND**

4. There is no evidence of renal (nephrotic syndrome) and gastrointestinal (for example, protein losing enteropathy, PLE) as causes of hypogammaglobulinemia;

OR

C. IgG sub-class deficiency (IgG1, IgG2, IgG3, IgG4) when:
   1. There is a history of recurrent sinopulmonary infections requiring antibiotic therapy; **AND**
   2. There is a lack of, or inadequate response to immunization (for example, but not limited to tetanus or pneumococcal antigen); **AND**
   3. The initial, pre-treatment levels of one or more serum IgG subclasses are below the lower limit of the age adjusted laboratory reference range or are more than two standard deviations below the age adjusted mean;

OR

D. Hyperimmunoglobulinemia E syndrome (HIE) when the following criteria are met:
   1. Confirmation of elevated level of serum IgE; AND
   2. Individual has clinical features including:
      a. Recurrent sinopulmonary and skin infections; **AND**
      b. Chronic eczematous dermatitis

Approval Duration for Primary Immunodeficiency: 1 year

OR

II. **Individual is using for one following secondary immunodeficiencies:**

A. B-cell chronic lymphocytic leukemia (CLL) with the following (NCCN 2A):
   1. A history of recurrent bacterial infection or an active infection not responding to antimicrobial therapy; AND
   2. Hypogammaglobulinemia shown by total IgG is less than 500 mg/dl;

OR

B. Multiple myeloma with the following: (NCCN 2A)
   1. History of a clinically severe infection or active clinically severe infection, **OR**
   2. Hypogammaglobulinemia shown by total IgG less than 400 mg/dL;

OR

C. Human immunodeficiency virus (HIV)-infected children, to prevent opportunistic bacterial infection in individuals with hypogammaglobulinemia (IgG less than 400mg/dL) or recurrent infections (IDSA/CDC 2013);

OR

D. Secondary hypogammaglobulinemia or agammaglobulinemia following chimeric antigen receptor (CAR) T cell treatment (Kymriah/Yescarta PI);

OR

E. Secondary hypogammaglobulinemia or agammaglobulinemia following chimeric antigen receptor (CAR) T cell treatment (Kymriah/Yescarta PI);

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Approval Duration for Secondary Immunodeficiency: 6 months

OR

III. **Individual is using in the context of transplant for one of the following:**

A. Hematopoietic stem cell transplant (HCT) for either of the following:

1. Allogeneic bone marrow transplant (BMT) recipients, in the first 100 days after transplantation, to reduce the risk of graft-versus-host disease associated with interstitial pneumonia (infectious or idiopathic) and infections (cytomegalovirus infections, varicella-zoster virus infection, and recurrent bacterial infection) (DrugPoints B IIa); **OR**
2. Prevention of bacterial infections in individuals who are immunosuppressed after allogenic HCT transplant), when there is severe hypogammaglobulinemia (IgG less than 400 mg/dl) (AHFS, ASBMT 2009);

OR

B. **Solid organ transplantation including either of the following:**

1. Desensitization prior to a solid organ transplantation for suppression of panel reactive anti-HLA antibodies in individuals with high panel reactive antibody (PRA or cPRA [corrected PRA]) levels to human leukocyte antigens (HLA) (AAAAI 2016) , or in individuals with a history of high levels of donor-specific antibodies (DSA) (KDIGO 2020, ISHLT 2016); **OR**
2. Transplant recipients at risk for CMV (TTS 2018, DP B IIb); **OR**
3. Transplant recipients experiencing antibody-mediated rejection with donor-specific antibodies (KDIGO 2009, ISHLT 2010);

Approval Duration in the context of transplant: 6 months

OR

IV. **Individual is using for treatment of one the following autoimmune diseases:**

A. Immune-mediated encephalitis, including paraneoplastic and autoimmune encephalitis (AE) when the following criteria are met (Zuliani 2019, Lancaster 2016):

