VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin Intravenous Utilization Management Medical Policy

- Asceniv™ (immune globulin intravenous liquid-sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous – AMDA Biologics)
- Flebogamma® DIF (immune globulin intravenous – Grifols USA)
- Gammagard Liquid, Gammagard S/D < 1 mcg/mL in 5% solution (immune globulin intravenous – Baxalta US)
- Gammaked™ (immune globulin intravenous caprylate/chromatography purified – Kedrion Biopharma)
- Gammaplex® (immune globulin intravenous – BPL)
- Gamunex®-C (immune globulin intravenous caprylate/chromatography purified – Grifols USA)
- Octagam® (immune globulin intravenous – Octapharma)
- Panzyga® (immune globulin intravenous-ifas – Octapharma USA)
- Privigen® Liquid (immune globulin intravenous – CSL Behring)

REVIEW DATE: 9/15/2021

OVERVIEW

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of these products (except Octagam 10%) are FDA-approved for replacement therapy in patients with primary immune deficiencies due to defects in humoral immunity. The following indications are FDA approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of infections in patients with hypogammaglobulinemia and/or recurrent infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**, to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[7,9,12,15]
- **Dermatomyositis (or polymyositis)**. Octagam 10% is indicated for the treatment of dermatomyositis in adults.[11] Patients with dermatomyositis treated with Octagam were under treatment with corticosteroids and/or maximally two immune-suppressants OR patients had previous failure or intolerance with a corticosteroid and at least one additional immunosuppressive drug.[33] IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32]
- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,4,6-9,11,12,15,23-25]
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.[6,26] The American Heart Association and the American Academy of Pediatrics recommend initial therapy 2 g of IVIG per kg as a single IV dose given over 10 to 12 hours.[26,27] The dose can be repeated if needed.
- **Multifocal motor neuropathy** in adults as maintenance therapy to improve muscle strength and disability.[5]
- **Primary humoral immune deficiency (PID**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and

severe combined immunodeficiencies.[1-10,12,15,16,25] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via IV or subcutaneous infusion for primary immunodeficiency.[5,7,9] IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[3,4,7-10,12,13,17,24,45]

IVIG is prepared from pooled plasma collected from a large number of human donors.[1-12,15,16,25] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans. Asceniv contains not only antibodies which satisfy the requirement to treat patients with primary immunodeficiencies, it also has elevated levels of respiratory syncytial virus (RSV) antibodies.[19]

IVIG also is used for many off-label indications. Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

- **Antibody-mediated rejection (AMBR) in transplantation**: Current strategies for treatment of antibody-mediated rejection include plasmapheresis, IVIG, and T-cell or B-cell-depleting agents.[76] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,77] Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes) recommends a combination of corticosteroids, plasmapheresis, IVIG, and anti-CD-20 antibody and lymphocyte-depleting antibody for antibody-mediated rejection.[77,78] As in desensitization therapy, much of the information of IVIG use is in patients with kidney transplants, but the same principles apply to transplantation of other organs and tissues. Immune globulin has been used in lung transplant patients to treat ABMR[20,4479] and a scientific statement from the American Heart Association states that primary therapy for ABMR in patients with heart transplants may include IVIG, plasmapheresis, high-dose corticosteroids, and anti-lymphocyte antibodies.[36]
- **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita):** Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) 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.[28-30] International expert recommendations for the management of pemphigus note that first-line treatment includes corticosteroids and anti-CD20 monoclonal antibodies. First-line corticosteroid-sparing agents include azathioprine and mycophenolate mofetil and other corticosteroid-sparing agents include IVIG.[2]
- **Cytomegalovirus (CMV) pneumonia in patients with cancer or transplant-related infection**: For CMV pneumonia, therapy consists of ganciclovir IV injection (or foscarnet IV injection if CMV is ganciclovir-resistant). The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 1.2021 – July 2, 2021) note IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.[31]
- **Desensitization therapy prior to and immediately after transplantation**: Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many of the same principles apply to transplantation of other organs and tissues.[34,35] Current protocols include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletions with rituximab for IV infusion).[18]
- **Guillain Barre syndrome (GBS)**: 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.[37]

The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.[38] IVIG is not indicated or proven to be effective in patients mildly affected with GBS.[32,38]

- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency)**: Clinical guidelines for immunoglobulin use by the National Health Service- England note secondary antibody deficiency can be hypogammaglobinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.[27] NCCN guidelines regarding management of immunotherapy-related toxicities (version 1.2020 – December 16, 2020) note that after anti-CD19 chimeric antigen receptor (CAR)-T cell therapy, monthly IVIG replacement for select patients with hypogammaglobulinemia and serious or recurrent infections can be considered.[74]
- **Hematopoietic cell transplantation (HCT) to prevent infections**: HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend IVIG for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is used to prevent infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL). Guidelines from the American Society for Blood and Marrow Transplantation make recommendations for IVIG dosing in HCT recipients to prevent infectious complication.[39] During the first 100 days after HCT, the dose in adults and adolescents is 0.5 g/kg per week. The IVIG dose should be individualized to maintain trough (pre-dose) serum IgG greater than 400 to 500 mg/dL. The dose in allogeneic pediatric HCT patients is 0.4 g/kg per month, adjusted to keep IgG > 400 mg/dL. Higher and more frequent dosing may be necessary in patients for prevention of early disease after HCT because the half-life of IVIG is reduced to between 1 to 10 days in this population. Dosing for > 100 days post-HCT is 0.5 g/kg given every 3 to 4 weeks. The dose is not adjusted using serum IgG level in patients with multiple myeloma or malignant macroglobulinemia. NCCN guidelines on prevention and treatment of cancer-related infections discussed similar recommendations.[31]
- **Human immunodeficiency virus (HIV)-associated thrombocytopenia**: Secondary ITP can occur in patients with HIV infection.[23,24] Treatment of secondary ITP (HIV-associated) with short-term corticosteroid therapy increases the platelet count in a similar manner as in non-HIV infected persons and does not appears to be associated with adverse effects. The American Society of Hematology guidelines for ITP recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV.[23,24]
- **HIV-infected infants and children to prevent recurrent infections**: IVIG is no longer recommended for primary prevention of serious infections in children infected with HIV unless hypogammaglobulinemia is present or functional antibody deficiency is demonstrated by recurrent infections.[40] In children with greater than two serious infections in a 1-year period and who cannot tolerate combination antiretroviral therapy, secondary prophylaxis is indicated. The first choice for secondary prophylaxis is trimethoprim-sulfamethoxazole and IVIG every 2 to 4 weeks is an alternative. Clinicians providing care for adolescents are advised to use the US Department of Health and Human Services Adult and Adolescent HIV-guideline for the care of post-pubertal adolescents (sexual maturity rating [SMR] four and five) and to use the pediatric guideline for guidance on the care of adolescents at SMR 3 or lower.[40]

- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy**: NCCN guidelines for the management of immunotherapy-related toxicities (version 3.2021 – May 14, 2021) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy; as treatment for severe myasthenia gravis; encephalitis; cardiovascular adverse events; inflammatory arthritis; musculoskeletal adverse events; moderate or severe Guillian-Barre syndrome; severe transverse myelitis; bullous dermatitis; and Stevens-Johnson syndrome/toxic epidermal necrolysis.[74] The American Society of Clinical Oncology (ASCO) also has practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.[75] These practice guidelines address the above mentioned indications along with other conditions (e.g., severe cutaneous adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome (LEMS)**: Limited but moderate- to high-quality evidence from randomized controlled trials have shown that 3,4-diaminopyridine or IVIG was associated with improved muscle strength score and compounded muscle action potential amplitudes. IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies.[18]
- **Multiple myeloma**: Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.[31] The NCCN guidelines on multiple myeloma (version 1.2022 – August 16, 2021) note that IVIG should be considered in the setting of recurrent, serious infections.[42]
- **Multiple sclerosis, acute severe exacerbation or relapses**: Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotrophic hormone, plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.[43] During pregnancy, relapses severe enough to require treatment can be safety managed with a short-term course of corticosteroids after the first trimester. Methylprednisolone is the preferable agent because it is metabolized before crossing the placenta.[43]
- **Myasthenia gravis**: Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.[65] Symptomatic and immunosuppressive treatment of myasthenia gravis includes pyridostigmine as initial therapy in most patients. Corticosteroids or immunosuppressive therapies are used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal immunosuppressive agent (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. In patients with refractory myasthenia gravis, chronic IVIG and chronic plasma exchange (PLEX), cyclophosphamide, or rituximab may be used. PLEX and IVIG are recommended as short-term treatments in patients with myasthenia gravis with life-threatening effects such as respiratory insufficiency or dysphagia; to prepare for surgery in patients with significant bulbar dysfunction; when rapid response is needed; when other treatments are not adequate; and before starting corticosteroids if necessary to prevent or minimize exacerbations. IVIG can be considered as maintenance therapy in patients with refractory myasthenia gravis or in patients with relative contraindications to immunosuppressive agents. Refractory myasthenia gravis is defined as the post intervention status is unchanged or worse after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning as defined by the patient or physician. The international consensus guidance statement for myasthenia gravis[65] recommends an initial dose of 2 g/kg given in divided doses over 2 to 5 days. For maintenance therapy, the recommended dose is 0.4 to 1 g/kg given every 4 weeks; an attempt to decrease frequency can be made over time. If additional treatment is required, the dose should be adjusted based on the response.

- **Passive immunization for measles (post-exposure prophylaxis)**: When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at ≥ 12 months, unless the patient is severely immunocompromised. The Advisory Committee on Immunization Practices (ACIP) recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complication from measles: infants < 12 months of age; pregnant women without evidence of measles immunity; and severely immunocompromised persons.[13] For infants < 12 months of age, intramuscular IG is used; infants 6 through 11 months of age can receive measles, mumps and rubella vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients. ACIP recommends 400 mg/kg as an IV infusion.[13]
- **Passive immunization for Varicella (chickenpox) [post-exposure prophylaxis]**: Children infected with HIV without a history of previous chickenpox or children who have not received two doses of varicella vaccine should receiving VariZIG® or, if not available, IVIG within 10 days after close contact with a person who has chickenpox or shingles.[41,46] VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferable within 4 days, and as late as 10 days after exposure.[47] Whether to administer VariZIG depends on three factors: 1) whether the patient lacks evidence of immunity to varicella; 2) whether the exposure is likely to result in infection; and 3) whether the patient is at greater risk for varicella complications than the general population.[48] In situations where administration of VariZIG does not appear possible within 10 days of exposure, IVIG is considered an alternative and should be given within 10 days of exposure48 (and ideally within 96 hours of exposure).[40] The dose is 400 mg/kg given once.[40,41,46]
- **Pure red blood cell aplasia secondary to chronic (persistent) parvovirus B19 infection and immunologic subtype**: In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[49] IVIG has been used to treat severe anemia secondary to chronic parovirus B19 infection in the context of solid-organ transplantation, HIV infection, or primary antibody deficiency.[49] A Canadian expert panel of hematologists recommend prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type pure red blood cell aplasia.[22] The panel considers IVIG a reasonable second-line option for this serious condition.
- **Stiff-Person Syndrome (Moersch-Woltman Syndrome)**: Per the European Federation of Neurological Societies, IVIG should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have severe disability in carrying out daily activities.[32]
- **Thrombocytopenia, feto-neonatal alloimmune**: Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.[50,51] First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive therapy.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of IVIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e.,

Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG products as well as the monitoring required for adverse events and long-term efficacy, some approvals require IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

If the prescriber is switching between IVIG products and a case has already been approved by a clinician, a new approval may be entered without another clinical review. The new approval should only be extended for the remaining doses and duration which were granted on the original review. The indication (or diagnosis code) and dosing need to be the same as the original review. If the indication or dosing is different, a new clinical review would need to be completed.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of immune globulin intravenous products is recommended in those who meet the following criteria:

FDA-Approved Indications

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1. **Primary Immunodeficiencies.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient meets ONE of the following (a, b, or c):
       Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.
       - **a)** Patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency, Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR
       - **b)** Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):
         - **(1)** Patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
         - **(2)** Patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); OR
         - **(3)** Patient has recurrent infections; OR
       - **c)** Patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following criteria (1 and 2):
         - **(1)** Patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); AND
         - **(2)** Patient has recurrent infections; AND
     - **ii.** The medication is prescribed by or in consultation with one of the following physician specialists: an allergist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and, according to the prescriber, is continuing to receive benefit from the product.
Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

Dosing. Approve the following dosing regimens (A, B, C, or D):
A) An initial loading dose of 1 g/kg given intravenously one time; OR
B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR
C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber; OR
D) Patients with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 4 months if the patient meets the following (i or ii and iii):
i. Patient has an immunoglobulin G (IgG) level < 500 mg/dL (5.0 g/L); OR
ii. Patient has a history of recurrent infections; AND
iii. The medication is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

Dosing. Approve the following dosing regimens (A, B, or C):
A. 0.4 g/kg given intravenously every 3 to 4 weeks; OR
B. 0.3 g/kg to 0.5 g/kg given intravenously once monthly; OR
C. The dose and interval have been adjusted to maintain a trough (pre-dose) IgG level of greater than 500 mg/dL.

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3. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets the following (i and ii):
i. Electrodiagnostic studies support the diagnosis of CIDP; AND
ii. The medication is prescribed by or in consultation with a neurologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

Dosing. Approve the following dosing regimens (A, B, or C):
A) An initial loading dose of 2 g/kg given intravenously in divided doses over 2 to 4 consecutive days; OR
B) A maintenance dose of 1 g/kg given intravenously over one day or divided into two doses of 0.5 g/kg given on 2 consecutive days. Either regimen is given every 3 weeks. OR
C) The dose and interval are adjusted according to clinical response with a maximum dose per treatment course of 2 g/kg.

4. Dermatomyositis or Polymyositis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):

i. Prior to starting any therapy for this condition, the patient meets one of the following (a or b):

a) Patient has or had an elevated creatinine kinase (CK) level, according to the prescriber; OR

b) Other measures support the diagnosis, according to the prescriber, including, but not limited to, skin manifestations, autoantibody testing, muscle biopsy results, electromyographic (EMG) findings; AND

ii. Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND

iii. Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; AND

Note: Examples of immunosuppressive agents include azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate mofetil.

iv. The medication is prescribed by or in consultation with a neurologist or a rheumatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.

Note: Examples of a response to therapy includes improved muscle strength, improved neuromuscular symptoms, and improved functional ability.

Dosing. Approve the following dosing regimens (A or B):

A) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 4 weeks; OR

B) 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days every 2 to 3 weeks.

5. Immune Thrombocytopenia (ITP). Approve for the duration noted if the patient meets ONE of the following (A, B, C, D, or E):

Note: The diagnosis of ITP encompasses previous nomenclature, such as Idiopathic Thrombocytopenia, Idiopathic Thrombocytopenic Purpura, Immune Thrombocytopenic Purpura.

A) Initial Therapy – Adult ≥ 18 Years of Age: Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient meets one of the following (a, b, or c):

a) Patient has tried a systemic corticosteroid (e.g., prednisone); OR

b) There is an urgent need to increase the platelet count quickly; OR

c) A systemic corticosteroid is contraindicated according to the prescriber; AND

ii. The medication is prescribed by or in consultation with a hematologist.

B) Initial Therapy – Patient is < 18 Years of Age. Approve for 1 year if prescribed by or in consultation with a hematologist.

C) Initial Therapy – To Increase Platelet Count Before Surgical or Dental Procedures. Approve for 1 month if prescribed by or in consultation with a hematologist.

D) Initial Therapy – Pregnant Patient. Approve for 6 months if prescribed by or in consultation with a hematologist.

E) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.

Note: Examples of responding to therapy include increased platelet counts, absence of significant bleeding, or preventing hemorrhage/ensuring an adequate platelet count in order for delivery in pregnant patients.

Dosing. Approve the following dosing regimens (A or B):
A) Up to 1 g/kg on 2 consecutive days OR up to 0.4 g/kg on 5 consecutive days (up to a total of 2 g per kg per treatment course); OR
B) The dose and interval between doses has been adjusted according to the platelet count and/or to prevent significant bleeding as determined by the prescriber.

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6. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

Dosing. Approve up to 2 g/kg given intravenously as a single dose or over multiple consecutive days. The dose may be repeated if needed.

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7. Multifocal Motor Neuropathy. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):
  i. The diagnosis is supported by weakness without sensory abnormalities, upper motor neuron signs, or marked bulbar involvement and meets one of the following (a, b, or c):
    a) The diagnosis is supported by nerve conduction studies that demonstrate motor conduction block or probable motor conduction block; OR
    b) The prescriber has determined the patient has multifocal motor neuropathy without conduction block; OR
    c) The diagnosis is supported by a motor nerve biopsy or by a magnetic resonance imaging (MRI) neurography; AND
  ii. The medication is prescribed by or in consultation with a neurologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has improvement in neurologic symptoms as determined by the prescriber
Note: Examples of improvement in neurologic symptoms include improvement in disability; grip strength improvement (measured with dynamometer); physical examination show improvement in neurological symptoms and strength.

Dosing. Approve the following dosing regimens (A or B):
A) Therapy is initiated with 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) One of the following maintenance dosing regimen is used (i, ii or iii):
  i. 0.5 g/kg to 2.4 g/kg given intravenously every month; OR
  ii. 1 g/kg given intravenously every 2 to 4 weeks; OR
  iii. 2 g/kg given intravenously every 1 to 2 months.

Other Uses with Supportive Evidence

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8. Antibody-Mediated Rejection in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve the following dosing regimens (A or B):
A) Up to 2 g/kg as an intravenous infusion (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR
B) The dosage is based on a transplant center's protocol.

