

Corporate Medical Policy

Immune Globulin Therapy

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Description of Procedure or Service

Human immune globulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Three formulations of human IgG are available for delivery by intravenous infusion (IVIg), by subcutaneous infusion (SCIg), or by intramuscular (IMIg) depot injections. IMIg has been largely abandoned in the United States because volume constraints and pain preclude delivery of sufficient product weekly into each buttock to yield therapeutic serum levels of IgG, leaving recipients susceptible to infections. Thus, this policy focuses on IVIg and SCIg for conditions that typically would be treated in an outpatient setting.

IVIg is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIg has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. The labeled indications approved by the U.S. Food and Drug Administration (FDA) for IVIg are listed in the following section. A variety of off-label indications have been investigated; some of the most common are briefly profiled here. Several IVIg products are available for clinical use in the United States.

This policy only addresses nonspecific pooled preparations of IVIg, including Carimune (ZLB Bioplasma), Flebogamma (Grifols), Gammagard (Baxter), Gamunex (Talecris Biotherapeutics), Octagam (Octapharma), Polygam S/D (Baxter) Privigen (CSL Behring LLC). This policy DOES NOT address other immunoglobulin preparations that are specifically used for passive immunization to prevent or attenuate infection with specific viral diseases such as respiratory syncytial virus, cytomegalovirus, or hepatitis B. (Coverage for RSV immune globulin (e.g., Synagis) is summarized in the Medical policy titled, "Respiratory Syncytial Virus Prophylaxis").

One SCIg product (Vivaglobin[®], ZLB Behring LLC, Kankakee, IL) has received FDA marketing approval for the treatment of patients with primary immune deficiency. Vivaglobin is a pasteurized, polyvalent human normal immune globulin product that is manufactured from large pools of human plasma by cold alcohol fractionation with no chemical or enzymatic alterations. Vivaglobin administration produces relatively stable steady-state serum levels of IgG that are representative of those seen in a normal human population.

IVIg Therapy

Inflammatory Myopathies

Inflammatory myopathies are broadly subdivided into polymyositis (PM), dermatomyositis (DM), and inclusion-body myositis (IBM). PM and DM are characterized clinically by proximal muscle weakness and pathologically by an inflammatory microangiopathy leading to subsequent muscle ischemia. In DM, these symptoms are accompanied by a characteristic erythematous rash. The inflammatory infiltrate in DM contains a high percentage of B cells and components of the complement cascade. In contrast, in PM the inflammatory infiltrates are not perivascular in location and contain activated T cells, natural killer

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cells, and macrophages. PM has no unique clinical features, and is typically a diagnosis of exclusion in patients with slowly progressive muscle weakness. Both PM and DM respond to corticosteroids or immunosuppressive drugs but can become refractory to such treatment. IBM is characterized clinically by slowly progressive muscle weakness and atrophy affecting proximal and distal muscle groups, particularly the quadriceps and the long finger flexors. Pathologically, IBM is characterized by granular inclusions within the muscle cells. Unlike DM or PM, IBM rarely responds to immunosuppressive therapy. For all of these conditions, IVIg has been investigated as a treatment, particularly for cases refractory to corticosteroids or immunosuppressive drugs.

Neuropathies

IVIg has been studied in a variety of neuropathies, most prominently Guillain-Barre syndrome (acute demyelinating neuropathy), chronic inflammatory demyelinating neuropathy (CIDP), and multifocal motor neuropathy. CIDP is a symmetrical polyneuropathy manifested as both motor and sensory deficits. The disease course may present as either a relapsing/fluctuating or slowly progressive disease. Some of the symptoms of CIDP may overlap with symptoms of chronic fatigue syndrome; therefore, when considering IVIg therapy, appropriate diagnosis is critical. In 1991, the American Academy of Neurology published criteria for the diagnosis of CIDP (See **Appendix**). Patients with both CIDP and Guillain-Barre syndrome may be initially treated with prednisone, followed by plasmapheresis or IVIg in more severe cases. The latest diagnostic criteria were proposed in 2005 by the Joint Task Force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS) based on available evidence and expert consensus in the medical literature. The Task Force members agreed to define clinical and electrophysiological criteria for CIDP with or without concomitant disease.

