I. POLICY

Intravenous Immune globulin (IVIg) Therapy

IVIg may be considered medically necessary for the following indications:

Primary immune deficiency syndromes, including combined immunodeficiencies.
- X-linked agammaglobulinemia (Bruton’s)
- X-linked hyper-IgM syndrome
- Severe combined immunodeficiency (SCID)
- Wiskott-Aldrich syndrome
- Ataxia telangiectasia
- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immune globulin:
  - Laboratory evidence of immunoglobulin deficiency (see Policy Guidelines)
  - Documented inability to mount an adequate immunologic response to inciting antigens (see Appendix)
  - Persistent and severe infections despite treatment with prophylactic antibiotics

Acute Humoral Rejection

Autoimmune Mucocutaneous Blistering Diseases in patients with severe, progressive disease, despite treatment with conventional agents (corticosteroids, azathioprine, cyclophosphamide, etc.)
- pemphigus
- pemphigoid
- pemphigus vulgaris
- pemphigus foliaceus
- Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)

Autoimmune and inflammatory disorders
- dermatomyositis refractory to treatment with corticosteroids; in combination with other immunosuppressive agents
- Kawasaki syndrome*;
Neuroimmunological
- myasthenia gravis in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
- myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange
- Guillain-Barre syndrome
- chronic inflammatory demyelinating polyneuropathy*; in patients with progressive symptoms for at least two months
- multifocal motor neuropathy
- Eaton-Lambert myasthenic syndrome; in patients who have failed to respond to anticholinesterase medications and/or corticosteroids.

Hematologic
- idiopathic thrombocytopenic purpura (ITP)
- treatment of acute, severe ITP (see policy guidelines)
- treatment of chronic ITP*; in patients with at least 6 months’ duration of disease, and with persistent thrombocytopenia despite treatment with corticosteroids and splenectomy
- neonatal alloimmune thrombocytopenia;
- allogeneic post-bone marrow transplant setting
- B cell chronic lymphocytic leukemia (CLL); in patients with hypogammaglobulinemia and persistent bacterial infections
- warm antibody autoimmune hemolytic anemia, refractory to corticosteroids and immunosuppressive agents
- anti-phospholipid syndrome
- severe anemia due to parvovirus B19

Infectious diseases
- HIV [human immunodeficiency virus]-infected patients
- toxic shock syndrome
- patients with primary defective antibody synthesis

Transplantation
- 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

* FDA-labeled indications
IVIg is considered not medically necessary as a treatment of relapsing/remitting multiple sclerosis.

Other applications of IVIg therapy are considered investigational, including, but not limited to, the following conditions:
- chronic progressive multiple sclerosis;
- refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus;
- recurrent spontaneous abortion (see below for related laboratory tests);
- inclusion-body myositis;
- 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, other than Eaton-Lambert myasthenic 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;
- immune-mediated neutropenia;
- nonimmune thrombocytopenia;
- cystic fibrosis;
- recurrent otitis media;
- diabetes mellitus;
- Behcet’s syndrome;
- adrenoleukodystrophy;
- stiff person syndrome;
- organ transplant rejection;
- uveitis;
- demyelinating optic neuritis;
Subcutaneous Immune Globulin (SCIG) Therapy
SCIG may be considered medically necessary for the treatment of primary immunodeficiencies*, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency (CVID), severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked agammaglobulinemia (XLA).

Policy Guidelines
Primary Immunodeficiency Syndromes. The diagnosis of immunodeficiency and post immunization titers must be taken in context with the clinical presentation of the patient and may vary dependent on the type of vaccine given and the prior immunization history of the patient. The following parameters are examples of criteria for diagnosis of the primary immunodeficiency syndromes.

- Laboratory evidence of immunoglobulin deficiency may include the following definitions:
  - Agammaglobulinemia (total IgG less than 200 mg/dL)
  - Persistent hypogammaglobulinemia (total IgG less than 400 mg/dL, or at least two standard deviations below normal, on at least two occasions)
  - Absence of B lymphocytes

- Inability to mount an adequate antibody response to inciting antigens may include the following definitions:
  - Lack of appropriate rise in antibody titer following provocation with a polysaccharide antigen. For example, an adequate response to the pneumococcal vaccine may be defined as at least a four-fold increase in titers for at least 50% of serotypes tested.
  - Lack of appropriate rise in antibody titer following provocation with a protein antigen. For example, an adequate response to tetanus/diphtheria vaccine may
According to a 2010 national guideline from Canada on immune globulin for primary immune deficiency, although higher trough levels of IVIg may be associated with clinical response; the goal of IVIg dose increases should be to improve clinical effectiveness and not merely to increase trough levels.

