

**Regence BlueCross BlueShield of Oregon • Regence BlueShield  
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**Medication Policy Manual**

**Policy No:** dru020

**Topic:** Immune Globulin Replacement Therapy (IVIG, SQ) **Date of Origin:** January 1996

- Carimune<sup>®</sup> NF
- Flebogamma<sup>®</sup>
- Gamastan<sup>®</sup>
- Gammagard S/D<sup>®</sup>
- Gammaplex<sup>®</sup>
- Gamunex<sup>®</sup>
- Iveegam<sup>®</sup>
- Privigen<sup>®</sup>
- Octagam<sup>®</sup>
- Vivaglobin<sup>®</sup> (only available SQ)

**Revised/Effective Date:** May 8, 2009

**Next Review Date:** May 8 2010

**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Intravenous immune globulin (IVIG) and subcutaneous immune globulin (Vivaglobin<sup>®</sup>) are preparations containing antibodies purified from human blood. They are used in the treatment of many different conditions resulting from immune deficiencies.

## Policy/Criteria

**I.** Most contracts require prior authorization approval of immune globulins prior to coverage. Immune globulins may be considered medically necessary when the following criteria below are met.

**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.

**OR**

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

**OR**

**C.** 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, and/or splenectomy. <sup>[45]</sup>

**OR**

**D.** Dermatomyositis, documented with EMG abnormalities and/or increased CPK levels, with associated severe disability, when steroid therapy is ineffective or not tolerated.

**OR**

**E.** Fetal alloimmune thrombocytopenia with documented diagnosis.

**OR**

**F.** HIV infected children (< 13 years of age) when the T4 cell count is greater than 200/mm<sup>3</sup>. <sup>[3]</sup>

**OR**

**G.** Hypogammaglobulinemia (acquired) associated with either chronic B-cell lymphocytic leukemia or post allogeneic bone marrow transplant and documented with laboratory findings (serum IgG).

**OR**

**H.** Hypogammaglobulinemic neonates (infectious disease prophylaxis) with low birth weight (less than 1500g) or in a setting with high baseline infection rate or morbidity. <sup>[1]</sup>

**OR**

**I.** 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:

1. Deteriorating pulmonary function tests.

**OR**

2. Rapid deterioration with symptoms for less than 2 weeks.

**OR**

3. Rapidly deteriorating ability to ambulate.

**OR**

4. Inability to walk independently for 10 meters.

**OR**

**J.** Inflammatory demyelinating polyneuropathy (chronic; CIDP) meeting all of criteria 1, 2, and 3 below:

1. Significant functional disability.

**AND**

2. Documentation of slowing of nerve conduction velocity on EMG/NCS.

**AND**

3. Documentation of elevated spinal fluid protein on lumbar puncture or a nerve biopsy confirming the diagnosis.

**OR**

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

**OR**

- L. ITP (chronic), when the platelet count is dangerously low (e.g., platelet count less than 30,000 cells/mm<sup>3</sup> in children, and less than 20,000 cells/mm<sup>3</sup> in adults).

**OR**

- M. ITP in pregnancy, when:

1. Refractory to steroids with platelet counts less than 10,000/mm<sup>3</sup> in the third trimester; <sup>[44]</sup>

**OR**

2. Platelet counts less than 30,000/mm<sup>3</sup> associated with bleeding before vaginal delivery or C-section; <sup>[44]</sup>

**OR**

3. Pregnant women who have developed autoimmune thrombocytopenia during a previous pregnancy; <sup>[44]</sup>

**OR**

4. Pregnant women who have platelet counts less than 50,000/mm<sup>3</sup> during the current pregnancy; <sup>[44]</sup>

**OR**

5. Pregnant women with a past history of splenectomy. <sup>[44]</sup>

**OR**

- N. Kawasaki syndrome during the first ten days of diagnosis.

**OR**

- O.** 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.

**OR**

- P.** Multifocal motor neuropathy in patients with anti-GM1 antibodies and conduction block.

**OR**

- Q.** Multiple myeloma in patients with stable disease and 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.<sup>[16]</sup>

**OR**

- R.** 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.

