Clinical Criteria

Subject: Immunoglobulins

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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
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	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)				
Panzyga	IV	x*	x (chronic)				
Privigen	IV	x*	x*(chronic)				x

*Includes pediatric indication

PI = Primary (Humoral) Immunodeficiency [such as 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

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, fetal alloimmune thrombocytopenia, autoimmune neutropenia, skin blistering disease, and dermatomyositis. Polymyositis is a very rare condition, but is thought to be similar to dermatomyositis.

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.

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
CIDP	• NCS show reduced conduction velocity, prolonged distal motor latencies, and dispersion and distance-dependent reduction of CMAP amplitude
MMN	• NCS show focal demyelination and conduction block

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. Carimune NF is the only IVIG that contains sucrose.

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:**

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 there is a diagnosis as evidenced by elevated level of serum IgE (AAAAI/ACAAI 2015);

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, **AND**
   2. Hypogammaglobulinemia shown by total IgG less than 500 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 2013);

OR

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

OR

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

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) levels to human leukocyte antigens (HLA) (AAAAI 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);

OR

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

A. 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 2011);

OR

B. Fetal alloimmune thrombocytopenia with the following: (ACOG 2016)
    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

C. Isoimmune hemolytic disease of the newborn, treatment of severe hyperbilirubinemia (AAP 2004);

OR

D. Autoimmune mucocutaneous blistering diseases (including pemphigus vulgaris, pemphigus foliaceous, bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullosa acquisita) when individual has had an inadequate response to, is intolerant of, or has a contraindication to other treatments such as corticosteroids or immunosuppressive agents (AAAAI 2016);

OR

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

OR

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

    AND

    3. 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;

OR

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

A. Lambert-Eaton myasthenic syndrome when: (AAAAI 2016)
    1. Individual is experiencing muscle weakness; **AND**
    2. Diagnosis confirmed by one of the following:

a. Characteristic electrodiagnostic findings using nerve conduction tests, repetitive nerve stimulation (RNS), exercise testing, or single fiber electromyography (SFEMG); **OR**
b. Presence of antibodies directed against voltage-gated calcium channels (VGCC);

OR

B. Guillain-Barre Syndrome (acute demyelinating polyneuropathy) (Drugpoints B IIa);

OR

C. Myasthenia Gravis when: (AAAAI 2016)
1. Individual's clinical presentation is characteristic of myasthenia gravis; **AND**
2. The diagnosis is confirmed by one of the following:
a. The presence of antibodies against the acetylcholine receptor (AChR-Ab) or muscle-specific tyrosine kinase (MuSK-Ab); **OR**
b. Characteristic electrodiagnostic findings using repetitive nerve stimulation (RNS) or single fiber electromyography (SFEMG);

AND

3. Individual is using for one of the following:
a. Worsening symptoms or exacerbation of myasthenia gravis; **OR**
b. Short-term therapy as immunosuppressive treatment is taking effect; **OR**
c. Maintenance therapy of myasthenia gravis when individual has had an inadequate response to, is intolerant of, or has a contraindication to other treatments such as steroids or immunosuppressants

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; **AND**
b. Nerve conduction studies (NCS) or diagnostic criteria confirm evidence of a demyelinating neuropathy; **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; **AND**
b. Continued need is demonstrated by attempts on an annual basis to titrate the dose or the interval of therapy result in worsening of symptoms;

OR

E. Multifocal Motor Neuropathy (MMN) for either of the following:
1. As an *initial* trial (up to 12 weeks) to treat MMN, when clinical presentation combined with electrodiagnostic testing, labs, or diagnostic criteria suggest or confirm MMN;
2. Continued use of Ig after initial trial for MMN when the following criteria are met:
a. Individual experienced improvement in strength and function after the initial trial; **AND**
b. Continued need is demonstrated by attempts on an annual basis to titrate the dose or the interval of therapy result in worsening of symptoms;

OR

F. Stiff-person syndrome when individual has had an inadequate response to, is intolerant of, or has a contraindication to other treatments such as benzodiazepines or baclofen (AAAAI 2016)

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 aneurysms and evidence of ongoing inflammation (such as elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) (AHFS, AHA 2004);

    AND

    3. Treatment for no more than 5 days (AHA 2004);

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 <500mg/dL) (NCCN 2a).

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

I. Alzheimer's disease; **OR**
II. Immune optic neuropathy; **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).

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.

A benefit plan may select any one or more of the following as preferred immunoglobulin: Asceniv, Bivigam, Carimune NF, Cutaquig, Cuvitru, Flebogamma DIF, Gammagard, Gammagard S/D less IgA, Gammaked, Gammaplex, Gamunex-C, Hizentra, Hyqvia, Octagam, Panzyga, Privigen. A list of the preferred immunoglobulin(s) is available here.

