**BENEFIT DESCRIPTION AND LIMITATIONS OF COVERAGE**

**ITEM:** Immune globulin intravenous injection IVIG (Carimune®, NF; Flebogamma®, Flebogamma® DIF; Gammagard®, Liquid; Gammagard®, Octagam®, Privigen™ Liquid; Gamunex®)

**PRODUCT LINES:** Commercial HMO/PPO/CDHP

**COVERED UNDER:**
- HMO: Medical
- PPO/CDHP: Medical

**DESCRIPTION:** Immune globulin intravenous (IVIG) products consist of concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that is prepared from pooled plasma collected from a large number of human donors. Replacement therapy for primary and secondary immunodeficiencies; interference with Fc receptors on the cells of the reticuloendothelial system for autoimmune cytopenias and ITP; possible role of contained antiviral-type antibodies.

**CPT/HCPCS Code:** J1566, 1569, J1568, J1572

**Company Supplying:** ZLB Behring LLC, Grifols Biologicals, S/D–Baxter Healthcare Corporation, Octapharma USA, Talecris Biotherapeutics®

**Setting:** Intravenous (IV)

**Coverage Criteria:** Express Scripts, Inc. monograph dated 01/13/2010

**Approval Period:** As stated by indication

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**Recommended Authorization Criteria**

Coverage of IVIG is recommended in those who meet the following criteria:

**FDA-Approved Indications**

1. **Immunodeficiency, primary humoral (treatment) (e.g., congenital agammaglobulinemia [X-linked agammaglobulinemia], congenital hypogammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia (with or without hyper IgM), severe combined immunodeficiency, Wiskott-Aldrich syndrome).** Approve for 12 months if prescribed by an immunologist or in consultation with an immunologist. Treatment is lifelong. FDA approved indications. Used for replacement in primary immunodeficiency disorders where antibody production is significantly impaired to increase IgG levels and to prevent or control recurrent and chronic bacterial infections and to control symptoms.
Also see Hyperimmunoglobulinemia E syndrome (Job’s syndrome) and Selective IgG subclass deficiency.

2. **Idiopathic or immune thrombocytopenic purpura (ITP) acute and chronic (treatment).** Platelet counts are expressed per mm$^3$ in this section.

Children with ITP. Approve for one of the following (a, b, c, or d).

a) If platelet count is < 20,000 and there is significant mucous membrane bleeding or if platelet count is < 10,000 and minor purpura, then approve for 12 months. Patients with severe, life-threatening bleeding should be hospitalized and treated with IVIG regardless of the platelet count. This is an ASH recommendation. Almost all intracranial hemorrhages occur at platelet counts < 20,000 and usually < 10,000. In clinical trials IVIG shortened the duration of severe thrombocytopenia.

b) If splenectomy is planned and platelet count is < 30,000, then approve for one month. ASH recommendation.

c) If platelet count is < 20,000 and inaccessibility or noncompliance is a concern, approve for 12 months. ASH recommendation.

d) If surgery, dental extractions, or other procedures likely to cause blood loss are needed, then approve for one month. British Society of Haematology recommendation.

Adults with ITP. Approve for one of the following (a, b, c, or d).

a) Patient has tried a corticosteroid and the platelet count is < 30,000 and there is acute bleeding. Approve IVIG for 12 months. According to ASH guidelines if platelet count is < 20,000 to 30,000 initial therapy is corticosteroids. ASH guidelines state that splenectomy is effective in normalizing platelet counts in patients who have been refractory to glucocorticoids for several weeks or years, but there are inadequate data to make evidence-based recommendations on the appropriate indications and timing for splenectomy and on when the benefits of splenectomy outweigh the potential risks. If ITP symptoms persist after treatment with glucocorticoids and splenectomy AND platelet count is < 30,000 AND there is active bleeding, then IVIG is indicated. According to ASH guidelines first choice options in these circumstances include IVIG, corticosteroids, accessory splenectomy, and no additional treatment; other agents may also be appropriate.

b) To increase platelet counts before major surgical procedures (e.g., splenectomy). Approve for one month. According to ASH guidelines, for elective splenectomy, preoperative therapy is IVIG or oral glucocorticoids in patients with platelet counts < 20,000 to reduce the risk of intraoperative and postoperative bleeding. IVIG is not indicated with platelet counts > 50,000. The British Society for Haematology guidelines for ITP state that treatment is needed in patients with ITP who are undergoing any procedure likely to induce blood loss and that IVIG is effective in increasing the platelet count in 75% of these patients. “Safe” platelet counts in adults are as follows: dentistry ≥10,000; extractions ≥ 30,000; regional dental block ≥ 30,000; minor surgery ≥ 50,000; and major surgery ≥ 80,000.

c) If the platelet count is < 20,000 and the patient is considered to be at risk for intracerebral bleeding, then approve IVIG for 12 months. According to ASH guidelines, if platelet count is < 20,000 and there is significant mucous membrane bleeding then the patient should be hospitalized. If there is severe life threatening bleeding, then hospitalize the patient and administer high dose corticosteroids, IVIG, and platelet transfusions.
d) If there will be predictable bleeding such as from surgery, dental procedures, pregnancy or labor, then approve IVIG for one month if the platelet counts are as follows. Dentistry ≤ 10,000, teeth extractions ≤ 30,000, regional dental block ≤ 30,000, minor surgery ≤ 50,000, major surgery ≤ 80,000. The British Society of Haematology guidelines for ITP state that treatment with IVIG is needed in adults with ITP who are undergoing any procedure likely to induce blood loss and that “safe” platelet counts are as follows: Dentistry ≥ 10,000, teeth extractions ≥ 30,000, regional dental block ≥ 30,000, minor surgery ≥ 50,000, major surgery ≥ 80,000.

Pregnant women with ITP. Approve for one of the following (a, b, c, d, e, f, or g).

a) Platelet count is 10,000 to 30,000 AND bleeding in third trimester, approve IVIG for three months. ASH recommendation.

b) Platelet count is 10,000 to 30,000 AND asymptomatic in third trimester. Approve IVIG for three months if glucocorticoids have been tried. ASH recommendation.

c) Platelet count is < 10,000 in third trimester, approve IVIG for three months. ASH recommendation.

d) Platelet count is < 10,000 in first or second trimester. Approve IVIG for three months if glucocorticoids have been tried. ASH recommendation.

e) Platelet count 10,000 to 30,000 and patient is bleeding in first or second trimester. Approve IVIG for three months if glucocorticoids have been tried. ASH recommendation.

f) Platelet count ≤ 50,000 for normal vaginal delivery if otherwise normal coagulation, approve IVIG for 2 weeks. British Society of Haematology guideline.

g) Platelet count ≤ 80,000 for cesarean section, spinal or epidural anesthesia in women with otherwise normal coagulation, approve IVIG for 2 weeks. British Society of Haematology guideline.

h) Platelet count 30,000 to 50,000 in the first or second trimester. Not recommended. ASH recommendation.

i) Platelet count > 50,000 in any trimester. Not recommended. ASH recommendation.

Newborns of mothers with ITP. Infants are hospitalized.

3. **Kawasaki disease (treatment adjunct).** Approve one dose in the acute phase. May approve a second dose in patients who fail to respond to the initial therapy. Patients should receive a single dose of IVIG together with aspirin within the first 10 days of illness, and if possible, within 7 days of illness. IVIG can also be given in children presenting after the 10th day of illness (i.e., the diagnosis was missed earlier) if they have persistent fever without other explanation or aneurysms and ongoing systemic inflammation. FDA approved indication. Efficacy of IVIG with aspirin in the acute phase of illness is well-established. Failure to respond is usually defined as persistent or recrudescent fever ≥ 36 hours after completing the initial IVIG infusion. Treatment with IVIG during the acute phase reduces the risk of coronary artery aneurysms or ectasia to < 5% vs. about 15 to 25% if untreated.