**OR**

- S.** 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.

**OR**

- T.** 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/or immunosuppressive therapy with azathioprine, methotrexate, or cyclophosphamide.

**OR**

- U.** Post-transfusion purpura in severely affected patients.
- V.** 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 such as:

1. 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**

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

**OR**

3. 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).

**OR**

4. 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.

**OR**

5. 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.

**OR**

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

**OR**

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

**OR**

- Y. Solid organ transplant in the treatment of antibody-mediated rejection:

1. 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**

2. Following solid organ transplant.

**OR**

- Z. 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.

**OR**

- AA. Systemic lupus erythematosus for severe active disease when other interventions are ineffective or not tolerated. Other interventions include, but are not limited to corticosteroids and immunosuppressive agents, such as cyclophosphamide or azathioprine.

## **II. Administration, Quantity Limitations, and Authorization Period**

- A. Regence does not consider immune globulins to be self-administered medications.
- B. When prior authorization is approved immune globulins may be authorized for the period defined in Table 1.
- C. Authorization shall be reviewed at least annually to confirm that current medical necessity criteria for the following conditions in Table 1 are met:

**TABLE 1**

Indication	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	2 weeks	3 months	6 months	1 year	Yes/No	Criteria
Acquired Factor VIII Inhibitor	One treatment per month			X		Yes	Documented initial response to IVIG and continued presence of Factor VIII inhibitor
Allogeneic bone marrow transplant	On days 7 and 2 prior to transplant, then once weekly for up to 90 days (total therapy duration of 97 days)			X		Yes	Reauthorization may be considered under hypogammaglobulinemia criteria
Autoimmune hemolytic anemia (warm type)	One treatment per month.			X		Yes	Documented initial response to IVIG and recurrence of clinically significant, symptomatic anemia.
Dermatomyositis	One treatment per month.		X			Yes	Objective evidence of efficacy of initial three-month treatment, such as improvement in muscle strength or decreased CPK levels.
Fetal alloimmune thrombocytopenia (FAIT)	One treatment per week.			X		Yes	Documented previous history of FAIT. Treatment not to exceed the duration of pregnancy.
HIV+ children (< 13 years)	One treatment per month.				X	Yes	Documentation of clinical improvement.
Hypogammaglobulinemia, acquired, associated with chronic B-cell lymphocytic leukemia or post allogeneic bone marrow transplant	One treatment per month.			X		Yes	Documentation of clinical improvement and current IgG levels that are in the low to normal range. Consideration of up to 1 year of therapy based on clinical benefit.
Hypogammaglobulinemic neonates (infectious disease prophylaxis)	One treatment per month.			X		Yes	Documentation of clinical improvement and current IgG levels that are in the low to normal range.

**TABLE 1 (Continued)**

Indication	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	2 weeks	3 months	6 months	1 year	Yes/No	Criteria
Inflammatory demyelinating polyneuropathy (acute)	One treatment per month.		X			Yes	Reauthorization may be considered under chronic IDP criteria
Inflammatory demyelinating polyneuropathy (chronic)	One treatment per month.			X		Yes	Documented initial response to IVIG and evidence of functional improvement.
ITP (acute)	Up to 4 doses given every other day.			X		No	Reauthorization may be considered under chronic ITP criteria.
ITP (chronic)	One treatment per month.			X		Yes	Platelet count below 30,000/mm <sup>3</sup> in children or below 20,000 mm <sup>3</sup> in adults. IVIG treatment only covered until conventional therapy takes effect.
ITP in pregnancy	One treatment per month.		X			Yes	Platelet count (see policy criteria). Treatment is not to exceed the duration of pregnancy.
Kawasaki syndrome	One treatment given within 10 days of symptom onset.	X				No	No further authorization shall be given.
Lambert-Eaton myasthenic syndrome	One treatment per month.			X		Yes	Documented initial response to IVIG and measurable improvement in muscle function/strength.
Multifocal motor neuropathy	One treatment per month.			X		Yes	Documented initial response to IVIG and measurable improvement in muscle function/strength.

