Medical Drug Clinical Criteria

Subject:	Immunoglobulins		
Document #:	CC-0003	**Publish Date:**	04/01/2025
Status:	Revised	**Last Review Date:**	11/15/2024

Table of Contents

Overview

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.

Summary of FDA-Approved indications for Immunoglobulins:

Agent	Route	PI	ITP	MMN	CLL	KS	CIDP	DM
Alyglo	IV	x						
Asceniv	IV	x*						
Bivigam	IV	x*						
Cutaquig	SC	x*						
Cuvitru	SC	x*						
Flebogamma DIF 5%	IV	x*						
Flebogamma DIF 10%	IV	x	x* (chronic)					
Gammagard	IV, SC	x*		x			x (IV)	
Gammagard S/D	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*					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*						
Yimmugo	IV	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

Other Uses:

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 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.

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.

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).

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

Chronic Inflammatory Demyelinating Polyneuropathy (or polyradiculoneuropathy) (CIDP): CIDP is an acquired, immune-mediated 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 <1ug/mL of IgA and may be better tolerated by a limited number of patients who have reacted to IG preparations with higher IgA. However, the concentration of IgA that will not provoke a reaction is unknown. Privigen and Hyqvia are contraindicated in patients with hyperprolinemia because they contain L-proline. Hyqvia is also contraindicated in patients with hypersensitivity to hyaluronidase or human albumin. Gammaplex is contraindicated in patients with a hereditary intolerance to fructose and in infants and neonates for whom sucrose or fructose tolerance has not been established. Octagam is contraindicated in patients with an acute hypersensitivity reaction to corn because it contains maltose.

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.

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.

Immunoglobulins

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, 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;

OR

E. Specific Antibody Deficiency (SAD) when:
1. There is a history of recurrent sinopulmonary infections requiring antibiotic therapy; **AND**
2. There is a lack of, or inadequate response to pneumococcal polysaccharide antigen; **AND**
3. There are normal concentrations of IgG, IgA, IgM, and IgG subclasses;

OR

F. Severe combined immunodeficiency [SCID] when:
1. Either of the following:
a. 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; **OR**
b. CD3+ T cell count of less than 300 cells /mm^3, *or* there is presence of maternal T cells in the circulation; **AND**
2. There is no evidence of renal (nephrotic syndrome) and gastrointestinal (for example, protein losing enteropathy) as causes of hypogammaglobulinemia;

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 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 functional IgG less than 400 mg/dL (i.e., polyclonal functional IgG may be estimated by subtracting M [monoclonal] spike value from total IgG);

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 2023);

OR

D. Secondary hypogammaglobulinemia or agammaglobulinemia following chimeric antigen receptor (CAR) T cell treatment (NCCN 2A/Label);

OR

E. Parvovirus B19 chronic infection and severe anemia associated with bone marrow suppression (NCCN 2A);

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 2022); **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 2022);

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;
            vii. Evidence of systemic inflammation such as fever, elevated C-reactive protein, or elevated sedimentation rate;
            viii. 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 muscle-specific 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* non-steroidal 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);

Approval Duration for MOG-related NMOSD:
Initial requests: 6 months
Continuation requests: 1 year

OR

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

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. 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) ; **OR**
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.

Step Therapy

Note: When an immunoglobulin is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

IG products and selected properties‡

Agent	Route	Osmolality (mOsm/kg)	Sodium	IgA (µg/mL)	Stabilizer or regulator
Alyglo 10%	IV	not stated	not stated	≤ 100	Glycine
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
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
Yimmugo 10%	IV	280 – 380	not stated	≤300	Glycine and polysorbate 80

‡ Per FDA Package Insert, unless otherwise noted; [π]Immune Deficiency Foundation (2021); [±]AAAAI (2016).

Commercial

Non-preferred Intravenous Immunoglobulins (IVIG) Step Therapy

A list of the preferred intravenous immunoglobulin(s) is available here.

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

A list of the preferred subcutaneous immunoglobulin(s) is available here.

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;

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.

Medicare

Non-preferred Intravenous Immunoglobulins (IVIG) Step Therapy

A list of the preferred intravenous immunoglobulin(s) is available here.

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

A list of the preferred subcutaneous immunoglobulin(s) is available here.

