



**BlueCross BlueShield
of Alabama**

Immune Globulins Medical Policy Prior Authorization Program Summary

Precertification/Prior Authorization may be required under certain plans. Please verify each member's benefits.

OBJECTIVE

The intent of the Immune Globulins medical drug criteria is to direct use to Food and Drug Administration approved label indications as well as indications supported by clinical guidelines and compendia. Currently available immune globulin preparations are produced from pooled human plasma involving a number of processes and there is limited supply of product. Use of immune globulins should be carefully considered. The prior authorization criteria for the immune globulins will consider use of these agents for unlabeled indications if there is evidence available or submitted by the prescriber supporting its intended use.

Target Drugs

Bivigam™ IVIG
Carimune® NF IVIG
Cuvitru™ SCIG
Flebogamma & Flebogamma® 5%, 10% DIF IVIG
GamaSTAN™ S/D, Immune Globulin IMIG
Gammagard® S/D IVIG
Gammagard® S/D IVIG IgA less than 1 mcg/mL
Gammagard® Liquid IVIG
Gammaked™ Liquid IVIG
Gammaplex® Liquid IVIG
Gamunex®-C SCIG/IVIG
Hizentra™ SCIG
HyQvia SCIG
Octagam® IVIG
Panzyga 10% IVIG
Privigen™ IVIG

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Immune Globulins will be approved when ALL of the following are met:

Choose ONE of the following:

1. The patient has been diagnosed with:
 - a. ONE of the following Primary immunodeficiencies:
 - i. Selective IgG subclass deficiency AND ALL of the following:
 1. Deficiency of 1 or more IgG subclasses (e.g. IgG1, IgG2, IgG3, or IgG4) < 2 standard deviations (SD) below age-specific mean, assessed on 2 separate occasions during infection free period
AND
 2. Poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination)
AND
 3. Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g. recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, etc.) despite aggressive management and treatment with antibiotics
OR
 - ii. Specific antibody deficiency (SAD) AND normal levels of immunoglobulin and normal levels of IgG subclasses with BOTH of the following:

1. Poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination)
AND
2. Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g. recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, etc.) despite aggressive management and treatment with antibiotics
OR
- iii. All other Primary immunodeficiencies [including, but not limited to, Common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA)/congenital agammaglobulinemia/Bruton's agammaglobulinemia, Autosomal Recessive Agammaglobulinemia (ARA), primary hypogammaglobulinemia, X-linked immunodeficiency, severe combined immunodeficiency (SCID), combined immunodeficiency syndromes (e.g. Ataxia Telangiectasia, DiGeorge syndrome, Wiskott-Aldrich Syndrome, zeta chain-associated protein 70, Hyper-IgM syndrome), any other humoral immunodeficiency] and ONE of the following:
 1. Agammaglobulinemia and ONE of the following:
 - a. Total IgG < 200 mg/dL (at baseline prior to immune globulin therapy) **OR**
 - b. Patients with an abnormal Bruton tyrosine kinase (BTK) gene/absence of BTK protein **OR**
 - c. Absence of B lymphocytes
OR
 2. Hypogammaglobulinemia and ALL of:
 - a. Total IgG < 700 mg/dL (at baseline prior to immune globulin therapy)
AND
 - b. Poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination
AND
 - c. Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g. recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, etc.) despite aggressive management and treatment with antibiotics
OR
- b. Chronic lymphocytic leukemia with reduced IgG and **BOTH** of the following:
 - i. The patient has hypogammaglobulinemia (total IgG < 700 mg/dL at baseline prior to immune globulin therapy)
AND
 - ii. ONE of the following:
 1. One severe bacterial infection within the last year **OR**
 2. Evidence of specific antibody deficiency
OR
- c. Prevention of bacterial infections in HIV-treated patients **AND** the patient is currently on antiretroviral therapy
OR
- d. Idiopathic thrombocytopenia purpura and **ONE** of the following:
 - i. The patient has failed conventional therapy (e.g. corticosteroids) **OR**
 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents (e.g. corticosteroids)
OR
- e. Dermatomyositis and **ONE** of the following:
 - i. The patient has failed conventional therapy (e.g. immunosuppressants, corticosteroids) **OR**
 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents **OR**
 - iii. The patient has been diagnosed with juvenile dermatomyositis
OR
- f. Polymyositis and **ONE** of the following:

