Important note
Even though this policy may indicate that a particular service or supply may be considered covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Senior Care members, this policy will apply unless Medicare policies extend coverage beyond this Medical Policy & Criteria Statement. Senior Care policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS’s Coverage Issues Manual can be found on the CMS website.

SERVICE: Immune Globulin Therapy

PRIOR AUTHORIZATION: Required

POLICY: SWHP may consider immune globulin (IVIG) medically necessary for patients with the following conditions:

Blood disorders
- Bone marrow transplant patients (for prevention of infection or GVH prevention)
- Multiple myeloma and immunoproliferative neoplasms
- Immune neutropenia
- Multiple myeloma without mention of remission
- Multiple myeloma in remission
- Plasma cell leukemia without mention of remission
- Plasma cell leukemia in remission
- Other immunoproliferative neoplasms without mention of remission
- Other immunoproliferative neoplasms in remission
- Agranulocytosis
- Common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked immunodeficiency
- Prevention of infection in patients with primary defective antibody synthesis
- Fetal alloimmune thrombocytopenia
- Autoimmune hemolytic anemia
- Agammaglobulinemia -primary humoral immunodeficiency
- Hypogammaglobulinemia -primary humoral immunodeficiency
- Chronic lymphocytic leukemia (CLL) with frequent infections
- Idiopathic thrombocytopenic purpura (ITP).

Infectious diseases
- HIV and AIDS
- Prevention of infection in HIV-infected children
- Prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ
- Solid organ transplant recipients at risk for cytomegalovirus infections and pneumonia.

Neurologic conditions
MEDICAL COVERAGE POLICY

SERVICE: Immune Globulin Therapy

Policy Number: 045
Effective Date: 09/03/2015
Last Review: 08/11/2015
Next Review Date: 08/31/2016

- Guillain Barre Syndrome (GBS)
- Chronic severe myasthenia gravis, for severe exacerbations causing disability
- Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindication to plasma exchange
- Myasthenia gravis in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complications from or failure of steroids and/or azathioprine.
- Hereditary and idiopathic peripheral neuropathy
- Peroneal muscular atrophy
- Hereditary sensory neuropathy
- Refsum's disease
- Idiopathic progressive polyneuropathy
- Multiple Sclerosis: for patients with relapsing-remitting disease (not primary or secondary progressive MS)
- Chronic inflammatory demyelinating polyneuropathy
- Demyelinating polyneuropathy associated with IgM paraproteinemia
- Multifocal motor neuropathy in patients with GM1 antibodies and conduction block

Other:
- Dermatomyositis/polymyositis
- Refractory dermatomyositis; in combination with other immunosuppressive agents
- Kawasaki disease
- Pemphigus vulgaris
- Prior to solid organ transplant; treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ
- Following solid organ transplant; treatment of antibody-mediated rejection

These conditions are covered ONLY for Medicare Advantage and Medicare Cost members (see attached LCD for other limitations):
- Pemphigus vulgaris and foliaceus
- Bullous pemphigoid
- Mucous membrane pemphigoid (also known as Cicatricial pemphigoid)
- Epidermolysis bullosa acquisita.

Conditions NOT covered because there is a lack of evidence suggesting efficacy:

Blood disorders
- Acquired factor VIII inhibitors
- Acute lymphoblastic leukemia
- Aplastic anemia
- Diamond-Blackfan anemia
- Hemophagocytic syndrome
- Nonimmune thrombocytopenia
- Red cell aplasia
- Thrombotic thrombocytopenic purpura.

Rheumatoletic diseases
- Behcet’s syndrome
- Inclusion body myositis, because it does not work in this disorder
- Rheumatoid arthritis and other connective tissue diseases including systemic lupus erythematosus
- Scleroderma
• Systemic Lupus Erythematosus
• Other vasculitides besides Kawasaki disease; including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., Wegener’s granulomatosis, polyarteritis nodosa), Goodpasture’s syndrome, and vasculitis associated with other connective tissue diseases.

Neurologic conditions
• Epilepsy
• Multiple sclerosis: primary progressive or secondary progressive types, because it has not been shown to offer additional health benefits to patients with these types of MS
• Paraneoplastic syndromes including but not limited to Lambert-Eaton syndrome
• Stiff-man syndrome.