Multifocal motor neuropathy is characterized by a conduction block of the motor axons. Patients frequently exhibit antibodies to GM1 ganglioside. Clinically, the disease presents as a very slow onset of weakness and muscular atrophy with preservation of sensation. Unlike other neuropathic disorders, this disease does not respond to steroids or plasmapheresis. Stiff person syndrome is a rare central nervous system disorder characterized by fluctuating muscle rigidity of truncal and proximal limb muscles with periodic spasms, resulting in a significant disability. The condition is thought to be immunologic in origin; elevated levels of anti-GAD antibodies are detected in most patients. Initial therapy is typically diazepam, but frequently the high doses required are poorly tolerated. IVIg has been investigated as an alternative therapy.

IVIg has also been investigated in neuropathies associated with paraproteinemia or a variety of paraneoplastic syndromes, including Eaton Lambert syndrome or neuropathy associated with anti-Yo or anti-Hu antibodies, seen in association with a variety of cancers including ovarian or small cell lung cancer.

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disease accompanied by a lymphocytic infiltration in lesions. Evidence relating to pathogenesis suggests genetic, infective, and/or immune mechanisms. IVIg has been investigated in patients with relapsing/remitting MS, for whom the treatment goals are to decrease the frequency and severity of future attacks and, if possible, to improve the functional deficit to some extent in patients with chronic progressive disease.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease characterized by autoantibodies directed against the acetylcholine receptors of the muscle end plate that induce muscle weakness and pronounced fatigability. Initial treatment focuses on the use of cholinesterase inhibitors to overcome the post-synaptic blockade. Immunosuppressant drugs, including corticosteroids and azathioprine, are also effective. In patients with severe weakness, plasma exchange is a short-term therapy. IVIg has also been investigated in patients with myasthenia gravis as a potential alternative to plasma exchange.

Kawasaki Syndrome and Other Vasculitides

Kawasaki syndrome is an acute multisystem vasculitis that primarily affects children, manifesting itself as a constellation of clinical signs and symptoms including fever, conjunctivitis, mucosal erythema,

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polymorphous rash, and cervical adenopathy. Although the symptoms are self-limited, up to 25% of untreated patients may develop potentially lethal coronary artery abnormalities. Although the mechanism of action of IVIg is not understood, its use early in the course of disease has been shown to reduce the prevalence of coronary artery abnormalities.

The success of IVIg in Kawasaki disease has led to the investigation of IVIg in other vasculitides, such as those associated with rheumatoid arthritis, Wegener's granulomatosis, and polyarteritis nodosa.

Recurrent Spontaneous Abortion

Recurrent spontaneous abortion (RSA) is defined as 3 or more pregnancies resulting in a spontaneous abortion prior to 16–20 weeks of gestational age. Patients with RSA frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss. Since these antibodies are associated with clotting abnormalities, treatment has included aspirin and heparin. Other more subtle immune etiologies have also been investigated. For example, a variety of cytokines and other mediators may be toxic to the conceptus. These cytokines may be detected in an embryo cytotoxicity assay in which activated lymphocytes from women with RSA are shown to be toxic to placental cell lines. Elevated levels of natural killer cells, which may be associated with antiphospholipid antibodies, have also been implicated in RSA. Another theory proposes that a lack of maternal blocking antibodies to prevent immunologic rejection of the fetus may be responsible. IVIg has been explored as a treatment based on its ability to influence both T- and B-cell function. In fact, IVIg may be offered to those patients with antiphospholipid antibodies without a prior history of RSA who are currently pregnant or contemplating pregnancy.