**TABLE 1 (Continued)**

Indication	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	2 weeks	3 months	6 months	1 year	Yes/No	Criteria
Multiple myeloma	One treatment per month.				X	Yes	Documentation of clinical improvement and current IgG levels that are in the low to normal range.
Myasthenia gravis (acute and chronic)	One treatment per month.			X		Yes	Documented initial response to IVIG and measurable improvement in muscle function/strength.
Pediatric intractable epilepsy	One treatment per month.			X		Yes	Documented initial response to IVIG and significantly reduced frequency and/or duration of seizures.
Polymyositis	One treatment per month.		X			Yes	Objective evidence of the efficacy of initial three-month treatment, such as improvement in muscle strength and/or decreased CPK levels.
Post-transfusion purpura	One or two treatments.	X				No	No further authorization shall be given.
Primary humoral immunodeficiency disease	One treatment per month.				X	Yes	Documented initial response to IVIG, current IgG levels that are in the low to normal range and evidence of clinical improvement, such as decreased occurrence of infections.
Pure red cell aplasia	One treatment per month.			X		Yes	Documentation of initial response to IVIG, parvovirus, and recurrence of significant anemia.

**TABLE 1 (Continued)**

Indication	Frequency	Authorization Duration				Reauthorization	
	IVIG may be given no more frequently than:	2 weeks	3 months	6 months	1 year	Yes/No	Criteria
Refractory pemphigus foliaceus	One treatment per month.			X		No	No further authorization shall be given beyond 6 months. Approval may be granted until conventional therapy takes effect.
Solid organ transplant	Up to 4 doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant.		X			No	No further authorization shall be given.
Stiff-Person syndrome	One treatment per month.		X			Yes	Objective evidence of the efficacy of initial 3-month treatment, such as improvement in mobility, ability to perform work-related or household tasks, and decreased fall frequency.
Systematic lupus erythematosus	One treatment per month.			X		Yes	Documentation of initial response to IVIG and evidence of clinical improvement.

**III.** 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.

**IV.** 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. Motor neuron syndromes
29. Multiple sclerosis
30. Narcolepsy/cataplexy
31. Neonatal hemochromatosis
32. Neonatal hemolytic disease
33. Nephropathy, membranous
34. Nephrotic syndrome
35. Nonimmune thrombocytopenia
36. Ophthalmopathy, euthyroid
37. Opsoclonus myoclonus
38. Otitis media, recurrent
39. Paraproteinemic neuropathy
40. Polyneuritis
41. Post-polio syndrome
42. Recurrent spontaneous abortion
43. Rheumatoid arthritis
44. Sinusitis, chronic
45. Stevens-Johnson Syndrome
46. Still's Disease
47. Surgery or trauma
48. Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)
49. Thrombotic Thrombocytopenic Purpura, neonatal autoimmune – severe thrombocytopenia. (TTP)

50. Thrombotic Thrombocytopenic Purpura, refractory to platelet transfusions. (TTP)
51. Tic disorder (DSM-IV)
52. Toxic epidermal necrolysis
53. Urticaria, delayed pressure
54. Uveitis
55. Vasculitic syndromes, systemic
56. Von Willebrand's syndrome
57. Wegener's granulomatosis

## Position Summary

### *Intravenous immune globulin (IVIG)*

- All IVIG preparations are generally considered therapeutically interchangeable. <sup>[32-34]</sup>
- Minor immunoglobulin A (IgA) and immunoglobulin G (IgG) subclass differences exist. <sup>[32-34]</sup>
- IVIG preparations with low IgA content are used to minimize reactions in patients with hypogammaglobulinemia and concurrent IgA deficiency or when anti-IgA antibodies are present in a recipient. <sup>[32-34]</sup>

### *Subcutaneous immune globulin*

- There is a single product approved for subcutaneous infusion (Vivaglobin<sup>®</sup>) <sup>[53]</sup>
  - \* Available as 16% solution for weekly infusion.
  - \* Indicated for patients with primary immune deficiency (PID).
  - \* Lower bioavailability than IVIG; must give higher dose to achieve same serum IgG concentrations.
  - \* Maximum volume of injection per subcutaneous site is 15 ml; requires a minimum of 3 injection sites per weekly infusion for an average patient.