- i. The patient has failed conventional therapy (e.g. immunosuppressants, corticosteroids) **OR**
 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents
- OR**
- g. Severe rheumatoid arthritis and **ONE** of the following:
 - i. The patient has failed conventional therapy (e.g. tumor necrosis factor antagonists, DMARDS, Remicade, Xeljanz, Xeljanz XR)
 - OR**
 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional therapy agents
- OR**
- h. Myasthenia Gravis (MG) and **ONE** of the following:
 - i. The patient is in acute myasthenic crisis with decompensation (e.g. acute episode of respiratory muscle weakness/respiratory failure/dysphagia/ aspiration/major functional disability responsible for the discontinuation of physical activity) **OR** has severe refractory MG (e.g. major functional disability/weakness)
 - OR**
 - ii. Immune globulin will be used prior to surgery (i.e. thymectomy) in a patient with MG crisis
 - OR**
 - iii. The patient failed/has not been controlled with maximally tolerated immunomodulator therapy (e.g. corticosteroids, mycophenolate, cyclosporine, and/or azathioprine)
 - OR**
 - iv. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all immunomodulator therapy agents
 - OR**
 - v. The patient has received plasma exchange within the last 30 days
- OR**
- i. Multiple sclerosis and **BOTH** of the following:
 - i. The patient has a diagnosis of relapsing remitting multiple sclerosis (RRMS) **AND**
 - ii. The patient has had an insufficient response, documented failure, or FDA labeled contraindication to TWO Disease Modifying Agents FDA indicated for RRMS: Avonex, Aubagio, Betaseron, Copaxone (Glatopa), Extavia, Gilenya, Lemtrada, Plegridy, Rebif, Tecfidera, Tysabri, or Zinbryta
- OR**
- j. Multiple myeloma **AND** the following:
 - i. The patient has stable disease (i.e. not progressive) **AND** has recurrent infections despite antibiotic prophylaxis **AND** is currently (within past 30 days) on chemotherapy
- OR**
- k. Acquired von Willebrand hemophilia and **ONE** of the following:
 - i. The patient has failed conventional therapy (e.g. DDAVP, corticosteroids, cyclophosphamide, von Willebrand factor replacement therapy, FEIBA (factor eight inhibitor bypassing activity), rituximab, or recombinant factor VIIa) **OR**
 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional agents
- OR**
- l. Hemolytic disease of the newborn and **BOTH** of the following:
 - i. The patient is using concurrent phototherapy **AND**
 - ii. The patient has either Rhesus or ABO hemolytic disease
- OR**
- m. Provision of passive immunity in **ONE** of the following susceptible individuals:

- i. Hepatitis A: The patient requires pre-exposure prophylaxis within 14 days **OR** the patient requires post exposure prophylaxis within 14 days **AND** falls under 1 of the following populations:
 - 1. Patients who cannot be vaccinated due to age (<12 months) **OR**
 - 2. Has a vaccination allergy or refusal of vaccination **OR**
 - 3. Infants born to mothers with acute hepatitis A prevention**OR**
- ii. Measles: For patients that have been exposed to measles within 6 days and is unvaccinated, and who has not previously had measles
OR
- iii. Rubella: The patient is a pregnant woman, who will not consider therapeutic abortion, and requires post exposure prophylaxis within 72 hours of exposure to reduce the risk of infection and fetal damage
OR
- iv. Varicella: For immunosuppressant patients that require post exposure prophylaxis because varicella zoster immune globulin is not available (cannot obtain vaccine within 96 hours of exposure)
OR
- n. Prevention of bacterial infection in HIV-infected children and **ALL** of the following:
 - i. Patient is <13 years old **AND**
 - ii. CD4 count is >200 μ L **AND**
 - iii. Patient's IgG is <400 mg/dL (at baseline prior to immune globulin therapy)**OR**
- o. Refractory pemphigus vulgaris and **ALL** of the following:
 - i. The patient has progressive, severe/extensive and/or debilitating disease
AND
 - ii. ONE of the following:
 - 1. The patient has failed conventional immunosuppressive therapy (e.g. azathioprine, cyclophosphamide, mycophenolate, corticosteroids)
OR
 - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all conventional immunosuppressive therapy agents**OR**
- p. Primary immune defects with absent B cells **OR**
- q. Prior to solid organ transplant, treatment for patients at high risk of antibody-mediated rejection (AMR) including highly sensitized patients and those receiving ABO incompatible organ **OR**
- r. Post solid organ transplant, treatment of AMR **OR**
- s. Adult HIV associated thrombocytopenia **OR**
- t. Prevention and treatment of neonatal sepsis **OR**
- u. Graves Ophthalmopathy **OR**
- v. Fetomaternal alloimmune thrombocytopenia **OR**
- w. Post transfusion purpura **OR**
- x. Guillain-Barre syndrome **OR**
- y. Chronic inflammatory demyelinating polyneuropathy (CIDP) **OR**
- z. Multifocal motor neuropathy **OR**
- aa. Paraprotein associated demyelinating neuropathy – (IgM, IgA, or IgG)
OR
- bb. Lambert-Eaton myasthenia syndrome (LEMS) **OR**
- cc. Intractable childhood epilepsy **OR**
- dd. Rasmussen syndrome **OR**
- ee. Kawasaki disease **OR**
- ff. CMV-induced pneumonitis in solid organ transplant **OR**
- gg. Rotaviral enterocolitis **OR**
- hh. Bacterial infections in lymphoproliferative disease **OR**
- ii. Prevention in acute graft vs. host disease (GVHD) after bone marrow transplant (BMT) **OR**