Fetal Alloimmune Thrombocytopenia

Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage is identified in about 10%–30% of affected neonates. At the present time, screening for this condition is unavailable, and thus the thrombocytopenia is only identified at the time of birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia and, similar to erythroblastosis fetalis, the severity of the thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIg.

Solid Organ Transplantation

Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common antibody-mediated rejection reaction (AMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AMR does not, and, as such, has also been referred to as “steroid-resistant rejection.” The risk of AMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a panel reactive antibody (PRA) screen, which combines the recipient's serum with samples of antigen containing cells taken from 60 individuals representative of the potential donor pool. The percentage of PRA is the percentage of positive reactions. Those with a PRA greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of AMR. As an immunomodulatory agent, IVIg has been widely used in the prevention and management of AMR, often in conjunction with plasma exchange (see policy No. 8.02.02). For example, in patients at high risk for AMR, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AMR develops.

SCIg Therapy

Primary immunodeficiencies (PID) are genetically caused immune system defects. A genetic basis for more than 80 different types of PID has been discovered, the most common being primary antibody deficiency (PAD) that is associated with low levels or total lack of normal circulating immunoglobulins. Individuals with PID are prone to recurrent bacterial infections, primarily in the upper and lower respiratory tract and in the gastrointestinal (GI) tract. In PID patients, infections are frequent and may

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cause progressive tissue damage that can be severe and life threatening. For example, recurrent infections in the lungs can cause bronchiectasis and respiratory failure. GI tract infections secondary to PID can result in nutritional deficiencies and poor growth. Less frequently, other infections may occur, such as enterovirus in the brain and muscle, or mycoplasma in bone and joint tissues. Antibiotics can be used to treat bacterial infections, but the majority of patients with PID require lifelong immunoglobulin replacement to prevent tissue damage. One SCIG product (Vivaglobin) has received FDA marketing approval for immunoglobulin replacement therapy in patients with PID. Other applications of this product are considered off-label in the United States and are not addressed in this policy.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for Immune Globulin Therapy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Immune Globulin Therapy is covered

IVIg may be considered medically necessary for the following indications when the diagnosis has been established by an appropriate clinical work-up:

- treatment of primary humoral immunodeficiencies*/primary immune deficiency diseases*, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and x-linked agammaglobulinemia,
- treatment of idiopathic, immune, chronic immune thrombocytopenic purpura (ITP)*,
- in post-bone marrow transplant setting,
- prevention of graft-versus-host disease in hematopoietic transplant patients,
- prevention of infection in:
 - HIV infected patients
 - patients with primary defective antibody synthesis
 - patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia
- refractory dermatomyositis, in combination with other immunosuppressive agents,
- Kawasaki syndrome*,
- chronic inflammatory demyelinating polyneuropathy*,
- Guillain-Barré syndrome,
- multifocal motor neuropathy in patients with anti-GM1 antibodies and conduction block,
- fetal alloimmune thrombocytopenia,
- Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications 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,
- prior to solid-organ transplant, treatment of patients at high risk of antibody-mediated rejection,

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- including highly sensitized patients, and those receiving an ABO incompatible organ,
- following solid-organ transplant, treatment of antibody-mediated rejection.

Subcutaneous immune globulin may be considered medically necessary for the treatment of patients with primary immune deficiency diseases (PIDD)*, including:

- congenital agammaglobulinemia,
- hypogammaglobulinemia,
- common variable immunodeficiency,
- severe combined immunodeficiency,
- Wiskott-Aldrich syndrome,
- X-linked agammaglobulinemia.

* *FDA-labeled indications*

When Immune Globulin Therapy is not covered

IVIg is considered not medically necessary as a treatment of relapsing/remitting multiple sclerosis.