- \* . Subcutaneous delivery may result in higher steady-state IgG levels due to less variation in IgG levels.
- \* Injection site swelling, redness, and itching were reported in the majority of patients (92%).

### *Dosing Considerations and Therapeutic Levels*

- A plasma IgG level of 200mg/dL is often a common minimum target for patients being considered for IVIG replacement therapy. <sup>[4]</sup>
- In patients with mild to moderate IgG deficiency with levels of 300mg/dL-400mg/dL, the decisions to treat are based on clinical symptoms and antigenic challenge. <sup>[31]</sup>
- Dosing adjustment in replacement therapy is based on clinical response and IgG levels. <sup>[4]</sup>
- 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. <sup>[4,31]</sup> Some patients may require an IgG level of 400-500 mg/dL above their baseline value for protection.
- 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. <sup>[56]</sup>
- The trough or steady state IgG level is obtained before scheduled infusions and frequently guides IVIG dose selection.

### *Clinical Efficacy*

#### FDA-LABELED INDICATIONS <sup>[1,4-5,27,34,37,43]</sup>

- 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]
- HIV-infected children < 13 years of age. <sup>[43]</sup>
  - \* IVIG has 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 mm<sup>3</sup>. <sup>[3]</sup>
  - \* The recommended dose is 400 mg/kg/month to maintain the serum IgG level.
- Allogeneic bone marrow transplant (BMT) <sup>[4,34-35]</sup>
  - \* 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. <sup>[43]</sup>

- 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. <sup>[4,34]</sup>
  - \* Monthly IVIG infusions of 400 mg/kg are recommended to maintain the serum IgG level.
- Idiopathic thrombocytopenia purpura (ITP)
  - \* Normal platelet count range is 115,000/mm<sup>3</sup> to 440,000/mm<sup>3</sup>.
  - \* Acute ITP
    - In various studies, 64% to 100% of IVIG recipients attained platelet counts greater than 100,000 cells/mm<sup>3</sup> within 7 days. <sup>[4,34]</sup>
    - 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 <sup>[4, 8-10]</sup>
    - 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 mm<sup>3</sup> in adults or less than 30,000 per mm<sup>3</sup> 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.

- 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. <sup>[4, 34-35]</sup> 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.

## OFF-LABEL INDICATIONS

- 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. <sup>[60]</sup>
- Dermatomyositis
  - \* High-dose IVIG is a safe and effective treatment for refractory dermatomyositis unresponsive to corticosteroid therapy. <sup>[5,7,28,33,36]</sup>
  - \* The recommended IVIG dose is 2 gm/kg per month.
- Fetal alloimmune thrombocytopenia
  - \* ACOG guidelines recommend IVIG as first line treatment for documented fetal thrombocytopenia. <sup>[58]</sup>
  - \* A trial comparing IVIG treatment with and without dexamethasone in siblings showed that: <sup>[2]</sup>
    - IVIG treatment was associated with an increase in mean platelet count of 69,000/mm<sup>3</sup>.
    - 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. <sup>[59]</sup>
- 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. <sup>[67]</sup>
- Inflammatory demyelinating polyneuropathy (IDP)
  - \* Acute IDP, including Guillain-Barré syndrome <sup>[57]</sup>
    - 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.
    - The usual IVIG dose is 400 mg/kg/day for 5 days, repeated every 6 weeks.
- ITP in pregnancy
  - \* The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia. <sup>[44]</sup>
  - \* 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.

- 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).<sup>[73]</sup>
  - \* The recommended dose of IVIG is 2 gm/kg administered over 2 – 5 days.
- Multifocal motor neuropathy in patients with anti-GM1 antibodies and conduction block
  - \* Small controlled trials demonstrate significant increase in muscle strength associated with IVIG administration, long-term benefits, and safety.<sup>[6,26]</sup>
  - \* The recommended IVIG dose is 2 gm/kg/month, administered over 2 – 5 days.
  - \* Conduction block is the hallmark of this disease. Additionally, patients with anti-GM1 antibodies show an increased chance of response to IVIG.
- 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.<sup>[69]</sup>
  - \* 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.<sup>[70]</sup>
  - \* There is no evidence to determine whether IVIG improves function or reduces steroid requirements for moderate to severe myasthenia gravis.<sup>[69]</sup>
  - \* The recommended dose of IVIG is 1 – 2 gm/kg/month administered over 2 – 5 days.<sup>[69]</sup>
- 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.

