Effective Date: 5/3/2018

**Immune Globulin Replacement Therapy**

**Medication Use Guidelines**

<table>
<thead>
<tr>
<th>Brand</th>
<th>FDA Approval</th>
<th>HCPCS</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivigam™</td>
<td>Biotest Pharmaceutical</td>
<td>J1566</td>
<td>Medical</td>
</tr>
<tr>
<td>Carimune® NF</td>
<td>CSL Behring</td>
<td>J1566</td>
<td>Medical</td>
</tr>
<tr>
<td>Cuvitru™ (SC only)</td>
<td>Baxalta</td>
<td>J1555 / J7799 (Medicare Use) / J1599 (Commercial Program)</td>
<td>Medical &amp; Pharmacy</td>
</tr>
<tr>
<td>Flebogamma® DIF</td>
<td>Grifols</td>
<td>J1572</td>
<td>Medical</td>
</tr>
<tr>
<td>GamaSTAN® S/D (IM)</td>
<td>Baxter Healthcare</td>
<td>J1569</td>
<td>Medical &amp; Pharmacy</td>
</tr>
<tr>
<td>Gammagard® Liquid (IV &amp; SC)</td>
<td>Baxter Healthcare</td>
<td>J1460 / J1560 CPT /90281</td>
<td>Medical</td>
</tr>
<tr>
<td>Gammagard® S/D</td>
<td>Baxter Healthcare</td>
<td>J1569</td>
<td>Medical</td>
</tr>
<tr>
<td>Gammadeplex®</td>
<td>Bio Products Laboratory</td>
<td>J1557</td>
<td>Medical</td>
</tr>
<tr>
<td>Gamunex® (IV &amp; SC)</td>
<td>Talecris</td>
<td>J1561</td>
<td>Medical &amp; Pharmacy</td>
</tr>
<tr>
<td>Hizentra® (SC only)</td>
<td>CSL Behring</td>
<td>J1559</td>
<td>Medical &amp; Pharmacy</td>
</tr>
<tr>
<td>HyQvia® (SC only)</td>
<td>Baxter</td>
<td>J1575</td>
<td>Medical &amp; Pharmacy</td>
</tr>
<tr>
<td>Octagam®</td>
<td>Octapharma</td>
<td>J1568</td>
<td>Medical</td>
</tr>
<tr>
<td>Privigen®</td>
<td>CSL Behring</td>
<td>J1459</td>
<td>Medical</td>
</tr>
</tbody>
</table>

I. **Policy/Criteria**

*Note: Requests must be supported by submission of chart notes and patient specific documentation.*

A. **Coverage of immune globulins is provided when criteria 1, 2, and 3 below are met:**

1. Requires treatment failure with or intolerance to two preferred IG products. AND
2. Coverage for Cuvitru and HyQvia is provided when used for FDA-approved indications only. AND
3. Requires one of the following criteria below:

   a. **Acquired Factor VIII inhibitor when conventional therapy is ineffective or not tolerated.**
      Examples of conventional therapy include, but are not limited to, immunosuppressive therapy with cyclophosphamide, steroids, or azathioprine.

   b. **Allogeneic bone marrow transplant recipients who are ≥ 20 years of age for up to 4 months following transplantation.**

   c. **Autoimmune encephalitis and when patient meets all the criteria below**
      i. Cerebral spinal fluid (CSF) antibody testing, electroencephalography (EEG) testing and a brain magnetic resonance image (MRI) has been done to rule out other causes
      
      ii. Other conditions have been ruled out

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d. Autoimmune hemolytic anemia (AIHA) when patient is diagnosed with warm type AIHA that does not respond to alternative therapies. Examples of alternative therapies include, but are not limited to, steroids, immunosuppressive agents, plasmapheresis, rituximab and/or splenectomy.

e. Dermatomyositis, documented with EMG abnormalities and/or increased CPK levels, with associated severe disability, when other interventions are ineffective or not tolerated. Other therapy interventions include, but are not limited to, corticosteroid therapy and immunosuppressive therapy with azathioprine, methotrexate, or cyclophosphamide.

f. Fetal alloimmune thrombocytopenia with documented diagnosis.

g. HIV infected children (< 13 years of age) when the CD4 cell count is greater than 200/mm³.

h. Hypogammaglobulinemia (acquired, secondary) associated with either chronic B-cell lymphocytic leukemia (CLL) or post allogeneic bone marrow transplant with laboratory findings (low serum IgG and/or patients with poor IgG response to the pneumococcal vaccine) and a history of recurrent infections.

i. Hypogammaglobulinemic neonates (infectious disease prophylaxis) with low birth weight (less than 1500g) or in a setting with high baseline infection rate or morbidity.

j. Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome. IVIG can be used as an alternative to plasma exchange in patients who meet one of criteria 1 through 4 below:
   i. Deteriorating pulmonary function tests. OR
   ii. Rapid deterioration with symptoms for less than 2 weeks. OR
   iii. Rapidly deteriorating ability to ambulate. OR
   iv. Inability to walk independently for 10 meters.

k. Inflammatory demyelinating polyneuropathy (chronic; CIDP) meeting all of criteria a, b, and c below:
   i. Significant functional disability. AND
   ii. Documentation of slowing of nerve conduction velocity on EMG/NCS. AND
   iii. Documentation of elevated spinal fluid protein on lumbar puncture or an MRI confirming the diagnosis.

l. Idiopathic thrombocytopenia purpura (ITP; acute), when a rapid increase in platelet count is necessary, such as in an acute bleeding episode or prior to surgery.

m. ITP (chronic), when the platelet count is dangerously low (e.g., platelet count less than 30,000 cells/mm³ in children, and less than 20,000 cells/mm³ in adults) for patients concurrently receiving corticosteroids.

n. ITP in pregnancy, when:
   i. Refractory to steroids with platelet counts less than 10,000/mm³ in the third trimester
   OR
   ii. Platelet counts less than 30,000/mm³ associated with bleeding before vaginal delivery or C-section.
   iii. Pregnant women who have developed autoimmune thrombocytopenia during a

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previous pregnancy.

iv. Pregnant women who have platelet counts less than 50,000/mm$^3$ during the current pregnancy

OR

v. Pregnant women with a past history of splenectomy.

o. Kawasaki syndrome during the first ten days of diagnosis.

p. Lambert-Eaton myasthenic syndrome when other treatment options are ineffective or not tolerated. Examples of other treatment options include, but are not limited to, pyridostigmine bromide, azathioprine, and prednisone.

q. Multifocal motor neuropathy (MMN) in patients with conduction block and appropriate testing (example: anti-GM1 antibodies).

r. Multiple myeloma in patients with stable disease and a high risk of recurrent infections despite prophylactic antibiotic therapy, patients with poor IgG response to the pneumococcal vaccine, or have low normal IgG levels during acute sepsis episodes.

s. Myasthenia gravis for the treatment of acute severe decompensation (e.g., respiratory failure, swallowing difficulties) or chronic decompensation, when other treatments are ineffective or not tolerated. Other treatment options include, but are not limited to, plasmapheresis, pyridostigmine, and immunosuppressive therapy such as azathioprine, cyclosporine, and cyclophosphamide.

t. Pediatric intractable epilepsy in candidates for surgical resection or when other interventions are ineffective or not tolerated. Examples of other interventions include, but are not limited to, anticonvulsant medications, ketogenic diets, and steroids.

u. Polymyositis in patients with severe active illness when other interventions have been ineffective or not tolerated. Other therapy interventions include, but are not limited to, corticosteroid therapy and immunosuppressive therapy with azathioprine, methotrexate, or cyclophosphamide.

v. Post-transfusion purpura in severely affected patients.

w. Primary humoral immunodeficiency diseases: A baseline IgG level is needed along with the laboratory findings specified below prior to the initiation of immune globulin for newly diagnosed primary humoral immunodeficiency diseases:

i. X-linked agammaglobulinemia (congenital agammaglobulinemia) diagnosis accompanied by marked deficits or absence of all five immunoglobulin classes (IgG, IgM, IgA, IgE, and IgD), decreased circulating B lymphocytes, and normal numbers of functioning T lymphocytes.

OR

ii. Hypogammaglobulinemia (a general term describing serum levels of IgG which are below the lower limits of normal).

a) Member has unexplained recurrent or persistent severe bacterial infections despite adequate treatment, including all of the following:

1. Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis, etc);
2. Prophylactic antibiotics;
3. Increased vigilance and appropriate antibiotic therapy for infections; and
4. Immunization with conjugate vaccines in patients who have not responded to polysaccharide vaccines.
iii. Common variable immunodeficiency (CVID); acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia documented with low to normal IgG levels and the inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax).

iv. Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM) accompanied by very low serum concentrations of IgG, IgA, and IgE, with normal or, more frequently, greatly elevated polyclonal IgM concentrations.

v. Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, accompanied by marked deficits in IgG, IgA and IgM, low lymphocyte counts, and absent or below normal levels of both B- and T- lymphocytes.

x. Pure red cell aplasia with documented parvovirus B19 infection and severe anemia.

y. Refractory pemphigus foliaceus resistant to conventional treatments, until conventional treatment takes effect. Conventional treatments include, but are not limited to immunosuppressive agents and plasmapheresis.

z. Solid organ transplant in the treatment of antibody-mediated rejection:
   i. Prior to solid organ transplant, when patient is at high risk for antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ. OR
   ii. Following solid organ transplant.

aa. Stiff-Person Syndrome when treatment with other agents is ineffective or not tolerated. Examples of other treatment options include, but are not limited to, diazepam, baclofen, clonazepam, valproic acid, and clonidine.

bb. (For GamaSTAN only) – Prophylactic post exposure for Hepatitis A, Measles (Rubeola), Varicella, and Rubella (in early pregnancy).