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9. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and

Epidermolysis Bullosa Acquisita). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following (a, b, or c):
  - **a)** Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber AND the patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; OR
    Note: Examples of immunosuppressive agents include azathioprine, cyclophosphamide, dapsone, methotrexate, cyclosporine, mycophenolate mofetil, and tacrolimus.
  - **b)** Patient has rapid, debilitating, progressive disease that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent; OR
  - **c)** The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect; AND
- **ii.** The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy can include healing of previous lesions or fewer new lesions.

Dosing. Approve the following dosing regimens (A, B, or C):

A) 2 g/kg per cycle given intravenously every 3 to 4 weeks. This dose is divided over 2, 3, or 5 consecutive days; OR

B) In patient with aggressive ocular disease, such as ocular cicatricial pemphigoid, 2 g/kg given intravenously may be given every 2 weeks in divided doses over 2, 3, or 5 consecutive days; OR

C) The frequency is gradually being slowly decreased as the lesions resolve and heal.

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10. Cytomegalovirus Pneumonia in a Patients with Cancer or Transplant-Related Infection. Approve for 2 months if prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

Dosing. Approve 400 mg/kg given intravenously every other day for 3 to 5 doses.

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11. Desensitization Therapy Prior to and Immediately after Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

Dosing. Approve the following dosing regimens (A or B):

A) Up to 2 g/kg per month administered intravenously (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]); OR

B) The dosage is based on a transplant center's protocol.

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12. Guillain Barre Syndrome. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (this is to provide one course of therapy) if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets one of the following (a or b):
  - **a)** The medication is initiated within 2 weeks and no longer than 4 weeks after onset of neuropathic symptoms; OR

Note: Examples of neuropathic symptoms include weakness, inability to stand or walk without assistance, and respiratory or bulbar weakness.

b) Patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG; AND

ii. The medication is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with Guillain Barre syndrome.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month (this is to provide a second course) about 3 weeks after the first course.

Dosing. Approve 2 g/kg administered intravenously in divided doses over 2 to 5 days.

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13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]). Approve for 6 months if the patient meets ONE of the following (A or B):

Note: Some examples of B-cell targeted therapy are chimeric antigen receptor (CAR)-T cell therapy (e.g., Kymriah [tisagenlecleucel injection], Abecma [idecabtagene vicleucel injection], Breyanzi [lisocabtagene maraleucel injection], Tecartus [brexucabtagene autoleucel injection], Yescarta [axicabtagene ciloleucel injection]), a rituximab product, Besponsa (inotuzumab ozogamicin injection).

Note: Refer to B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Infections and Multiple Myeloma for diagnosis-specific criteria.

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii and iii):

i. Patient has an immunoglobulin G (IgG) level of < 500 mg/dL (5.0 g/L) [excluding paraprotein]; AND

ii. Patient has recurrent or severe infections or there is a high risk of infection according to the prescriber; AND

iii. The medication is being prescribed by or in consultation with an oncologist, hematologist, infectious disease physician, or immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

Dosing. Approve the following dosing regimens (A, B, or C):

A) 0.4 g/kg to 0.6 g/kg given intravenously once a month; OR

B) 0.2 g/kg to 0.8 g/kg given intravenously once every 3 to 4 weeks; OR

C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

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14. Hematopoietic Cell Transplantation to Prevent Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient has had a HCT within the previous year; AND

ii. Patient has an immunoglobulin G (IgG) level < 500 mg/dL (5.0 g/L) OR the patient has multiple myeloma or malignant macroglobulinemia; AND

iii. According to the prescriber, the patient has a significant risk of having frequent and/or severe infections; AND

iv. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level, controlling the number of infections, or a decrease in the number of infections.

Dosing. Approve the following dosing regimens (A, B, or C):

A) During the first 100 days after HCT, the patient meets ONE of the following (i or ii):
- **i.** Adults and adolescents: 0.5 g/kg per week given intravenously and the dose is adjusted to maintain trough (pre-dose) serum IgG greater than 400 mg/dL; OR
- **ii.** Pediatric patient with allogeneic HCT: 0.4 g/kg per month given intravenously and the dose is adjusted to keep IgG greater than 400 mg/dL; OR

B) Greater than 100 days post-HCT, the dose is 0.5 g/kg given intravenously every 3 to 4 weeks, and the dose is adjusted to keep IgG greater than 400 mg/dL; OR

C) The dosage is based on a transplant center's protocol.

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15. Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia. Approve for 1 month if the patient meets the following (A and B):

A) Patient meets one of the following (i or ii):
- **i.** Patient is receiving combination antiretroviral therapy; OR
- **ii.** Patient has clinically significant bleeding complications according to the prescriber; AND

B) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician who specializes in the treatment of HIV infection.

Dosing. Approve the following dosing regimens (A or B):

A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 days; OR

B) Up to 1 g/kg one time given intravenously up to once weekly.

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16. Human Immunodeficiency Virus (HIV), to Prevent Recurrent Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is < 18 years of age; AND
- **ii.** Patient is receiving combination antiretroviral therapy; AND
- **iii.** Patient has ONE of the following (a, b, or c):
  - **a)** Hypogammaglobulinemia (i.e., IgG < 400 mg/dL [4.0 g/L]); OR
  - **b)** Functional antibody deficiency is demonstrated by poor specific antibody titers (that is, the patient does not develop specific antibody responses against protein and polysaccharide antigens); OR
  - **c)** Functional antibody deficiency is demonstrated by the patient having recurrent (two or more per year), serious infections (e.g., bacteremia, meningitis, pneumonia) despite administration of combination antiretroviral therapy and appropriate antimicrobial prophylaxis; AND
- **iv.** The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the frequency and/or severity of infections have decreased according to the prescriber.

Dosing. Approve the following dosing regimens (A or B):

A) The dose is 0.4 g/kg given intravenously infusion every 2 to 4 weeks; OR

B) The dose and interval are adjusted according to clinical effectiveness.
Note: Examples of adjusting according to clinical effectiveness may include the need to increase the dose or frequency based on frequency or severity of infections, hospitalizations, days of school or work missed, failure to thrive.