4. **B-cell chronic lymphocytic leukemia (CLL) in patients with hypogammaglobulinemia and/or with previous history of a serious bacterial infection.** Approve for 12 months in patients with
hypogammaglobulinemia and/or with previous history of a serious bacterial infection. Hypogammaglobulinemia for these patients is IgG < 640 mg/dL [< 6.4 g/L]. A serious bacterial infection is one requiring an antibiotic for treatment. FDA labeled indication. In placebo-controlled trials, IVIG significantly reduced bacterial infections. According to a Canadian expert panel of hematologists, IVIG is recommended for infection prophylaxis in these adults who have either a recent episode of a life-threatening infection thought to be caused by low levels of polyclonal immunoglobulins or recurrent episodes of clinically significant infections (e.g., pneumonia) that are caused by low levels of polyclonal immunoglobulins. IVIG is an option for acute life-threatening infections in these patients. This panel of hematologists recommended re-evaluation every 4 to 6 months when used for prophylaxis but there was no consensus on specific criteria to use for duration of treatment with IVIG.

5. **Chronic inflammatory demyelinating polyneuropathy (or polyradiculoneuropathy) (CIDP).** Approve for 12 months. FDA-approved to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse. IVIG is recommended as an equivalent alternative to plasma exchange in children and adults. In the pivotal trial for CIDP, IVIG was effective at improving certain motor functions for up to 48 weeks after initial therapy. In previous short-term, controlled trials, IVIG improved disability more than prednisolone and the quality of life was better with IVIG because adverse effects were less. Neurological disability score improved similarly with IVIG and plasma exchange. IVIG was also significantly more effective than placebo in improving muscle strength. About 2/3 of patients responded to IVIG and about 1/3 of these need no further treatment and 2/3 required repeated courses of IVIG. Benefit from IVIG lasts for 2 to 12 weeks, so treatment must be repeated.

**Other Uses with Supportive Evidence**

6. **Allogeneic bone marrow transplantation** or hematopoietic stem cell transplantation (HSCT) (i.e., blood or marrow HSCT). Approve for 12 months of therapy at any time after transplantation in patients who have severe hypogammaglobulinemia (IgG < 400 mg/dL). The requirement for IgG < 400 mg/dL does not apply to patients who underwent transplantation for multiple myeloma or malignant macroglobulinemia because their total IgG concentration is affected by their underlying paraproteinemia. In the first 100 days after transplantation, IVIG should not be routinely given to HSCT recipients to prevent bacterial infection. However, IVIG is recommended for routine use in HSCT recipients (adults, adolescents, pediatric) with unrelated marrow grafts (allogeneic) who experience severe hypogammaglobulinemia (IgG < 400 mg/dL) within the first 100 days after transplant. To prevent late disease (> 100 days after HSCT), routine monthly IVIG administration to HSCT recipients is not recommended as a means of preventing bacterial infections. In a randomized trial where IVIG or no IVIG prophylaxis were given from day 90 to day 360 post bone marrow transplantation (patients received methotrexate plus cyclosporine for graft-versus-host disease [GVHD] prophylaxis), the incidence of bacteremia, sepsis, localized infection, survival, obliterative bronchiolitis, or the incidence or mortality of chronic GVHD were not reduced with IVIG. Patients with severe demonstrable hypogammaglobulinemia (e.g., IgG levels < 400 mg/dL) can continue receiving IVIG. IVIG supplementation is often used in patients with
severe infections and IgG levels < 400 mg/dL to maintain levels until infections resolve.

Gamimune® N, a brand of IVIG that has been discontinued, was FDA-approved for the treatment of bone marrow transplant patients ≥ 20 years of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic etiologies, and acute GVHD in the first 100 days posttransplant. Currently marketed IVIG products do not have this indication.

**GVHD, acute (within first 100 days after transplantation).** Not recommended. (See Exclusions)

**GVHD, chronic, prevention.** Not recommended. (See Exclusions)

**HSCT in allogeneic recipients from HLA-identical sibling donors.** Not recommended. (See Exclusions)

**Autologous bone marrow transplantation or HSCT.** Not recommended in autologous transplants. (See Exclusions)

Although IVIG is used for immune system modulation, IVIG is not recommended for cytomegalovirus (CMV) disease prophylaxis in HSCT recipients. (See Exclusions)

7. **Human immunodeficiency virus (HIV) infected infants and children younger than 13 years of age, for prevention of recurrent bacterial infections.** Approve for 12 months for one of the following a, b, or c.
   a. infants and children with recurrent, serious bacterial infections, defined as 2 or more serious bacterial infections, such as bacteremia, meningitis, or pneumonia during a 1-year period despite administration of highly active antiretroviral therapy (HAART) and prophylactic cotrimoxazole (TMP-SMZ) or other antimicrobials or
   b. in HIV-infected infants and children with hypogammaglobulinemia (IgG < 400 mg/dL [4.0 g/L]) or
   c. absence of detectable antibody to measles in children who have received two measles immunizations and who live in regions with a high prevalence of measles or
   **Passive immunization for measles in HIV-infected infants and children younger than 13 years of age.** Approve single dose, if IM IG is contraindicated. IM injection is contraindicated with severe thrombocytopenia or any coagulation disorder. Passive immunization for measles with IM IG is given to symptomatic or asymptomatic HIV-infected children who are exposed to measles regardless of immunization status. Passive immunization is not required in children who have received IVIG within 2 weeks of exposure.

**Passive immunization for varicella in HIV-infected infants and children younger than 13 years of age.** Approve a single dose if varicella zoster immune globulin (VariZIG®) is not available for one of the following a or b.
   a. child is without previous varicella infection or has not received 2 doses of varicella vaccine or
   b. children with moderate to severe immune compromise even if they have been immunized.
These children should receive VariZIG or, if not available, IVIG within 96 hours after close contact with a person who has chickenpox or shingles. Post exposure prophylaxis with acyclovir, VariZIG or if VariZIG is not available, IVIG should be considered for HIV-infected children with moderate to severe immune compromise even if they have been immunized. Children who have received IVIG within 2 weeks of exposure do not require additional passive immunization. Also see, Varicella, postexposure prophylaxis.

Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and the Infectious Diseases Society of America (IDSA) guidelines do not include recommendations for use of IVIG in treatment of serious or recurrent bacterial infections. Studies that showed IVIG was beneficial for prevention of bacterial infections in HIV-infected children were done before HAART was available. HAART that suppresses HIV replication to undetectable levels has decreased the incidence of opportunistic infections (Pneumocystis pneumonia [PCP], CMV retinitis, mycobacterium avium complex [MAC] infection, toxoplasmosis) dramatically. U. S. Public Health Service (USPHS) and IDSA guidelines for preventing opportunistic infections in HIV-infected persons recommend that infants and children with hypogammaglobulinemia (IgG < 400 mg/dL) receive IVIG to prevent serious bacterial infections. IVIG should also be considered for HIV-infected children who have recurrent serious bacterial infections even though such treatment might not provide additional benefit to children who are receiving daily TMP-SMZ for PCP prophylaxis. Also see HIV-associated thrombocytopenia, children.

Gamimune N, a brand of IVIG that has been discontinued, was FDA-approved for pediatric HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalization and to increase the time free of serious bacterial infection. Currently marketed IVIG products do not have this indication. There is no evidence that IVIG confers incremental benefit to antiretroviral therapy and prophylactic antibiotics given according to current standards of practice. In children with advanced HIV disease who are receiving zidovudine, IVIG decreases the risk of serious bacterial infections, but this benefit is apparent only in children who are not receiving TMP-SMZ as prophylaxis and for children with CD4 T lymphocyte counts > 200 to 400 cells/mm$^3$.

8. **Adult Still’s disease.** Approve for 12 months if patient has tried a corticosteroid and methotrexate and a biologic agent (etanercept, infliximab, or anakinra) or if these therapies are contraindicated. No controlled trials are available using IVIG. Case reports indicate IVIG may be effective in some patients who do not respond to nonsteroidal anti-inflammatory drugs and in the treatment of flares in recent onset of disease.

9. **Autoimmune hemolytic anemia (AIHA).** Approve for 12 months in patients with warm-antibody AIHA who have tried corticosteroids or had a splenectomy or if these treatments are contraindicated. Evidence does not support routine use of IVIG, but IVIG may have a role in patients with warm-type AIHA that does not respond to corticosteroids or splenectomy.