B. Administration, Quantity Limitations, and Authorization Period:
   a. BCBSM/BCN does not consider intravenous immune globulins to be self-administered medications and is covered under the medical benefit. Subcutaneously administered IVIG may be considered under the pharmacy benefit.

   b. When prior authorization is approved immune globulins may be authorized for the period defined in Table 1. Please note the frequency of administration does not apply to all patients. Depending on response to therapy, there is a small set of patients that will require more frequent administrations. One treatment course where the total dose is administered over a period of more than 1 day will be allowed (ex: the usual IVIG dose of CIDP is 400 mg/kg/day for 5 days for a total of 2 g/kg/day).

   c. When prior authorization is approved immune globulins may be authorized at the usual doses listed in Table 2. Initial dosing will be approved at the lower end of the dose range. Increase in dose and dosing interval will be authorized based on indication and literature support of the dose/dosing interval. Authorization shall be reviewed at least annually to confirm that current medical necessity criteria for the
following conditions in Table 1 are met.

d. Subcutaneous administration of immune globulin is considered an alternative to intravenous administration of immune globulin and may be considered medically necessary when one of the criteria in Section I is met.

e. Coverage for HyQvia is authorized for every four week dosing interval after the ramp-up period unless the four week dosing interval is ineffective or not tolerated.

C. IVIG is considered investigational when used for all other conditions, including, but not limited to:

1. Acute lymphocytic leukemia
2. Acute renal failure
3. Adrenoleukodystrophy
4. Adult HIV infection
5. Alzheimer's disease
6. Aplastic anemia
7. Asthma
8. Atopic dermatitis
9. Autism
10. Behçet's syndrome (Behçet’s disease)
11. Cardiomyopathy, recent-onset dilated
12. Chronic fatigue syndrome
13. Clostridium difficile, recurrent
14. Cystic fibrosis
15. Diabetes
16. Diamond-Blackfan anemia
17. Endotoxemia
18. Heart block, congenital
19. Hemolytic anemia
20. Hemolytic transfusion reaction
21. Hemophagocytic syndrome
22. Human T-lymphocyte virus-1 myelopathy
23. Hyper IgE syndrome
24. Immune mediated neutropenia
25. Inclusion body myositis
26. Infectious disease in high risk neonates and adults following surgery or trauma
27. Lumbosacral plexopathy
28. Miller-Fisher syndrome
29. Motor neuron syndromes
30. Multiple sclerosis
31. Narcolepsy/catataplexy
32. Neonatal hemochromatosis
33. Neonatal hemolytic disease
34. Nephropathy, membranous
35. Nephrotic syndrome
36. Neuromyelitis optica
37. Nonimmune thrombocytopenia
38. Ophthalmopathy, euthyroid
39. Opsoclonus myoclonus
40. Otitis media, recurrent

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41. Paraproteinemic neuropathy
42. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
43. Polyneuritis
44. Post-polio syndrome
45. Recurrent spontaneous pregnancy loss-abortion
46. Rheumatoid arthritis
47. Sinusitis, chronic
48. Stevens-Johnson Syndrome
49. Still’s Disease
50. Surgery or trauma
51. Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)
52. Thrombotic Thrombocytopenic Purpura, neonatal autoimmune–severe thrombocytopenia (TTP)
53. Thrombotic Thrombocytopenic Purpura, refractory to platelet transfusions (TTP)
54. Tic disorder (DSM-IV)
55. Toxic epidermal necrolysis
56. Urticaria, delayed pressure
57. Uveitis
58. Vasculitic syndromes, systemic
59. Von Willebrand’s syndrome
60. Wegener’s granulomatosis

a. Requests for use of IVIG in non-FDA approved indications must include documentation of a trial and failure of standard therapies for that diagnosis when applicable.