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17. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab injection), Opdivo (nivolumab injection), Yervoy (ipilimumab injection), Tecentriq (atezolizumab injection), Bavencio (avelumab injection), Imfinze (durvalumab injection), Libtayo (cemiplimab injection), Jemperli (dostarlimab injection).

A) Initial Therapy. Approve for 1 month if the patient meets the following (i, ii, or iii):
- **i.** Patient has tried a systemic corticosteroid and has not adequately responded to therapy; OR
  Note: Examples of systemic corticosteroids include prednisone, methylprednisolone.
- **ii.** The medication is being started with a systemic corticosteroid; OR
- **iii.** A corticosteroid is contraindicated per the prescriber.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy, as determined by the prescriber, and the prescriber has determined extended therapy is required.

Dosing. Approve the following dosing regimens (A, B, or C):
A) Up to 0.4 g/kg given intravenously daily for 5 days; OR
B) Up to 2 g/kg given intravenously over 2 to 5 days; OR
C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

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18. Lambert-Eaton Myasthenic Syndrome (LEMS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (to allow for one course of therapy) if the patient meets the following (i, ii, and iii):
- **i.** Patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient has paraneoplastic LEMS; OR
  - **b)** Patient has non-paraneoplastic LEMS AND has tried a systemic corticosteroid (e.g., prednisone) or another immunosuppressive agent (e.g., azathioprine), or has a contraindication to corticosteroids and/or immunosuppressive agents, according to the prescriber; AND
- **iii.** The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a response or continued effectiveness, according to the prescriber.
Note: Examples of a response to therapy include improved muscle strength or other clinical response.

Dosing. Approve the following dosing regimens (A or B):
A) Up to 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR
B) Maintenance therapy every 4 weeks with up to 2 g/kg with the dose being adjusted based on clinical symptoms.

19. Multiple Myeloma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following (i and ii):
- **i.** Patient has severe, recurrent infections according to the prescriber; AND
- **ii.** The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year.

Dosing. Approve 0.4 g/kg to 0.5 g/kg given intravenously every 3 to 4 weeks.

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20. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses. Approve for 1 month (this is to provide one course of therapy) if the patient meets the following (A, B, and C):

A) Patient meets one of the following (i or ii):
- **i.** Patient has either not responded to OR has had a significant adverse reaction with systemic corticosteroids (e.g., methylprednisolone sodium succinate injection) OR plasma exchange; OR

  Note: A trial of Acthar H.P. gel [repository corticotropin injection; adrenocorticotropic hormone, ACTH] would also count toward meeting this requirement.
- **ii.** A systemic corticosteroid is contraindicated, according to the prescriber; AND

B) Patient meets one of the following (i or ii):
- **i.** Patient is already on maintenance therapy for MS or will be starting maintenance therapy for MS; OR

  Note: Maintenance therapy does NOT include IVIG. Examples of maintenance therapy for MS would include: Avonex (interferon beta-1a injection), Plegridy (peginterferon beta-1a injection), Rebif (interferon beta-1a injection), Betaseron (interferon beta-1b injection)/Extavia (interferon beta-1b injection), Copaxone (glatiramer injection)/Glatopa (glatiramer injection), Gilenya (fingolimod capsule), Lemtrada (alemtuzumab injection), Aubagio (teriflunomide tablet), Mavenclad (cladribine tablet), Mayzent (siponimod tablet), Tecfidera (dimethyl fumarate capsule), Vumerity (diroximel fumarate capsule), Zeposia (ozanimod capsule), Tysabri (natalizumab injection), Novantrone (mitoxantrone injection), Bafiertam (monomethyl fumarate capsule), Kesimpta (ofatumumab injection), Ocrevus (ocrelizumab injection), Ponvory (penesimod tablet).
- **ii.** Patient is pregnant or patient is post-partum and the prescriber has determined maintenance therapy is not clinically appropriate; AND

C) The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

Dosing. Approve the following dosing regimens (A or B):

A) A single 1 g/kg given intravenously ; OR

B) 0.4 g/kg per day IV infusion for 5 consecutive days.

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21. Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A, B, C or D):

A) Initial Therapy for Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy) if the patient meets the following (i and ii):
- **i.** Patient meets ONE of the following conditions (a, b, c, or d):
  - **a)** Patient has an exacerbation of myasthenia gravis; OR
  - **b)** Patient requires stabilization of myasthenia gravis before surgery; OR
  - **c)** Patient has been started on an immunosuppressive drug and is waiting for full effect; OR

Note: Examples of immunosuppressive drugs include azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, or tacrolimus.

d) Patient is starting therapy with a corticosteroid and IVIG is being given to prevent or minimize exacerbations; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Cuurrently Receiving Immune Globulin Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy).

C) Initial Therapy for Maintenance. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient has refractory myasthenia gravis; AND

ii. Patient has tried pyridostigmine; AND

iii. Patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus AND has had an inadequate response; AND

iv. The medication is prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Immune Globulin for Maintenance Therapy. Approve for 1 year if the patient is responding according to the prescriber.

Note: Examples of responding to therapy include improvement in weakness (bulbar, limb, or respiratory), improvement with ocular symptoms.

Dosing. Approve the following dosing regimens (A, B, or C):

A) Short-term use: 2 g/kg given intravenously in divided doses over 2 to 5 consecutive days; OR

B) Maintenance therapy: 0.4 g/kg to 1 g/kg given intravenously every 4 weeks; OR

C) The dose and interval between doses has been adjusted based on clinical response as determined by the prescriber.

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22. Passive Immunization for Measles (Post-Exposure Prophylaxis). Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):

Note: For patients with primary immune deficiency, see criteria for PID.

A) Patient is pregnant and meets the following (i and ii):

i. Patient has been exposed to measles; AND

ii. Patient does not have evidence of immunity to measles (i.e., the patient does not have a history of the disease or age-appropriate vaccination); OR

B) Patient meets ALL of the following (i, and ii):

i. Patient is immunocompromised; AND

ii. Patient has been exposed to measles.