Infectious
• Chronic sinusitis
• Recurrent otitis media.

Other
• Adrenoleukodystrophy
• Asthma
• Chronic fatigue syndrome
• Cystic fibrosis
• Diabetes mellitus
• Hemolytic uremic syndrome
• Idiopathic lumbosacral flexopathy
• Recurrent fetal loss
• Recurrent Spontaneous Abortion
• Bullous pemphigoid (Medicare Advantage and Medicare Cost members)
• Pemphigus foliaceus (Medicare Advantage and Medicare Cost members)
• Cicatricial pemphigoid (mucous membrane pemphigoid) (Medicare Advantage and Medicare Cost members)
• Epidermolysis bullosa aquisita (except for Medicare Advantage and Medicare Cost members)
• Recurrent spontaneous pregnancy loss
• Idiopathic environmental illness
• Myasthenia gravis in patients responsive to immunosuppressive treatment
• Post-infectious sequelae
• Organ transplant rejection
• Uveitis
• Demyelinating optic neuritis
• Recent-onset dilated cardiomyopathy
• Other disorders not listed above.

OVERVIEW:
• Immune globulin (IVIG) derived from human plasma, is a collection of antibodies pooled together from multiple human donors. It is a mixture of various normal human antibodies, and, when administered by intravenous infusion, provides immediate antibody levels.

• High dose immune globulin therapy can provide lifesaving treatment for patients with primary immunodeficiencies, and has become an important therapy for various neurologic diseases and immune system abnormalities.
MEDICAL COVERAGE POLICY

SERVICE: Immune Globulin Therapy

Policy Number: 045
Effective Date: 09/03/2015
Last Review: 08/11/2015
Next Review Date: 08/31/2016

CMS:

NCD: Medicare covers intravenous immune globulin (IVIG) when criteria are met. See the Medicare Benefit Policy Manual (Pub. 100-2) Chapter 15 - Covered Medical and Other Health Services, Section 50.6 Coverage of Intravenous Immune Globulin for Treatment of Primary Immune Deficiency Diseases in the Home at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

LCD: L32712 Novitas Solutions

POLICY HISTORY:

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REFERENCES:
The following scientific references were utilized in the formulation of this medical policy. SWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to SWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Arthritis Foundation
2. National Office, 1330 West Peachtree Street, Atlanta, Georgia 30309 Toll-free Information Line: 1-800-283-7800
3. Myasthenia Gravis Foundation of America 222 S. Riverside Plaza, Suite 1540, Chicago, IL 60606 Telephone - (312) 258-0522 or (800) 541-5454, Fax - (312) 258-0461 Email Address - MGFA@AOL.COM Web: http://www.med.unc.edu/mgfa/mgf-home.htm
4. Neurological Institute, P.O. Box 5801, Bethesda, MD 20824 (301)496-5751, (800)352-9424. The NINDS conducts and supports a wide range of research on neurological disorders, including Guillain-Barre syndrome.
5. Guillain-Barre Syndrome Foundation International P.O. Box 262, Wynnewood, PA 19096, (215) 667-0131 Printed information and assistance to Guillain-Barre patients.
7. Lupus Foundation of America, Massachusetts Chapter - Northeast 425 Watertown St., Newton, MA 02158, (617) 332-9014
8. CMS /Medicare website: www.cms.gov
Appendix

LCD ID L32712

Jurisdiction Texas

LCD Title Intravenous IMMUNE GLOBULIN (IVIG)

Original Effective Date For services performed on or after 08/13/2012

Revision Effective Date For services performed on or after 05/08/2014

Coverage Indications, Limitations, and/or Medical Necessity

Notice: It is not appropriate to bill Medicare for services that are not covered (as described by this entire LCD) as if they are covered. When billing for non-covered services, use the appropriate modifier.