10. **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita).** Approve for 12 months if patient has tried conventional therapy
(systemic corticosteroids AND immunosuppressive agents [e.g., azathioprine, cyclophosphamide, dapsone, methotrexate, cyclosporine, mycophenolate mofetil (Cellcept®)] (or has contraindications to conventional therapy) OR the disease is rapidly progressive, extensive, or debilitating. For mucous membrane pemphigoid [cicatricial pemphigoid] conventional therapy is dapsone AND cyclophosphamide, azathioprine, or mycophenolate mofetil, etc. Conventional therapy is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy. The total duration of treatment with IVIG can be at least 2 years or longer. The interval between infusions is increased gradually and prolonged clinical remission has been reported with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, and mucous membrane pemphigoid [cicatricial pemphigoid]. In a randomized, double-blind, placebo-controlled trial, the therapeutic efficacy of single-cycle, high-dose IVIG administered over 5 consecutive days was assessed in patients (n = 61) with pemphigus vulgaris and pemphigus foliaceus, who were relatively refractory to systemic corticosteroids. Time to escape from the protocol (TEP) was used as the primary efficacy endpoint; defined as the length of the period until a patient stayed on the protocol without any additional treatment. The TEP was significantly longer in patients randomized to receive high dose (400 mg) IVIG compared to placebo (P < 0.001). Pemphigus activity score was also significantly decreased from baseline in patients who received IVIG compared to placebo.

11. Autoimmune-mediated diabetic proximal neuropathy (severe diabetic polyradiculopathy and/or plexopathy and many other terms). Approve for 3 months of IVIG if patient has tried immunosuppressive therapy. Long-term therapy with IVIG is not recommended. This condition resembles CIDP (see above). IVIG and immunosuppressants have been reported to improve strength and functioning in case series in clinically heterogeneous groups of patients. The natural history of diabetic proximal neuropathy is gradual spontaneous improvement. If weakness is severe, IVIG or plasma exchange may be used. Controlled trials are needed. A Canadian expert panel of neurologists did not recommend IVIG for diabetic polynueopathy, mononeuropathy, or proximal limb neuropathy because the evidence is very limited and patients in the case series were clinically heterogeneous. They recommended that patients with diabetes who have a CIDP phenotype should follow the therapy for CIDP.

12. Churg-Strauss syndrome (allergic granulomatosis and angiitis). Approve for 12 months in patients who have tried corticosteroids and cyclophosphamide. In case series and case reports, IVIG has been effective when used in addition to corticosteroids and cyclophosphamide.

13. CMV interstitial pneumonia in allogeneic bone marrow transplant or HSCT patients. Approve for 2 months. For CMV disease, especially CMV pneumonia, therapy consists of intravenous ganciclovir and IVIG in combination. Whether adding IVIG adds efficacy is controversial, and there is no data to support adding IVIG for the treatment of any manifestation of CMV disease other than pneumonia. CMV immune globulin (Cytogam®) may be preferred instead of IVIG for interstitial pneumonia. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) recommends the combination of ganciclovir and IVIG for the therapy of CMV pneumonia. For other
types of CMV disease, the EBMT recommends ganciclovir or foscarnet without IVIG.

For CMV prophylaxis and preemptive therapy, see Exclusions.

14. **Dermatomyositis.** Approve for 12 months in patients who have not responded to conventional therapy (systemic steroids, immunosuppressants, e.g., azathioprine, methotrexate, cyclosporine) or if these therapies are contraindicated or not tolerated, and if IVIG is used in conjunction with at least one other drug therapy. In a double-blind, placebo-controlled crossover trial, patients with treatment resistant dermatomyositis who received IVIG for 3 months had significant improvement in muscle strength and neuromuscular symptoms and in rash. IVIG may be used in patients with severe active illness for whom other interventions have been unsuccessful or intolerable. IVIG has been used to maintain response.

15. **Encephalomyelitis, acute disseminated.** Approve one course (2 to 5 days) in patients who have tried high-dose corticosteroids or when there is contraindication to corticosteroids. In case reports, IVIG has been effective in some patients who did not respond to high-dose corticosteroids. According to a Canadian expert panel of neurologists, IVIG is indicated for second-line therapy in monophasic and relapsing acute disseminated encephalomyelitis.

16. **End stage heart failure awaiting transplant, to lower allosensitization (may or may not be on a left ventricular assist device [LVAD]) or post-transplant.** Approve for 12 months in patients with high levels of preformed anti-HLA antibodies (high panel peak reactive antibody [PRA] levels > 20%) who are being managed by a transplant center. In a study in sensitized LVAD recipients who were awaiting cardiac transplant, treatment with IVIG reduced serum reactivity to HLA class I antigens, decreased the risk of positive cross-match reactions, and shortened the waiting time for cardiac transplantation. In another study, in 35 sensitized patients who had orthotopic heart transplantation, IVIG was used with plasmapheresis pre-transplant to allow successful cardiac transplantation and to improve survival. There were various causes for sensitization in these patients.

17. **End stage renal disease (ESRD) awaiting transplant, to lower allosensitization (preparation for renal transplant) or post renal transplant to treat rejection.** Approve for 12 months in patients with high levels of preformed anti-HLA antibodies (high panel PRA levels > 20%) who are being managed by a transplant center. IVIG has been used in highly sensitized patients to reduce allosensitization, ischemia-reperfusion injuries, and acute rejections episodes in renal and cardiac allograft recipients. In a double-blind trial in patients with ESRD, IVIG was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients; waiting time for transplant was decreased.

18. **End stage lung or liver disease awaiting transplant, to lower allosensitization (preparation for lung or liver transplant).** Approve for 12 months in patients with high levels of preformed anti-HLA antibodies (high panel PRA levels > 20%) who are being managed by a transplant center. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.) IVIG has been used in highly sensitized patients to reduce
allosensitization, ischemia-reperfusion injuries, and acute rejections episodes in renal and cardiac allograft recipients. Limited information is available in lung transplant patients.

19. **Epilepsy, pediatric intractable.** Approve for 12 months of therapy in children with seizures that are refractory to at least 2 drugs for seizures and a corticosteroid. Exceptions are not recommended for West syndrome (infantile spasms). Exceptions are not recommended in adults. Evidence does not support routine use of IVIG but IVIG may have a role in certain syndromes (e.g., Lennox-Gastaut syndrome, Rasmussen syndrome, Landau-Kleffner syndrome, mixed seizures of early onset with immune deficiency (IgA or IgG subclass deficiency)) as a last resort, especially in patients who may be candidates for surgical resection. Controlled trials are needed on well-defined populations. The Canadian expert panel of neurologists does not recommend IVIG for pediatric intractable epilepsy.

20. **Evans syndrome.** Refer to ITP or to warm autoimmune hemolytic anemia (AIHA) criteria depending on which symptoms are predominant. Patients are initially treated as having either ITP or warm AIHA depending on presentation and the diagnosis is often made retrospectively.

21. **Factor VIII inhibitors, acquired (acquired hemophilia A).** Approve for 12 months in patients who have received a corticosteroid, cyclophosphamide and/or azathioprine for immunosuppression or if bleeding is life-threatening. Published reports (case series and case reports) using the combination of prednisolone and IVIG are limited. Corticosteroids are the mainstay of therapy and may be used alone or in combination with cyclophosphamide or azathioprine or IVIG. IVIG has a similar response rate to prednisolone (about 30%), but the onset of effect is more rapid with IVIG (about 5 days with IVIG and 3 to 6 weeks with prednisolone). Combination therapy with prednisolone and cyclophosphamide produces response in 60 to 70% of patients. Some patients do not respond to or become refractory to immunosuppressive therapy or only have a partial response to other therapies. According to a Canadian expert panel of hematologists, immunosuppression is achieved with prednisone and cyclophosphamide and in their opinion there is no convincing evidence of clinical benefit of IVIG, and routine use is not recommended. IVIG may be considered one option among adjunctive therapies in urgent situations.