Dosing. Approve the following dosing regimen: 0.4 g/kg intravenously administered one time.

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23. Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]. Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):

A) Patient has HIV and meets the following(i, ii, and iii):

i. VariZIG® (varicella zoster immune globulin [human] for intramuscular injection) is not available or cannot be administered within 10 days of exposure; AND

ii. Patient does not have evidence of immunity to varicella (i.e., patient does not have a history of the disease or age-appropriate vaccination); AND

iii. The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist; OR

B) Patient does not have HIV and meets the following (i, ii, iii, and iv):
- **i.** VariZIG (varicella zoster immune globulin [human] for intramuscular injection) is not available or cannot be administered within 10 days of exposure; AND
- **ii.** Patient does not have evidence of immunity to varicella (i.e., patient does not have a history of the disease or age-appropriate vaccination); AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient is immune compromised; OR
  - **b)** Patient is pregnant; AND
- **iv.** The medication is prescribed by or in consultation with an infectious diseases specialist or immunologist.

Dosing. Approve 0.4 g/kg given intravenously one time.

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24. Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic [Persistent] Parvovirus B19 Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 2 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has a chronic immunodeficiency condition; AND
  Note: Examples of a chronic immunodeficiency condition include patients with HIV infection, solid organ transplants (e.g., renal, liver), chemotherapy for hematologic malignancy.
- **ii.** Patient has clinically significant anemia as determined by the prescriber OR the patient is transfusion dependent; AND
- **iii.** The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 3 months if the patient responded with an increase in hemoglobin to previous IVIG therapy but relapse when off IVIG or in patients who respond and require maintenance therapy to prevent relapse.

Dosing. Approve the following dosing regimens (A, B, or C):

A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days (one course) for up to two courses; OR

B) 0.4 g/kg to 0.5 g/kg given intravenously daily for 5 days; OR

C) 0.4 g/kg given intravenously once every 4 weeks.

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25. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has tried a systemic corticosteroid (e.g., prednisone); AND
- **ii.** Patient has tried either cyclophosphamide OR cyclosporine; AND
- **iii.** The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month if the patient has responded with an increase in hemoglobin and reticulocytossis according to the prescriber.

Dosing. Approve 0.5 g/kg given intravenously for 4 weeks.

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26. Stiff-Person Syndrome (Moersch-Woltman Syndrome). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i and ii):
- **i.** Patient meets ONE of the following criteria (a or b):
  - **a)** Patient has tried a benzodiazepine (e.g., diazepam) OR baclofen; OR

b) Patient has contraindications to both a benzodiazepine AND baclofen according to the prescriber; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy includes reduced stiffness or frequency of spasms, ability to walk unassisted.

Dosing. Approve the following dosing regimens (A or B):

A) 2 g/kg given intravenously over a period of 2 to 5 consecutive days every month; OR

B) For maintenance therapy, the dose is adjusted to provide the minimum effective dosage of IVIG. Maximum dose is 2 g/kg given intravenously.

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27. Thrombocytopenia, Feto-neonatal Alloimmune. Approve for 6 months if the pregnant mother or newborn patient is prescribed the medication by or in consultation with a hematologist or an obstetrician.

Dosing. Approve the following dosing regimens (A, B, C, or D):

A) For the mother: 1 g/kg given intravenously every week; OR

B) For the mother: 2 g/kg given intravenously every week; OR

C) For the mother: 1 g/kg given intravenously twice weekly; OR

D) For the newborn: 1 g/kg to 2 g/kg given intravenously dosed per the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin intravenous is not recommended in the following situations:

1. **Adrenoleukodystrophy.** Evidence does not support IVIG use.[18]

2. **Alzheimer's Disease (AD).** In one multicenter, double-blind, Phase III, placebo-controlled trial, 390 patients with mild to moderate AD were randomized to therapy with IVIG 400 mg/kg or 200 mg/kg or to placebo given every 2 weeks for 18 months.[61] There was no statistically significant difference in the rate of cognitive decline when compared with placebo. Also, there was not a statistically significant change in functional ability when compared to placebo. Large placebo-controlled trials with a longer observation period are needed to establish efficacy, determine the optimal dosing regimen, and to confirm the safety of IVIG in the general AD population.[52,53]

3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG.[18]

4. **Anemia, Aplastic.** Evidence does not support IVIG use.[22]

5. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

6. **Atopic Dermatitis.** Limited data exist to determine the utility of intravenous immunoglobulin in the management of atopic dermatitis.[55]

7. **Autism.** Evidence does not support IVIG use.[18] Well controlled, double-blind trials are needed.

8. **Chronic Fatigue Syndrome.** Evidence does not support IVIG use.[56] One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.[56] Although scores were improved in IVIG and placebo treatment groups, no significant between group difference was demonstrated.

9. **Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy).** There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g of IVIG per kg produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients.[57] In a randomized, placebo-controlled, multicenter trial, low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate-to-severe complex regional pain syndrome.[58] Well-controlled large-scale trials are needed.

10. **Crohn's Disease.** There is insufficient evidence to recommend IVIG. In one single center case collection report, 19 patients with acute Crohn's disease (Crohn's Disease Activity Index [CDAI] 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days.[59] Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has a role in the treatment of Crohn's disease.

11. **Cystic Fibrosis.** There is insufficient evidence to recommend IVIG. In one single-center retrospective case review of 16 children with cystic fibrosis, IVIG was reportedly effective.[60] Well-designed, controlled trials are needed.[18]

12. **Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use.[18,62,63] In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.[62] No beneficial effect was shown with IVIG compared with control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

13. **Fibromyalgia Syndrome.** There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy received IVIG 400 mg/kg given daily for 5 days.[64] Pain, tenderness, and strength reportedly improved. Double-blind, placebo-controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.

14. **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%.[66] In another controlled trial in patients with recent onset dilated cardiomyopathy and 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.