The use of intravenous immune globulin should be reserved for patients with serious defects of antibody function. The goal is to provide immune globulin to those who lack it. Medicare will provide coverage for intravenous immune globulin when it is used in treatment of the following conditions:

- Primary immunodeficiency.
- Immune-mediated Thrombocytopenia (ITP).
- Kawasaki disease.
- Human Immunodeficiency Virus (HIV) (for pediatric use only).
- Bone marrow transplantation.
- Chronic B-cell lymphocytic leukemia.

Intravenous Immune Globulin (IVIG) can replace missing antibodies and decrease infection in primary immune deficiency and chronic lymphocytic leukemia, increase platelets in idiopathic thrombocytopenic purpura, prevent complications in Kawasaki disease and possibly decrease morbidity in some other conditions.

IVIG is the preferred treatment method for patients who require immediate increase in intravascular immunoglobulin antibody levels and are unable to produce sufficient amounts of Immunoglobulin G (IgG) antibodies. The therapeutic effect of IVIG is immediate, well tolerated and less likely to produce side effects if infused at the properly indicated rate(s). Sensitivity to these reactions is usually related to the infusion rate. Caution should be exercised in the administration of intravenous immune globulin; reactions may cause a rapid fall in blood pressure and clinical anaphylaxis.

IVIG is covered for treatment of the following biopsy-proven conditions:

- Pemphigus vulgaris.
- Pemphigus foliaceus.
- Bullous pemphigoid.
• Mucous membrane pemphigoid (aka, cicatricial pemphigoid), benign mucous membrane pemphigoid, with or without mention of ocular movement.
• Epidermolysis bullosa acquisita.

Patients must meet at least one of the following criteria:
• Failed conventional therapy. Contractors have the discretion to define what constitutes failure of conventional therapy.
• Conventional therapy is contraindicated. Contractors have the discretion to define what constitutes contraindications to conventional therapy.
• Have rapidly progressive disease in which a clinical response could not be affected quickly enough using conventional agents. In these situations, IVIG therapy would be given along with conventional treatment(s) and the IVIG would be used only until conventional therapy could take effect.

Note: In addition, IVIG for the treatment of autoimmune mucocutaneous blistering disease must be used only for short-term therapy and not as a maintenance therapy.

Other preparations of IVIG are available:
• RhoD immune globulin for use in preventing postpartum Rhesus isoimmunization.
• Cytomegalovirus immune globulin for use in treating or preventing cytomegaloviral disease in transplant recipients.
• Hepatitis B immune globulin intravenous for use in treating prevention of hepatitis B recurrence following liver transplantation in hepatitis B surface antigen (HBsAG)-positive liver transplant patients. (FDA approved April 6, 2007.)

Physicians should avoid prescribing IVIG except for patients with severe immune deficiency and who have low antibody levels or for those whom have other well-established indications for therapy with IVIG as described within this LCD.

Primary Humoral Immunodeficiencies:
IVIG will be covered for use as replacement therapy in patients with primary immunodeficiencies in whom severe impairment of antibody capacity is present in the following conditions:
• Congenital agammaglobulinemia.
• Common variable immunodeficiency.
• Wiskott-Aldrich syndrome
• X-linked immunodeficiency with hyper-IgM.
• Severe combined immunodeficiencies.
• Deficient qualitative and/or quantitative antibody production.
• Have at least one bacterial infection directly attributable to this deficiency.
**Idiopathic Thrombocytopenic Purpura (ITP):**
IVIG will be covered for both acute and chronic refractory ITP.

Acute ITP, IVIG is covered for:

- Management of acute bleeding due to severe thrombocytopenia (platelet counts usually less than 30,000/ul).
- To increase platelet counts prior to invasive surgical procedures, e.g. splenectomy.
- Severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage.

Chronic refractory ITP is covered for patients meeting all of the following conditions:

- Prior treatment with corticosteroids and splenectomy.
- Duration of illness of greater than six months.
- Age of 10 years or older.
- No concurrent illness/disease explaining thrombocytopenia.
- Platelet counts persistently at or below 20,000/ul.

**Chronic Lymphocytic Leukemia (CLL):**
IVIG will be covered when used to prevent recurrent bacterial infections in patients with B-cell chronic lymphocytic leukemia meeting all of the following conditions:

- Must have unequivocally documented CLL.
- An immunoglobulin G (IgG) level of less than 600 mg/dl.
- Recent history of serious bacterial infection(s) requiring either oral or parenteral antibiotic therapy.