22. **Graves ophthalmopathy (orbitopathy).** Approve for 9 months of therapy if patient has tried an intravenous corticosteroid (e.g., methylprednisolone) or has contraindication to systemic corticosteroids. Intravenous corticosteroids and orbital radiotherapy alone or in combination are the most effective medical therapies. In two small trials, IVIG and oral corticosteroids had similar efficacy in reducing the eye changes in Graves’ ophthalmopathy (soft tissue involvement, diplopia, proptosis). Adverse effects were more frequent with the oral corticosteroids. In one study IVIG was given every 21 days for 12 cycles. Soft tissue involvement improved or disappeared in 25 of 28 patients on IVIG, 5 to 6 months after starting therapy.
   • Approve for 12 months if IVIG is initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms (weakness, inability to stand or walk without assistance, respiratory or bulbar weakness). (Patients are hospitalized.)
   • Approve for 12 months if the patient relapses and the patient had an initial response to IVIG. Treatment with IVIG after 4 weeks from onset is indicated since some patients may relapse and the relapse may be severe enough to warrant a repeat course of IVIG. IVIG is recommended as an equivalent alternative to plasma exchange in children and adults. IVIG is the treatment of choice, since plasma exchange (which is equivalent to treatment with IVIG) is not always readily available. In controlled trials, IVIG was as effective or more effective than plasma exchange in improving strength, time to unaided walking, or discontinuation of ventilation. The American Academy of Neurology recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms. The effects of IVIG and plasma exchange are equivalent in hastening recovery, and multiple complications were less frequent with IVIG than with plasma exchange. The Canadian expert panel of neurologists recommended that the use of IVIG for Guillain-Barré syndrome also apply to patients with Miller Fisher and other variants of Guillain-Barré. In a retrospective review of 92 patients with Miller Fisher syndrome, the authors concluded that IVIG and plasmapheresis seem not to have influenced patients’ outcomes.

24. HIV-associated thrombocytopenia, adults.
   • Approve for one month in nonsplenectomized patients who are Rh₀ [D] antigen-positive who have tried Rh₀ [D] immune globulin AND patient has significant bleeding OR platelet count less than 20,000/mm³. Patients with a contraindication to Rh₀ [D] immune globulin are not required to have tried it.
   • Approve for one month in splenectomized patients or in patients who are Rh₀ [D] antigen-negative AND patient has significant bleeding OR platelet count < 20,000/mm³.

Treatment choices are similar to those for ITP, and IVIG is only indicated with significant bleeding. Corticosteroids are usually effective but cause many adverse effects in these immunocompromised patients. Splenectomy and Rh₀ [D] immune globulin may be effective. Platelet counts may increase with HAART. Evidence for IVIG is mostly based on case reports and cohort studies and most studies predate the current standard practices for treatment of HIV. In one small study, 9 Rh₀ [D] positive nonsplenectomized adults and children with HIV infection with platelet counts <20,000 to 30,000/mm³ were randomized to Rh₀ [D] immune globulin or IVIG for 3 months and then crossed over to the other therapy. The mean increase in platelet count was 77,000 with Rh₀ [D] immune globulin and 29,000 with IVIG (P = 0.07); mean duration of effect was 41 days with Rh₀ [D] immune globulin vs. 19 days with IVIG (P = 0.01). Rh₀ [D] immune globulin is FDA approved in non-splenectomized, Rh₀ [D] positive patients for the treatment of childhood acute or chronic ITP, chronic ITP in adults, and ITP secondary to HIV infection (adults and children). The safety and efficacy of Rh₀ [D] immune globulin has not been evaluated in patients who are splenectomized or in patients who are Rh₀ [D] negative. A Canadian expert panel of hematologists recommends IVIG as a treatment option for this condition when there is active bleeding or when platelet counts are < 10,000/ mm³. Their recommendations do not discuss use of Rh₀ [D] immune globulin.
25. **HIV-associated thrombocytopenia, infants and children.** Approve for 5 days of therapy if platelet count is < 20,000 IVIG and is being used in children who are on antiretroviral therapy. A Canadian expert panel of hematologists recommends IVIG as a treatment option for this condition when there is active bleeding or when platelet counts are < 10,000/mm$^3$. They do not discuss using Rh$_0$[D] immune globulin for this indication.

26. **Hyperimmunoglobulinemia E (hyper-IgE) syndrome (Job’s syndrome) (treatment).** Approve for 12 months. IVIG is effective in the treatment of severe eczema, atopic dermatitis, and recurrent respiratory infections in these patients. IVIG also decreases enhanced IgE production. This is a rare syndrome and IVIG use is based on case reports. This is a primary immunodeficiency.

27. **IgM paraproteinemic demyelinating neuropathy (or other paraproteinemic demyelinating neuropathies).** Approve for 12 months. When compared to placebo in a small, short-term (4 weeks), double-blind, crossover trial, IVIG produced a modest but statistically significant decrease in overall disability and a significant improvement in many secondary outcome measures (e.g., time to walk 10 meters, grip strength, and sensory symptom scores). However, the short duration of follow-up makes it unclear whether this is clinically significant. Long term studies are needed. IVIG is used in severe cases. IVIG or plasma exchange are recommended for initial therapy in patients with significant disability or rapid worsening, although efficacy is unproven. In patients with moderate or severe disability, immunosuppressive therapy (e.g., chlorambucil, cyclophosphamide) should be considered; long-term efficacy remains unproven. The Canadian expert panel of neurologists does not recommend IVIG for IgM paraproteinemic neuropathy. Less common paraproteinemic demyelinating neuropathies (i.e., Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Monoclonal gammopathy cold Agglutinins and Disialoganglioside antibodies [CANOMAD] or neuropathy with an IgA or IgG paraprotein) may respond to IVIG.

28. **Inclusion body myositis.** Approve for 12 months. In a placebo-controlled crossover trial IVIG improved muscle strength (not statistically significant), but duration of swallowing function was improved significantly. In a controlled trial where patients on prednisone were randomized to placebo or IVIG once monthly for 3 months there was no significant difference in muscle strength between the groups. Some patients may have a modest transient benefit from IVIG that is sufficient to justify a trial of IVIG, especially in those with severe dysphagia. Further larger and longer term (> 6 months) trials are needed. Inclusion body myositis is usually resistant to steroids and immunosuppressive therapy. The Canadian expert panel of neurologists does not recommend IVIG for inclusion body myositis, noting that a small number of patients showed some improvement with IVIG but there is no evidence of sustained benefit.

29. **Juvenile rheumatoid arthritis (JRA), juvenile idiopathic arthritis.** Approve for 12 months in patients who have tried at least 2 other drug therapies and are being treated by a rheumatologist or in consultation with a rheumatologist. IVIG has been used in children with polyarticular or systemic JRA that was unresponsive to standard therapy (corticosteroids, methotrexate, abatacept [Orencia®], adalimumab [Humira®], etanercept [Enbrel®]).
30. **Lambert-Eaton myasthenic syndrome (treatment).** Approve for 12 months in patients who are receiving immunosuppressive agents (e.g., steroids, azathioprine) or who are receiving specific treatment for paraneoplastic Lambert-Eaton myasthenic syndrome. In a placebo-controlled crossover trial, a single dose of IVIG produced significant improvement in muscle strength and reduced serum calcium channel antibody titers. Plasma exchange, steroids, and immunosuppressive agents have not been studied in randomized controlled trials. IVIG may be useful as adjunctive therapy in difficult to treat patients.

31. **Leukemia, acute lymphoblastic.** Approve for 12 months in children with hypogammaglobulinemia and either a history of severe invasive infection or with recurrent sinopulmonary infections. According to a Canadian expert panel of hematologists, IVIG is not recommended for routine use in children with hematologic malignancies with or without hypogammaglobulinemia. Two exceptions are recommended by the expert panel. In children with hematologic malignancies with acquired hypogammaglobulinemias and either a history of severe invasive infection or recurrent sinopulmonary infections, IVIG may be an option. The second exception is children registered in clinical trials that include IVIG in the protocol for treatment of hematologic malignancies (and/or hematopoietic stem cell transplantation) even without severe or recurrent infection.

32. **Marburg disease (a variant of multiple sclerosis).** Approve for 12 months. The Canadian panel of expert neurologists agreed IVIG may be considered among the treatment options considering the life-threatening nature of this condition.

33. **Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).** Approve for 12 months. Responds to IVIG, plasma exchange, and prednisone. Therapy is the same as for CIDP.

34. **Multifocal motor neuropathy (treatment).** Approve for 12 months. In several placebo-controlled trials, IVIG improved muscle strength and neurological disability scores. IVIG is the only proven effective treatment (plasma exchange and corticosteroids are not effective) and is considered first-line treatment. IVIG is beneficial in maintenance treatment but the disease continues to progress over many years. Some patients with multifocal motor neuropathy do not respond to IVIG and should not be retreated with IVIG.