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 two preferred subcutaneous Ig agents; **OR**

III. 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; **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.

[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 Limits

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

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

90283	Immune globulin, (IgIV), human, for intravenous use
90284	Immune globulin, (SCIg), human, for use in subcutaneous infusions, 100 mg each

ICD-10 Diagnosis

	All diagnoses

HCPCS

J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1552	Injection, immune globulin (alyglo), 500 mg
J1554	Injection, immune globulin (Asceniv), 500 mg
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
J1561	Injection, immune globulin, (Gamunex, 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 immunoglobulin
J1576	Injection, immune globulin (13anzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg
J3590	Unclassified biologics [when specified as Yimmugo (immune globulin intravenous, human-dira)]
S9338	Home infusion therapy; immunotherapy, administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment, per diem

Document History

Revised: 11/15/2024
Document History:

- 04/01/2025 – Step therapy table updates.
- 01/17/2025 – Step therapy table updates.
- 11/15/2024 – Annual Review: Update criteria for use in multiple myeloma. Step therapy update. Coding Reviewed: Add HCPCS J1552 effective 1/1/2025 and delete HCPCS J1599 for Alyglo.
- 10/23/2024 – Step therapy table updates.

- 08/16/2024 – Select Review: Add new agent Yimmugo to document. Coding Reviewed: Added HCPCS J3590 for Yimmugo (immune globulin intravenous, human-dira). Removed HCPCS J1460 and J1560, these intramuscular immunoglobulins products are addressed in CC-0039; removed CPT 90281. Updated coding description for: J1558 (removed Effective 7/1/2020 wording); J1561 (added Gamunex).
- 07/01/2024 – Step therapy table updates.
- 03/11/2024 – Select Review: Add new agent Alyglo to document. Update summary of FDA indications for Gammagard liquid and Hyqvia. Coding Reviewed: Added HCPCS J1599 for Alyglo.
- 03/29/2024 – Step therapy table updates.
- 11/17/2023 – Annual Review: Update criteria to add indication for specific antibody deficiency. Update criteria to expand on indication for severe combined immune deficiency. Wording, formatting, and reference updates. Coding Reviewed: No changes.
- 03/13/2023 – Select Review: Update criteria to clarify initiation requests for various indications. Coding Reviewed: No changes. Effective 7/1/2023 Added HCPCS J1576. Deleted HCPCS J1599.
- 11/18/2022 – Annual Review: Update criteria to add continuation criteria for Autoimmune mucocutaneous blistering diseases, Dermatomyositis or polymyositis, Lambert-Eaton myasthenic syndrome, Myasthenia Gravis, and Stiff-person syndrome. Add approval durations for various indications. Update multiple myeloma criteria per NCCN guidelines to allow for use with history of infections or low IgG levels. Add dosing limits for DM, CLL, and Stiff-person syndrome per label and/or compendia. Wording, formatting, and reference updates. Coding Reviewed: No changes.
- 09/30/2022 – Step therapy table updates.
- 07/25/2022 – Step therapy table updates. Administrative update to add documentation.