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.
<table>
<thead>
<tr>
<th>Indications</th>
<th>Frequency</th>
<th>Authorization Duration</th>
<th>Reauthorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired Factor VIII inhibitor</td>
<td>One treatment per month</td>
<td>2 weeks</td>
<td>3 months</td>
</tr>
<tr>
<td>Allogeneic bone marrow transplant</td>
<td>On days 7 and 2 prior to transplant, then once weekly for up to 90 days (total therapy duration of 97 days)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia (warm type)</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>Fetal alloimmune thrombocytopenia (FAIT)</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>HIV + children (&lt; 13 years)</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypogammaglobulinemia, acquired, associated with chronic B-cell lymphocytic leukemia or post allogeneic bone marrow transplant</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypogammaglobulinemia neonates (infectious disease prophylaxis)</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome</td>
<td>One treatment per month</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Inflammatory demyelinating polyneuropathy (chronic; CIDP)</td>
<td>One treatment per month</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>ITP (acute)</td>
<td>Up to 4 doses given every other day</td>
<td>X</td>
<td>No</td>
</tr>
<tr>
<td>Indication</td>
<td>Frequency</td>
<td>Authorization Duration</td>
<td>Reauthorization</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>ITP (chronic)</td>
<td>One treatment per month</td>
<td>2 week, 3 months, 6 month</td>
<td>Yes</td>
</tr>
<tr>
<td>ITP in pregnancy</td>
<td>One treatment per month</td>
<td>6 month</td>
<td>Yes</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>One treatment given within 10 days of symptom onset.</td>
<td>2 week, 3 months, 6 month</td>
<td>No</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>One treatment per month</td>
<td>6 month, 1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>One treatment per month</td>
<td>6 month, 1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>One treatment per month</td>
<td>6 month, 1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Myasthenia gravis (acute and chronic)</td>
<td>One treatment per month</td>
<td>6 month, 1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Pediatric intractable epilepsy</td>
<td>One treatment per month</td>
<td>6 month, 1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>One treatment per month</td>
<td>6 month</td>
<td>Yes</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>One or two treatments</td>
<td>6 month</td>
<td>No</td>
</tr>
<tr>
<td>Primary humoral immunodeficiency diseases</td>
<td>One treatment per month</td>
<td>6 month, 1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>One treatment per month</td>
<td>6 month</td>
<td>Yes</td>
</tr>
<tr>
<td>Refractory pemphigus foliaceus</td>
<td>One treatment per month</td>
<td>6 month</td>
<td>No</td>
</tr>
<tr>
<td>Indication</td>
<td>Frequency</td>
<td>Authorization Duration</td>
<td>Reauthorization</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------</td>
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</tr>
<tr>
<td>Solid organ transplant</td>
<td>Up to 4 doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant.</td>
<td>2 week</td>
<td>X</td>
</tr>
<tr>
<td>Stiff-Person Syndrome</td>
<td>One treatment per month</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>One treatment per month</td>
<td>6 months</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Once for &lt; 3 month stay in endemic region. Repeat every 4 to 6 months for &gt; 3 month stay in endemic region</td>
<td>1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Measles (Rubeola)</td>
<td>Once post suspected exposure if fewer than 6 days previously</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Varicella</td>
<td>Once immediately post exposure</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Rubella (in early pregnancy)</td>
<td>Once</td>
<td></td>
<td>Yes</td>
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<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Acquired Factor VIII inhibitor</td>
<td>1000 mg/kg for 2 days OR 400 mg/kg for 5 days</td>
</tr>
<tr>
<td>Allogeneic bone marrow transplant</td>
<td>500 mg/kg on day 7 and day 2 prior to transplantation and then once weekly thereafter for 90 days after transplantation</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia (warm type)</td>
<td>400 mg/kg/day for 5 days</td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td>400 mg/kg/day for 5 days</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>2000 mg/kg every month</td>
</tr>
<tr>
<td>Fetal alloimmune thrombocytopenia (FAIT)</td>
<td>1000 mg/kg every week, 2gm/kg/week in refractory cases</td>
</tr>
<tr>
<td>HIV + children (&lt; 13 years)</td>
<td>400 mg/kg every 4 weeks</td>
</tr>
<tr>
<td>Hypogammaglobulinemia, acquired, associated with chronic B-cell lymphocytic leukemia or post allogeneic bone marrow transplant</td>
<td>400mg/kg IV every 4 weeks</td>
</tr>
<tr>
<td>Hypogammaglobulinemic neonates (infectious disease prophylaxis)</td>
<td>400 - 600mg/kg/month, administered as a single dose, or up to several months in duration</td>
</tr>
<tr>
<td>Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome</td>
<td>400 mg/kg/day for 5 days</td>
</tr>
<tr>
<td>Inflammatory demyelinating polyneuropathy (chronic; CIDP)</td>
<td>Loading dose: 2000 mg/kg, given in divided doses over 2 to 4 consecutive days Maintenance dose: 1000 mg/kg every 3 weeks OR 500 mg/kg/day, for 2 consecutive days every 3 weeks 400 mg/kg/5 days, repeated every 6 weeks</td>
</tr>
<tr>
<td>ITP (acute)</td>
<td>1000 mg/kg/day for 2 consecutive days OR 400 mg/kg once daily for 2-5 consecutive days</td>
</tr>
<tr>
<td>ITP (chronic)</td>
<td>1 – 2 gm/kg as a single dose or divided into equal amounts and given over 2-5 days</td>
</tr>
<tr>
<td>ITP in pregnancy</td>
<td>400 mg/kg/day for 5 days</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>2000mg/kg as a single dose OR 400 mg/kg/day for 4 days</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>2000 mg/kg administered over 2-5 days</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>2000 mg/kg/month, administered over 2-5 days</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>400 mg/kg every month</td>
</tr>
<tr>
<td>Myasthenia gravis (acute and chronic)</td>
<td>1-2 gm/kg/month IV, given over 2 to 5 days</td>
</tr>
<tr>
<td>Pediatric intractable epilepsy</td>
<td>2000 mg/kg over 4 days followed by 1000 mg/kg over 2 days every month for 6 months</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>2000 mg/kg/month given over 2 to 5 days</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>500 mg/kg/day for 2 consecutive days</td>
</tr>
<tr>
<td>Primary humoral immunodeficiency diseases</td>
<td>100 – 800 mg/kg /month</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>400 mg/kg/day for 5-10 days OR 1000 mg/kg/day for 3 days</td>
</tr>
<tr>
<td>Refractory pemphigus foliaceus</td>
<td>1-2 gm/kg over 3 days every 4 weeks</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>2000 mg/kg/month for 4 months</td>
</tr>
<tr>
<td>Stiff-Person Syndrome</td>
<td>400 mg/kg/day for 3 - 5 days</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>400 mg/kg/day for 5 days</td>
</tr>
</tbody>
</table>

