Medical and Behavioral Health Policy
Section: Medicine
Policy Number: II-51
Effective Date: 05/19/2014

Blue Cross and Blue Shield of Minnesota medical policies do not imply that members should not receive specific services based on the recommendation of their provider. These policies govern coverage and not clinical practice. Providers are responsible for medical advice and treatment of patients. Members with specific health care needs should consult an appropriate health care professional.

IMMUNE GLOBULIN THERAPY

Description: 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. This policy addresses intravenous immunoglobulin (IVlg) and subcutaneous immunoglobulin (SCIg).

IVlg is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVlg 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 SCIg products have also received FDA approval for the treatment of patients with certain primary immunodeficiencies. These products include: Hizentra®, Gamunex®-C, Gammaked®, and Gammagard Liquid®.

Definitions:

Immunoglobulins: Any of a group of large glycoproteins that are secreted by plasma cells and that function as antibodies in the immune response by binding with specific antigens. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM.

Hypogammaglobulinemia: An abnormally low concentration of gamma globulin in the blood, resulting in increased risk of infection.

Policy:

I. INTRAVENOUS IMMUNE GLOBULIN
The use of intravenous immune globulin may be considered MEDICALLY NECESSARY in the treatment of the following conditions:

A. Primary Immunodeficiencies
   1. X-linked agammaglobulinemia (X-LA or Bruton’s disease);
   2. Common variable immune deficiency when the following
criteria are met;
  a. Significant and clearly documented recurrent infections (e.g., recurrent pneumonias, frequent episodes of bacterial sinusitis, and not just isolated chronic sinusitis); AND
  b. Onset of symptoms after two (2) years of age; AND
  c. Abnormally low serum levels of IgM and/or IgA (2 standard deviations below the age-adjusted mean) IN ADDITION TO abnormally low serum levels of IgG, as demonstrated by EITHER of the following:
    • Total serum IgG level < 200mg/dL; OR
    • Total serum IgG level ≥ 200 and < 400mg/dL OR at least 2 standard deviations below the normal age-adjusted mean AND
    ➢ A demonstrated impaired response to immunization with protein AND/OR polysaccharide antigens:
      o For protein antigens: Serum antibody titers to tetanus and/or diphtheria should be obtained before immunization with tetanus and/or diphtheria vaccine and then three to four weeks after immunization. An abnormal response is defined as less than a four-fold rise in antibody titer
      o For polysaccharide antigens: Serum antibody titers to pneumococcus should be obtained before immunizations and then three to six weeks after immunization with a polyvalent pneumococcal polysaccharide vaccine (such as Pneumovax). An abnormal response is defined as less than a four-fold rise in titer;
    AND
    ➢ Exclusion of other possible causes of hypogammaglobulinemia;
AND
  d. Documentation must include the patient’s serum immunoglobulin levels AND the age-adjusted reference ranges for the laboratory performing the tests.
3. IgG subclass deficiencies
  a. Significant and clearly documented recurrent infections (e.g., recurrent pneumonias, frequent episodes of bacterial sinusitis, and not just isolated chronic sinusitis); AND
  b. Abnormally low levels of one or more IgG subclasses (2 standard deviations below the age-adjusted mean) in patients with normal levels of total IgG and IgM; AND
  c. A demonstrated impaired response to immunization with protein AND/OR polysaccharide antigens:
    • For protein antigens: Serum antibody titers to
tetanus and/or diphtheria should be obtained before immunization with tetanus and/or diphtheria vaccine and then three to four weeks after immunization. An abnormal response is defined as less than a four-fold rise in antibody titer.

- For polysaccharide antigens: Serum antibody titers to pneumococcus should be obtained before immunization and then three to six weeks after immunization with a polyvalent pneumococcal polysaccharide vaccine (such as Pneumovax). An abnormal response is defined as less than a four-fold rise in titer;

**AND**

- Documentation must include the patient’s serum immunoglobulin levels AND the age-adjusted reference ranges for the laboratory performing the tests.

4. X-linked immunodeficiency with hyper IgM;
5. Immunodeficiency with thrombocytopenia and eczema (Wiscott-Aldrich syndrome);
6. Hyperimmunoglobulin E syndrome;
7. Severe combined immune deficiency;
8. Cellular immunodeficiency with immunoglobulins (Nezelof syndrome);
9. Thymic hypoplasia (DiGeorge’s syndrome);
10. Pediatric human immunodeficiency virus (HIV) infection;
11. Kawasaki disease (mucocutaneous lymph nodes syndrome);
12. Acquired hypogammaglobulinemia caused from either of the following two malignancies:
   a. Chronic lymphocytic leukemia
   b. Multiple myeloma.

**B. Hematologic Disorders**

1. Idiopathic thrombocytopenic purpura;
2. Neonatal alloimmune thrombocytopenia - as antenatal treatment in women who have previously had an infant with alloimmune thrombocytopenia or as neonatal treatment for the infant;
3. Warm antibody autoimmune hemolytic anemia, refractory to corticosteroids and splenectomy;
4. Pure red cell aplasia due to parvovirus B19.

**C. Musculoskeletal System and Connective Tissue Disorders**

1. Dermatomyositis that has not responded to treatment with prednisone and immunosuppressant therapy (e.g., azathioprine, methotrexate);
2. Polymyositis that has not responded to treatment with prednisone and immunosuppressant therapy (e.g., azathioprine, methotrexate).

**D. Nervous System Disorders**

1. Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome);
2. Chronic inflammatory demyelinating polyneuropathy
3. Myasthenia gravis
   a. Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness);
   b. Myasthenia gravis in patients with chronic debilitating disease (e.g., restricted daily activities and symptomatic at rest or worse) despite treatment with cholinesterase inhibitors, or complications from or failure of steroids and/or azathioprine;

E. Organ and Stem-Cell Transplantation
1. Prior to solid organ transplantation, for treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients and those receiving an ABO incompatible organ;
2. Following organ transplantation, for treatment of antibody-mediated rejection;
3. Following hematopoietic stem-cell transplantation, for treatment of related immunodeficiencies.