1. Individual has been evaluated for possible neoplasm associated with encephalitis; **AND**
2. As an initial trial (up to 12 weeks) when diagnosis is confirmed by the following"
   a. Detection of a specific autoantibody associated with AE, including but not limited to:
      i. NMDAR, LGI1, Caspr2, AMPAR, GABA-A or GABA-B receptor, IgLON5, DPPX, GlyR, mGluR1, mGluR2, mGluR5, Neurexin 3-alpha, or dopamine-2 receptor (D2R); **AND**

b. Clinical presentation includes neurological symptoms (for example, memory deficits, seizures, movement disorders, speech disturbances, behavioral changes, or psychiatric symptoms); AND
c. Alternative etiologies of encephalitis syndrome have been ruled out, such as infectious etiologies, other neurological disorders, or other autoimmune conditions.

3. Continued use of Ig after initial trial when the following criteria are met:
   a. There are clinically significant improvements in symptoms on physical examination; **AND**
   b. . Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals, or previous discontinuation resulted in relapse); **AND**
   c. Cancer screening continues.

Approval Duration for AE:
Initial requests: 12 weeks
Continuation requests: 1 year

OR

B. Immune thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) with either of the following:
   1. Active bleeding (for example, but not limited to hematuria, petechiae, bruising, gastrointestinal bleeding, gingival bleeding); **OR**
   2. Platelet count less than 30,000 mcL (ASH 2019);

Approval Duration for ITP: 6 months

OR

C. Fetal alloimmune thrombocytopenia with the following: (ACOG 2019)
   1. Antibodies to paternal platelet antigen are found in maternal serum; AND
   2. One of the following is demonstrated:
      a. There has been a previously affected pregnancy; **OR**
      b. There is a family history of maternofetal alloimmune thrombocytopenia; **OR**
      c. Fetal blood sample shows thrombocytopenia;

OR

D. Isoimmune hemolytic disease of the newborn, treatment of severe hyperbilirubinemia (AAP 2022);

OR

E. Autoimmune mucocutaneous blistering diseases (including pemphigus vulgaris, pemphigus foliaceous, bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullosa acquisita) when the following criteria are met (AAAAI 2016, Murrell 2020):
    1. Individual has had an inadequate response to, is intolerant of, or has a contraindication to other treatments such as corticosteroids or immunosuppressive agents.
    2. As continued use after initial trial for autoimmune mucocutaneous blistering diseases when the following criteria are met:
        a. There is clinically significant improvements in symptoms on physical examination; **AND**
        b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for mucocutaneous blistering diseases:
Initial requests: 6 months
Continuation requests: 1 year

OR

F. Autoimmune neutropenia when active infection has been excluded as a cause of neutropenia (AAAAI 2016, DP B IIb);

Approval Duration for neutropenia: 6 months

OR

G. Dermatomyositis or polymyositis when the following criteria are met: (AHFS, AAAAI 2016)
    1. For initial requests:
        a. Individual has had an inadequate response to, is intolerant of, or has a contraindication to other treatments, including corticosteroids and non-steroidal immunosuppressive agents; **AND**
        b. Diagnosis is confirmed by the presence of at least 4 of the following 8 characteristics (Tanimoto 1995):
            i. Weakness in the trunk or proximal extremities;
            ii. Elevated serum creatinine kinase or aldolase levels;
            iii. Muscle pain not otherwise explained;
            iv. Characteristic electromyography findings (short duration, polyphasic motor unit potentials with spontaneous fibrillation potentials);
            v. Presence of anti-Jo-1 antibody (histidyl-tRNA synthetase); vi. Arthralgias or arthritis without joint destruction;
            vi. Evidence of systemic inflammation such as fever, elevated C-reactive protein, or elevated sedimentation rate;
            vii. Inflammatory myositis seen on muscle biopsy;

AND

c. If using for dermatomyositis, there are skin lesions characteristic of dermatomyositis (such as heliotrope lesions on eyelids, Gottron's papules, erythematous plaques over extensor joints of extremities) present.