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D. Background Information

FDA-Labeled Indications
1. Primary humoral immunodeficiency diseases
2. HIV-infected children < 13 years of age
3. Allogenic bone marrow transplant (BMT)
4. Chronic B-Cell Lymphocytic Leukemia (CLL)
5. Idiopathic thrombocytopenia purpura (ITP)
6. Kawasaki syndrome
7. Multifocal motor neuropathy

E. Clinical Efficacy
a. FDA-Labeled Indications
1. Primary humoral immunodeficiency diseases
   • X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life.
   • Common variable immunodeficiency (CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia) is characterized by low to normal IgG levels and inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax). Most patients experience severe recurrent and/or chronic infections.
   • Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, are rare, inherited syndromes.
   • Immunoglobulin reference ranges vary depending on the age of the patient and the particular assay method used. The usual immune globulin maintenance dose is 100-800mg/kg/month and therapy is usually life-long.
   • A serum IgG level should be drawn every 3 months, before infusion, and IVIG dose adjusted accordingly.
   • Serum trough levels should be maintained at 400 – 600 mg/dL. Documentation of the rationale should be provided in the event that a trough level greater than 600 mg/dL is required. [Medicare]
   • HyQvia has not been studied for use in indications other than Primary Immunodeficiency in adults. Safety has not been established in children.
   • Cuuvitru has not been studied for use in indications other than primary Immunodeficiency in adults and pediatric patients two years of age and older.
   • When IGHy (HyQvia) or IVIG was administered at 3- or 4-week treatment intervals, serum IgG trough levels were similar, regardless of the administration route (IGHy or IGIV) or patient age.
2. HIV-infected children < 13 years of age
   • IVIG has been shown to decrease the frequency of bacterial infections, increase the time free from serious bacterial infections, and decrease the frequency of hospitalization in children with AIDS.
   • There is no evidence to suggest that IVIG gives incremental benefit to antiretroviral therapy and prophylactic antibiotics.
   • In children with advanced HIV disease who are receiving zidovudine, IVIG decreases the risk of serious bacterial infections. However, this benefit is apparent only in children who are not receiving co-trimoxazole as prophylaxis and for children with a CD4 count of greater than 200 to 400 per mm3.
   • The recommended dose is 400 mg/kg/month to maintain the serum IgG level.
3. Allogenic bone marrow transplant (BMT)

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• **IVIG is safe and effective in reducing the incidence and severity of infections and graft-vs.-host disease in allogeneic BMT recipients greater than 20 years old**
• **Mortality after 100 days is unaffected by IVIG.**
• **Little to no benefit is apparent among younger patients or in autologous transplants.**
• **The usual dosage is 500 mg/kg administered on day 7 and day 2 prior to transplantation and then once weekly thereafter. Therapy generally continues for 90 days after the transplant.**