Non-preferred Immunoglobulins Step Therapy

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

I. Individual is currently receiving and stabilized on the requested non-preferred agent; **OR**
II. If designated, individual has had a trial and inadequate response or intolerance to one preferred Ig agent; **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. The preferred Ig agent is not acceptable due to concomitant clinical condition(s), such as but not limited to the following:
    A. Renal insufficiency/impairment; **OR**
    B. Non-O blood type; **OR**
    C. Severe IgA deficiency; **OR**
    D. Diabetes/prediabetes; **OR**
    E. Cardiovascular disease; **OR**
    F. Hyperprolinemia; **OR**
    G. Hypernatremia; **OR**
    H. High-risk for thrombosis, such as but not limited to:
        1. Hyperviscosity syndromes (such as cryoglobulinemia, monoclonal gammopathies, polyclonal hyperglobulinemia); **OR**
        2. Hypercoagulable conditions;

    OR

    I. Documented 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

V. If all subcutaneous Ig (SCIG)- only dose forms (Cutaquig, Cuvitru, Hizentra, Hyqvia) are designated as non-preferred, the desired agent may be approved for individuals requesting for any of the following:
    A. Difficult vein access that precludes use of an intravenous immune globulin (IVIG); **OR**
    B. History of serious systemic reaction to IVIG expected to be avoided by using SCIG; **OR**
    C. History of inconsistent serum levels of immunoglobulin G (IgG) with IVIG.

[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.

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

90281	Immune globulin (Ig), human, for intramuscular use [when specified for disease treatment as described in this document]
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
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
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
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg (Panzyga)
J3490	Unclassified drugs when specified as [Cutaquig]
J3590	Unclassified biologicals when specified as [Cutaquig]
C9399	Unclassified drugs or biologicals when specified as [Cutaquig] Hospital OUTPATIENT SERVICES ONLY
S9338	Home infusion therapy; immunotherapy, administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment, per diem

Document History

Revised: 06/10/2019
Document History:

- 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. American Academy of Pediatrics. RedBook: 2018: Report of the Committee on Infectious Diseases. 31st Edition. Available at https://redbook.solutions.aap.org/book.aspx?bookid=2205
2. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297-316.
3. American College of Obstetricians and Gynecologists (ACOG).Practice Bulletin No. 166. Thrombocytopenia in pregnancy. Obstet Gynecol. 2016; 128(3):e43-53.
4. American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012; 98(5):1103-1111.
5. 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.
6. 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 on: October 24, 2018.
7. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2019. URL: http://www.clinicalpharmacology.com. Updated periodically.
8. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation (ISHLT) Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010; 29(8):914-956.
9. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: June 2019.
10. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
11. 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
12. Kotton D.K., Caliendo A.M., Huprikar S., Chou S., Danziger-Isakov L., Humar A. The Transplantation Society International CMV Consensus Group. The third international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation. 2018;102:900–931.
13. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2019; Updated periodically.
14. NCCN Clinical Practice Guidelines in Oncology™. © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on May 31, 2019.
    a. Multiple myeloma. V2.2019. Revised November 16, 2018.
    b. Management of Immunotherapy-Related Toxicities. V2.2019. Revised April 8, 2019
    c. Chronic Lymphocytic Leukemia/small lymphocytic lymphoma. V5.2019. Revised May 23, 2019.
15. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011; 117(16):4190-4207. Available from: http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx. Accessed on: September 4, 2018.
16. Newburger JW, Takahashi M, Gerber MA et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004; 110:2747-71.
17. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol. 1995; 22(4):668-674.
18. 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.
19. Panel on Opportunistic Infections in HIV-exposed and HIV-infected children, US Department of Health and Human Services (HHS). Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. (October 18, 2018).

20. 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. J Allergy Clin Immunol. 2017;139(3S):S1–46.

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.

ING-CC-0003 Immunoglobulins

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
5/1/2018	Gamunex-C Octagam	Asceniv Bivigam CarimuneNF Cutaquig Cuvitru Flebogamma Gammagard Gammagard S/D Gammaked Gammaplex Hizentra HyQvia Privigen

*Effective 2/9/19 Cuvitru, Hizentra and HyQvia are non-preferred agents

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
TBD	Gamunex-C Octagam	Asceniv Bivigam CarimuneNF Cutaquig Cuvitru Flebogamma Gammagard Gammagard S/D Gammaked Gammaplex Hizentra HyQvia Privigen