Intravenous immunoglobulin therapy is considered investigational for all other indications, including, but not limited to, the treatment of the following conditions:

- refractory rheumatic arthritis and other connective tissue disease including systemic lupus erythematosus,
- chronic progressive multiple sclerosis,
- recurrent spontaneous abortion,
- inclusion body myositis,
- refractory dermatomyositis, as monotherapy,
- dermatomyositis in patients responsive to immunosuppressive therapy,
- polymyositis, including refractory polymyositis,
- Myasthenia Gravis in patients responsive to immunosuppressive treatment,
- 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,
- thrombotic thrombocytopenic purpura,
- hemolytic uremic syndrome,
- paraneoplastic syndromes, including but not limited to Eaton Lambert syndrome,
- demyelinating polyneuropathy associated with IgM paraproteinemia,
- epilepsy,
- chronic sinusitis,
- asthma,
- chronic fatigue syndrome,
- aplastic anemia,
- Diamond-Blackfan anemia,
- red cell aplasia,
- acquired factor VIII inhibitors,
- hemophagocytic syndrome,
- acute lymphoblastic leukemia,
- multiple myeloma,

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- immune-mediated neutropenia,
- nonimmune thrombocytopenia,
- cystic fibrosis,
- recurrent otitis media,
- diabetes mellitus,
- Behcet's syndrome,
- adrenoleukodystrophy,
- autoimmune mucocutaneous blistering diseases: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullous acquisita,
- post-infectious sequelae,
- stiff person syndrome,
- organ transplant rejection,
- uveitis,
- demyelinating optic neuritis,
- recent-onset dilated cardiomyopathy,
- Fisher syndrome,
- pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),
- autism.
- Subcutaneous immunoglobulin therapy is considered investigational for indications other than primary immune deficiency diseases.

Immunoglobulin therapy is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency who have known antibody against IgA.

Policy Guidelines

Prophylaxis with IVIg in patients undergoing hematopoietic stem cell transplantation may reduce the incidence of infections, acute graft versus host disease, and interstitial pneumonitis. For BCBSNC policy, the source of hematopoietic stem cells may be from bone marrow, peripheral blood or umbilical cord blood.

The previous policy statement regarding IVIg for multiple sclerosis was based on a 1998 BCBSA TEC Assessment, which concluded that IVIg met the TEC criteria. Therefore, it was considered medically necessary in the previous version of this policy. However, in 2002 the American Academy of Neurology published a technology assessment on therapies for multiple sclerosis. This assessment provided a rating of the recommendations, including A (established as effective), B (probably effective, ineffective, or harmful), C (possibly effective, ineffective or harmful), or U (data inadequate). This assessment offered the following recommendation regarding IVIg:

The studies of intravenous immunoglobulin (IVIg) to date have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in relapsing-remitting multiple sclerosis (Type C recommendation).

The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (Type C recommendation).

In contrast, the American Academy of Neurology recommended the use of interferon beta (Type B recommendation) and glatiramer acetate (Type A recommendation). This assessment suggests that IVIg is no longer considered a drug of choice for relapsing-remitting multiple sclerosis, and thus the policy statement in this policy has been revised to indicate that IVIg is not medically necessary. A literature

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search for the period of 2002 to December 2004 did not identify any additional randomized trials that would prompt reconsideration of the conclusions of the American Academy of Neurology assessment.

Patients with chronic inflammatory demyelinating neuropathy (CIDP) should meet the diagnostic criteria established by the American Academy of Neurology. In addition, intravenous immunoglobulin infusion (IVIg) treatment should be limited to CIDP patients who do not respond to initial therapy with prednisone and are experiencing serious clinical worsening documented by neurological exam. In patients treated for chronic diseases, such as CIDP, multifocal motor neuropathy, and dermatomyositis, the effect of IVIg is transitory and therefore periodic infusions of IVIg are needed to maintain treatment effect. The frequency of transfusions is titrated to the treatment response; typically, biweekly or monthly infusions are needed. Continued treatment with IVIG is warranted only if it continues to be efficacious.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 90283, 90284, J1459, J1460, J1557, J1559, J1561, J1562, J1566, J1568, J1569, J1572, J1599