4. **Chronic B-Cell Lymphocytic Leukemia (CLL) with hypogammaglobulinemia**
   - **IVIG therapy reduces the incidence of bacterial infections to approximately 50% of the incidence without IVIG administration.**
   - **Monthly IVIG infusions of 400 mg/kg are recommended to maintain the serum IgG level.**

5. **Idiopathic thrombocytopenia purpura (ITP)**
   - **Normal platelet count range is 115,000/mm³ to 440,000/mm³.**
   - **Acute ITP**
     - In various studies, 64% to 100% of IVIG recipients attained platelet counts greater than 100,000 cells/mm³ within 7 days.
       - A maximum of 1 gm/kg/day for three or four doses of IVIG on alternate days is recommended.
       - Acute ITP is usually seen in children and typically resolves spontaneously within 2 months.
   - **Chronic ITP**
     - Current evidence does not support that IVIG alters the natural course of chronic ITP, affects long-term morbidity/mortality, or increases the rate of long-term remission.
     - IVIG is not indicated for the maintenance of platelet counts in chronic ITP.
     - Steroids and/or splenectomy are considered the first-line treatment of choice for chronic ITP.
     - IVIG may be considered in patients with dangerously low platelet counts (less than 10,000 to 20,000 per mm³ in adults or less than 30,000 per mm³ in children), and therefore may be at an increased risk for significant bleeding, such as intracranial hemorrhage.
     - The usual dose of IVIG is 1 to 2 gm/kg divided into equal amounts and given over 2 to 5 days.

6. **Kawasaki syndrome**
   - **IVIG in conjunction with aspirin given within the first 10 days of illness can reduce the incidence of coronary artery abnormalities by 65% - 78%, compared with treatment with aspirin alone. IVIG is not effective if more than ten days have elapsed from onset of symptoms.**
   - The usual dose of IVIG is 2 gm/kg as a single dose, or 400 mg/kg daily for 4 days.

7. **Multifocal motor neuropathy**
   - **Small controlled trials demonstrate significant increase in muscle strength associated with IVIG administration, long-term benefits, and safety.**
   - **Baxter International's Gammagard Liquid is the first immunoglobulin treatment FDA approved for MMN patients in the United States, June 2012.**
   - **The recommended IVIG dose is 2 gm/kg/month, administered over 2 – 5 days.**

**b. Off-Label Indications**

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1. Acquired Factor VIII inhibitor
   - A sufficient treatment course is usually 6-12 weeks before attempting a different
     immunosuppressive agent. Patients are generally treated until remission (elimination of
     the inhibitor) occurs, which may take several months.
   - Treatment regimens of 1 gm/kg for 2 days or 400 mg/kg for 5 days have been studied.
     In one study, only 6 of 19 patients responded to IVIG within 40 days of treatment.

2. Autoimmune encephalitis
   - Evidence for the effectiveness of IVIG in autoimmune encephalitis comes from one large systematic
     review by Nosadini et al 2015.
   - IVIG when used in combination with other immunomodulatory treatments has better outcomes
     compared to patients with no immunotherapy.
   - The usual dose of IVIG is 0.4 gm/kg/day for 5 days and subsequent replacement of IVIG is usually
     considered at 3 to 4 weeks.

3. Autoimmune hemolytic anemia
   - In a retrospective study of 73 patients, a response was observed in 40% of cases, only
     15% achieving hemoglobin levels of 10 g/dL or greater; children were more likely to
     respond (54%).
   - In a recent guideline, high-dose immunoglobulin was not recommended for use in
     AIHA, except under certain life-threatening circumstances.

4. Dermatomyositis
   - High-dose IVIG is a safe and effective treatment for refractory dermatomyositis
     unresponsive to corticosteroid therapy.
   - The recommended IVIG dose is 2 gm/kg per month.

5. Fetal alloimmune thrombocytopenia
   - ACOG guidelines recommend IVIG as first line treatment for documented fetal
     thrombocytopenia.
   - A trial comparing IVIG treatment with and without dexamethasone in siblings showed
     that:
     - IVIG treatment was associated with an increase in mean platelet count of 69,000/mm$^3$.
     - There were no instances of intracranial hemorrhages, although hemorrhage had
       occurred previously in 10 untreated siblings.
   - The recommended dose of IVIG is 1 gm/kg/week, increasing to 2 gm/kg/week in
     refractory cases.