2. As continued use after initial trial for dermatomyositis or polymyositis when the following criteria are met:
   a. There is clinically significant improvements in symptoms on physical examination; **AND**
   b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for dermatomyositis or polymyositis:
Initial requests: 6 months
Continuation requests: 1 year

OR

V. **Individual is using for treatment of one of the following neurologic diseases:**

A. Lambert-Eaton myasthenic syndrome when the following criteria are met: (AAAAI 2016)
   1. For initial requests:
      a. Individual is experiencing muscle weakness; **AND**
      b. Diagnosis confirmed by one of the following:
         i. Characteristic electrodiagnostic findings using nerve conduction tests, repetitive nerve stimulation (RNS), exercise testing, or single fiber electromyography (SFEMG); **OR**
         ii. Presence of antibodies directed against voltage-gated calcium channels (VGCC)
   2. As continued use after initial trial for Lambert-Eaton myasthenic syndrome when the following criteria are met:
      a. There is clinically significant and objective improvement in neurological symptoms on physical examination (for example, an objective change in patient function that is clinically meaningful, such as patient can now work or perform tasks that they previously could not); **AND**
      b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for Lambert-Eaton myasthenic syndrome:
Initial requests: 12 weeks
Continuation requests: 1 year

OR

B. Guillain-Barre Syndrome (acute demyelinating polyneuropathy) when: (Drugpoints B IIa)
   1. Individual's clinical presentation is characteristic of Guillain-Barre Syndrome, including (Willison 2016):
      a. Progressive weakness in the legs and/or arms; **AND**
      b. Absent or depressed tendon reflexes (i.e., areflexia) in affected limbs; **AND**
   2. Initial treatment with immune globulin occurs within eight (8) weeks of onset of symptoms (AAN 2016); **AND**
   3. Individual is not on concomitant plasmapheresis therapy; **AND**
   4. Treatment for no more than 5 days (i.e., one course of therapy)

Approval Duration for Guillain-Barré Syndrome: 1 course of therapy (5 days)

OR

C. Myasthenia Gravis when the following criteria are met: (AAAAI 2016, Neurol Clin 2018, Neurology 2016/2020)
   1. For initial requests:
      a. Individual's clinical presentation is characteristic of myasthenia gravis; **AND**
      b. The diagnosis is confirmed by one of the following (Juel 2007):
         i. The presence of antibodies against the acetylcholine receptor (AChR-Ab) or musclespecific tyrosine kinase (MuSK-Ab); **OR**
         ii. Characteristic electrodiagnostic findings using repetitive nerve stimulation (RNS) or single fiber electromyography (SFEMG);

      AND

      c. Individual is using for one of the following:
         i. Exacerbation of myasthenia gravis or acute myasthenic crisis; **OR**
         ii. Short-term therapy as immunosuppressive treatment is taking effect; **OR**
         iii. Maintenance therapy of myasthenia gravis when individual has had an inadequate response to, is intolerant of, or has a contraindication to all of the following:
            - Pyridostigmine; **AND**
            - Corticosteroids; **AND**
            - Non-steroidal immunosuppressants. Inadequate response to non-steroidal immunosuppressants is defined as unchanged or worsening symptoms despite one of the following:
               - At least a twelve (12) month trial of azathioprine or mycophenolate; OR

- At least a two (2) month trial of cyclosporine, cyclophosphamide, tacrolimus, or methotrexate.