35. **Multiple myeloma.** Approve for 12 months in patients with stable (plateau phase) disease (> 3 months from diagnosis) and who have severe recurrent bacterial infections. These patients usually have hypogammaglobulinemia and IVIG is used as prophylaxis. In a randomized placebo-controlled trial, prophylactic use of IVIG reduced serious and life-threatening infections in immunosuppressed patients with multiple myeloma. According to a Canadian expert panel of hematologists, IVIG is recommended for infection prophylaxis in these adults who have either a recent episode of a life-threatening infection thought to be caused by low levels of polyclonal immunoglobulins or recurrent episodes of clinically significant infections (e.g., pneumonia) that are caused by low levels of polyclonal immunoglobulins. IVIG is an option for acute life-threatening infections in these patients. This panel of hematologists recommended re-evaluation every 4 to 6 months when used for prophylaxis but
there was no consensus on specific criteria to use for duration of treatment with IVIG.

36. **After the first neurological event suggestive of demyelinative disease (multiple sclerosis).** Approve for 12 months. In a single-center, placebo-controlled trial, patients with their first neurological event suggestive of demyelinative disease (multiple sclerosis) had less probability of developing clinically definite multiple sclerosis when they received IVIG every 6 weeks for one year compared to placebo. Patients on IVIG had a significant reduction in the volume and number of T2-weighted lesions and in the volume of gadolinium-enhancing lesions compared with placebo. IVIG treatment significantly lowered the incidence of a second attack and reduces disease activity as measured by brain magnetic resonance imaging.

37. **Multiple sclerosis, relapsing remitting.** Approve for 12 months if standard therapy with an interferon (e.g., Betaseron®, Avonex®, Rebif®) or glatiramer (Copaxone®) has been tried or is contraindicated. Women who are pregnant or breast feeding or immediately postpartum are not required to use an interferon or glatiramer. IVIG has been beneficial in controlled trials in preventing relapses in relapsing remitting multiple sclerosis, but additional studies are needed. The studies of IVIG have usually involved small number of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is possible that IVIG reduces the attack rate in relapsing remitting multiple sclerosis. In a retrospective analysis of pregnant women with relapsing remitting multiple sclerosis, patients who received IVIG during pregnancy and postpartum or postpartum only had lower relapse rates than those who were untreated. Randomized, double-blind trials are needed to confirm these findings, to determine the optimal dose, and to compare IVIG with beta interferon and glatiramer. Current evidence suggests IVIG is of little benefit in slowing disease progression.

38. **Multiple sclerosis with refractory optic neuritis.** Approve for 12 months in patients with severe, refractory, optic neuritis who have had no recovery of vision after 3 months of standard therapy (corticosteroids) or if corticosteroids are contraindicated. A Canadian expert panel of neurologists recommends IVIG in patients with acute exacerbation of multiple sclerosis who have severe, refractory optic neuritis who have had no recovery of vision after 3 months of standard therapy. Preliminary evidence suggests IVIG might be of benefit. This panel did not recommend a dose or duration of therapy with IVIG.

39. **Myasthenia gravis, crisis.** Approve for one month for patients who are in crisis and have severe weakness that is poorly controlled by other agents (anticholinesterase drugs [e.g., pyridostigmine], steroids, immunosuppressants [e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil], plasma exchange [plasmapheresis]) OR for patients in crisis where plasma exchange is not feasible or desired. [These patients are hospitalized.] In one randomized study, IVIG for either 3 or 5 days was similar in efficacy to plasma exchange in patients with severe exacerbations of myasthenia gravis. Evidence does not support routine use of IVIG. IVIG may be considered in patients with severe myasthenia gravis to treat acute severe decompensation when other treatments have been unsuccessful or are contraindicated.
Myasthenia gravis, severe exacerbation. Approve for 12 months for severe exacerbation (i.e., worsening weakness) as assessed by the physician in patients on immunosuppressive therapy while waiting for the full effect of immunosuppressive drug. Patient must be on an immunosuppressive drug. In a randomized, double-blind, placebo-controlled trial in 51 patients with myasthenia gravis and worsening weakness, IVIG-treated patients had a clinically meaningful improvement in the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity at day 14 and day 28. The greatest improvement occurred in patients with more severe disease (QMG Score for Disease Severity > 10.5).

40. Neutropenia, immune-mediated (autoimmune). Approve for one month of therapy if patient has tried two other therapies (a corticosteroid, antibiotics, filgrastim (Neupogen®) or pegfilgrastim (Neulasta®)). Evidence does not support routine use of IVIG, but IVIG may have a role in severe illness that does not respond to other modalities or when the latter are contraindicated. Symptomatic treatment with antibiotics is usually adequate, but for severe infections due to neutropenia or for surgical preparation, filgrastim, corticosteroids, and IVIG have been effective. Primary autoimmune neutropenia is usually benign and self-limiting. Secondary autoimmune neutropenia is often due to an underlying malignancy. Limited information is available on the use of IVIG.

41. Opsoclonus myoclonus (infantile polymyoclonia, acute cerebellar encephalopathy, oculocerebellomyoclonic syndrome, dancing eyes-dancing feet syndrome). Approve for 12 months. Symptoms have improved with ACTH or IVIG or plasma exchange. There are no controlled trials (rare condition). ACTH is usually the initial therapy but is not used long-term due to adverse effects. IVIG is usually used before plasma exchange due to the difficulty of obtaining venous access for plasma exchange in children. Maintenance therapy is usually required. In case reports treatment with IVIG has continued for about one year. Objective evidence of clinical improvement should be required for sustained use of IVIG.

Optic neuritis, in multiple sclerosis. See Multiple sclerosis with refractory optic neuritis above.

Pemphigus. See autoimmune mucocutaneous blistering diseases.

42. Polymyositis. Approve for 12 months in patients who have not responded to conventional therapy (steroids, immunosuppressants [e.g., methotrexate, azathioprine, cyclosporine]) or if these therapies are contraindicated or not tolerated. In uncontrolled series, IVIG has been effective in polymyositis.

43. Post transfusion purpura. Approve for one five-day course of therapy. IVIG may be considered as first-line therapy in severely affected patients (i.e., platelet count usually < 10,000 2 to 14 days after transfusion and bleeding). There are multiple case reports indicating IVIG is effective in some patients. This syndrome is so rare that case series reports are all that is available for evidence.

44. Pure red cell aplasia in patients with parvovirus B19 infection (parvovirus B19 infection with chronic and severe anemia). Approve for 12 months. IVIG can cure parvovirus B19 infection and reverse the anemia. Maintenance therapy has been used in patients who relapse.
45. **Pure red cell aplasia, immunologic subtype.** Approve for 12 months if patient has tried prednisone and either cyclophosphamide or cyclosporine. Based on case reports about 50% of patients benefit with IVIG therapy.

46. **Pyoderma gangrenosum.** Approve for 6 months if patient has tried two other systemic therapies (e.g., intrallesional injections of corticosteroids or cyclosporine [for localized pyoderma gangrenosum]; systemic corticosteroids, immunosuppressants such as azathioprine/6-mercaptopurine, mycophenolate mofetil, cyclosporine, cyclophosphamide, chlorambucil; or dapsone, or infliximab). IVIG has been effective in a few cases where other therapies had failed.

47. **Scleromyxedema.** Approve for 12 months if patient has tried one other therapy (e.g., corticosteroid, thalidomide, cytotoxic agent [e.g., cyclophosphamide, melphalan], psoralen plus UVA [PUVA], extracorporeal photopheresis, retinoids, plasmapheresis, interferon-α, cyclosporine). In case reports, patients who received IVIG had improvement in cutaneous and systemic manifestations of the disease. IVIG was continued to maintain remission. This is a rare disorder and no randomized controlled studies are available for any treatment.

48. **Selective IgG subclass deficiency.** Approve for 6 months if patient meets all of the following criteria.
   a. Patient has a history of recurrent or persistent, severe bacterial infections and
   b. Infections are not responding adequately to treatment and prophylaxis with antibiotics (or multiple antibiotic hypersensitivities interfere with treatment) and
   c. IVIG is prescribed by an immunologist or in consultation with an immunologist and
   d. Patient has impaired antibody response to either protein (e.g., tetanus, diphtheria) and/or polysaccharide antigens (pneumococcus, meningococcus, *Hemophilus influenza* type b).