6. Hypogammaglobulinemic neonates
   - Treatment with IVIG is usually reserved for patients with recurrent severe infections, not
     responding to antibiotic prophylaxis.
   - The usual IVIG dose is 400 – 600 mg/kg/month, administered as a single dose, or up to
     several months in duration.

7. Inflammatory demyelinating polyneuropathy (IDP)
   - Acute IDP, including Guillain-Barré syndrome
     - The American Academy of Neurology recommends the use of IVIG in
       non ambulant adult patients with Guillain-Barré syndrome within 2 – 4
       weeks of neuropathic symptom onset.
     - The recommended IVIG dose is 400 mg/kg/day for 5 days. If relapse
       occurs within 1-2 weeks of initial therapy, an additional treatment course
       of IVIG may be effective. Further treatment does not improve outcomes
       and is not recommended.
   - Chronic IDP
     - Treatment options include plasmapheresis, IVIG, and corticosteroids.
8. ITP in pregnancy
- The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia.
- Platelet function is typically normal so it is not necessary to maintain platelet count in the normal range.
- The first line of treatment is prednisone, usual dose 1-2mg/kg/day.
- IVIG is useful in cases that are resistant to steroids and when a rapid rise in platelets is necessary. A response typically occurs within 6 – 72 hours of IVIG treatment.

9. Lambert-Eaton myasthenic syndrome (LEMS)
- LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes.
- Patients reported improved limb, respiratory muscle, and bulbar muscle strength with IVIG, compared to placebo in a small randomized crossover trial (n = 9).
- The recommended dose of IVIG is 2 gm/kg administered over 2 – 5 days.

10. Myasthenia gravis
- Randomized trials examining short-term treatment of myasthenia gravis with IVIG have shown no difference between IVIG and plasma exchange or IVIG and methylprednisolone.
- IVIG may be useful in treating patients with severe myasthenia gravis who fail to respond to the maximum tolerated doses of corticosteroids and/or immunosuppressants.
- There is no evidence to determine whether IVIG improves function or reduces steroid requirements for moderate to severe myasthenia gravis.
- The recommended dose of IVIG is 1 – 2 gm/kg/month administered over 2–5 days.

11. Pediatric epilepsy
- The efficacy was evaluated in a retrospective, multicenter study comprising 64 consecutive patients treated with immunoglobulins for either epileptic encephalopathy or refractory epilepsy.
- Nine patients (14%) demonstrated complete resolution and 10 (15.6%) exhibited partial improvement. Of these 19 responders (29.7%), eight relapsed.
- Although intravenous immunoglobulin is not suitable for all cases of epilepsy, it may prove efficacious for specific epileptic syndromes.

12. Polymyositis
- Polymyositis is an inflammatory myopathy with no unique clinical features. It is typically a diagnosis of exclusion in patients with slowly progressive muscle weakness.
- Traditional therapies include immunosuppressive medications or steroids.
- The recommended dose of IVIG is 2 gm/kg/month administered over 2–5 days.

13. Post-transfusion purpura
- Post-transfusion purpura is a rare condition that can occur in patients undergoing blood transfusions. It typically develops approximately one-week after blood transfusion.
- IVIG may be considered first-line therapy in severely affected patients.
- The recommended dose of IVIG is 500 mg/kg/day for two consecutive days.
- Rapid platelet recovery has been seen within days of treatment.

14. Pure red cell aplasia
- Parvovirus B19 infects and lyases red cell precursors, which can cause pure red cell aplasia. IVIG therapy is usually reserved for patients with chronic parvovirus infection.
and chronic anemia.

- Chronic parvovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parvovirus and anemia may spontaneously resolve.
- The usual dose of IVIG is 400 mg/kg/day for 5 – 10 days or 1 gm/kg/day for 3 days. Initial treatment courses may be indicated with recurrence of anemia and increase in parvovirus B19 DNA.

15. Refractory pemphigus foliaceus
- IVIG is typically given in combination with conventional treatments, such as immunosuppressive agents and plasmapheresis, and is discontinued once conventional treatment takes effect. IVIG is not considered a maintenance therapy for pemphigus foliaceus.
- The usual dose of IVIG is 1-2 gm/kg administered over 3 days. This regimen may be repeated every 3-4 weeks.

16. Solid organ transplant
- Antibody-mediated rejection (AMR) is a potential cause of acute organ rejection after transplant. Pre-treatment with IVIG (desensitization) may reduce the risk of AMR.
- A randomized, double-blind trial comparing IVIG to placebo in 101 highly sensitized renal transplant candidates concluded that IVIG is better than placebo in improving transplantation rates.
- A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant.