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

From Policy Entitled: Intravenous Immune Globulin Therapy

TEC Bulletin 12/95

2/96 FDA approval of RespiGam (RSV-IGIV) to prevent respiratory syncytial virus in children under 24 months)

1/97 - Recommendations from the American Academy of Pediatrics, member alert

BCBSA Medical Policy Reference Manual - 9/23/98

BCBSA Medical Policy Reference Manual - 11/1/98

USPDI - 19th Edition, 1999; Vol. 1, pp. 1686-1690, 3024-3025 & 3147.

Medical Policy Advisory Group - 12/99

Canadian Journal of Neurological Sciences; *IGIV in Neurology--Evidence and Recommendations*; Brill V, Allenby K, Midroni G, O'Connor PW, Vajsar J. May 26, 1999 (2):139-52

American Academy of Neurology; *Intravenous Immunoglobulin for the Treatment of Acquired Myasthenia Gravis*; James F. Howard, Jr., M.D.; December 1998;51(Suppl 5)S30-S36

Consultant review - 2/2001

BCBSA Medical Policy Reference Manual - Policy 8.01.05-Review date 12/18/02

USPDI - 23rd Edition, 2003; Vol. 1, pp. 1527-1532

Specialty Matched Consultant Review - 4/2003

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 4/16/04.

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USPDI - 25th Edition, 2005; Vol. 1, pp. 1652-1658

Specialty Matched Consultant Review - 3/28/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 4/1/05.

Policy retitled: Immune Globulin Therapy

U.S. Food and Drug Administration. Product Approval Information-Licensing Action for Immune Globulin Subcutaneous (Human). Retrieved on 1/17/07 from <http://www.fda.gov/cber/products/igsczlb010906.htm>

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 12/14/05.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 4/25/06

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 7/20/06.

Specialty Matched Consultant Review - 5/23/07

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 12/11/08

U.S. Food and Drug Administration (FDA). Immune Globulin Intravenous (IGIV) Indications. Updated 8/1/07. Retrieved 2/12/09 from <http://www.fda.gov/cber/products/igivlist.htm>

Gibson J, Kornberg A, Riminton S. Criteria for the clinical use of intravenous immunoglobulin in Australia. Canberra, ACT: National Blood Authority 2007. Retrieved 2/12/09 from <http://www.nba.gov.au/ivig/Criteria/foreword.html>

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525-S553. Retrieved 2/12/09 from http://www.aaaai.org/members/resources/initiatives/ivig_toolkit/2006_ivig_evidence_review.pdf

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision. *Eur J Neurol*. 2010 Mar;17(3):356-63

Policy Implementation/Update Information

From Policy Entitled: Intravenous Immune Globulin Therapy

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|-------|---|
| 7/94 | Evaluated: Eligible for coverage for the treatment of refractory dermatomyositis. Investigational for the treatment of chronic progressive or relapsing-remitting multiple sclerosis and refractory rheumatoid arthritis. |
| 11/94 | Evaluated: Investigational for treatment of recurrent fetal loss and chronic inflammatory demyelinating polyneuropathy |
| 1/96 | Evaluated: Investigational for treatment of refractory SLE related cytopenia, nephritis, CNS involvement, vasculitis, pericarditis, or pleural effusion (TEC Bulletin, June 1995) |
| 6/96 | Revised: Added FDA approval of REspiGam to prevent respiratory syncytial virus in children under 24 months |
| 1/97 | Revised: Updated RespiGam and indications for use. Added CHD to list under investigational. |
| 9/99 | Reformatted, Medical Term Definitions added. |
| 12/99 | Medical Policy Advisory Group |
| 2/00 | The policy was revised to include eligibility of coverage for Myasthenia Gravis based on |