2. As continued use after initial trial for myasthenia gravis when the following criteria are met:
   a. There is clinically significant and objective improvement in neurological symptoms on physical examination (for example, an objective change in patient function that is clinically meaningful, such as patient can now work or perform tasks that they previously could not); **AND**
   b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for myasthenia gravis:
Initial requests: 12 weeks
Continuation requests: 1 year

OR

D. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):
   1. As an initial trial (up to 12 weeks) when the following criteria are met:
      a. There is muscle weakness or sensory dysfunction caused by neuropathy in more than one limb for at least two (2) months; **AND**
      b. Evidence of a demyelinating neuropathy confirmed by one of the following:
         i. Per the EFNS/PNS guidelines, individual has one of the following electrodiagnostic findings (EFNS/PNS 2021):
            - Prolongation of motor distal latency in 2 nerves
            - Reduction of motor conduction velocity in 2 nerves
            - Prolongation of F-wave latency in 2 nerves
            - Absence of F-waves in at least 1 nerve
            - Motor conduction block in at least 1 nerve
            - Abnormal temporal dispersion in at least 2 nerves
            - Distal compound muscle action potential (CMAP) duration increase in at least 1 nerve;

            OR
         ii. Per the AAN guidelines, individual has three (3) of the following electrodiagnostic findings (AAN 1991):
            - Reduced conduction velocity in at least 2 nerves
            - Partial conduction block in at least 1 nerves
            - Prolonged distal motor latency in at least 2 nerves
            - Absent or prolonged F-wave latency in at least 2 nerves; **OR**
         iii. Cerebrospinal fluid (CSF) analysis shows albuminocytologic dissociation or elevated CSF protein with a white blood cell count of less than 10/mm3 (EFNS/PNS 2021); **AND**

c. Other polyneuropathies such as IgM neuropathy, hereditary neuropathy, and diabetic neuropathy have been ruled out.

2. As continued use after initial trial for CIDP when the following criteria are met:
   a. There is clinically significant improvement in neurological symptoms on physical examination (for example, an objective change in patient function that is clinically meaningful, such as patient can now work of perform tasks that they previously could not); **AND**
   b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for CIDP:
Initial requests: 12 weeks
Continuation requests: 1 year

OR

E. Multifocal Motor Neuropathy (MMN) for either of the following:
   1. As an initial trial (up to 12 weeks) to treat MMN, when diagnosis is confirmed by all of the following criteria (EFNS/PNS 2010, AANEM 2003):
      a. Stepwise or slowly progressive, focal, asymmetric limb weakness for at least one (1) month; **AND**
      b. Motor involvement of at least two (2) nerves; **AND**
      c. Sensory nerve conduction studies are normal, with the exception of minor vibration loss in the lower limbs; **AND**
      d. Absence of all of the following upper motor neuron signs, or presence of such can be explained by a comorbid condition (for example, history of stroke):
         i. Spastic tone
         ii. Clonus
         iii. Extensor plantar response
         iv. Pseudobulbar palsy.
   2. Continued use of Ig after initial trial for MMN when the following criteria are met:
      a. There is clinically significant and objective improvement in neurological symptoms on physical examination (for example, an objective change in patient function that is clinically meaningful, such as patient can now work or perform tasks that they previously could not); **AND**
      b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for MMN:
Initial requests: 12 weeks
Continuation requests: 1 year

OR

F. Stiff-person syndrome when the following criteria are met (AAAAI 2016):
    1. For initial requests:
        a. Individual has had an inadequate response to, is intolerant of, or has a contraindication to other treatments such as benzodiazepines or baclofen (AAAAI 2016).
    2. Continued use of Ig after initial trial when the following criteria are met:
        a. There is clinically significant and objective improvement in neurological symptoms on physical examination (for example, an objective change in patient function that is clinically meaningful, such as patient can now work or perform tasks that they previously could not); **AND**
        b. Continued need is demonstrated by clinical effect (for example, patient has a positive response and stable on current dose, or worsening of symptoms occurs from a dose decrease or increase in dose intervals);

Approval Duration for stiff-person syndrome:
Initial requests: 12 weeks
Continuation requests: 1 year