- jj. Delayed pressure urticaria **OR**
- kk. Prevention of acute humoral rejection in renal transplant **OR**
- ll. Pediatric autoimmune psychiatric disorders associated with streptococcal infections **OR**
- mm. Severe invasive group A streptococcal disease **OR**
- nn. Severe, persistent, high-dose asthma **OR**
- oo. Toxic epidermal necrolysis and Stevens-Johnson syndrome **OR**
- pp. Low serum IgG levels induced by chemotherapy or following hematopoietic stem cell transplant (HSCT) for malignancy **OR**
- qq. Stiff-man syndrome (Moersch-Woltmann) **OR**
- rr. Monoclonal gammopathy **OR**
- ss. The use of the immune globulin product is supported by clinical evidence or the prescriber has submitted documentation in support of therapy with immune globulin for the intended diagnosis

AND

- 2. ONE of the following:
 - a. The dose is supported by FDA labeling, compendia, or clinical evidence **OR**
 - b. The prescriber submitted clinical evidence supporting the requested dose for the intended use

Length of approval: 12 months unless otherwise indicated below (refer to Table 1)

Renewal Evaluation

Immune Globulins will be renewed when ALL of the following are met:

- 1. The patient has been previously approved for the requested agent through the Medical Drug Review Process

AND

- 2. ONE of the following:
 - a. The patient was previously approved for immune globulin (IG) therapy for short term use (i.e. ≤ 3 months) (refer to Table 1) **AND** the following:
 - i. The prescriber has provided clinical documentation supporting continued use of the requested agent
 - OR**
 - b. The patient was previously approved for chronic immune globulin (IG) therapy (e.g. for a diagnosis not noted in Table 1) **AND** one of the following:
 - i. The patient has had clinical improvement OR disease stabilization (e.g. IgG level has improved from pre-treatment levels with the requested agent, reduction in the number and/or severity of difficult to treat infections, reduction in seizure frequency)
 - OR**
 - ii. The prescriber has provided clinical documentation supporting continued use of the requested agent

AND

- 3. ONE of the following:
 - a. The dose is supported by FDA labeling, compendia, or clinical evidence **OR**
 - b. The prescriber submitted clinical evidence supporting the requested dose for the intended use

Length of Approval: 12 months unless otherwise indicated below (refer to Table 1)

Table 1

Indication	Length of Approval
Measles, Rubella, Varicella	Once
Adult HIV associated thrombocytopenia	1 month
Rotaviral enterocolitis	1 month
Delayed pressure urticaria	1 month
Prevention of acute humoral rejection in renal transplant	1 month
CMV induced pneumonitis in solid organ transplant	3 months
Guillain-Barre Syndrome	3 months
Hepatitis A	3 months
Idiopathic thrombocytopenia purpura	3 months
Acquired von Willebrand hemophilia	3 months
Hemolytic disease of the newborn	3 months
Lambert-Eaton myasthenia syndrome	3 months
Myasthenia gravis crisis	3 months
Kawasaki disease	3 months
Prior to solid organ transplant, treatment for patients at high risk of antibody-mediated rejection (AMR) including highly sensitized patients and those receiving ABO incompatible organ	3 months
Post solid organ transplant, treatment of AMR	3 months
Prevention and treatment of neonatal sepsis	3 months
Severe invasive group A streptococcal disease	3 months
Toxic epidermal necrolysis and Steven Johnsons syndrome	3 months
Graves Ophthalmopathy	3 months
Post transfusion purpura	3 months
Prevention in acute graft vs. host disease (GVHD) after bone marrow transplant (BMT)	3 months
Pediatric autoimmune psychiatric disorders associated with streptococcal infections	3 months

Your health plan does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Your health plan administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in your health plan's administration of plan contracts.