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- specific criteria per information received from the December 1998 article written by Dr. Howard and the May 1999 publication stated above. Typographical error corrected. Last Review and Next Review dates changed. Coding system changes.
- 10/00 System coding changes.
- 12/00 New 2001 HCPCS code J1563 added. System coding changes.
- 03/01 Consultant review. No changes to policy. Reaffirm.
- 4/01 Revised. Removed first statement under "what is not covered". It was a duplicate diagnosis.
- 5/03 Specialty Matched Consultant Review 4/03. Revised Description section for clarity. Typos corrected. Deleted codes J1561, J1562, 90288, 90371, 90379, 90386 from Billing/Coding section as codes have either been deleted or are not applicable to this policy. Added code J1564 to Billing/ Coding section. Kawasaki Syndrome is now a labeled indication. Eaton-Lambert syndrome is now an off-label indication. Under "When covered" added "steroid" to 2.h.ii; added refractory polymyositis as 2.i; Toxic shock syndrome as 2.j; Hemolytic Disease of the newborn as 2.k. Under "When not covered" added diagnoses 30-38.
- 4/04 Benefits Application and Billing/Coding sections updated for consistency.
- 4/21/05 Specialty Matched Consultant review 3/28/05. Under When Covered section -added the following statement to Guillain-Barré syndrome - "*when presenting within 4 weeks of neuropathic symptoms if nonambulant and 2 weeks if ambulant*". New HCPCS codes, Q9941, Q9942, Q9943, Q9944 added in Billing/Coding section of policy. Notification given 4/21/05. Effective date 7/7/2005.
- 1/19/06 Removed deleted codes J1563, J1564, Q9941, Q9942, Q9943, & Q9944 from Billing/Coding section and added new 2006 CPT codes J1566 & J1567.
- 2/16/06 Removed #2.h.i-ii indications for Myasthenia Gravis under "When Covered" section and added the following: **2.h.** Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange and **2.i.** Myasthenia Gravis in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complication from or failure of steroids and/or azathioprine. Removed #5 statement under "When not Covered" section. #5 now reads, "Myasthenia Gravis in patients responsive to immunosuppressive treatment." Notification given 2/16/06. Effective date 4/27/06.
- 3/2/06 Due to a scheduling change for the 4/27/06 website update, the effective date for the revisions to this policy noticed on 2/16/06 is 4/24/06.
- 4/24/06 Added the following statement to When Covered section; 1.c. and 1.e. second bullet-both regarding bone marrow transplant patients: "(for BCBSNC policy, the source of hematopoietic stem cells may be from bone marrow, peripheral blood or umbilical cord blood)".
- 7/10/06 Typos corrected.

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- 3/12/07 "Intravenous" dropped from name of policy, Policy section, When Covered section header and When Not Covered section header since policy now includes subcutaneous route of administration of immune globulin. Information regarding subcutaneous formulation of immunoglobulin added to Description section. Under When Covered section added criteria for intravenous immunoglobulin in the setting of solid organ transplant. Also added "Subcutaneous immune globulin may be considered medically necessary for the treatment of patients with primary immune deficiency diseases (PID)." Under When Not Covered section, added contraindication to immune globulin therapy. Code J1562 added to Billing/Coding section (previously deleted code reinstated for subcutaneous injection immune globulin). Key words, terms and definitions and reference sources added. (pmo)