17. Stiff Person Syndrome
- Sixteen patients were randomized to IVIG or placebo for 3 months, then crossed over to the alternate treatment after a 1 month washout period. IVIG patients demonstrated decreased stiffness scores, decreased frequency of falls, ability to walk more easily without assistance, and improved ability to perform work-related tasks. Benefits lasted 6 weeks to 1 year without additional treatment.
- The usual dose of IVIG is 400 mg/kg/day for 3 – 5 days.

18. Systemic Lupus Erythematosus
- Small case series suggest some benefit from treatment with IVIG when compared to cyclophosphamide.
- The usual dose of IVIG is 400 mg/kg/day for 5 days.

c. Investigational Conditions
The University Hospital Consortium (UHC), an alliance of 68 academic health centers, performed a critical assessment of off-label IVIG uses.
The UHC determined published data to be inadequate to support the use of IVIG in various conditions.

1. Asthma:
   - Further trials in asthma patients are necessary to delineate patient subsets that would best benefit from IVIG therapy, and define optimal dosing in this condition.

2. HIV
   - The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes.

3. Multiple sclerosis
   - Progressive: There is not substantial evidence to support IVIG in the treatment of chronic progressive multiple sclerosis.
4. **Opsoclonus-myoclonus**
   - A rare neurological syndrome characterized by an unsteady gait, brief shock-like muscle spasms, and irregular rapid eye movements.
   - Evidence supporting the use of IVIG in this condition consists of retrospective chart reviews and case reports. However, a randomized phase II trial is currently investigating the use of IVIG in treating children with opsoclonus-myoclonus associated with neuroblastomas.

5. **Post-Polio**
   - Two published trials of post-polio syndrome failed to demonstrate a statistically significant benefit compared to placebo in improvement of muscle strength.

6. **Recurrent pregnancy loss or recurrent spontaneous abortion: due to anti-phospholipid or anti-cardiolipin antibodies**
   - Recurrent pregnancy loss is defined as three or more pregnancies resulting in spontaneous abortion prior to 20 weeks of gestational age. These women often have immunologic abnormalities, particularly antiphospholipid antibodies.
   - IVIG has not been established as a safe or effective therapy to prevent recurrent spontaneous abortion in women with immunologic abnormalities, such as elevated natural killer cells, defective cytokines, or defective growth factors.
   - One randomized controlled trial comparing IVIG to thyroid replacement therapy for the prevention of miscarriages found IVIG to be less effective. There was a statistically significant higher rate of live birth among women treated with thyroid replacement therapy.
   - A small randomized controlled trial in 85 women with a history of three or more spontaneous abortions before 10 weeks of gestation compared low molecular heparin (LMW) plus aspirin with IVIG therapy. The percentage of live births in the LMW plus aspirin versus the IVIG treatment group was 72.5% and 39.5%, respectively.
   - A randomized controlled trial in 82 women with a history of idiopathic secondary miscarriage compared live birth rates in those who received intravenous immune globulin versus placebo infusion (saline). There was no statistical difference between treatment groups.
   - ACOG recommendations state:
     - If results are positive for the same antibody on two consecutive tests 6 to 8 weeks apart, initiate heparin and low-dose aspirin with next pregnancy attempt.
     - IVIG is not effective in preventing recurrent pregnancy loss.

7. **Alzheimer’s Disease**
   - A small sample of four patients received intravenous immune globulin (IVIG) treatment at a dose of 0.4 g/kg every two weeks and showed no further cognitive decline in patients with Alzheimer's disease.

8. **Additional conditions for which published data is determined to be inconclusive or inadequate to support the use of IVIG include Alzheimer’s disease, atopic dermatitis, recurrent *C. difficile*, narcolepsy/cataplexy, neonatal hemochromatosis, chronic sinusitis, tic disorder, delayed...**
F. Dosing Considerations and Therapeutic Levels

1. A plasma IgG level of 200 mg/dL is often a common minimum target for patients being considered for IVIG replacement therapy.

2. In patients with mild to moderate IgG deficiency with levels of 300 mg/dL-400mg/dL, the decisions to treat are based on clinical symptoms and antigenic challenge.

3. Dosing adjustment in replacement therapy is based on clinical response and IgG levels.

4. The minimum serum concentration of IgG necessary for protection has not been firmly established. However, maintenance of serum trough IgG levels above 500 mg/dL has been considered a sufficient target to prevent most systemic infections. Some patients may require an IgG level of 400-500 mg/dL above their baseline value for protection.

5. In patients with severe hypogammaglobulinemia or agammaglobulinemia, IgG levels (trough) should be checked every three to six months in growing children and every six to twelve months in adults.

6. The trough or steady state IgG level is obtained before scheduled infusions and frequently guides IVIG dose selection.

References


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