Acute, severe ITP may be defined by the following parameters:
- acute ITP with major bleeding, e.g., life-threatening bleeding and/or clinically important mucocutaneous bleeding
- acute ITP with severe thrombocytopenia and at high risk for bleeding complications
- acute ITP with severe thrombocytopenia and a slow or inadequate response to corticosteroids
- acute ITP with severe thrombocytopenia and a predictable risk of bleeding in the future, e.g., a procedure or surgery with a high bleeding risk.

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) should meet the diagnostic criteria established by the American Academy of Neurology, particularly if the patient also is diagnosed with chronic fatigue syndrome. (See Appendix A for the diagnostic criteria.) In addition, by 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. 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.

Patients with multifocal motor neuropathy should meet established diagnostic criteria such as those published by Van Asseldonk and colleagues in *Lancet Neurology* in 2005 (See Appendix B for the diagnostic criteria).
The following is an adaptation of recommendations that have been made for IVIg dosing in a consensus report from the IVIg advisory committee:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary immunodeficiency disorders</td>
<td>0.4-0.6 g/kg every 28 days</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>0.4 g/kg for 5 doses</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>0.25-0.4 g/kg × 5 doses</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>0.4 g/kg for 5 doses</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenia</td>
<td>0.4 g/kg/d × 5 days</td>
</tr>
<tr>
<td>Acute humoral rejection</td>
<td>1 g/kg/d for 2 doses</td>
</tr>
</tbody>
</table>

**Cross-reference:**
- **MP-7.006** Pregnancy-Related Testing for Genetic, Chromosomal, Metabolic, and Immunologic Abnormalities
- **MP-2.304** Pervasive Developmental Disorders
- **MP-4.031** Plasma Exchange
- **MP-2.068** Extracorporeal Photophoresis after Solid-Organ Transplant and for Graft-Versus Host Disease, and Cutaneous T-Cell Lymphoma

**II. PRODUCT VARIATIONS**

[N] = No product variation, policy applies as stated

[Y] = Standard product coverage varies from application of this policy, see below

- [N] Capital Cares 4 Kids
- [N] Indemnity
- [N] PPO
- [N] SpecialCare
- [N] HMO
- [N] POS
- [Y] SeniorBlue HMO*
- [Y] FEP PPO**
- [Y] SeniorBlue PPO*

* For treatment of Autoimmune Mucocutaneous Blistering Diseases, refer to Centers for Medicare and Medicaid (CMS) National Coverage Determination (NCD) 250.3 Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases. For IVIG given in the home for treatment of primary immunodeficiency, refer to NHIC LCD 27260 Intravenous Immune Globulin and Local Coverage Article for Intravenous Immune Globulin effective January 2011 (A46761). For the treatment of second-line therapy in acute relapse of relapsing multiple sclerosis (MS), refer to Novitas Solutions Local Coverage Determination LCD L32937 Intravenous Immune Globulin (IVIG).

Also, for off-label uses of drugs and biologicals, refer to the following Medicare Benefit Policy Manual sections: “FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if determined that the use is medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice.”
III. DESCRIPTION/BACKGROUND

This policy addresses the use of human immune globulin therapy for preventing and/or treating a wide variety of disorders in the outpatient setting. Both intravenous infusion (IVIg) and subcutaneous infusion (SCIg) of immune globulin are addressed. However, the policy only considers nonspecific pooled preparations of IVIg, not other preparations used for passive immunization to specific antigens.

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.

Intravenous infusion immune globulin 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. Several IVIg products are available for clinical use in the United States. The labeled indications approved by the U.S. Food and Drug Administration (FDA) for IVIg are listed in the Policy section. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (e.g., Guillain-Barre syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.
This policy only addresses nonspecific pooled preparations of IVIg; it 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.

Subcutaneous infusion immune globulin is used for treating patients with primary immunodeficiencies (PID). 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. The first FDA-approved SCIg product, 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.

Applications of this product for conditions other than primary immunodeficiencies are considered off-label in the United States and are not addressed in this policy. In recent years, other SCIg products have also received FDA-marketing approval.