15. **Human Immunodeficiency Virus (HIV) Infection, Adults, for Prophylaxis of Infections.** IVIG is not listed in the recommendations for post exposure prophylaxis for occupational exposures to HIV; antiretroviral therapy should be used in certain circumstances after exposure to HIV infection.[67]

16. **In Vitro Fertilization (IVF).** There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

17. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.[18]

18. **Post-Polio Syndrome.** There is insufficient evidence to recommend IVIG. A 2015 Cochrane Review concluded there was moderate- and low-quality evidence that IVIG has no beneficial effect on activity limitations in the short term and long term, respectively.[69] The evidence for effectiveness of IVIG on muscle strength is inconsistent.

19. **Recurrent Spontaneous Pregnancy Loss (RSPL) [Including a Patient with Antiphospholipid Antibody-Positive].** Evidence does not support IVIG use.[70-73] In one double-blind pilot study, IVIG did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen.[70] In another double-blind trial (n =82 of whom 47 had an index pregnancy) live birth rates did not differ significantly between IVIG-treated and placebo-treated women.[71] The American Society for Reproductive Medicine practice committee states that several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss and this treatment is not recommended.[73]

20. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of IVIG.[14,18] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Primary Immunodeficiencies (PID)**: In Initial Therapy, the wording of "or another confirmed primary immunodeficiency" was added. For Continuation Therapy, the examples of benefits from the product were moved to a Note and the wording "according to the prescriber" was added. In **Dosing**, the examples of clinical response were removed. In Dosing related to patients with primary immunodeficiency and exposure to measles, the wording of "previous exposure or risk of future measles exposure" was added. The specific measles dosing regimens were removed and the wording that the minimum dose has been determined by the prescriber was added. **B-Cell Chronic Lymphocytic Leukemia for Prevention of Bacterial Infections**: Added "having a positive response to therapy according to the prescriber" and placed current examples of a positive response as a note. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy**: For Continuation Therapy, moved examples of a clinically significant improvement to a note. Removed a neurologist or in consultation with a neurologist for continuation criteria. **Idiopathic (Immune) Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia [IT] Acute and Chronic** was updated to Immune Thrombocytopenia (ITP). The following note was added: The diagnosis of Immune Thrombocytopenia (ITP) encompasses previous nomenclature, such as Idiopathic Thrombocytopenia, Idiopathic Thrombocytopenic Purpura, Immune Thrombocytopenic Purpura. In Initial Therapy for adults ≥ 18 years of age (previously > 17 years of age), criteria were updated to require the patient try a systemic corticosteroid, or there is an urgent need to increase platelet count quickly, or to allow if a systemic corticosteroid is contraindicated according to the prescriber. Previous criteria that separated out adults and children with acute bleeding and those with persistent or chronic disease were removed. Previous criteria of specifying platelet counts for adults with acute bleeding, persistent or chronic disease, and to increase platelet counts prior to surgery were removed. The requirement for adults that a corticosteroid be started with immune globulin if there is an urgent need to increase the platelet count quickly was removed. In Initial Therapy for children and adolescents (< 18 years of age) [previously ≤ 17 years of age], to increase platelet counts before surgical procedures, and pregnant patients, the criteria were updated to only include a requirement for the prescriber's specialty. Previous criteria that addressed children and adolescents with inaccessibility issues, activity level, and noncompliance were removed. The specific wording regarding pregnant patients, including "before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia" and "pregnant patient in any trimester" was removed and replaced with the general term of "pregnant patients". The duration of approval was updated from 2 weeks and 3 months, per the respective classifications, to 6 months for any pregnant patient. For Continuation Therapy, a requirement was added that the patient has responded to therapy according to the prescriber; and the examples of responding to therapy were moved to a Note. In **Dosing**, specific dosing regimens were removed. The wording of "up to" 1 g per kg on 2 consecutive days, "up to" 0.4 g per kg on 5 consecutive days (up to a total of	08/19/2020

	2 g per kg per treatment course), and the dose and interval between doses has been adjusted according to the platelet count and/or to prevent significant bleeding "as determined by the prescriber" was added. **Kawasaki Disease**: The criteria were updated from approval of a single dose to an approval duration of 3 months. The criterion that the patient had signs and symptoms required for a second dose of immune globulin was removed since the intent of the criteria assumed the patient was given a first dose of the product in the hospital. In **Dosing**, the wording of "up to" and "as a single dose or over multiple consecutive days" and "the dose may be repeated if needed" was added. Also, the references to length of infusion and to signs of fever or inflammation were removed. **Multifocal Motor Neuropathy (MMN)**. For Continuation Therapy, moved examples of a clinically significant improvement to a note. Removed a neurologist or in consultation with a neurologist for continuation criteria. **Antibody-Mediated Rejection (ABMR) in Solid Organ Transplantation (e.g., Kidney, Heart, Lung, Liver)** was updated to Antibody-Mediated Rejection (ABMR) in Transplantation. In **Dosing**, the reference to case-by-case review was removed. Also, an addition of criterion was added as up to 2 g per kg as an intravenous infusion (as a single dose or divided in smaller doses) OR based on a transplant center's protocol. **Autoimmune Mucocutaneous Blistering Diseases**. In the initial therapy criteria, examples of immunosuppressive agents were updated to notes. In the continuation criteria, examples of response to therapy were updated to notes. **Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Cancer or Transplant-Related Infection** was updated to Cytomegalovirus (CMV) Pneumonia in Patients with Cancer or Transplant-Related Infection. **Dermatomyositis or Polymyositis**. In the initial therapy criteria, examples of immunosuppressive agents were updated to notes. In the continuation criteria, examples of response to therapy were updated to notes. **Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation** was updated to Desensitization Therapy Prior to and Immediately after Transplantation. In Continuation Therapy, the criterion regarding the timing of administration was removed. Criteria was updated to approve for 1 year if the product is prescribed by or in consultation with a physician affiliated with a transplant center. **Guillain Barre Syndrome (GBS).** Neuropathic symptoms were moved from criterion to a note. **Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficieny [SID])**. Added IgG level in units of g/L. Continuation criteria: updated wording to having a positive response to therapy according to the prescriber and moved examples of a positive response to a note. In **Dosing**, the reference to case-by-case review was removed. Dosing was updated as 0.4 to 0.5 g per kg to 0.4 to 0.6 g per kg. Also, the criterion was added as 0.2 to 0.8 g per kg once every 3 to 4 weeks and dosing adjusted based on clinical response as determined by the prescriber. **Hematopoietic Cell Transplantation (HCT) to Prevent Bacterial Infection**. Added IgG level in units of g/L. Continuation criteria: updated wording to having a positive response to therapy according to the prescriber and moved examples of a positive response to a note. In **Dosing**, the following criterion was added: The immune globulin dosage is based on a transplant center's protocol. **Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia**. Dosing section- added "up to" to both dosing criteria. **Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections**. Added IgG level in units of g/L. Dosing criteria- removed "between infusions" and added a note of examples of adjusting the dose according to clinical effectiveness. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy**. Initial therapy criteria- moved examples of systemic corticosteroid therapy to a note. Dosing criteria: Added "up to" and "as an IV infusion" wording. Added criterion regarding the dose and interval between doses has been adjusted based on clinical response as determined by the prescriber. **Lambert-Eaton Myasthenic Syndrome (LEMS).** Continuation criteria- moved examples of a response to therapy to a note. In **Dosing**, the wording "up to" was added. Dosing criteria- added the wording "up to" on criteria A).	

