

Corporate Medical Policy

Immune Globulin Therapy

File Name: immune_globulin_therapy
Policy Number: DRU4140
Origination: 07/1994
Last CAP Review: 3/2009
Next CAP Review: 3/2011
Last Review: 4/2009

Description of Procedure or Service

Therapeutic immune globulin is a preparation of plasma proteins derived from the pooled plasma of adult donors. Largely comprised of IgG antibodies, therapeutic immune globulin provides passive immunization by increasing the recipient's serum levels of circulating antibodies. IgG antibodies have multiple functions, including binding to and neutralizing bacterial toxins; opsonization of pathogens; activation of complement; and suppression of pathogenic cytokines and phagocytes through binding to CD5, interleukin-1a, interleukin 6, tumor necrosis factor-alpha, and T-cell receptors. Therapeutic immune globulin may diminish pathogenic mechanisms in some autoimmune diseases by binding to and inhibiting the activity of autoantibodies.

Several IVIg products are available for clinical use and can be delivered by intravenous infusion (IVIg), by subcutaneous infusion (SCIg), or by intramuscular (IMiG) depot injections. IMiG has been largely abandoned in the U.S. 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. This policy focuses on IVIg and SCIg for conditions that typically would be treated in an outpatient setting.

Each product may have different FDA approved indications, therefore, specific product information, product availability, and patient characteristics should be taken into account when selecting therapy. Some of the main FDA approved indications include the treatment of primary immune deficiency disorder, prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia, prevention of coronary artery aneurysms in Kawasaki disease, and increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding.

Coverage for RSV immune globulin (e.g., Synagis) is summarized in the Evidence Based Guideline-EBG.DRU4170 "Respiratory Syncytial Virus Prophylaxis"

*****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

Please refer to Certificate for availability of benefits. This policy relates only to the services or supplies described herein. Benefits may vary according to benefit design, therefore certificate language should be

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reviewed before applying the terms of the policy.

When Immune Globulin Therapy is covered

- A. IVIg may be considered medically necessary for the following indications when the diagnosis has been established by an appropriate clinical work-up:
1. 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,
 2. treatment of idiopathic, immune, chronic immune thrombocytopenic purpura (ITP),
 3. in post-bone marrow transplant setting,
 4. prevention of graft-versus-host disease in hematopoietic transplant patients,
 5. prevention of infection in:
 - a. HIV infected patients
 - b. patients with primary defective antibody synthesis
 - c. patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia
 6. refractory dermatomyositis, in combination with other immunosuppressive agents,
 7. Kawasaki syndrome,
 8. chronic inflammatory demyelinating polyneuropathy,
 9. Guillain-Barré syndrome,
 10. multifocal motor neuropathy in patients with anti-GM1 antibodies and conduction block,
 11. fetal alloimmune thrombocytopenia,
 12. relapsing/remitting multiple sclerosis,
 13. Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange,
 14. 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,
 15. 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,
 16. following solid-organ transplant, treatment of antibody-mediated rejection.
- B. Subcutaneous immune globulin may be considered medically necessary for the treatment of patients with primary immune deficiency diseases (PIDD), including:
1. congenital agammaglobulinemia,
 2. hypogammaglobulinemia,
 3. common variable immunodeficiency,
 4. severe combined immunodeficiency,
 5. Wiskott-Aldrich syndrome,
 6. X-linked agammaglobulinemia.

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When Immune Globulin Therapy is not covered

- A. Intravenous immunoglobulin therapy is considered investigational for all other indications, including, but not limited to, the treatment of the following conditions:
1. refractory rheumatic arthritis and other connective tissue disease including systemic lupus erythematosus,
 2. chronic progressive multiple sclerosis,
 3. recurrent spontaneous abortion,
 4. inclusion body myositis,
 5. refractory dermatomyositis, as monotherapy,
 6. dermatomyositis in patients responsive to immunosuppressive therapy,
 7. polymyositis, including refractory polymyositis,
 8. Myasthenia Gravis in patients responsive to immunosuppressive treatment,
 9. 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,
 10. thrombotic thrombocytopenic purpura,
 11. hemolytic uremic syndrome,
 12. paraneoplastic syndromes, including but not limited to Eaton Lambert syndrome,
 13. demyelinating polyneuropathy associated with IgM paraproteinemia,
 14. epilepsy,
 15. chronic sinusitis,
 16. asthma,
 17. chronic fatigue syndrome,
 18. aplastic anemia,
 19. Diamond-Blackfan anemia,
 20. red cell aplasia,
 21. acquired factor VIII inhibitors,
 22. hemophagocytic syndrome,
 23. acute lymphoblastic leukemia,
 24. multiple myeloma,
 25. immune-mediated neutropenia,
 26. nonimmune thrombocytopenia,
 27. cystic fibrosis,
 28. recurrent otitis media,
 29. diabetes mellitus,
 30. Behcet's syndrome,
 31. adrenoleukodystrophy,

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32. autoimmune mucocutaneous blistering diseases: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullous acquisita,
 33. post-infectious sequelae,
 34. stiff person syndrome,
 35. organ transplant rejection,
 36. uveitis,
 37. demyelinating optic neuritis,
 38. recent-onset dilated cardiomyopathy,
 39. Fisher syndrome,
 40. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),
 41. autism.
- B. Subcutaneous immunoglobulin therapy is considered investigational for indications other than primary immune deficiency diseases.
- C. 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.

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 Codes: 90283, 90284, J1459, J1561, J1562, J1566, J1568, J1569, J1572

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

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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.

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.

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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

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 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.

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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 (PIDD)." 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)

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)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and 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.