Prime Therapeutics LLC is an independent limited liability company providing pharmacy benefit management services.

DRAFT

FDA APPROVED INDICATIONS AND DOSAGE^{1-10,18-20,23,26,27,29,30,55,56}

	PID	CLL	ITP	KAWASAKI SYNDROME	OTHER	ROUTE	DOSE FORM
Bivigam™	✓					IV	10% solution
Carimune® NF	✓		✓			IV	Lyophilized powder
Cuvitru™ 20%	✓					SC	20% solution
Flebogamma®	✓					IV	5% solution
Flebogamma®	✓						10% Solution
5% DIF							
Flebogamma®	✓		✓ ^d				
10% DIF							
GamaSTAN™ S/D					✓ ^a	IM	16.5% solution
Gammagard® S/D, 5%, 10%	✓	✓	✓	✓		IV	Lyophilized powder
Gammagard® S/D, 5%	✓	✓	✓	✓		IV	5% solution
Gammagard Liquid®	✓				✓ ^c	SC, IV	10% solution
Gammaked	✓		✓		✓ ^b	SC (PID only), IV	10% solution
Gammaplex Liquid®	✓		✓			IV	5% solution
Gamunex®-C	✓		✓		✓ ^b	SC (PID only), IV	10% solution
Hizentra™	✓					SC	20% solution
Hyqvia	✓					SC	10% solution
Octagam®	✓					IV	5% solution 10% solution
Panzyga 10%	✓		✓			IV	10% solution
Privigen™	✓		✓			IV	10% solution

PID=primary immunodeficiencies, CLL=chronic lymphocytic leukemia, HIV=human immunodeficiency virus, ITP=idiopathic thrombocytopenic purpura

^a Prophylactic therapy for Hepatitis A, measles, Varicella, and Rubella

^b Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

^c Multifocal Motor Neuropathy (MMN)

^d Treatment of ITP in patients 2 years of age or older

Safety

Each IVIG product line may have unique tolerability and safety profiles due to the proprietary differences in the manufacturing processes.²⁷

Serious adverse events affecting renal, cardiovascular, central nervous, integumentary, and hematologic systems have been reported in the literature.²⁷

Common mild adverse events reported include low grade fever, headache, nausea, malaise, and myalgia. Tension headache is the most common adverse event occurring in 26% to 61% of patients. The incidence of adverse events, depending on the disease and patient population studies ranges from 2% to 25% per infusion.²⁸ Boxed warnings for one or more of thrombosis, renal dysfunction, and acute renal failure are a part of all immune globulin labeled products.

Primary immunodeficiency

Primary immunodeficiency is a disorder that involves low levels of most all immunoglobulin (Ig) classes, lack of B lymphocytes, and frequent bacterial infections. This overarching category includes congenital or x-linked agammaglobulinemia or hypogammaglobulinemia, common variable immunodeficiency (CVID), X-linked immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and hyper IgM syndrome. Agammaglobulinemia can be described by 3 major types: X-linked, early onset, and late onset. The majority of early onset patients (approximately 90%) and absence of B cell have abnormalities of the Bruton tyrosine kinase (*Btk*) gene. Late-onset is usually referred to as common variable immunodeficiency. In patients with agammaglobulinemia all circulating immunoglobulin levels (IgG, IgA, IgM, IgE) are low. Serum IgG level < 100 mg/dL should be concerning although some patients with X-linked agammaglobulinemia (XLA) may have IgG levels as high as 200-300 mg/dL but these levels do not necessarily exclude a diagnosis of XLA.⁴⁰ Evaluation of hypogammaglobulinemia should include quantitative measurement of serum immunoglobulins and if those levels are normal and humoral immunodeficiency is still suggested, antibody response to specific antigens (polysaccharide and protein antigens) should be determined. Immunization with unconjugated pneumococcal vaccine is used to assess response to polysaccharides by comparison of pre- and post-immunization titers (generally, a 4-fold rise is considered adequate).⁴²