F. Dermatologic Disorders
1. Autoimmune Mucocutaneous Blistering Diseases
   Treatment of the following conditions in patients with severe, progressive disease despite treatment with conventional medical therapy (e.g., corticosteroids, azathioprine, cyclophosphamide):
   a. Pemphigus vulgaris;
   b. Pemphigus foliaceus;
   c. Bullous pemphigoid;
   d. Mucous membrane pemphigoid;
   e. Bullous systemic lupus erythematosus (SLE);
   f. Epidermolysis bullosa acquisita
2. Toxic epidermal necrolysis (TEN)

II. SUBCUTANEOUS IMMUNE GLOBULIN
The use of subcutaneous immune globulin (SClg) therapy may be considered MEDICALLY NECESSARY for the treatment of primary immunodeficiencies (FDA-labeled indications), including the following:
A. Congenital agammaglobulinemia;
B. Severe combined immunodeficiency;
C. Wiskott-Aldrich syndrome;
D. X-linked agammaglobulinemia (XLA);
E. Common variable immune deficiency (CVID) when the following criteria are met:
   1. Significant and clearly documented recurrent infections (e.g., recurrent pneumonias, frequent episodes of bacterial sinusitis, and not just isolated chronic sinusitis); and
   2. Onset of symptoms after two (2) years of age; and
   3. Abnormally low serum levels of IgM and/or IgA (2 standard deviations below the age-adjusted mean) IN ADDITION
TO abnormally low serum levels of IgG, as demonstrated
by EITHER of the following:

a. Total serum IgG level < 200mg/dL; OR

b. Total serum IgG level ≥ 200 and < 400mg/dL OR at
least 2 standard deviations below the normal age-
adjusted mean AND

• A demonstrated impaired response to immunization
with protein AND/OR polysaccharide antigens:
  ➢ For protein antigens: Serum antibody titers to
tetanus and/or diphtheria should be obtained
before immunization with tetanus and/or
diphtheria vaccine and then three to four weeks
after immunization. An abnormal response is
defined as less than a four-fold rise in antibody
titer
  ➢ For polysaccharide antigens: Serum antibody
titers to pneumococcus should be obtained
before immunizations and then three to six
weeks after immunization with a polyvalent
pneumococcal polysaccharide vaccine (such as
Pneumovax). An abnormal response is defined
as less than a four-fold rise in titer;

AND

• Exclusion of other possible causes of
hypogammaglobulinemia

AND

4. Documentation must include the patient’s serum
immunoglobulin levels AND the age-adjusted reference
ranges for the laboratory performing the tests.

III. DOCUMENTATION FOR RENEWAL REVIEW
Renewal of pre-authorization for all medical necessity indications
for intravenous AND subcutaneous immune globulin must include
documentation supporting sustained treatment-related response,
such as substantial improvement in disease condition or a
reduction in disease progression.

IV. INVESTIGATIVE INDICATIONS
The use of intravenous immune globulin OR subcutaneous
immune globulin is considered INVESTIGATIVE in ALL other
circumstances, including the following conditions:

A. Chronic fatigue syndrome;
B. Multiple sclerosis (relapsing-remitting and chronic,
progressive);
C. Recurrent fetal loss;
D. Chronic sinus infections *(unless the sinus infection is a
symptom of one of the primary immunodeficiencies listed
above. Chronic sinus infection is common in most primary
immunodeficiencies listed, especially antibody deficiency with
normal or near-normal immunoglobulins);
E. Inclusion body myositis;
F. Asthma;
G. POEMS syndrome (polyneuropathy, organeomegaly, endocrinopathy, monoclonal gammopathy, and skin changes);
H. Autistic spectrum disorders;
I. PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections);
J. Fisher syndrome;
K. Opsoclonus-myoclonus.

Coverage: Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for certain services addressed in the medical policies.

Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. Receipt of benefits is subject to all terms and conditions of the member’s summary plan description (SPD). As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Blue Cross reserves the right to revise, update and/or add to its medical policies at any time without notice.

For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.

Refer to the Pre-Certification/Pre-Authorization section of the Medical Behavioral Health Policy Manual for the full list of services, procedures, prescription drugs, and medical devices that require Pre-certification/Pre-Authorization. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

Coding: The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

CPT:
90283 Immune globulin (IgIV), human, for intravenous use
90284 Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96367 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new
drug/substance, up to 1 hour (list separately in addition to code for primary procedure)

**HCPCS:**

J1459 Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1556 Injection, immune globulin (Bivigam), 500 mg
J1557 Injection, immune globulin, (gammaplex), intravenous, non-
lyophilized (e.g. liquid), 500 mg
J1559 Injection, immune globulin (hizentra), 100 mg
J1561 Injection, immune globulin, (gamunex-c/gammaked), non-
lyophilized (e. G. Liquid), 500 mg
J1562 Injection, immune globulin (Vivaglobin), 100 mg
J1566 Injection, immune globulin, intravenous, lyophilized
(e.g.,powder), not otherwise specified, 500 mg
J1568 Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569 Injection, immune globulin, (gammagard liquid), non-lyophilized, (e. G. Liquid), 500 mg
J1572 Injection, immune globulin (Flebogamma/Flebogamma Dif),
intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599 Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg

**Deleted Codes:** C9130, C9270

**Policy History:**

**Developed September 21, 1990**

**Most recent history:**

Revised March 9, 2011
Revised March 14, 2012
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Revised March 12, 2014

**Cross Reference:**

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