OR

G. Myelin Oligodendrocyte Glycoprotein (MOG)- related Neuromyelitis Optica Spectrum Disorder (NMOSD) for either of the following (Hacohen 2019):
    1. As an initial trial for the diagnosis of MOG-related neuromyelitis optica spectrum disorder (NMOSD); **AND**
        a. Individual is confirmed to be seropositive for myelin oligodendrocyte glycoprotein (MOG) antibodies; **AND**
        b. Individual is seronegative for aquaporin-4 (AQP4) antibodies; **AND**
        c. Individual is using for one of the following:
            i. As induction treatment for an acute episode after an inadequate response to, intolerance, or contraindication to corticosteroids; **OR**
            ii. Individual has further relapse after maintenance treatment with corticosteroids and nonsteroidal immunosuppressants.
    2. Continued maintenance use after initial treatment for MOG-related NMOSD when the following criteria is met:
        a. Individual has experienced a clinical response with immune globulin (for example, a reduction in frequency of relapse);

OR

VI. **Individual is using for treatment of one of the following miscellaneous indications:**

A. A. Measles (rubeola) post-exposure prophylaxis: (AHFS)

1. Individual is using for post-exposure prophylaxis to prevent or modify measles (rubeola); **AND**
2. Administered within 6 days of exposure and not given concomitantly with a vaccine containing the measles virus; **AND**
3. Eligible, exposed, non-immune individuals will receive a vaccine containing the measles virus greater than or equal to 8 months after immunoglobulin administration (CDC 2013); **AND**
4. Used in the following individuals considered at risk for severe disease and complications (CDC 2013):
   a. No evidence of measles immunity, in particular in pregnant women; **OR**
   b. Severely immunocompromised individuals;

OR

B. Varicella post-exposure prophylaxis: (AHFS) 1. Individual is using as post-exposure prophylaxis of varicella infection in susceptible individuals (such as, immunocompromised); AND 2. The varicella-zoster immune globulin (human) (VZIG) is unavailable;

OR

C. Tetanus: (AHFS)
   1. Individual is using as treatment or post-exposure prophylaxis of tetanus when tetanus immune globulin (TIG) is unavailable;

OR

D. Kawasaki Syndrome when:
   1. Treatment initiated within 10 days of onset; **OR**
   2. Treatment Initiated beyond 10 days of onset if individual has unexplained persistent fever, or coronary artery abnormalities with evidence of ongoing inflammation (such as elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) (AHA 2017); **AND**
   3. Treatment for no more than 5 days (AFHS);

OR

E. Toxic shock syndrome caused by staphylococcal or streptococcal organisms (AAP 2018, AHFS);

OR

F. Treatment of cancer-related CMV pneumonia if individual has hypogammaglobulinemia (IgG less than 500mg/dL) (NCCN 2A).

Approval Duration for cancer-related CMV pneumonia: 6 months

Requests for Immunoglobulin therapy may not be approved for the following:

I. Alzheimer's disease; **OR**
II. II. Immune optic neuropathy, with the exception of MOG-related NMOSD; **OR**
III. Multiple sclerosis; **OR**
IV. Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS);

V. Treatment to prevent recurrent spontaneous abortion in pregnant women with a history of recurrent spontaneous abortion (ASRM 2012); **OR**