Diagnosis involves laboratory evaluations (Serum IgA, IgG, and IgM levels, circulating T and B lymphocytes and T cell function), imaging (CT scan of chest detecting pulmonary abnormalities), histology of lymph nodes (reactive follicular or atypical hyperplasia, and granulomatous inflammation), bronchoscopy (infectious processes), and lymph node biopsy. The prevalence in the United States is 1 case per 50,000 population. A 20-year survival rate is 64%-67% for males and females respectively.²⁹ New diagnostic criteria for common variable immune deficiency has been proposed but to date not validated. The proposed definition of a confirmed diagnosis includes aspects of both laboratory values and clinical symptoms.⁴⁷ Diagnostic criteria discussed by the American Academy of Allergy and Immunology (AAAAI) for hypogammaglobulinemia include low IgG level (< 700 mg/dL or at least two standard deviations below the mean) or an inability to mount a significant response to antigenic challenge or both in patients with recurrent bacterial infections coupled with a lack of response to protein or polysaccharide vaccine challenges (i.e. patients who cannot make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both). These patients are recommended for immune globulin replacement.⁴⁸ The European society of immune deficiencies (ESID) registry has published a working definition for several primary immunodeficiencies including agammaglobulinemia, severe combined immunodeficiency, and CVID. The working definition also includes both laboratory values and clinical symptoms. The working definition is based on more recent registry information than the diagnostic requirements discussed by AAAAI and is being used by the European society of immune deficiencies however neither definition has been validated.⁴⁹

Immune globulin is the current mainstay of therapy for patients with primary immunodeficiencies. Immune globulin protects against infection by providing protective antibodies and humoral immunity. A study in 31 children with X-linked agammaglobulinemia showed that immune globulin reduced the incidence of infection from 0.4 per patient year to 0.06 per patient year ($p < 0.001$).¹⁵ In a study of adults with common variable immunodeficiency, immune globulin reduced the incidence of bacterial pneumonia from 84% before treatment to 11% after treatment with immune globulin.¹⁵

Treatment guidelines published in 2010 from the National Advisory Committee on Blood and Blood Products and Canadian Blood Services concluded there is sufficient evidence that immunoglobulin therapy reduces the rate of infection and hospitalization in patients with primary immune deficiency, which likely leads to a lower mortality and improved quality of life. These guidelines also recommend when considering primary immune deficiency in patients with

autoimmune hematological diseases that quantitative IgA, IgG, and IgM levels be drawn and evaluated prior to beginning therapy with immune globulin. Primary immune deficiency may require indefinite therapy.⁴¹

Idiopathic thrombocytopenic purpura (ITP)

ITP is a syndrome in which a decreased number platelets leads to bleeding tendency, easy bruising, or extravasation of blood from the capillaries into the skin and mucous membranes. This illness occurs in otherwise healthy individuals.³⁰ Patients are often asymptomatic but may exhibit signs of bleeding including bruising, purpura, and mild mucosal hemorrhage. Splenomegaly is exclusive of an ITP diagnosis.³⁰ As part of a complete blood count (CBC), isolated thrombocytopenia is the hallmark of ITP. Anemia and/or neutropenia may indicate other diseases. A peripheral blood smear may show the following: normal morphology of red blood cells and leukocytes and normal morphology of platelets with varying numbers of large platelets. The value of bone marrow evaluation in diagnosing ITP is unresolved. Prevalence in the United States is estimated at 5 cases and 2 cases per 100,000 in children and adults respectively. The primary cause of long-term morbidity and mortality is hemorrhage.³⁰

Corticosteroids are the drugs of choice for initial management of acute disease.³⁰ Use of IVIG in ITP is often reserved for patients who need an immediate increase in platelet count or in patients who have failed corticosteroids.¹⁵

Kawasaki disease (KD)

KD is an acute febrile vasculitic disease of early childhood. It has good prognosis with treatment and is characterized by a remittent fever, erythematous rash (often on the trunk), and red swollen lips and tongue.^{17,31} Cardiac complications including coronary artery aneurysm, myocardial infarction, congestive heart failure (CHF), and arrhythmias are the most common cause of death in patients with Kawasaki disease.¹⁶ Diagnosis criteria (established by the American Heart Association) include fever > 5 days and 4 of the 5 main clinical features:

- Changes in peripheral extremities – initial reddening/swelling of palms and soles, followed by membranous desquamation of finger and toe tips
- Generalized polymorphous rash but may be limited to groin or lower extremities
- Erythema, fissuring, and crusting of lips or strawberry tongue
- Painless bulbar conjunctival injection, bilaterally
- Acute cervical lymphadenopathy with lymph node diameter > 1.5 cm, typically unilaterally

If a patient has 4 or more of the criteria above, guidelines advise a diagnosis of KD can be made on day 4 of the fever. No specific laboratory test is used to diagnose KD. The actual cause of Kawasaki disease is unknown but is thought to be infectious in nature. Epidemics occur primarily in late winter and spring with 3-year intervals.³¹