	Myasthenia Gravis. Moved examples of immunosuppressive drugs to notes. Dosing criteria- added criterion regarding the dose and interval between doses has been adjusted based on clinical response as determined by the prescriber. Also added the wording "up to". **Passive Immunization for Measles (Post-Exposure Prophylaxis).** Moved examples of severe immunocompromised status into a note. **Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic [Persistent] Parvovirus B19**. Moved examples of chronic immunodeficiency conditions to a note. **Stiff-Person Syndrome (Moersch-Woltman Syndrome)**. Continuation therapy – moved examples of response to therapy to a note. **Thrombocytopenia, Feto-neonatal Alloimmune.** In **Dosing**, the reference to case-by-case review was removed. The option for neonatal being dosed by the prescriber was added.	
Selected Revision	For continuation criteria, removed the wording "intravenous."	09/2/2020
Annual Revision	Removed Carimune from the policy (obsolete). **Primary Immunodeficiencies:** The prescriber specialty of allergist/immunologist was updated to allergist (immunologist is listed separately). **B-Cell Chronic Lymphocytic Leukemia for Prevention of Infections:** The descriptor of "bacterial" was removed from the condition of approval. Additionally, the descriptor of "bacterial" was removed from the criterion regarding recurrent infections. The Dosing was updated to be: "greater than 500 mg/dL" (previously was "about 500 mg/dL and up to 700 mg/dL"). **Dermatomyositis or Polymyositis:** This indication was moved from "Other Uses with Supportive Evidence" to an FDA-approved indication. Prior to starting therapy, a requirement for an elevated kinase level, according to the prescriber, was added, unless other measures support the diagnosis, including, but not limited to, skin manifestations, autoantibody testing, muscle biopsy results, electromyographic findings. Dosing that referred to monthly use was updated to be once every 4 weeks. **Multifocal Motor Neuropathy:** The indication "Multifocal Motor Neuropathy (Treatment)" was changed as listed. A requirement was added that the diagnosis to be supported by weakness without sensory abnormalities, upper motor signs, or marked bulbar involvement. Additionally, a requirement was added for one of the following: the diagnosis is supported by nerve conduction studies that demonstrate motor conduction block or probable motor conduction block; the prescriber has determined the patient has multifocal motor neuropathy without conduction block; or the diagnosis is supported by a motor nerve biopsy or by a magnetic resonance imaging neurography. **Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita):** In the Dosing, the word "initially" was removed (not needed). **Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]):** Additional examples of chimeric antigen receptor T-cell therapy were added. The descriptor of "bacterial" was removed from the criterion regarding recurrent or severe infection. **Hematopoietic Cell Transplantation to Prevent Infection:** The indication "Hematopoietic Cell Transplantation to Prevent Bacterial Infection" was changed to as listed. Additionally, the descriptor of "bacterial" was removed from the criterion regarding frequent and/or severe infections. In Dosing, the phrase "greater than 400 to 500 mg per/dL" for serum IgG was updated to "greater than 400 mg/dL". **Human Immunodeficiency Virus-Associated Thrombocytopenia:** For Dosing, the phrase "for platelet counts less than 20 x 10^9/L or 20,000/µL to 30 x 10^9/L or 30,000/µL per mm3 and this dose is repeated once weekly if needed" was changed to "up to once weekly." **Human Immunodeficiency Virus Infected Infants and Children to Prevent Recurrent Infections:** The indication "Human Immunodeficiency Virus-Infected Infants and Children to Prevent Recurrent Bacterial Infections" was changed to as listed. Additionally, the word "bacterial" was removed from the criterion regarding recurrent, serious infections. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy:** Added additional examples of checkpoint inhibitors.	09/15/2021

	Multiple Myeloma: The word "bacterial" was removed from the criterion regarding severe, recurrent infections. **Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses:** The requirement was added that the patient is already on maintenance therapy or will be starting maintenance therapy for MS. An exception was added for pregnant and post-partum patients if the prescriber determined maintenance therapy is not clinically appropriate. **Multiple Sclerosis, Post-Partum to Prevent Relapses:** This condition and related criteria were removed. **Myasthenia Gravis:** Approval criteria were clarified related to continuation of therapy in patients using immune globulin for short-term (acute) use. Examples of a response to therapy were added for continuation of treatment in patients receiving immune globulin for maintenance therapy. Dosing was changed to remove the wording "up to" for maintenance dosing. **Passive Immunization for Measles (Post-Exposure Prophylaxis):** The requirement that the medication be given within 6 days of exposure was removed. The word "severely" was removed from the criterion related to immunocompromised patients. A note regarding examples of severely immunocompromised patients was removed. In Dosing, the wording "as soon as possible after exposure" was removed. **Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]:** The requirement that VariZIG is not available was updated to add "or it cannot be administered within 10 days of exposure".	