VI. When the above criteria are not met and for all other indications.

IG products and selected properties‡

Agent	Route	Osmolality (mOsm/kg)	Sodium	IgA (µg/mL)	Stabilizer or regulator
Asceniv 10%	IV	370 – 510[π]	100 to 140 mmol/L	<200	Glycine and polysorbate 80
Bivigam 10%	IV	370 – 510	100 to 140 mmol/L	≤200	Glycine and polysorbate 80
Carimune NF	IV	192 – 1074*	<20 mg NaCl per gm of protein	720[±]	Sucrose
Cutaquig 16.5%	SC	310 – 380	<30 mmol/L	≤600	Maltose
Cuvitru 20%	SC	280 – 292	none	80	Glycine
Flebogamma DIF 5%	IV	240 – 370	trace	<50	D-sorbitol
Flebogamma DIF 10%	IV	240 – 370	trace	<100	D-sorbitol
Gammagard 10%	IV, SC	240 – 300	none	37	Glycine
Gammagard S/D 5%	IV	636	8.5 mg/mL	<1	Glucose and glycine
Gammaked 10%	IV, SC	258	trace	46	Glycine
Gammaplex 5%	IV	420 – 500	30 to 50 mmol/L[π/±]	<10	D-sorbitol, glycine, and polysorbate 80
Gammaplex 10%	IV	280	<30 mmol/L	<20	Glycine and polysorbate 80
Gamunex-C 10%	IV, SC	258	trace	46	Glycine
Hizentra 20%	SC	380 [π/±]	trace	≤50	L-proline and polysorbate 80
Hyqvia 10%	SC	240 – 300	none	37	Glycine
Octagam 5%	IV	310 – 380	≤30 mmol/L	≤200	Maltose
Octagam 10%	IV	310 – 380	≤30 mmol/L	106	Maltose
Panzyga 10%	IV	240 – 310	trace	100	Glycine
Privigen 10%	IV	240 – 440	trace	≤25	L-proline
Xembify 20%	SC	280 – 404	none	contains IgA (not defined)	Glycine and polysorbate 80

‡ Per FDA Package Insert, unless otherwise noted; [π]Immune Deficiency Foundation (2021); [±]AAAAI (2016); *Carimune NF osmolality dependent upon protein concentration and diluent.

Step Therapy

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

Non-preferred Intravenous Immunoglobulins (IVIG) Step Therapy

Requests for a non-preferred intravenous immunoglobulin agent may be approved when the following criteria are met:

I. Documentation is provided that individual is currently receiving and stabilized on the requested non-preferred agent; OR

II. Documentation is provided that individual has had a trial and inadequate response or intolerance to two preferred intravenous Ig agents; OR

III. The preferred agents are not FDA-approved and do not have an accepted off-label use per the off-label use policy for the prescribed indication and the requested non-preferred agent does; OR IV. Documentation is provided that the preferred Ig agents are not acceptable due to concomitant clinical condition(s), which requires an Ig agent with specific properties. Examples include, but not limited to the following:

A. Severe IgA deficiency (<7 mg/dL of IgA), or IGA deficiency with antibodies against IgA, requiring agent with very low IGA content; **OR**

B. Hypersensitivity, as manifested by a severe systemic/allergic or anaphylactic reaction, to any ingredient which is not also present in the requested non-preferred agent; **OR**
C. Clinically significant reaction, including, but not limited to, hemolysis or renal dysfunction/impairment, that may be lessened by use of a non-preferred agent with different properties;

Subcutaneous Immunoglobulins (SCIG)-only Step Therapy

Requests for a preferred subcutaneous immunoglobulin (SCIG)-only agent may be approved when the following criteria are met:

I. Documentation is provided that individual is currently receiving and stabilized on the requested preferred agent; **OR**
II. Documentation is provided that individual has had a trial and inadequate response or intolerance to intravenous immunoglobulins (IVIG) due to one of the following: A. History of serious systemic reaction to IVIG expected to be avoided by using SCIG; OR B. History of inconsistent serum levels of immunoglobulin G (IgG) with IVIG; **OR**
III. Documentation is provided that individual has difficult vein access AND rationale has been provided for why Gamunex-C cannot be administered subcutaneously.