- 11/19/2021 – Annual Review: Update criteria to add paraneoplastic encephalitis indication. Update the CIDP criteria to remove the word “partial” from the motor conduction block for the EFNS/PNS diagnostic criteria per guideline update. Updated references. Coding Reviewed: No changes. Effective 7/1/2022 Added HCPCS J1551 for Cutaquig. Removed HCPCS J3490, J3590, C9399.
- 11/20/2020 – Annual Review: Update criteria for hyperimmunoglobulinemia E syndrome to include clinical features of disease. Update criteria for multiple myeloma to update minimum threshold for IgG levels per NCCN 2A update. Update criteria for solid organ transplant to allow for corrected PRA and history of high DSA levels per guidelines. Update IG criteria to allow for new indication of autoimmune encephalitis. Clarify use of previous agents for dermatomyositis and polymyositis. Update criteria for Guillain-Barre syndrome to include clinical presentation features, treatment guidance, and approval duration. Update criteria for multifocal motor neuropathy to expand on diagnostic requirements, and requirements for continuation of use, and clarify approval duration. Update IG criteria to allow for new indication of MOG-related NMOSD. Update non-approvable criteria to allow exceptions for MOG-related NMOSD under immune optic neuropathy. Add administrative note for use in cancer-related CMV pneumonia. Wording and formatting changes. Coding Reviewed: Added HCPCS C9072 for Asceniv (Effective 1/1/2021). Effective 4/1/2021 Added HCPCS J1554 for Asceniv. Removed C9072. Removed term Asceniv from J1599.
- 05/15/2020 – Select Review: Update criteria for myasthenia gravis to include specific drug failures, and add failure of pyridostigmine as requirement. Update criteria for CIDP to include requirement regarding disease duration, specific electrodiagnostic criterion, and objective measures for continuation. Remove annual evaluation of clinical effect requirement from CIDP criteria, and clarify language for clinical effect. Clarify initial approval duration for CIDP. Coding Reviewed: Added HCPCS J1558 for Xembify (Effective 7/1/2020), Delete the term Xembify 6/30/2020- J3490, J3590, C9399
- 11/15/2019 – Annual Review: Add new product Xembify (subcutaneous immunoglobulin) to clinical criteria and step therapy. Update criteria for use in Kawasaki disease to include coronary artery abnormalities. Minor wording and formatting changes. Coding reviewed: Added Xembify to J3490, J3590, C9399.
- 09/23/2019 - Administrative update to add drug specific quantity limit.
- 06/10/2019 – Select Review: Add new products, Asceniv (intravenous immunoglobulin) and Cutaquig (subcutaneous immunoglobulin) to indication table and as potential preferred products in step therapy. Coding reviewed: Added new HCPCS J3490, J3590, and C9399 for Cutaquig, Asceniv drug is listed under J1599
- 11/16/2018 – Annual Review: Initial review of Immunoglobulin clinical criteria. Clarify definition of “refractory” in certain indications. Add use in Multiple Myeloma and CMV pneumonia per NCCN recommendations. Update HIV indication to apply to hypogammaglobulinemic patients. Update definition of hypogammaglobulinemia to IgG <400mg/dL per guidelines. Add use in antibody-mediated rejection per guidelines. Update definition of ITP per guidelines and for consistency with other agents. Update criteria in Myasthenia Gravis to include use in exacerbation or refractory disease. Simplify and clarify diagnostic criteria in neurologic conditions. Bring post- exposure prophylaxis of certain infections in scope. Add references for off label indications and other wording and formatting changes. HCPCS Coding review: no change. ICD-10 Coding review: no change.

