

## Medical Policy



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### Title: Immune Globulin Therapy

#### Professional

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Revision Date(s): November 11, 1999;  
April 20, 2000; August 9, 2001;  
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Current Effective Date: April 1, 2007

#### Institutional

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Revision Date(s): April 21, 2005; August  
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#### DESCRIPTION

Immune globulin is a substance obtained from human blood plasma that function to protect against infectious agents. Administration is usually intravenously or subcutaneous.

Subcutaneous infusion of immune globulin (SCIG) is an alternative method of administration, especially in patients with difficult venous access. SCIG at a dose of 160 mg/kg per week can raise the level of IgG comparable with those obtained with IVIG at a dose of 400-600 mg/kg per month. SCIG is well accepted by patients and is mostly done at home. The risk of infusion reactions is even less than for IV infusions.

**POLICY** - All immune globulin therapy will be reviewed for medical necessity prior to payment. See Utilization Section for details. Indications for immune globulin include:

1. Immunodeficiency states:  
One of the following six is required:
  - a. A functional immune deficiency manifested by recurrent serious infections. Needs to be demonstrated by the lack of antibody response to pneumococcal vaccine with pre and post antibody titers (patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal

- response to pneumococcal immunization) and recurrent significant infections or
- b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis. Testing for pneumococcal antibody response is not needed.
  - c. B Cell Lymphocytic Leukemia (CLL) (e.g. multiple myeloma, chronic lymphocytic leukemia with low immunoglobulin levels or B cell lymphoma).
  - d. Transient hypogammaglobulinemia of childhood
    - Similar to a functional immune deficiency but transient, usually six months, then IVIG should be gradually withdrawn. Need testing for pneumococcal antibody response.
    - Consider in children less than age 5.
  - e. Partial antibody deficiency (subclass of deficiency)
    - This may refer to a deficiency of one of the four subclasses. This in itself does not indicate instituting IVIG therapy even if patient presents with multiple infection (sinusitis or other upper respiratory infection). Attempts need to be made to find underlying cause and to see if patient has normal immune response. By giving Pneumovax (pneumococcal at a minimum and may include tetanus or hemophilus influenza in addition) and checking antibody levels before and after ascertain if patient has normal immune response.
    - If normal response is obtained, then subclass level deficiency should not be treated. The only exception to this would be in case of a life threatening hospitalization from a specific disease.
  - f. Profound neutropenia in neonatal sepsis (WBC 5,000 or below) –Allow for a single dose.
2. Idiopathic thrombocytopenia (ITP)
    - a. Acute Idiopathic thrombocytopenia (ITP)
      - 1) Management of acute bleeding, due to severe thrombocytopenia (platelet counts usually less than 30,000/ul;
      - 2) To increase platelet counts prior to invasive surgical procedures, e.g., splenectomy;
      - 3) In patients with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage
    - b. Chronic Refractory ITP
      - 1) Prior to treatment with corticosteroids and splenectomy and;
      - 2) Duration of illness of greater than six months and;
      - 3) Age of 10 years or older and;
      - 4) No concurrent illness/disease explaining thrombocytopenia and;
      - 5) Platelet counts persistently at or below 20,000/ul.
  3. HIV associated thrombocytopenia - Allow treatment (same as ITP)
  4. Immune thrombocytopenic purpura of pregnancy – Allow for 5 days.
  5. Neonatal alloimmune thrombocytopenia - Allow for 5 days.
  6. Kawasaki Syndrome

7. Organ transplant - graft versus host disease. Allow treatment, but treatment should be short-term unless it is "chronic" graft versus host.
8. Guillain Barré Syndrome - Allow for no longer than 1 month.
9. Bone Marrow transplant
10. Landau-Kleffner Syndrome – Allow for six-weeks with documented speech improvement, only if patient has completed a course of prednisone. Additional treatment requires prior approval.
11. Polymyositis - Allow for six months if no response to steroids and observe for relapse.
12. Dermatomyositis - Allow for six months if no response to steroids and observe for relapse.
13. HIV associated polyneuropathy.
14. Multifocal motor neuropathy.
15. Chronic inflammatory demyelinating polyneuropathy (CIDP)
16. Myasthenia gravis - Only when all other treatments fail.
17. Intractable seizure - Not recommended unless all other measures fail.
18. Rasmussen encephalitis
19. Systemic juvenile rheumatoid arthritis - Only for refractory patient cases.
20. Systemic lupus - Not recommended except for refractory cases.
21. Steroid dependent asthmatic, allow only if:
  - a. All modalities have failed.
  - b. Unstable patient requiring frequent hospital care. A trial should be allowed and if there is a decrease of frequency of hospital admissions and stabilization of patient's pulmonary function it should be allowed.
22. Pemphigus - only when all other treatments fail.
23. Prior to renal transplantation with high levels of panel reactive antibodies (PBA)

**NOTE:**

When it is determined IVIG is to be given for the duration of the patient's life, reviews will be conducted not for medical necessity but for patient benefits.