   After 6 months review for effect on frequency of infections. If frequency of infections has decreased then approve for another 6 months. After 12 months (total) discontinue IVIG. The patient should be re-evaluated after 12 months of therapy. After being off of IVIG for at least 5 months, the patient should be tested again for antibody response while off IVIG. If antibody response is still impaired, follow criteria above (a, b, c, and d) and approve for 2 years. After 2 years, re-evaluate while off IVIG for at least 5 months.

   Use of IVIG replacement therapy for selective IgG subclass deficiency is not as clear cut as for X-linked agammaglobulinemia and common variable immunodeficiency. Controlled trials are not available. In case reports IVIG reduced the episodes of sinusitis and otitis media in children with selective IgG antibody deficiency and recurrent infections who did not improve after prophylactic antibiotic therapy. Other case reports also indicate that IVIG prophylaxis is effective in reducing the number of infections and use of antibiotics in patients with selective IgG subclass deficiency. Patients with selective IgG subclass deficiency have normal or near normal serum IgG concentrations. Impaired antibody responses, not a deficiency of an IgG subclass protein, is associated with an increased incidence of infection and a beneficial response to IVIG. Many children outgrow their selective IgG subclass deficiency; in teenagers and adults the deficiency usually persists.
49. **Small bowel transplant to lower allosensitization (preparation for small bowel transplant) or post small bowel transplant to treat rejection.** Approve for 12 months in patients with high levels of preformed anti-HLA antibodies (high panel PRA levels > 20%) who are being managed by a transplant center. Very limited information is available. In a pilot study, highly sensitized patients (n = 6) with intestinal failure (short gut syndrome) who were awaiting isolated small bowel transplant received IVIG and immunosuppressive therapy pre-transplant. Four of the 6 patients had PRA reduction and received intestinal transplantation. Patients continued on IVIG post-transplant at days 1, 7 and 21. The waiting time for transplant and mortality was similar to non-sensitized patients.

50. **Stiff-person syndrome (Moersch-Woltman syndrome).** Approve for 12 months if patient has tried a benzodiazepine, baclofen, or gabapentin. In a small double-blind, placebo-controlled crossover trial, IVIG decreased stiffness scores significantly and decreased heightened sensitivity scores.

51. **Systemic lupus erythematosus (SLE).** Approve for 12 months if patient has tried azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab or a corticosteroid. Evidence does not support routine use of IVIG but IVIG may be used in patients with severe active SLE for whom other interventions have been unsuccessful or intolerable. Well-controlled trials are needed to determine which subsets of patients will benefit the most from IVIG. IVIG is used to treat severe thrombocytopenia or immune neutropenia. Its role in non-hematologic manifestations of lupus is less clear. It has been used effectively to treat lupus nephritis. First line therapy for active SLE is corticosteroids and antimalarial drugs (hydroxychloroquine). Second-line drugs are azathioprine, methotrexate, cyclophosphamide, or rituximab.

52. **Thrombocytopenia refractory to platelet transfusions.** Approve for 12 months. Evidence does not support routine use of IVIG but IVIG may have a role in patients with severe thrombocytopenia of documented immune basis for whom other modalities are unsuccessful or contraindicated.

53. **Thrombocytopenia, fetal alloimmune.** Approve maternal antenatal infusion of IVIG for 6 months. Antenatal therapy with IVIG is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia. IVIG reduces the risk of intracranial hemorrhage and increases the fetal platelet count. In newborns with fetal/neonatal alloimmune thrombocytopenia, first-line therapy is antigen-negative compatible platelets and IVIG is adjunctive.

**Transplantation.** See End stage heart failure, renal disease, lung or liver disease. See Small bowel transplant.

54. **Urticaria, chronic autoimmune.** Approve for 6 months of therapy in patients with chronic autoimmune urticaria who have tried all of the following medications:
   a. a first generation antihistamine (e.g., chlorpheniramine, diphenhydramine, hydroxyzine),
   b. a second generation antihistamine (e.g., loratadine, cetirizine (Zyrtec®), fexofenadine, desloratadine (Clarinex®)),
   c. an H2-receptor antagonist (e.g., ranitidine, cimetidine, doxepine),
d. a corticosteroid, and
e. at least one of the following: cyclosporine, montelukast (Singulair®).

After initial 6 months approve for another 6 months if patient is improved. Further authorization after 12 months total is not recommended.

One cycle (5 days) of IVIG was beneficial in 9 of 10 patients with chronic autoimmune urticaria who had poor responses to antihistamines with 3 of the patients having prolonged remission. In a single center open-label study, 29 patients with autoimmune urticaria received 0.15 mg/kg of IVIG every 4 weeks for a minimum of 6 months and a maximum of 51 months. There was clinical improvement in 26 patients with reduced urticaria or angioedema and decreased use of antihistamines. The onset of clinical benefit ranged from 1 to 13 months (mean 4.5 months) and was gradual and progressive. Nineteen of 26 patients had complete remission of symptoms. Efficacy persisted for at least 12 months after treatment. In other cases IVIG was not effective. IVIG also induced remission or improved symptoms in 5 of 8 patients with severe unremitting delayed pressure urticaria (some with autoimmune urticaria) who had not responded to other therapies or were controlled only with systemic corticosteroids. None of these reports were controlled trials. Practice guidelines state that alternative regimens may be necessary in refractory forms of chronic urticaria and mention IVIG in this list of alternatives.

55. **Uveitis, noninfectious.** Approve for 6 months in patients who have tried corticosteroids and at least one immunosuppressive drug (methotrexate, cyclosporine, mycophenolate mofetil], azathioprine). For acute uveitis, corticosteroids are used. For chronic uveitis, long term immunosuppressive therapy, often with 2 or 3 drugs, is used. There are no controlled trials using IVIG to treat uveitis, and IVIG is considered an alternative when almost all other therapies have failed. In one report IVIG for 6 months was effective in increasing visual acuity in patients with birdshot retinochoroidopathy (an autoimmune posterior uveitis).

After 6 months approve for another 6 months if there is improvement and/or reduction in dose of corticosteroid and/or immunosuppressive drug. Further authorization after 12 months total is not recommended.

56. **Varicella, postexposure prophylaxis (passive immunization).** Approve a single dose in the following patients (a, b, c, d, or e) who are without evidence of immunity to varicella (i.e., with history of disease or age-appropriate vaccination) and if VariZIG is not available:
   a. Immunocompromised patients or
   b. Neonates whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after) (these babies are probably hospitalized) or
   c. Premature infants born at ≥ 28 weeks of gestation who are exposed during the neonatal period and whose mothers do not have evidence of immunity or
   d. Premature infants born at < 28 weeks gestation or who weigh ≤ 1000 g at birth and were exposed during the neonatal period, regardless of maternal history of varicella disease or vaccination or
   e. Pregnant women.
VariZIG is indicated for postexposure prophylaxis in these patients and is given as soon as possible after exposure and as late as 96 hours after exposure. The patient groups listed are recommended by the Advisory Committee on Immunization Practices (ACIP). In situations where administration of VariZIG does not appear possible within 96 hours of exposure, IVIG is considered an alternative and should be given within 96 hours of exposure. The dose is 400 mg/kg given once. For pregnant women who cannot receive VariZIG, clinicians can choose either IVIG or closely monitor the women for signs or symptoms of varicella and institute acyclovir therapy if illness occurs.

57. Vasculitic syndromes, systemic (Wegener’s granulomatosis or microscopic polyangiitis). Approve for 12 months in patients with anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (Wegener’s granulomatosis or microscopic polyangiitis) if patient has tried a corticosteroid and either cyclophosphamide or azathioprine. Evidence does not support routine use of IVIG but IVIG may be used in patients with severe active illness for whom other interventions have been unsuccessful or intolerable. In a double-blind placebo controlled trial in 34 patients, IVIG for 5 days was effective in reducing disease activity in patients with ANCA-associated systemic vasculitis (Wegener’s granulomatosis, microscopic polyangiitis) who were refractory to conventional therapy. The effect lasted for 3 months. In a prospective, open-label study 22 patients with systemic vasculitides with relapses during therapy with corticosteroids and/or immunosuppressants, were given IVIG for 4 days every month for 6 months. IVIG was effective in inducing complete remission in 16 of 22 patients at month 6 and in 13 of 22 patients at month 9. ANCA is a serological marker for disease activity in patients with ANCA+ systemic vasculitis. In one report in patients with severe IgA nephropathy, proteinuria, hematuria and renal function improved with IVIG therapy. Minimal information is available on the effect of IVIG on glomerulonephritis in patients with ANCA-associated systemic vasculitis.