Regulatory Status
Several IVIg have been approved by the FDA. These include Carimune (ZLB Bioplasma), Flebogamma (Grifols), Gammagard (Baxter), Gamunex (Talecris Biotherapeutics), Octagam (Octapharma), Polygam S/D (Baxter) Privigen (CSL Behring LLC).

Several SCIg products have received FDA marketing approval for primary immunodeficiencies. These include Vivaglobin® (ZLB Behring LLC, Kankakee, IL), Hizentra® (ZLB Behring LLC, Kankakee, IL), Gamunex-C® (Talecris Biotherapeutics, Inc., Research Triangle Park, NC), and Gammaked® (Kedrion Biopharma, Cambridge, MA).

IV. DEFINITIONS

ANTIBODY is a protein substance produced in response to a unique antigen. The substance developed combines with a specific antigen to destroy or control it.

IMMUNE GLOBULIN is a drug created from serum containing antibodies. It is used to supply necessary antibodies to patients with immunoglobulin deficiencies and to provide passive immunity against common viral infections (e.g., hepatitis A and measles).

INTRAVENOUS refers to within or into a vein.

OFF LABEL refers to the use of a drug to treat a condition for which it has not been approved by the U.S. Food and Drug Administration (FDA), especially when such may relieve unpleasant symptoms or prove compassionate. Drug effects that have been observed but not specifically
proven (and for which no application has been made) may be exploited for unproven or "off-label" uses by licensed medical practitioners.

V. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VI. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VII. REFERENCES


<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>IMMUNE GLOBULIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.023</td>
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</table>


Durable Medical Equipment Regional Carrier (DMERC) Region A Local Coverage Determination (LCD) 27260 Intravenous Immune Globulin Effective 01/01/12. [Website]: http://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=46761&ver=10&ContrId=137&ContrVer=1&LCDId=27260&CntrctrSelected=137*1&Cntrctr=137&name=NHIC%2c%2BCorp.%2b(16003%2c%2bDME%2bMAC)&LCntrctr=137*1&kq=1829415601&ua=highwire&IsPopup=y& Accessed February 27, 2013.


Taber’s Cyclopedic Medical Dictionary, 19th edition.


VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
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<tr>
<th>CPT Codes®</th>
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<tbody>
<tr>
<td>90283</td>
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<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1556</td>
<td>Injection, immune globulin (bivigam), 500 mg</td>
</tr>
<tr>
<td>J1557</td>
<td>Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin (Gamanex/Gamanex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1562</td>
<td>Injection, immune globulin (Vivaglobin), 100 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin (Octagam) intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin (Gammagard) intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
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<td>J1572</td>
<td>Injection, immune globulin (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
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<td>J1599</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg</td>
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<tr>
<td>ICD-9-CM Diagnosis Code*</td>
<td>Description</td>
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<tr>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------</td>
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<tr>
<td>040.82</td>
<td>Streptococcus infection in conditions classified elsewhere and of unspecified site</td>
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<tr>
<td>041.00 – 041.9</td>
<td>Bacterial infection, code range</td>
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<tr>
<td>042.0</td>
<td>Human immunodeficiency virus (HIV) disease</td>
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<tr>
<td>204.10</td>
<td>Chronic lymphoid leukemia, without mention of having achieved remission</td>
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<tr>
<td>204.11</td>
<td>Chronic lymphoid leukemia in remission</td>
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<td>279.00</td>
<td>Unspecified hypogammaglobulinemia</td>
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<td>279.2</td>
<td>Combined immunity deficiency</td>
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<td>279.3</td>
<td>Other selective immunoglobulin deficiencies</td>
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<tr>
<td>279.04</td>
<td>Congenital hypogammaglobulinemia</td>
</tr>
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<td>279.05</td>
<td>Immunodeficiency with increased igm</td>
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<tr>
<td>279.06</td>
<td>Common variable immunodeficiency</td>
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<tr>
<td>279.12</td>
<td>Wiskott-aldrich syndrome</td>
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<td>Combined immunity deficiency</td>
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<td>279.3</td>
<td>Unspecified immunity deficiency</td>
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<td>287.3 – 287.39</td>
<td>Primary thrombocytopenia</td>
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<td>287.4 – 287.49</td>
<td>Secondary thrombocytopenia</td>
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<td>287.5</td>
<td>Unspecified thrombocytopenia</td>
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<td>289.81</td>
<td>Primary hypercoagulable state</td>
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<td>334.8</td>
<td>Spinocerebellar disease</td>
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<td>354.0 – 355.9</td>
<td>Mononeuritis, code range</td>
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<td>Acute infective polyneuritis</td>
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<td>Chronic inflammatory demyelinating polyneuritis</td>
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<td>Myasthenia gravis with (acute) exacerbation</td>
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<td>358.1</td>
<td>Myasthenic syndromes in diseases classified elsewhere</td>
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<td>4260-4269</td>
<td>Conduction disorders, code range</td>
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<td>695.14</td>
<td>Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome</td>
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<tr>
<td>694.4 – 694.5</td>
<td>Pemphigus/pemphigoid code range</td>
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<tr>
<td>446.1</td>
<td>Acute febrile mucocutaneous lymph node syndrome (Kawasaki disease)</td>
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<td>710.3</td>
<td>Dermatomyositis</td>
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<tr>
<td>757.39</td>
<td>Other specified congenital anomaly of skin</td>
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<tr>
<td>776.1</td>
<td>Transient neonatal thrombocytopenia</td>
</tr>
<tr>
<td>V42.81</td>
<td>Status post-bone marrow transplant</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
The following ICD-10 diagnosis codes will be effective October 1, 2014:

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<th>ICD-10-CM Diagnosis Code*</th>
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<tr>
<td>A48.3</td>
<td>Toxic shock syndrome</td>
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<tr>
<td>B95.0-B95.8</td>
<td>Streptococcus, staphylococcus and enterococcus as the cause of diseases classified elsewhere code range</td>
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<tr>
<td>B20</td>
<td>Human immunodeficiency virus [HIV] disease</td>
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<tr>
<td>C91.10-C91.12</td>
<td>Chronic lymphocytic leukemia of b-cell type code range</td>
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<tr>
<td>D59.1</td>
<td>Other autoimmune hemolytic anemias (includes warm type)</td>
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<td>D68.61</td>
<td>Anticardiolipin syndrome (includes antiphospholipid syndrome)</td>
</tr>
<tr>
<td>D80.0-D80.9</td>
<td>Immunodeficiency with predominantly antibody defects code range</td>
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<td>D83.0-D83.9</td>
<td>Common variable immunodeficiency code range</td>
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<td>G35</td>
<td>Multiple sclerosis</td>
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<tr>
<td>G60.0 – G60.9</td>
<td>Hereditary and idiopathic neuropathy</td>
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<tr>
<td>G61.0</td>
<td>Guillain-Barre syndrome</td>
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<td>G70.01</td>
<td>Myasthenia gravis with (acute) exacerbation</td>
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<tr>
<td>G73.3</td>
<td>Myasthenic syndromes in other diseases classified elsewhere</td>
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<tr>
<td>I 44.0 – I45.9</td>
<td>Other conduction disorders</td>
</tr>
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<td>L10.0 – L10.9</td>
<td>Pemphigus code range</td>
</tr>
<tr>
<td>L12.0 – L12.9</td>
<td>Pemphigoid code range</td>
</tr>
<tr>
<td>L51.3</td>
<td>Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome</td>
</tr>
<tr>
<td>M30.0</td>
<td>Mucocutaneous lymph node syndrome</td>
</tr>
<tr>
<td>M33.90 – M33.99</td>
<td>Dermatopolymyositis unspecified</td>
</tr>
<tr>
<td>P61.0</td>
<td>Transient neonatal thrombocytopenia</td>
</tr>
<tr>
<td>Z94.81</td>
<td>Bone marrow transplant status</td>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**IX. POLICY HISTORY**

<table>
<thead>
<tr>
<th>MP 2.023</th>
<th>CAC 5/27/03</th>
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<tr>
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<td>CAC 9/25/07</td>
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<td>CAC 7/29/08</td>
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7/1/09 Administrative Change Cross-reference added for Pervasive Developmental Disorders