The goal of treatment is to prevent coronary artery disease. Immune globulin is the mainstay of treatment.³¹ A meta-analysis of randomized control trials (RCTs) found a significant decrease in new coronary artery aneurysms with the use of immune globulin.¹⁵

Chronic lymphocytic leukemia (CLL), bone marrow transplant, pediatric HIV

CLL is a disorder characterized by progressive accumulation of functionally incompetent lymphocytes. Patients present with a wide range of symptoms including enlarged lymph nodes, liver or spleen, recurring infections, loss of appetite, fatigue, abnormal bruising, or night sweats. Approximately 25-25% of patients will be asymptomatic upon diagnosis. Peripheral blood flow cytometry is the most valuable test to confirm a diagnosis of CLL. Patients with early stage disease are not treated with chemotherapy until they become symptomatic. Up to 25% of patients demonstrate autoimmune anemia, thrombocytopenia, or both. Patients experiencing frequent bacterial infections associated with hypogammaglobulinemia are likely to benefit from monthly infusions of IVIG.³²

CLL, bone marrow transplant (BMT), and HIV are all associated with immunosuppression and an increased risk of infection. Immune globulin can provide additional protection against infection by supplementing humoral immunity. Trials comparing immune globulin to placebo in these disease states have shown decreased bacterial infections but not a decrease in mortality.¹⁵ The advent of antimicrobial prophylaxis and Highly Active Anti-Retroviral

Therapy (HAART) (in the case of HIV) has decreased the need for immune globulin.

Hepatitis A (HAV)^{37,38}

The disease is usually transmitted via the fecal-oral route either by person-to-person contact or ingestion of contaminated food or water. Transmission is facilitated by poor personal hygiene, poor sanitation, and intimate contact (e.g., intra-household or sexual exposure). Illicit drug users are the most common source of HAV. The incubation period for HAV infection following exposure to the virus ranges from 15-50 days (average of 28 days). Use in HAV patients is to provide passive immunity for pre-exposure or post-exposure prophylaxis in susceptible individuals who are at risk of or have been exposed to the virus. Immune globulin (GamaSTAN S/D) is used for short-term protection against HAV in unvaccinated patients.

Measles^{37,38,39}

Measles is a highly contagious respiratory disease caused by the measles virus. Measles spread through the air by breathing. Symptoms of measles include fever, runny nose, cough and rash all over the body. Immune globulin (GamaSTAN S/D) is used to prevent or modify symptoms of measles in susceptible persons (unvaccinated and has not had measles) exposed to the disease within 6 days previously.

Rubella^{37,38}

Rubella, also known as German Measles, or three-day measles is a contagious viral infection caused by the rubella virus. The virus is spread through the air or close contact. Immune globulin (GamaSTAN S/D) is recommended as post exposure prophylaxis in susceptible pregnant women who are exposed to a confirmed case of rubella early in pregnancy, and who will not consider terminating the pregnancy under any circumstances. These women should receive immune globulin within 72 hours of rubella exposure.

Varicella^{37,38}

Varicella, commonly called the chickenpox, is a common childhood disease. It is caused by the varicella-zoster virus (VZV). The virus is spread through airborne particles, droplets in exhaled air, and fluid from the blisters or sores. Symptoms include fever, weakness, rash and usually appear 14-16 days. Immune globulin (GamaSTAN S/D) is recommended for post exposure prophylaxis when Varicella-Zoster Immune Globulin is unavailable (e.g. cannot be obtained within 96 hours of exposure).

Compendia Supported Indications

Immune globulin is available in different forms and by different manufacturers with varying uses. Primary literature will often refer to immunoglobulin as a category without calling out a specific branded product therefore literature on one product's use versus another is limited.

For the purposes of the criteria, indications deemed appropriate are those that are supported by at least two compendia where one of the compendia is DrugDex with a level of evidence of 2B and strength of recommendation of B or supported in guidelines with highest level of evidence recommendation. Some indications have been added with limited evidence due to the life threatening nature of the condition.

Described in detail below are notable and common supported uses of Immune globulin. However, due to the significant amount of non-labeled but supported uses, each one will not be discussed in detail.