- 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. <sup>[1]</sup>
  - \* The recommended dose of IVIG is 500 mg/kg/day for two consecutive days. Rapid platelet recovery has been seen within days of treatment.
  
- Pure Red Cell Aplasia
  - \* Parvovirus B19 infects and lyses 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. <sup>[71]</sup>
  
- 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.
  
- 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. <sup>[27]</sup>

- \* 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. <sup>[68]</sup>
- \* A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant. <sup>[27]</sup>
- 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. <sup>[27]</sup>
  - \* The usual dose of IVIG is 400 mg/kg/day for 3 – 5 days.
- Systemic Lupus Erythematosus
  - \* Small case series suggest some benefit from treatment with IVIG when compared to cyclophosphamide. <sup>[27]</sup>
  - \* The usual dose of IVIG is 400 mg/kg/day for 5 days.

*Investigational Conditions* <sup>[1,5,13-15,17-20,27,46-52]</sup>

- 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. <sup>[1]</sup>
- 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. <sup>[17-20]</sup>
- HIV: The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes. <sup>[3]</sup>

- Multiple sclerosis, progressive: There is not substantial evidence to support IVIG in the treatment of chronic progressive multiple sclerosis. <sup>[28-30, 64]</sup>
- Multiple sclerosis; relapsing-remitting type: IVIG may provide some benefit in reducing the acute exacerbation rate in relapsing-remitting multiple sclerosis. <sup>[5,27,54]</sup>
  - \* Trials are generally limited to small numbers of patients and have lacked complete data on clinical outcomes.
  - \* Current evidence suggests little benefit with regard to slowing disease progression.
  - \* The American Academy of Neurology does not consider IVIG to be a first-line therapy in the treatment of relapsing-remitting multiple sclerosis.
- Opsoclonus-myoclonus
  - \* Opsoclonus-myoclonus is 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. <sup>[73,74]</sup>
- Post-Polio: Two published trials of post-polio syndrome failed to demonstrate a statistically significant benefit compared to placebo in improvement of muscle strength. <sup>[65, 66]</sup>
- 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. <sup>[27]</sup>
  - \* 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. <sup>[13-15, 62]</sup>

- \* 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. <sup>[61]</sup>
  
- \* 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. <sup>[55]</sup>
  
- 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 pressure urticaria, and toxic epidermal necrolysis . <sup>[27,46-52, 63]</sup>

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**Cross References**

BlueCross BlueShield Association Medical Policy # 8.01.05; Intravenous Immune Globulin Therapy

Epogen<sup>®</sup>, Procrit<sup>®</sup> epoetin alfa dru012

<b>Codes</b>	<b>Number</b>	<b>Description</b>
CPT	90780-90781	IV infusion for therapy
CPT	90284	Immune globulin (SCIg), human, for SC use
CPT	90283	Immune globulin (IVIg), human, for IV use
HCPCS	J1566	Injection, Immune Globulin, (Carimune), IV
HCPCS	J1562	Unclassified Biologics, Immune globulin subcutaneous, (Vivaglobin)
HCPCS	J1568	Injection, Immune Globulin, (Octagam), IV, non-lyophilized, (e.g., liquid), 500 MG
HCPCS	J1566, J1569	Injection, Immune Globulin, (Gammagard), IV, non-lyophilized, (e.g., liquid), 500 MG
HCPCS	J1572	Injection, Immune Globulin, (Flebogamma), IV, non-lyophilized, (e.g., liquid), 500 MG
HCPCS	J1566	Injection, Immune Globulin, (Iveegam), IV,
HCPCS	J1566	Injection, Immune Globulin (Polygam), IV,
HCPCS	J1561	Injection, Immune Globulin, (Gamunex), IV, non-lyophilized, (e.g., liquid), 500 MG