Churg-Strauss syndrome and Kawasaki disease are also systemic vasculitic diseases. See other criteria for these diseases.

58. Von Willebrand’s syndrome, acquired. Approve one course (2 to 5 days) in patients with life or limb threatening hemorrhages who are also receiving other therapies. Patients are probably hospitalized. Controlled trials are not available. IVIG has been used in patients who did not respond to desmopressin (DDAVP) in combination with replacement of von Willebrand factor and factor VIII with Humate-P®. According to a Canadian expert panel of hematologists, IVIG is not recommended routinely but may be one option among adjunctive therapies in urgent situations (e.g., active bleeding, preoperatively).

EXCLUSIONS

Coverage of IVIG is not recommended in the following circumstances:

1. Adrenoleukodystrophy. Evidence does not support IVIG use.

2. Alzheimer’s disease. Evidence does not support IVIG use. In a small phase 1 study, patients with mild to moderate Alzheimer’s disease received various doses of IVIG from a lot with high titers of anti-amyloid beta antibody. After 6 months
of treatment none of the patients had a decrease in cognitive function and most had an improvement. A phase 2 study is underway and 6 month results have been reported. A large retrospective case-control analysis found a significant association between IVIG use and Alzheimer's disease diagnosis. Patients who received IVIG (mainly for cancers) were less likely to be diagnosed with Alzheimer's disease (or Alzheimer's related diseases) than those who did not receive IVIG. Large placebo-controlled trials with a longer observation period are needed.

3. **Amyotrophic lateral sclerosis.** There is insufficient evidence to recommend IVIG.

4. **Anemia, aplastic.** Evidence does not support IVIG use.

5. **Anemia, Diamond-Blackfan.** Evidence does not support IVIG use.

6. **Asthma.** Evidence does not support IVIG use. Data showing the beneficial effects of IVIG are limited. Further randomized controlled trials are needed in carefully defined groups with persistent requirements for high doses of systemic corticosteroids. Uncontrolled studies suggest efficacy, but 2 of 3 randomized controlled trials showed no significant effect. Some patients with hypogammaglobulinemia and recurrent infections also may have asthma and can be evaluated by a pharmacist and/or a physician on a case-by-case basis to determine a coverage recommendation for the client.

7. **Atopic dermatitis.** Evidence does not support IVIG use. IVIG has been reported to be effective in severe therapy-resistant atopic dermatitis. Most guidelines for the treatment of atopic dermatitis do not list IVIG as a treatment. Guidelines from the American Academy of Dermatology state that data about the efficacy of IVIG for atopic dermatitis is conflicting and definitive conclusions about its role in the treatment of atopic dermatitis cannot be made. Double-blind, placebo-controlled trials that are at least 4 months long are needed.

8. **Autism.** Evidence does not support IVIG use.

9. **Autologous bone marrow transplantation or HSCT.** Not recommended in autologous transplants because the benefit is slight. Routine use of IVIG among autologous recipients is not recommended.

10. **Behcet’s syndrome, ocular manifestations.** Evidence does not support IVIG use. In an uncontrolled case series IVIG was effective in controlling the acute ocular inflammation in patients with Behcet’s syndrome who were refractory to corticosteroids and cyclosporine. A controlled trial is needed.

11. **BK virus associated nephropathy (BKVAN) in kidney transplant patient.** Limited information is available. Standard treatment is to reduce the dose of immunosuppressive therapy and therapy with cidofovir (Vistide®) or leflunomide. In a report from one center, 8 patients with BKVAN were treated with IVIG (and reduction of immunosuppressive therapy); 88% of patients still had functioning allografts after a mean of 15 months. Prospective randomized, multi-center trials are needed to validate these results.

12. **Chronic fatigue syndrome.** Evidence does not support IVIG use.
13. **Crohn’s disease.** There is insufficient evidence to recommend IVIG. In a single center case collection report, 19 patients with acute Crohn’s disease (Crohn’s disease activity index 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days. Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Spontaneous remissions cannot be excluded. Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has role in the treatment of Crohn’s disease.

14. **Cystic fibrosis.** Evidence does not support IVIG use. Some of these patients may be hypogammaglobulinemic and if so will be evaluated by a pharmacist and/or a physician on a case-by-case basis to determine a coverage recommendation for the client.

15. **CMV disease prophylaxis in bone marrow transplant or HSCT recipients.** IVIG is not recommended. IVIG has been used in the past for CMV prophylaxis, but CMV prophylaxis is currently based on using seronegative blood in seronegative recipients, screening for CMV antigenemia, and prophylaxis with ganciclovir in some patients. However, it is recommended for other indications in these patients. See Other Uses with Supportive Evidence.

16. **CMV infection, that is, preemptive therapy for CMV infection or treatment of CMV disease, in allogeneic bone marrow transplant or HSCT patients.** Not recommended. Preemptive therapy is defined as receiving therapy when there is evidence of active, but asymptomatic, CMV infection and is based on tests that rapidly detect CMV viremia or antigenemia. Preemptive therapy is used in most cases instead of prophylaxis for CMV management. First-line preemptive therapy for CMV infection is ganciclovir or foscarnet. Although most studies using IVIG for preemptive therapy were randomized, the patient populations were heterogeneous, the IVIG dose varied, most but not all used ganciclovir, and they were not adequately controlled. IVIG monotherapy does not appear to be effective for preemptive therapy. Current CDC, IDSA, and the American Society of Blood and Marrow Transplantation guidelines do not include recommendations for use of IVIG in preemptive therapy of CMV infections.

17. **Diabetes mellitus.** Evidence does not support IVIG use. Antibodies against islet cell antigens are implicated in the autoimmune pathogenesis of type 1 diabetes mellitus. In a 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes. No beneficial effect was shown with IVIG compared to control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

18. **Endotoxemia.** Evidence does not support IVIG use.

19. **GVHD, acute (within first 100 days after transplantation).** Not recommended. Current recommendations do not include using IVIG for this indication. IVIG is recommended in patients with severe hypogammaglobulinemia after transplantation to prevent bacterial infection and acute GVHD. (See Allogeneic bone marrow transplantation above under Other Uses with Supportive Evidence.)

20. **GVHD, chronic, prevention.** Not recommended. Chronic defined as persisting or developing after 100 days. IVIG has been recommended for use in producing
immune system modulation for preventing GVHD, but in a randomized trial where IVIG or no IVIG prophylaxis were given from day 90 to day 360 post-transplantation, the incidence or mortality of chronic GVHD was not reduced with IVIG. (See Allogeneic bone marrow transplantation above under Other Uses with Supportive Evidence.)

21. Heart block, congenital. Evidence does not support IVIG use.

22. Heart failure, chronic. There is insufficient evidence to recommend IVIG. In one randomized, placebo-controlled trial, IVIG given monthly for 26 weeks improved left ventricular ejection fraction (LVEF) in patients with chronic heart failure and LVEF < 40%. In another controlled trial in patients with recent onset dilated cardiomyopathy LVEF < 40%, IVIG, given for 2 consecutive days with no maintenance IVIG, did not improve LVEF more than placebo. Larger trials are needed in well defined populations (cause and severity) to determine if IVIG has a role in the treatment of heart failure.

23. HSCT in allogeneic recipients from HLA-identical sibling donors. Not recommended. In a placebo-controlled trial, prophylactic IVIG had no benefit over placebo for prophylaxis of infection, interstitial pneumonia, GVHD, transplantation-related mortality at 6 months, or survival at 24 months. IVIG is recommended in patients with severe hypogammaglobulinemia after transplantation to prevent bacterial infection and acute GVHD. (See Allogeneic bone marrow transplantation above under Other Uses with Supportive Evidence.)

24. Hemolytic disease of the newborn. Patients are hospitalized. IVIG has been reported to decrease the need for exchange transfusions, reduce length of hospital stay, and reduce the duration of phototherapy. The Canadian expert panel of hematologists recommends IVIG only for hemolytic disease of the newborn with established jaundice and not for prophylaxis.