Specific antibody deficiency and IgG subclass deficiency

Patients who suffer recurrent infections because they lack, or have very low levels of one, or two IgG subclasses, but whose other immunoglobulin levels, including total IgG are normal have selective IgG subclass deficiency. Each subclass serves different functions in protecting against infection. For example, IgG1 and IgG3 subclasses have antibodies that protects against proteins such as toxins produced by diphtheria and tetanus bacteria. In contrast, antibodies against polysaccharide coating producing bacteria (e.g. pneumococcus and Haemophilus influenzae) are predominately of the IgG2 subtype. Patients present more frequently with recurrent ear infections, sinusitis, bronchitis and pneumonia. Some patients will have an increased frequency of infection beginning around 2 years of age while others may have a much later onset. These infections in general are not as severe as those suffered by patients with combined IgG, IgA and IgM (e.g. X-linked agammaglobulinemia or common variable immunodeficiency) deficiency. Normal values are typically between two standard deviations below or above the average for a person's age but these

values should be re-evaluated over a period of months before calling the person’s level’s abnormal. Diagnosis should include the person’s ability to produce specific antibodies in response to childhood vaccines and clinical status. A subset of patients have normal immunoglobulin levels and normal IgG subclasses but still don’t produce protective antibody levels in response to vaccines or bacteria. These patients are thought to have Specific Antibody Deficiency (SAD) and are typically groups with IgG subclass deficiency patients.⁴³

Graves disease

This is an autoimmune disease characterized by hyperthyroidism. Graves disease represents a part of more extensive autoimmune processes which can lead to dysfunction of multiple organs. It is associated with pernicious anemia, vitiligo, autoimmune adrenal insufficiency, and systemic lupus erythematosus. Graves ophthalmopathy is one several disease manifestations. For active disease, therapy mainstays are high-dose glucocorticoids, orbital radiotherapy, both, or orbital decompression. Other therapies evaluated in treatment include immune globulin and somatostatin analogs.³⁴

Dermatomyositis

Dermatomyositis is an idiopathic inflammatory myopathy that most commonly affects the skin and muscles and may impact joints. These patients often present with skin diseases including eruption on exposed surfaces, pruritus of skin lesions, scaly scalp or hair loss. Systemic symptoms include arthralgia, dyspnea, dysphagia, arrhythmia, dystonia or malignancy. Diagnosis involves heliotrope, Gottron papules, erythema, or flat, red rash of face and upper trunk. Prednisone is first line therapy for dermatomyositis. Immune globulin is used in patients who have failed corticosteroids and immunosuppressants.³⁵

Polymyositis

Polymyositis is an idiopathic inflammatory myopathy causing muscle weakness, elevated muscle enzyme levels and is similar to dermatomyositis. Polymyositis and dermatomyositis share many clinical features. Initial treatment for polymyositis involves corticosteroids. As with dermatomyositis, steroids and immunosuppressive agents are first line. Immune globulin has been used for short-term treatment in steroid-resistant patients.³⁶

Myasthenia Gravis – Crisis

Myasthenia gravis (MG) is an autoimmune disorder of peripheral nerves. Antibodies form against acetylcholine (aCh) nicotinic postsynaptic receptors. A reduction in these receptors results in progressively reduced muscle strength with repeated use of the muscle and recovery of muscle strength following a rest period. MG affects approximately 20 people per 100,000 population. It is twice as common in women as men and the overall prevalence is estimated to be 150-200 per million. Approximately 80 to 90% of myasthenics have circulating antibodies to aCh receptor (AChR+). An additional 7% of patients with generalized MG have antibodies to muscle-specific tyrosine kinase (MuSK) and a remaining 8% are classified as seronegative.⁵⁴ Exacerbations of MG can result in crisis. Myasthenia crisis is often caused by infection however there are up to 30% of patients in whom no identifiable cause is found.⁵⁰

Conflicting evidence exists for the treatment of myasthenia crisis. Plasmapheresis or plasma exchange removes circulating humoral factors from the blood. It is used as adjunct to other immunomodulatory therapies and as a tool for crisis management.⁵¹ American Academy of Neurology (AAN) evidence based guidelines on the use of plasmapheresis in neurological disorders concluded that there is insufficient evidence for the use of plasmapheresis in crisis patients.⁵² AAN also published evidence based guidelines for the use of intravenous immune globulin in the treatment of neuromuscular disorders and found that the use of IVIG is probably effective in treating patients and there is insufficient evidence to compare the efficacy of IVIG and plasmapheresis in the treatment of MG.⁵³ Other published literature supports the use of plasma exchange in crisis patients.^{51, 54} Gwathmey et al reports for AChR+ patients IVIG and plasma exchange are thought to be equally effective but for patients with MuSK positive patients plasma exchange is considered superior.⁵⁴