**Denied Medical Conditions:**

1. Infertility and Spontaneous abortion deny experimental/investigational.
2. Frequent sinus/pulmonary infection only, deny not medically necessary.
3. Shingles deny not medically necessary.
4. Prevention of bacterial infection associated with HIV (adults), deny not medically necessary.
5. Amyotrophic Lateral Sclerosis (ALS), deny experimental/investigational.

**DOCUMENTATION**

1. Information needed when reviewed for medical necessity are:
  - a. Detailed history & physical

- b. Pre and post pneumococcal vaccine titer (may include tetanus, or hemophilus influenza in addition)
- c. Date of pneumococcal vaccination (may include tetanus, or hemophilus influenza in addition)

### **UTILIZATION**

All claims are subject to medical review. At a minimum, the medical record must include the requirements listed in the Documentation Section. Providers may:

- Submit medical records prior to treatment for predetermination of medical necessity, or
- Submit medical records with the claim for medical necessity review.

### **CODING**

#### **REVENUE CODE**

0636

#### **CPT/HCPCS**

90283	Immune Globulin (IgIV), human, for intravenous use
90399	Unlisted immune globulin (use this code for SCIG)
J1562	Immune Globulin, subcutaneous, 100 mg
J1566	Immune Globulin, IV, lyophilized (e.g., powder), 500mg
J1567	Immune Globulin, IV, non-lyophilized (e.g., liquid), 500mg
J3490	Unclassified drugs (use this code for SCIG)
Q9941	Injection, Immune Globulin, Intravenous, Lyophilized, 1 gram
Q9942	Injection, Immune Globulin, Intravenous, Lyophilized, 10 gram
Q9943	Injection, Immune Globulin, Intravenous, Non-Lyophilized, 1 gram
Q9944	Injection, Immune Globulin, Intravenous, Non-Lyophilized, 10 gram

#### **DIAGNOSIS CODES**

**These diagnoses are otherwise subject to medical policy as stated above.**

204.10	Lymphoid leukemia; Chronic, without mention of remission
204.11	Lymphoid leukemia; Chronic, in remission
284.9	Aplastic anemia, unspecified
287.3	Primary thrombocytopenia
357.0	Acute infective polyneuritis
446.1	Acute febrile mucocutaneous lymph node syndrome [MCLS]
357.81	Chronic inflammatory demyelinating polyneuritis
694.4	Pemphigus
710.3	Dermatomyositis
710.4	Polymyositis
V42.81	Organ or tissue replace by transplant; bone marrow

**REVISIONS**

April 21, 2005	<p>Deleted Policy #1 - Immunodeficiency diagnosis:</p> <ol style="list-style-type: none"> <li>a. Functional immune deficiency (must meet the two bullets listed below to approve, otherwise will be denied as not medically necessary).</li> <li>b. Immunodeficiency syndrome (must meet the two bullets listed below to approve, otherwise will be denied as not medically necessary).</li> <li>c. Acquired Immunodeficiency - CVID (must meet the two bullets listed below to approve, otherwise will be denied as not medically necessary). <ul style="list-style-type: none"> <li>• Impaired quantitative total IgG levels of less than 200 mg/dl and a history of life-threatening infections such as bacterial meningitis and sepsis. In these situations, testing for responses to antigenic stimulation would not be prudent and IVIG therapy should be allowed when these conditions exist.</li> <li>• In all other cases, a functional immune deficiency needs to have been demonstrated by the lack of antibody response to antigen stimulation (pneumococcal at a minimum and may include tetanus, or hemophilus influenza in addition) to which most normal patients would respond, I.E., pre and post immunization antibody levels. These results must be reviewed and correlated with the relevant clinical findings.</li> </ul> </li> </ol>
	<p>Added a new Policy #1 - Immunodeficiency states: One of the following two is required:</p> <ol style="list-style-type: none"> <li>a. A functional immune deficiency needs to be demonstrated by the lack of antibody response to pneumococcal vaccine with pre and post antibody titers; or</li> <li>b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis.</li> <li>c. B Cell Lymphocytic Leukemia (CLL) (e.g. multiple myeloma, chronic lymphocytic leukemia with low immunoglobulin levels or B cell lymphoma).</li> </ol>
	<p>Deleted #2 "Idiopathic thrombocytopenia (ITP)</p> <ol style="list-style-type: none"> <li>a. Allow as first line of treatment if platelets are under 30,000. 20,000 (if 20,000 or above patient should be observed).</li> <li>a. Administer 1gm/kg x 3 days or until platelets reach 50,0000 (1/2 of patients will need a second round of treatment in 4-8 weeks until platelets are 50,000).</li> <li>b. Procedures may be repeated monthly for 8 months, if no improvement after 8 months splenectomy should be performed.</li> </ol>