Requests for a non-preferred subcutaneous immunoglobulin (SCIG)-only agent may be approved when the following criteria are met:

I. Documentation is provided that individual is currently receiving and stabilized on the requested non-preferred agent; **OR**
II. Documentation is provided that individual has had a trial and inadequate response or intolerance to intravenous immunoglobulins (IVIG) due to one of the following:
    A. History of serious systemic reaction to IVIG expected to be avoided by using SCIG; **OR**
    B. History of inconsistent serum levels of immunoglobulin G (IgG) with IVIG; **OR**
    C. Documentation is provided that individual has difficult vein access AND Gamunex-C cannot be administered subcutaneously;

    AND
III. Documentation is provided that individual has had a trial and inadequate response or intolerance to two preferred SCIG-only agents;

    OR
IV. Documentation is provided that the preferred SCIG-only agent is not acceptable due to concomitant clinical condition(s), which requires an Ig agent with specific properties. Examples include, but not limited to the following:
    A. Severe IgA deficiency (<7 mg/dL of IgA), or IgA deficiency with antibodies against IgA, requiring agent with very low IgA content; **OR**
    B. Hypersensitivity, as manifested by a severe systemic/allergic or anaphylactic reaction, to any ingredient which is not also present in the requested non-preferred agent; **OR**
    C. Clinically significant reaction, including, but not limited to, hemolysis or renal dysfunction/impairment, that may be lessened by use of a non-preferred agent with different properties;

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OR

V. The preferred SCIG-only agents are not FDA-approved and do not have an accepted off-label use per the off-label use policy for the prescribed indication and the requested non-preferred agent does.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness

Quantity Limitations

Intravenous Immunoglobulin Quantity Limits

Drug	Limit Per Indication
Intravenous Immunoglobulins	**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):** 1000 mg/kg (may be divided over two days) as frequently as every 3 weeks (DP)† **Chronic Lymphocytic Leukemia (CLL):** 500 mg/kg monthly (NCCN) **Dermatomyositis (DM):** 2000 mg/kg administered in divided doses over 2 to 5 days every 4 weeks (Octagam 10% label) **Guillain-Barré Syndrome:** 400 mg/kg daily for 5 days **OR** 2000 mg/kg administered in divided doses over 2 to 5 days (DP, AHFS) **Idiopathic thrombocytopenic purpura (ITP):** 2000 mg/kg administered in divided doses over 2 to 5 days or 1000 mg/kg every other day for up to 3 doses (DP) **Kawasaki Syndrome:** 2000 mg/kg per dose for up to two doses (AHFS) **OR** 400mg/kg/day for 4 days **Multifocal Motor Neuropathy (MMN):** 2400 mg/kg every 4 weeks (Gammagard label)^ **Myasthenia Gravis:** 2000 mg/kg administered in divided doses over 2 to 5 days (DP) **Primary Immunodeficiencies**: 800 mg/kg as frequently as every 3 weeks*
Override Criteria	
†For CIDP initiation of therapy, may approve loading doses of up to 2000 mg/kg in divided doses over 2 to 5 consecutive days	

^For MMN, may approve as frequent as every 2 weeks based on response (AHFS)

*For primary immunodeficiencies, may approve a higher dose when the treating physician has indicated that it is necessary based on the individual's clinical response

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description

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HCPCS	J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
	J1460	Injection, gamma globulin, intramuscular, 1 cc [when specified for disease treatment as described in this document]
	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 (Effective 7/1/2020)
	J1559	Injection, immune globulin (Hizentra), 100 mg
	J1560	Injection, gamma globulin, intramuscular, over 10 cc [when specified for disease treatment as described in this document]
	J1561	Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
	J1566	Injection, immune globulin, intravenous lyophilized (e.g., powder), not otherwise specified, 500 mg [Carimune, Gammagard S/D]
	J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
	J1569	Injection, immune globulin, (Gammagard Liquid), 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 immuneglobulin
	J1576	Injection, immune globulin (panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg
	J1554	Injection, immune globulin (Asceniv), 500 mg
	J1551	Injection, immune globulin (Cutaquig), 100 mg
	S9338	Home infusion therapy; immunotherapy, administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment, per diem

ICD-10 Diagnosis

All diagnoses

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 03/10/2024	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria; coding reviewed: No change	3/25/2024	5/9/2024
Policy Inception 03/13/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023