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<thead>
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Gamunex added to list of IVIG preparations in background/description. References updated.
<table>
<thead>
<tr>
<th>CAC 9/28/10</th>
<th>Consensus review.</th>
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<tbody>
<tr>
<td>CAC 10/25/11</td>
<td>Consensus review</td>
</tr>
</tbody>
</table>
| CAC 4/24/12 | Adopt BCBSA. The following were added as medically necessary: 
**Primary immune deficiency syndromes, including combined immunodeficiencies**
- X-linked hyper-IgM syndrome 
- Ataxia telangiectasia
**Autoimmune Mucocutaneous Blistering Diseases**, in patients with severe, progressive disease despite treatment with conventional agents (corticosteroids, azathioprine, cyclophosphamide, etc.)
- Pemphigus 
- pemphigoid* 
- pemphigus vulgaris 
- pemphigus foliaceus 
- Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)
**Neuroimmunological**
- Eaton-Lambert myasthenic syndrome; in patients who have failed to respond to anticholinesterase medications and/or corticosteroids
**Infectious diseases**
- toxic shock syndrome
IVIg is considered **not medically necessary** as a treatment of relapsing/remitting multiple sclerosis. Previously this indication was listed as investigational.

The following indications were added as investigational:
- Fisher syndrome 
- pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); 
- autism 
- complex regional pain syndrome 
- Alzheimer’s disease 
- IgG sub-class deficiency 
- Sepsis
FEP variation updated.
| CAC 6/4/13 | Minor revision. “Neonatal” added to bullet point on sepsis in the investigational statement. Crohn’s disease, opsoclonus-myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis and polyradiculoneuropathy (other than CIDP) were all added as examples of investigational indications. Severe anemia associated with parvovirus B19 was added as a medically necessary indication under hematologic indications. |

**12/19/2013- New 2014 Code updates made.**

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X. APPENDIX

Appendix A:

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 1 limb or a peripheral nerve nature, developing over at least 2 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:
   a. <80% of lower limit of normal (LLN) is amplitude >80% of LLN
   b. <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.
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:
   a. >125% of upper limit of normal (LEN) is amplitude >80% of LLN
   b. >150% of LEN if amplitude <80% of LLN.

4. Absent F waves or prolonged minimum
   a. >120% of ULN if amplitude >80% of LLN
   b. >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, 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 is 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.

V. 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)

VI. 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

VII. 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
     - 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

VIII. **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)

**Appendix B:**

**Diagnostic Criteria for Diagnosis of Multifocal Motor Neuropathy (MMN)**
The following are proposed diagnostic criteria adapted from a 2005 article by Van Asseldonk and colleagues (Lancet Neurology; 4: 309-319)

I. **Clinical criteria**
   1. Slow or stepwise progressive limb weakness
   2. Asymmetrical limb weakness
3. Fewer than seven affected limb regions (on each side: upper arm, lower arm, upper leg, or lower leg)
4. Tendon reflexes in affected limbs are decreased or absent
5. Signs and symptoms more pronounced in arms than in legs
6. 20–65 years old at disease onset
7. No objective sensory abnormalities except for vibration sense
8. No bulbar signs or symptoms
9. No upper-motor-neuron features
10. No other neuropathies
11. No myopathy (e.g., dystrophy, inclusion-body myositis)

II. Laboratory criteria
1. CSF protein less than 1 g/L
2. High anti-GM1 titre
3. High signal intensity on T2-weighted MRI of the brachial plexus

III. Electrodiagnostic criteria
1. Definite motor conduction block: Compound muscle action potential (CMAP) area reduction on proximal versus distal stimulation of at least 50% over a long segment (between erb and axilla, upper arm, lower arm, lower leg), or a CMAP amplitude reduction on proximal versus distal stimulation of at least 30% over a short distance (2·5 cm) detected by inching. CMAP amplitude on stimulation of the distal part of the segment with motor conduction block of at least 1 mV
2. Probable motor conduction block: CMAP amplitude reduction on proximal versus distal stimulation of at least 30% over a long segment of an arm nerve. CMAP amplitude on stimulation of the distal part of the segment with motor conduction block of at least 1 mV
3. Slowing of conduction compatible with demyelination: Motor conduction velocity (MCV) <75% of the lower limit of normal; DML or shortest F wave latency 130% of the upper limit of normal or absence of F waves all after 16–20 stimuli. CMAP amplitude on distal stimulation of at least 0·5 mV

Definite MMN: 1–11 on clinical criteria, 1 on laboratory criteria, and 1 and 4 on electrodiagnostic criteria

Probable MMN: 1–3 and 6–11 on clinical criteria, 1 on laboratory criteria, and 2 and 4 on electrodiagnostic criteria

Possible MMN: 1 and 7–11 on clinical criteria, 2 or 3 on laboratory criteria, and 3 and 4 on electrodiagnostic criteria