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- 7/2/07 Specialty Matched Consultant review. No changes to criteria. Added HCPCS codes Q4087, Q4088, Q4091 and Q4092 effective July 1, 2007 to Billing/Coding section. Reference source added. (pmo)
- 12/31/07 Coding update. Deleted codes 90291, Q4087, Q4088, Q4091 and Q4092. Added codes 90284, J1561, J1568, and J1569. (adn)
- 3/24/08 Added code J1572 (Flebogamma) and code Q4097 (Privigen) to the Billing/Coding section. (adn)
- 01/05/09 Coding update. Code Q4097 replaced with Code J1459. (adn)
- 7/6/09 Description section revised for clarity. Reformatted "When IVIg Is Covered" section into an outline and added the following indications: in post-bone marrow transplant setting and refractory dermatomyositis in combination with other immunosuppressive agents. The following indications were deleted from the "When IVIg is Covered" section: refractory polymyositis, toxic shock syndrome, hemolytic disease of the newborn and Lambert-Eaton syndrome. Subcutaneous immune globulin may be considered medically necessary for treatment of patients with primary immune deficiency diseases including: congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and x-linked agammaglobulinemia. The following were added to the "When IVIg is Not Covered" section: refractory dermatomyositis as monotherapy, dermatomyositis in patients responsive to immunosuppressive therapy, polymyositis including refractory polymyositis, Fisher syndrome and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Deleted Code J1567. References updated. Specialty Matched Consultant review 4/8/09. (adn)
- 9/28/09 Description section extensively revised. Specific FDA-labeled indications noted in the When IVIg Is Covered section. Relapsing/remitting multiple sclerosis (formerly Item 12) was deleted from the list of covered indications. The following statement was added to the When IVIg Is Not Covered section, "IVIg is considered not medically necessary as a treatment of relapsing/remitting multiple sclerosis." Notification given 9/28/09. Effective date 1/01/10. (adn)
- 6/22/10 Policy Number(s) removed (amw)
- 1/4/2011 Added new HCPCS codes J1559 and J1599 to Billing/Coding section. Also added HCPCS code J1460 due to deletion of J codes J1470-J1550.(lpr)
- 4/12/11 Added code C9270 to Billing/Coding section. Specialty Matched Consultant Advisory Panel review. The following information was added to the Policy Guidelines section: "Patients with chronic inflammatory demyelinating neuropathy (CIDP) should meet the diagnostic criteria established by the American Academy of Neurology. In addition, intravenous immunoglobulin infusion (IVIg) treatment should be limited to CIDP patients who do not respond to initial therapy with prednisone and are experiencing serious clinical worsening documented by neurological exam. In patients treated for chronic diseases, such as CIDP, multifocal motor neuropathy, and dermatomyositis, the effect of IVIg is transitory and therefore periodic infusions of IVIg are needed to maintain treatment effect. The frequency of transfusions is titrated to the treatment response; typically, biweekly or monthly infusions are needed. Continued treatment with IVIG is warranted only if it continues to be efficacious." Added Appendix to policy with diagnostic criteria for CIDP. Specialty Matched Consultant review 2/2011. (adn)
- 1/1/12 Coding update. Deleted code C9270 and replaced with J1557. (adn)

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is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.

Appendix

Diagnostic Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The following criteria are adapted from the Task Force Report of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (Neurology 1991; 41(5):617-8) The report included mandatory, supportive, and exclusionary diagnostic criteria. Only the mandatory criteria are excerpted here. The criteria are based on a combination of clinical observations, physiologic studies, pathologic features (i.e., nerve biopsy), and studies of the cerebrospinal fluid (CSF).

I. Clinical

Mandatory

1. Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than one limb or a peripheral nerve nature, developing over at least two months.
2. Hypo- or areflexia. This will usually involve all 4 limbs.

II. Physiologic Studies

Mandatory

Nerve conduction studies including studies of proximal nerve segments in which the predominant process is demyelination.

Must have 3 of 4:

1. Reduction in conduction velocity (CV) in 2 or more motor nerves:
 - <80% of lower limit of normal (LLN) is amplitude >80% of LLN
 - <70% of LLN is amplitude <80% of LLN
2. Partial conduction block or abnormal temporal dispersion in 1 or more motor nerves: either peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow.

Criteria suggestive of partial conduction block: <15% change in duration between proximal and distal sites and >20% drop in negative peak (p) area or peak to peak (p-p) amplitude between proximal and distal sites.