	<p>Added a new Policy #2 - "Idiopathic thrombocytopenia (ITP) Acute Idiopathic thrombocytopenia (ITP)</p> <ol style="list-style-type: none"> <li>Management of acute bleeding, due to severe thrombocytopenia (platelet counts usually less than 30,000/ul;</li> <li>To increase platelet counts prior to invasive surgical procedures, e.g., splenectomy;</li> <li>In patients with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage</li> </ol> <p>Chronic Refractory ITP</p> <ol style="list-style-type: none"> <li>Prior to treatment with corticosteroids and splenectomy and;</li> <li>Duration of illness of greater than six months and;</li> <li>Age of 10 years or older and;</li> <li>No concurrent illness/disease explaining thrombocytopenia and;</li> <li>Platelet counts persistently at or below 20,000/ul.</li> </ol>
	Deleted #4 "B-Cell lymphocytic leukemia (CLL)"
	Deleted # 26 "Multiple myeloma - When a patient is on chemotherapy for multiple myeloma, chronic lymphocytic, or leukemia with low immunoglobulin levels and frequency infections".
	Added the following codes: 90399, J3490, Q9941, Q9942, Q9943, and Q9944.
August 18, 2005	In "Policy section" 1.a. added, "manifested by recurrent serious infections".
	In "Policy section" 1.b. added, "Testing for pneumococcal antibody response is not needed."
	In "Policy section" old #25 moved to new #1.d., and added two bullets: <ul style="list-style-type: none"> <li>Similar to a functional immune deficiency but transient, usually six months, then IVIG should be gradually withdrawn. Need testing for pneumococcal antibody response.</li> <li>Consider in children less than age 5.</li> </ul>
	In "Policy section" old #17 moved to new #1.e.
	In "Policy" section, deleted old #14 "Prevention of bacterial infection associated with HIV (pediatric)".
	In "Policy" section, numbers 4 through 26 of old policy renumbered.
December 15, 2005	In "Coding" CPT/HCPCS section, deleted HCPCS codes J1563 and J1564 and added HCPCS codes J1566 and J1567.
March 1, 2006	In "Coding" title added "NOTE: Use of any diagnosis code does not guarantee reimbursement. Medical necessity will be based on documentation in the clinical record."
	In "Coding" Covered Diagnosis section, added ICD-9 code 357.81.

January 12, 2007 with an effective date of April 1, 2007	In "Policy" section 1., a., added "(patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization)" based on consultant review and recommended by the Medical Director.
	In "Policy" section, added #23 "Prior to renal transplantation with high levels of panel reactive antibodies (PBA)" as recommended by the Medical Director.
	In "Coding" title deleted "NOTE: Use of any diagnosis code does not guarantee reimbursement. Medical necessity will be based on documentation in the clinical record."
	In "Coding" CPT/HCPCS section, added HCPCS codes J1562 due to the 2007 CPT changes.
	In "Reference" Government Agency; Medical Society; and Other Authoritative Publications section added #2.

## **REFERENCES**

1. Dalakas, M. (1998). "The Use of Intravenous Immunoglobulin for Neurologic Diseases." Neurology 51, supplement 5: S1-S45. This is an excellent 45-page review supplement to the "green journal" (Neurology). It deals with many aspects of neurological use, from theory to practice. There are original data and evaluations.
2. Park, C. Lucy: Common Variable Immunodeficiency. EMedicine.com. Updated 5-26-2004.
3. Ratko, T. A., D. A. Burnett, et al. (1995). "Recommendations for off-label use of intravenously administered immunoglobulin preparations. University Hospital Consortium Expert Panel for Off-Label Use of Polyvalent Intravenously Administered Immunoglobulin Preparations [see comments]." JAMA 273(23): 1865-70. A well-quoted review paper on general off-label uses; it has a very useful reference table.
4. Rosa, T. (1998). "Primary Immunodeficiencies." Mayo Clin Proc 73(September): 865-872. This paper details every accepted use of IV-Ig in primary immunodeficiencies.
5. Stiehm ER, Casillas AM. Finkelstein JZ, et al: Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: use of an old method with a new product. J Allergy Clin Immunol 1998 Jun; 101(6 Pt 1): 848-9[Medline].
6. Yu, Z. and V. A. Lennon (1999). "Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases." N Engl J Med 340(3): 227-8. A proposed mechanism that may differ from traditional explanations of how IV-Ig works. The second author is a respected neuroimmunologist.

**Government Agency; Medical Society; and Other Authoritative Publications**

1. "Availability of immune globulin intravenous for treatment of immune deficient patients--United States, 1997-1998." MMWR Morbidity Mortal Wkly Report, (1999) 48(8): 159-62. A CDC statement detailing their views on IV-Ig shortage.
2. BCBSKS Medical Consultant, Practicing Board Certified in Allergy, Immunology and Pediatrics (Case Number 10728013), December 15, 2006.