References

1. Aggarwal R, Charles-Schoeman C, Schessl J, Dimachkie MM, Beckmann I, Levine T. Prospective, double-blind, randomized, placebo-controlled phase III study evaluating efficacy and safety of octagam 10% in patients with dermatomyositis ("ProDERM Study"). *Medicine (Baltimore)*. 2021;100(1):e23677. doi:10.1097/MD.0000000000023677 Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7793357/pdf/medi-100-e23677.pdf.
2. American Academy of Pediatrics. RedBook: 2021: Report of the Committee on Infectious Diseases. 32nd Edition. Available at https://publications.aap.org/redbook/book/347/Red-Book-2021-2024-Report-of-the-Committee-on.

3. American Academy of Pediatrics. Diagnosis and Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2022. 150 (3): e20220588959. Available at https://doi.org/10.1542/peds.2022-058859. Accessed October 18, 2024.
4. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 207. Thrombocytopenia in pregnancy. Obstet Gynecol. 2019; 133:e181. Accessed October 18, 2024.
5. American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012; 98(5):1103-1111.
6. Bonilla FA, Khan DA, Ballas ZK, et al. Joint task force on practice parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology; Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186–1205. Accessed October 18, 2024.
7. Centers for Disease Control and Prevention. Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013. Summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013; 62(RR-4):1-40. Available from: http://www.cdc.gov/mmwr/pdf/rr/rr6204.pdf. Accessed October 18, 2024.
8. Chung, SA, Langford CA, Maz M, et. al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Care and Research. Vol. 73, No. 8. August 2021, pp 1088-1105. Available at https://www.rheumatology.org/Portals/0/Files/Guideline-Management-ANCA-Associated-Vasculitis-2021.pdf. Accessed on October 18, 2024.
9. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed on October 18, 2024.
10. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
11. Farmakidis C, Pasnoor M, Dimachkie MM, et. al. Treatment of Myasthenia Gravis. Neurologic Clinics (Neurol Clin) 2018; 36:311. Accessed October 18, 2024.
12. Hacohen Y, Banwell B. Treatment Approaches for MOG-Ab-Associated Demyelination in Children. Current Treatment Options in Neurology. January 2019. 21(1):2. DOI: 10.1007/s11940-019-0541-x. Accessed on October 18, 2024.
13. Hughes RA, Donofrio P, Bril V, et al. ICE Study Group. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol. 2008 Feb;7(2):136-44. doi: 10.1016/S1474-4422(07)70329-0. Erratum in: Lancet Neurol. 2008 Sep;7(9):771.
14. Hughes RA, Wijdicks EF, Barohn R, et al. Practice parameter: Immunotherapy for Guillain–Barré syndrome. Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN). Neurology Sep 2003, 61 (6) 736-740; DOI: 10.1212/WNL.61.6.736. Reaffirmed January 22, 2022. Accessed October 18, 2024.
15. Immune Deficiency Foundation. Immunoglobin Products. Available at: https://primaryimmune.org/about-primary-immunodeficiencies-treatments/immunoglobulin-products. Accessed October 22, 2024.
16. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society [EFNS/PNS] guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J Peripher Nerv Syst. 2010 Dec;15(4):295-301. doi: 10.1111/j.1529-8027.2010.00290.x. Accessed October 22, 2024.
17. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis. 2007; 2:44. Available at file:///C:/Users/AF38863/Downloads/1750-1172-2-44.pdf. Accessed October 22, 2024.
18. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group: KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant, 9 (Suppl 3) (2009), pp. S1-S157. Accessed October 22, 2024.
19. Kidney Disease: Improving Global Outcomes (KDIGO) Kidney Transplant Candidate Work Group. KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation. 2020;104: S1 – S103. Accessed October 22, 2024.
20. Kotton D.K., Caliendo A.M., Huprikar S., Chou S., Danziger-Isakov L., Humar A. The Transplantation Society [TTS] International CMV Consensus Group. The third international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation. 2018;102:900–931. Accessed October 22, 2024.
21. Lancaster, E. The Diagnosis and Treatment of Autoimmune Encephalitis. *J Clin Neurol.* 2016 Jan;12(1):1-13. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712273/pdf/jcn-12-1.pdf. Accessed October 22, 2024.
22. Lancaster, E. Autoantibody Encephalitis: Presentation, Diagnosis, and Management. *J. Clin Neurol*. 2022; 18(4):373-390. Available at https://www.thejcn.com/pdf/10.3988/jcn.2022.18.4.373. Accessed October 22, 2024.
23. Léger JM, De Bleecker JL, Sommer C, et al. PRIMA study investigators. Efficacy and safety of Privigen(®) in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study). J Peripher Nerv Syst. 2013 Jun;18(2):130-40. doi: 10.1111/jns5.12017.
24. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation [ISHLT] (Consensus Document) J Heart Lung Transplant. 2016 Apr;35(4):397-406. Accessed October 22, 2024.
25. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; Updated periodically.
26. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association (AHA). *Circulation.* 2017;135(17):e927-e999. Accessed October 22, 2024.
27. Murrell DF, Peña S, Joly P, et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. J Am Acad Dermatol. 2020 Mar;82(3):575-585.e1. Accessed October 22, 2024.

28. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Reaffirmed July 2022. *Neurology*. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124 Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884987/pdf/NEUROLOGY2020099945.pdf. Accessed on October 22, 2024.
29. NCCN Clinical Practice Guidelines in Oncology™. National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on October 22, 2024.
    a. Multiple myeloma. V1.2025. Revised September 17, 2024.
    b. Chronic Lymphocytic Leukemia/Small lymphocytic lymphoma. V1.2025. Revised October 1, 2024.
    c. Prevention and Treatment of Cancer-Related Infections. V3.2024. Revised September 23, 2024.
    d. Management of Immunotherapy-Related Toxicities. V1.2024. Revised December 7, 2023.
30. Neunert C, Terrell DR, Arnold CM, et al. American Society of Hematology [ASH] 2019 guidelines for immune thrombocytopenia. *Blood Adv* 2019; 3 (23): 3829–3866. Available at https://doi.org/10.1182/bloodadvances.2019000966. Accessed October 22, 2024.
31. Olney RK, Lewis RA, Putnam TD, Campellone JV. AAEM Practice Topic in Electrodiagnostic Medicine. American Association of Electrodiagnostic Medicine. Consensus criteria for the diagnosis of multifocal motor neuropathy. Muscle Nerve 2003;27:117-121. Available at https://www.aanem.org/getmedia/afd29b39-2179-421e-bac7-f88b4294a27d/CCDiagoseMMN.pdf. Accessed October 22, 2024.
32. Otani IM, Lehman HK, Jongco AM, et. al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. Volume 149, Issue 5, P1525-1560. May 1, 2022. Available at https://www.jacionline.org/article/S0091-6749(22)00152-X/fulltext. Accessed October 22, 2024.
33. Panel on Opportunistic Infections in Children with and Exposed to HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV. Department of Health and Human Services. Updated July 3, 2024. Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-pediatric-opportunistic-infections/whats-new. Accessed on October 23, 2024.
34. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, El-Gamal Y, Harville TO, Hossny E, Mazer B, et al. Update on the use of immunoglobulin in human disease: a review of evidence. Work Group Report of the American Academy of Allergy, Asthma & Immunology (AAAAI) 2016. J Allergy Clin Immunol. 2017;139(3S):S1–46.
35. Report from an Ad Hoc Subcommittee of the American Academy of Neurology (AAN) AIDS Task Force. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991;41:617-618. Accessed on October 23, 2024.
36. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016; 87:419. Updated 2020. Accessed on October 23, 2024.
37. Shahrizaila N, Lehmann H, Kuwabara S. Guillain-Barre Syndrome. Lancet. 2021 Mar 27;397(10280):1214-1228. doi: 10.1016/S0140-6736(21)00517-1. Epub 2021 Feb 26. Accessed October 23, 2024.
38. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol. 1995; 22(4):668-674. Accessed on October 23, 2024.
39. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective (Consensus group including ASBMT, CDC, ISDA). Biol Blood Marrow Transplant 2009; 15(10):1143-1238. Accessed on October 23, 2024.
40. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. *Eur J Neurol*. 2021;28(11):3556-3583. doi:10.1111/ene.14959 Available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/ene.14959. Accessed on October 23, 2024.
41. Van Schaik IN, Bril V, van Geloven N, et al. PATH study group. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2018 Jan;17(1):35-46. doi: 10.1016/S1474-4422(17)30378-2. Epub 2017 Nov 6. Erratum in: Lancet Neurol. 2018 Jan;17 (1):26. Erratum in: Lancet Neurol. 2018 Aug;17(8):661.
42. Velleca A, Shullo MA, Dhital K, et al. The International Society of Heart and Lung Transplantation (ISHLT) Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2022; Volume 42, Issue 5, E1-E141, May 2023. Accessed October 23, 2024.
43. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet 2016; 388:717. October 23, 2024.
44. Yeung, MY. Kidney Transplantation in Adults: Overview of HLA sensitization and crossmatch testing. UpToDate. September 2024. Accessed on October 23, 2024.
45. Zuliani L, Nosadini M, Gastaldi M, et. al. Management of antibody-mediated autoimmune encephalitis in adults and children: literature review and consensus-based practical recommendations. Neurological Sciences 2019. 40:2017-2030. https://doi.org/10.1007/s10072-019-03930-3. Accessed on October 23, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

CC-0003 Immunoglobulins

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
10/01/2024	Intravenous: Gamunex-C* Octagam Subcutaneous^: Cutaquig Hizentra Xembify	Intravenous: Alyglo Asceniv Bivigam Flebogamma DIF Gammaked* Gammagard* Gammagard S/D Gammaplex Panzyga Privigen Subcutaneous: Cuvitru HyQvia
02/01/2025	Intravenous: Gamunex-C* Octagam Subcutaneous^: Cutaquig Hizentra Xembify	Intravenous: Alyglo Asceniv Bivigam Flebogamma DIF Gammaked* Gammagard* Gammagard S/D Gammaplex Panzyga Privigen Yimmugo Subcutaneous: Cuvitru HyQvia

*Gamunex-C, Gammaked, and Gammagard may be administered intravenously or subcutaneously.
^Subcutaneous preferred products require step through intravenous product.

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
N/A	N/A	N/A

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents

02/01/2025	Intravenous: Gamunex-C* Octagam Subcutaneous: Cutaquig Hizentra Xembify	Intravenous: Alyglo Asceniv Bivigam Flebogamma DIF Gammaked* Gammagard* Gammagard S/D Gammaplex Panzyga Privigen Subcutaneous: Cuvitru HyQvia
04/1/2025	Intravenous: Gamunex-C* Octagam Subcutaneous: Cutaquig Hizentra Xembify	Intravenous: Alyglo Asceniv Bivigam Flebogamma DIF Gammaked* Gammagard* Gammagard S/D Gammaplex Panzyga Privigen Yimmugo Subcutaneous: Cuvitru HyQvia

*Gamunex-C, Gammaked, and Gammagard may be administered intravenously or subcutaneously.