25. Hemophagocytic syndrome. Evidence does not support IVIG use. Patients would be hospitalized.

26. Human immunodeficiency syndrome (HIV) infection, adults, for prophylaxis of infections. Evidence does not support IVIG use. HAART should be used.

27. In vitro fertilization (IVF). Evidence does not support IVIG use. Randomized placebo-controlled trials do not support the use of IVIG in women with repeated unexplained IVF failure.


29. Multiple sclerosis, primary progressive. Evidence does not support IVIG use. Clinical trials are needed. Also see studies for secondary progressive below.

30. Multiple sclerosis, secondary progressive. Evidence does not support IVIG use. In a placebo-controlled trial in patients in an advanced stage of secondary progressive multiple sclerosis, IVIG therapy for 27 months had no beneficial effect on time to confirmed expanded disability status scale (EDSS, primary outcome) progression (hazard ratio 1.11 [95% CI 0.08-1.53] for IVIG vs. placebo). The annual relapse rate was 0.46 for both groups. No significant
differences between the treatment groups were found in any of the other clinical outcome measures or in the change of T2-lesion load over time. In another placebo-controlled trial, patients with primary progressive (n = 34) or secondary progressive (n = 197) multiple sclerosis were randomized to IVIG once monthly or placebo for 2 years. Mean duration of multiple sclerosis was 14 to 15 years and mean EDSS scores were about 5.5 at baseline. In the intent-to-treat population (both groups combined) IVIG delayed progression by 12 weeks compared to placebo and diminished the rate of patients with sustained progression by 15%; this effect was significant in those with primary progressive disease. In all, 51% of patients withdrew from the study. The study was not powered to show differences between the primary and secondary progressive groups and the number of patients with primary progressive disease was too small to draw valid conclusions. EDSS scores were similar with IVIG and placebo. Treatment with IVIG cannot be recommended for patients with secondary or primary progressive multiple sclerosis.

31. **Myelopathy, HTLV-I associated.** Evidence does not support IVIG use.

32. **Neonates, for suspected or proven infection.** Evidence does not support IVIG use. There is not sufficient evidence to support routine administration of IVIG to prevent mortality from suspected or subsequently proven infections in neonates. Further research is needed.

33. **Neonates, high-risk hypogammaglobulinemic.** Evidence does not support IVIG use.

34. **Neonates, high-risk, preterm, low birth weight, infections in (prophylaxis and treatment adjunct).** Evidence does not support IVIG use. IVIG results in a 3% reduction in sepsis and a 4% reduction in any serious infection, but is not associated with reductions in other important outcomes; IVIG does not have any significant effect on mortality from any cause or from infections. Early studies suggested prophylactic IVIG reduced nosocomial infections in low birth weight infants but these studies had many deficiencies. In a large prospective trial, prophylactic IVIG did not reduce the incidence of nosocomial infections in premature infants who weighed 501 to 1500 grams at birth. Morbidity, mortality, and duration of hospitalization were not different between IVIG and placebo.

35. **Nephropathy, membranous.** Evidence does not support IVIG use.

36. **Nephrotic syndrome.** Evidence does not support IVIG use.

37. **Neuropathy, paraproteinemic.** Evidence does not support IVIG use. Treatment of paraproteinemic neuropathies associated with multiple myeloma, amyloidosis, and Waldenstrom’s macroglobulinemia should be to treat the underlying disease. IVIG is not indicated. Also see IgM Paraproteinemic demyelinating neuropathies above.

38. **Ophthalmopathy, euthyroid.** Evidence does not support IVIG use.

39. **Otitis media, recurrent.** Evidence does not support IVIG use.

40. **Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).** Evidence does not support IVIG use.
Patients should be in a formal research protocol. In a randomized controlled trial, 29 children with new onset or severe exacerbations of obsessive compulsive disorder or tic disorder after streptococcal infections were randomized to IVIG, plasma exchange, or placebo. Patients who received either IVIG or plasma exchange improved compared to placebo. However, there are many limitations to this study. Additional studies are needed to determine the role of immunomodulatory therapies and antibiotic prophylaxis in PANDAS. The Canadian expert panel of neurologists recommends IVIG as an option for treatment of PANDAS and states that diagnosis requires expert consultation.

41. **Plexopathy, progressive lumbrosacral.** Evidence does not support IVIG use.

42. **Post-polio syndrome.** There is insufficient evidence to recommend IVIG. In a double-blind, trial, 135 patients (most were clinically unstable and had severely atrophic muscles in both legs) were randomized to either IVIG or placebo initially and then repeated 3 months later. At 6 months, median muscle strength differed by 8.3% in favor of IVIG (P = 0.029) with 15% being considered clinically significant; quality of life measured by Short Form-36 questionnaire was not significantly different between therapies. This study was not large enough to identify patients who were most likely to improve the most.

43. **Pure red cell aplasia due to myelodysplastic syndrome.** Evidence does not support IVIG use. This condition does not usually respond to immunosuppressive therapy or IVIG.

44. **Recurrent spontaneous pregnancy loss (RSPL) [including antiphospholipid antibody-positive women].** Evidence does not support IVIG use. According to guidelines from the American College of Obstetricians and Gynecologists, IVIG is not effective for preventing recurrent early (<15 weeks of gestation) pregnancy loss. Patients with a positive test for lupus anticoagulant or anticardiolipin antibodies should be treated with heparin and low dose aspirin during the next pregnancy attempt. In a double-blind pilot study, IVIG did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen. The American Society for Reproductive Medicine also concluded after reviewing 5 randomized controlled trials which assessed IVIG treatment for RSPL, that IVIG is not effective for primary RSPL. For secondary (indicates an antecedent pregnancy) RSPL, there was a higher percentage of successful pregnancies with IVIG, but the number of patients was not sufficient to rule out a chance finding. They concluded that IVIG as a treatment for RSPL is experimental and should only be used in a randomized clinical trial setting.

45. **Renal failure, acute.** Evidence does not support IVIG use.

46. **Rheumatoid arthritis.** Evidence does not support IVIG use.

47. **Sickle cell disease.** Evidence does not support IVIG use. A Canadian expert panel of hematologists states that IVIG is not recommended for routine treatment of non-life-threatening delayed hemolytic transfusion reactions in patients with sickle cell disease but could be used for serious, life-threatening reactions.

48. **Surgery or trauma, for prophylaxis of infections.** Evidence does not support IVIG use.
49. **Systemic sclerosis (systemic scleroderma).** Evidence does not support IVIG use. In a small open label trial, IVIG reduced skin fibrosis in patients with systemic sclerosis. Placebo-controlled trials are needed. In the natural course of the disease, skin atrophy may develop which would affect the measurement of skin involvement, and it is not known how IVIG would affect the other manifestations of systemic sclerosis (blood vessels, visceral organs). According to American College of Rheumatology guidelines for clinical trial design and outcomes in systemic sclerosis "randomized, double-blind, placebo-controlled trials are preferred. The treatment and follow-up period must be long enough to permit observation of any disease modification, which is likely to require 18-36 months, unless an extraordinarily effective therapy is identified. Responses selected should be quantitative, consistently and accurately reflect activity of systemic sclerosis in major target organs (not solely the skin), be sensitive to change, and be standardized, with limited variability.”

50. **Thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS).** Evidence does not support IVIG use. A Canadian expert panel of hematologists states that IVIG may be one option among adjunctive therapies when first-line therapy has failed.

51. **Thrombocytopenia, heparin-induced.** IVIG is contraindicated. IVIG could potentially increase the risk of thrombosis.

52. **Thrombocytopenia, nonimmune.** Evidence does not support IVIG use.

53. **Toxic necrotizing fasciitis due to group A streptococcus.** Patients are hospitalized.

54. **Toxic shock syndrome.** Patients are hospitalized.

55. **Transfusion reaction.** Evidence does not support IVIG use. According to the Canadian expert panel of hematologists there is no role for IVIG in routine management of hemolytic transfusion reaction but is an option in urgent situations. Patients are hospitalized.

56. **Transplantation, solid organ (e.g., heart, kidney) for prophylaxis or treatment of cytomegalovirus (CMV) infections.** Antiviral therapy is currently used. Antiviral agents (ganciclovir, valganciclovir (Valcyte™)) and CMV immune globulin (Cytogam®) are effective in preventing and treating CMV in solid organ transplant recipients.

57. **West syndrome (infantile spasms).** There is insufficient evidence to recommend IVIG.

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