**Human Immunodeficiency Virus (HIV) Infection:**
IVIG will be covered for patients infected with HIV to reduce significant bacterial infection meeting all of the following conditions:

- Age younger than 14 years old.
- Evidence of either qualitative or quantitative humoral immunologic defects.
- Current bacterial infections, despite appropriate antimicrobial prophylaxis.

**Chronic Inflammatory Demyelinating Polyneuritis (CIDP):**
The diagnosis of this condition must be documented in the medical record and must be consistent with published diagnostic criteria for this condition.


Patients responsive to an initial course of IVIG will be eligible for maintenance therapy coverage only if unequivocal neurological deterioration occurs at some future point in time. It is expected an initial trial of IVIG for CIDP to last 3 months. If no significant improvement as outlined in the above guidelines, therapy should be discontinued. Maintenance therapy should be at the lowest dose of IVIG possible. Although patients will vary in response, after a one to two year period of stable therapy, attempts to reduce should be occurring. Continued dosing without attempts to reduce the dosing and check responses
would be considered inappropriate and subject to pre and post pay reviews.

**Multifocal Motor Neuropathy:**
IVIG may be considered for first line of treatment of patients who have progressive, symptomatic multifocal motor neuropathy that has been diagnosed on the basis of electrophysiology findings that rule out other possible conditions that may not respond to this treatment.

**Dermatomyositis, Polymyositis:**
The routine use of IVIG is not usually recommended for polymyositis or dermatomyositis. IVIG may be used in patients with severe active illness for whom other interventions have been unsuccessful, have become intolerable or are contraindicated.

Refractory myopathies are, by definition, diseases that are unresponsive or poorly responsive to high-dose steroids either alone or in combination with other immunosuppressive agents (azathioprine, cyclophosphamide, methotrexate). Also included in this definition are patients responsive to but intolerant of continual high-dose steroids as reflected by severe adverse side effects (e.g., steroids myopathy or severe osteoporosis) in whom trials of other immunosuppressive agents, unless contraindicated, have been unsuccessful in achieving significant long-term steroid dose reductions.

Three other coverage conditions which must all be met, in addition to the above, are:
- Biopsy-proven disease.
- At least a four- to six-month trial of prednisone or prednisone combination therapies.
- Lack of response/poor response to therapies as reflected by persistently elevated serum Creatine Kinase (CK) levels and/or lack of improvement on muscle strength improvement scales.

Inclusion body myositis is generally refractory to all therapies and its rate of progression appears to be unaltered by most therapies. IVIG will not be covered for use in patients with inclusion body myositis.

**Immune Modulation prior to Transplantation**
IVIG has not been proven safe and effective when used for immune modulation of highly sensitized patients prior to transplantation and is therefore not covered for this indication.

**LCD Individual Consideration**
Certain unusual uses of IVIG may be covered on an LCD Individual Consideration basis. Such situations are described in the four conditions below.

**Autoimmune Hemolytic Anemia:**
The routine use of IVIG is not usually recommended. IVIG may have a role in patients with warm-type autoimmune hemolytic anemia that does not respond to corticosteroids or splenectomy or those for whom the latter two treatments are contraindicated. Coverage determination will require **LCD Individual Consideration**.
**Multiple Sclerosis (MS):**
The current evidence is inadequate to assess the value of IVIG in the treatment of multiple sclerosis. IVIG may be useful in persons as a second-line therapy in acute relapses of Relapsing Remitting Multiple Sclerosis (MS), but is generally not considered effective for maintenance therapy of MS or in slowing disease progression. **LCD Individual Consideration** may be given when IVIG is used in the treatment of an acute relapse of Relapsing Remitting MS.

**Systemic Lupus Erythematosus:**
The routine use of IVIG is not usually recommended. IVIG may be used in patients with severe active systemic lupus erythematosus for whom other interventions have been unsuccessful, have become intolerable or are contraindicated. Coverage determination will require **LCD Individual Consideration.**