ADDITIONAL INDICATIONS SUPPORTED BY EVIDENCE^{13, 21, 22, 24, 25, 46}

IVIG EVIDENCE BASED INDICATIONS		
Indication	Guideline	Recommendation / Evidence Level

IVIG EVIDENCE BASED INDICATIONS		
Indication	Guideline	Recommendation / Evidence Level
Primary immune defects with absent B cells	AAAAI	B, 2b
Impaired specific antibody production (normogammaglobulinemia, agammaglobulinemia, hypogammaglobulinemia)	AAAAI / NHS	B, 2b / C, 3
Prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving ABO incompatible organ	NHS	Grey Indication / 1b
Following solid organ transplant, treatment of antibody-mediated rejection	NHS	Grey Indication / 1b
Chronic lymphocytic leukemia with reduced IgG and history of infections	AAAAI / NHS	A, 1b / A, 1b
Adult HIV associated thrombocytopenia	NHS	A, 1b
Prevention in neonatal sepsis	AAAAI	A, 1a
Graves Ophthalmopathy	AAAAI	A, 1b
Dermatomyositis	AAAAI / NHS	B, 2a / B, 2a
Polymyositis	AAAAI	B, 2a
Severe rheumatoid arthritis	AAAAI	B, 2b
*Fetomaternal alloimmune thrombocytopenia	AAAAI / NHS	C, 3
*Post transfusion purpura	AAAAI / NHS	C, 3
Guillain-Barre syndrome	AAAAI / NHS	A, 1a / A, 1a
Chronic demyelinating polyneuropathy	AAAAI / NHS	A, 1a / A, 1a
Multifocal motor neuropathy	AAAAI / NHS	A, 1a / A, 1a
Paraprotein associated demyelinating neuropathy - (IgM)	AAAAI / NHS	A, 1b / A, 1b
Paraprotein associated demyelinating neuropathy - (IgG or IgA)	NHS	A, 1b
Lambert-Eaton myasthenia syndrome (LEMS)	AAAAI / NHS	A, 1b / A, 1b
Myasthenia Gravis - myasthenia crisis	AAAAI / NHS	B, 1b-2a / B, 1a
Stiff-man syndrome	AAAAI / NHS	A, 1b / A, 1b
Monoclonal gammopathy - Multiple sclerosis	AAAAI	A, 1a
Intractable childhood epilepsy	AAAAI	A, 1a
Rasmussen syndrome	AAAAI / NHS	B, 2b
CMV-induced pneumonitis in solid organ transplant	AAAAI / NHS	A, 1b / A, 1b

IVIG EVIDENCE BASED INDICATIONS		
Indication	Guideline	Recommendation / Evidence Level
Treatment of neonatal sepsis	AAAAI	A, 1a
Rotaviral enterocolitis	AAAAI	A, 1b
Bacterial infections in lymphoproliferative disease	AAAAI	B, 1b
Delayed pressure urticaria	AAAAI	B, 2b
Prevention of acute humoral rejection in renal transplant	AAAAI	A, 1b
Pediatric autoimmune psychiatric disorders associated with streptococcal infections	AAAAI	B, 2b
Severe invasive group A streptococcal disease	NHS	B, 1b
Severe, persistent, high-dose asthma	AAAAI	A, 1b
Toxic epidermal necrolysis and Stevens-Johnson syndrome	AAAAI / NHS	B, 2a / B, 2a
Low serum IgG levels following HSCT for malignancy	NHS	B, 2b
Multiple myeloma	NHS	A, 1b
Acquired von Willebrand hemophilia	NHS	B, 2a
Hemolytic disease of the newborn	NHS	B, 3

*Adding with limited evidence due to life threatening nature

Recommendation	Assigned
Requires at least 1 randomized controlled trial as part of literature of overall good quality and consistency address recommendation. (Evidence levels 1a, 1b).	A
Requires the availability of well conducted clinical studies or randomized clinical trials on the topic of recommendation (Evidence levels 2a, 2b)	B
Requires evidence obtained from expert committee reports, opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical study quality. (Evidence levels 3, 4)	C

Evidence	Assigned
From meta-analysis of randomized controlled studies	1a
From at least 1 randomized controlled study	1b
From at least 1 controlled trial without randomization	2a
From at least one other type of quasi-experimental study	2b
From non-experimental descriptive studies, such as cohort studies, correlation, or case-control studies	3
From expert committee reports or opinions or clinical experience of respected authorities or both	4

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Your health plan does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Your health plan administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in your health plan's administration of plan contracts.