Criteria for abnormal temporal dispersion and possible conduction block: >15% change in duration between proximal and distal sites and >20% drop in p area or p-p amplitude between proximal and distal sites and >20% drop in p or p-p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block as they are derived from studies of normal individuals. Additional studies, such as stimulation across short segments or recording of individual motor unit potentials, are required for confirmation.

3. Prolonged distal latencies in 2 or more nerves:
 - >125% of upper limit of normal (LEN) is amplitude >80% of LLN
 - >150% of LEN if amplitude <80% of LLN.
4. Absent F waves or prolonged minimum
 - >120% of ULN if amplitude >80% of LLN
 - >150% of ULN if amplitude <80% of LLN.

III. Pathologic Features

Mandatory

Nerve biopsy showing unequivocal evidence of demyelination and remyelination.

Demyelination by either electron microscopy (>5 fibers) or teased fiber studies >12% of 50 fibers,

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minimum of 4 internodes each, demonstrating demyelination/remyelination.

IV. CSF Studies

Mandatory

1. Cell count <10 per cubic mm if HIV-seronegative or <50 per cubic mm if HIV seropositive
2. Negative VDRL

The following criteria are adapted from the Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst.* 2005;10:220-228. The EFNS/PNS diagnostic criteria were designed to balance specificity and sensitivity.

I. Inclusion Criteria

1. Typical CIDP - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and absent or reduced tendon reflexes in all extremities
2. Atypical CIDP

One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs):

- Predominantly distal weakness (distal acquired demyelinating symmetric, DADS)
- Pure motor or sensory presentations, including chronic sensory immune polyradiculoneuropathy affecting the central process of the primary sensory neuron
- Asymmetric presentations (multifocal acquired demyelinating sensory and motor, MADSAM, Lewis-Sumner syndrome)
- Focal presentations (e.g., involvement of the brachial plexus or of one or more peripheral nerves in one upper limb)
- Central nervous system involvement (may occur with otherwise typical or other forms of atypical CIDP)

II. Exclusion Criteria

Diphtheria, drug or toxin exposure likely to have caused the neuropathy

Hereditary demyelinating neuropathy, known or likely because of family history, foot deformity, mutilation of hands or feet, retinitis pigmentosa, ichthyosis, liability to pressure palsy

Presence of sphincter disturbance

Multifocal motor neuropathy

Antibodies to myelin-associated glycoprotein

III. Electrodiagnostic Criteria

1. Definite

At least one of the following:

- At least 50% prolongation of motor distal latency above the upper limit of normal values in two nerves, or
- At least 30% reduction of motor conduction velocity below the lower limit of normal values in two nerves, or
- At least 20% prolongation of F-wave latency above the upper limit of normal values in two nerves (>50% if amplitude of distal negative peak CMAP, 80% of lower limit of normal values), or

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- Absence of F-waves in two nerves if these nerves have amplitudes of distal negative peak CMAPs at least 20% of lower limit of normal values + at least one other demyelinating parameter* in at least one other nerve, or
- Partial motor conduction block: at least 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve, or
- Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in at least two nerves, or
- Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) of at least 9 ms in at least one nerve + at least one other demyelinating parameter* in at least one other nerve

2. Probable

At least 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding posterior tibial nerve, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve

3. Possible

As in (1) but in only one nerve

CMAP, compound muscle action potential. To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. Temperatures should be maintained at least 33° C at the palm and 30° C at the external malleolus (good practice points).

** Any nerve meeting any of the criteria*

IV. Supportive Criteria

Elevated cerebrospinal fluid protein with leukocyte <10/mm³ (level A recommendation)

Magnetic resonance imaging showing gadolinium enhancement and /or hypertrophy of the cauda equine, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexus (level C recommendation)

Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination in >5 fibers by electron microscopy or in >6 of 50 teased fibers

Clinical improvement following immunomodulatory treatment (level A recommendation)