PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Intravenous Prior Authorization Policy

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

REVIEW DATE: 08/19/2020; Selected revision 9/2/2020

OVERVIEW

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

All of the US licensed 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 bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial 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]
- **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]
- **Multifocal motor neuropathy (MMN)** 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 (CVID), X-linked agammaglobulinemia (XLA) [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies (SCID).[1-10,12,15,16,25] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous (SC) 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.[3,4,7-10,12,13,17,25,45]

IVIG are 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 (PID), 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, intravenous immunoglobulin, 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[20,79,80], 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]
- **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) and IVIG in combination. The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 2.2020 – June 5, 2020) note IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.[31]
- **Dermatomyositis or polymyositis**. IVIG may be used in patients with dermatomyositis with severe active illness for whom other interventions have been unsuccessful or intolerable.[32,33] IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32] In uncontrolled series, IVIG has been effective in polymyositis.
- **Desensitization Therapy Prior to and Immediately after Transplantation**. Patients with preexisting anti-human leukocyte antigen (HLA) antibodies (sensitized patients) are more likely to have a positive cross match with possible donors and have a lower likelihood of receiving a transplant with longer wait times. 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 Rituxan® (rituximab injection 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 mildly affected GBS patients.[32,38]
- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency [SID])**. 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]
- **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 the following for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is indicated to prevent bacterial 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 bacterial infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL).
- **Human Immunodeficiency Virus (HIV)-associated thrombocytopenia**. Secondary ITP can occur in patients with HIV infection.[23,24] Effective viral suppression using antiretroviral therapy improves HIV-associated cytopenias, including thrombocytopenia. 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 appear to be associated with adverse effects. The American Society of Hematology guidelines for immune thrombocytopenia recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV.[23,24]
- **Human Immunodeficiency Virus (HIV)-infected infants and children to prevent recurrent bacterial infections**. IVIG is no longer recommended for primary prevention of serious bacterial infections in HIV-infected children unless hypogammaglobulinemia is present or functional antibody deficiency is demonstrated by recurrent bacterial infections.[40] In children with greater than two serious bacterial infections in a 1-year period and who cannot tolerate cART, secondary prophylaxis is indicated. The first choice of therapy 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] IV and V) and to use the pediatric guideline for guidance on the care of adolescents at SMR III or lower.[40]
- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy**. NCCN guidelines for the management of immunotherapy-related toxicities (version 1.2020 – December 16, 2020) 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; Stevens-Johnson syndrome/toxic epidermal necrolysis.[74] The American Society of Clinical Oncology 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 diagnoses (e.g., severe cutaneous skin adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).

- **Lambert-Eaton Myasthenic Syndrome (LEMS)**. LEMS is a rare presynaptic autoimmune disorder of neuromuscular transmission that is characterized by proximal muscle weakness, depressed tendon reflexes, and autonomic dysfunction.[18] 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 4.2020 – May 8, 2020) recommend that IVIG should be considered in the setting of recurrent, life-threatening infections.[42]
- **Multiple sclerosis (MS), 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 safely 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]
- **Multiple sclerosis (MS), post-partum to prevent relapses**. None of the disease modifying therapy for multiple sclerosis have been approved for use in women who are nursing. IVIG is the treatment of choice for post-partum mothers with MS who are nursing.[44]
- **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 Rituxan 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.

- **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 they are 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 aged < 12 months intramuscular IG is used; infants aged 6 through 11 months can receive MMR vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients.
- **Passive immunization for Varicella (chickenpox) [post-exposure prophylaxis]**. HIV-infected children without a history of previous chickenpox or children who have not received two doses of varicella vaccine should receive VariZIG or, if not available, IVIG within 10 days (ideally within 4 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, preferably 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] 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.[46]
- **Pure red blood cell aplasia (PRCA) 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 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 PRCA.[22] It considers IVIG a reasonable second-line option.
- **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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of IVIG products. 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 as well as the monitoring required for adverse events and long term efficacy, initial approval requires IVIG products to be prescribed by or in consultation with a physician who specialized in the condition being treated.

Automation: None.

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

FDA-Approved Indications

1. **Primary Immunodeficiencies (PID).** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
     - **i.** The 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)** The 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 (SCID), 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)** The patient has a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):
         - **(1)** The 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)** The patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); OR
         - **(3)** The patient has recurrent infections; OR
       - **c)** The patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following criteria (1 and 2):
         - **(1)** The patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); AND
         - **(2)** The patient has recurrent infections; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.
   - **B)** Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product, according to the prescriber.
     Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

2. **B-Cell Chronic Lymphocytic Leukemia for Prevention of Bacterial Infections.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following criteria (i or ii, and iii):
     - **i.** The patient has an immunoglobulin G (IgG) level < 500 mg/dL (5.0 g/L); OR
     - **ii.** The patient has a history of recurrent bacterial 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 is 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.

3. Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP). 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 criteria (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 of therapy 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. The patient may not have a full response after the initial 3 months, but there should be some response.

4. 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 Immune Thrombocytopenia (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. The patient meets one of the following (a, b, or c):
a) The 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.

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

6. Multifocal Motor Neuropathy (Treatment). Approve the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 6 months if 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.

Other Uses with Supportive Evidence

7. **Antibody-Mediated Rejection (AMBR) in Transplantation**. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

8. **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 criteria (i and ii):
      i. The patient meets ONE of the following criteria (a, b, or c):
         a) The 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) The 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.

9. **Cytomegalovirus (CMV) Pneumonia in 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.

10. **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 ALL of the following criteria (i, ii and iii):
      i. The patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND
      ii. The 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.
      iii. The medication is prescribed by or in consultation with a neurologist or 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.

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.

12. Guillain Barré Syndrome (GBS). 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 [divided doses given over 2 to 5 days]) if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets one of the following (a or b):

a) The medication is initiated within 2 weeks and no longer than 4 weeks of 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) The 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 GBS.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month (this is to provide a second course [divided doses given over 2 to 5 days]) about 3 weeks after the first course.

13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]). Approve for the duration noted 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], a rituximab product, Besponsa [inotuzumab ozogamicin]).

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

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

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

ii. The patient has recurrent or severe bacterial 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 diseases physician, or immunologist.

B) Patients 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 or a decrease in the number of infections.

14. Hematopoietic Cell Transplantation (HCT) to Prevent Bacterial 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 criteria (i, ii, iii, and iv):

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

ii. The 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 bacterial 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.

15. Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia. Approve for 1 month if the patient meets the following criteria (A and B):
A) The patient meets ONE of the following criteria (i or ii):
i. The patient is receiving combination antiretroviral therapy for their HIV infection; OR
ii. The 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 infections.

16. Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial 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 criteria (i, ii, iii, and iv):
i. The patient is < 18 years of age; AND
ii. The patient is receiving combination antiretroviral therapy; AND
iii. The 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 bacterial 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.

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), Opdivo (nivolumab), Yervoy (ipilimumab), Tecentriq (atezolizumab), Bavencio (avelumab), Imfinzi (durvalumab).

A) Initial Therapy. Approve for 1 month if the patient meets the following criteria (i, ii, or iii):
i. The 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.

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 [divided doses given over 2 to 5 days]) if the patient meets the following criteria (i, ii, and iii):

i. The patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND

ii. The patient meets ONE of the following (a or b):

a) The patient has paraneoplastic LEMS; OR

b) The 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.

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 criteria (i and ii):

i. The patient has severe recurrent bacterial 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.

20. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses. Approve for 1 month (this is to provide one course of therapy [either a single dose or in divided doses given over 1 to 5 days]) if the patient meets BOTH of the following criteria (A and B):

A) The patient meets ONE of the following criteria (i or ii):

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

21. Multiple Sclerosis (MS), Post-Partum to Prevent Relapses. 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 criteria (i and ii):

i. The patient is not currently receiving a disease modifying therapy (DMT) for MS to prevent relapses; AND

Note: Disease modifying therapy can include Avonex® (interferon beta-1a injection, IM), Plegridy® (peginterferon beta-1a SC injection), Rebif® (interferon beta-1a injection, SC), Betaseron®/Extavia® (interferon beta-1b injection), Copaxone®/Glatopa™ (glatiramer acetate injection, SC), Gilenya® (fingolimod capsules), Lemtrada™ (alemtuzumab injection for IV use), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimoid tablets), Tecfidera® (dimethyl fumarate capsules), Vumerity® (diroximel fumarate capsules), Zeposia® (ozanimod capsules), Tysabri® (natalizumab injection), Novantrone® (mitoxantrone injection).

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

B) Patient is Currently Receiving Immune Globulin. Approve for a second 6 months of therapy if the patient is not taking a disease modifying therapy (DMT) for MS.
Note: Disease modifying therapy can include: Avonex (interferon beta-1a injection, IM), Plegridy (peginterferon beta-1a SC injection), Rebif (interferon beta-1a injection, SC), Betaseron/Extavia (interferon beta-1b injection), Copaxone/Glatopa (glatiramer acetate injection, SC), Gilenya (fingolimod capsules), Lemtrada (alemtuzumab injection for IV use), Aubagio (teriflunomide tablets), Mavenclad (cladribine tablets), Mayzent (siponimoid tablets), Tecfidera (dimethyl fumarate capsules), Vumerity (diroximel fumarate capsules), Zeposia (ozanimod capsules), Tysabri (natalizumab injection), Novantrone (mitoxantrone injection).

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

A) Initial Therapy for Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy to be given in divided doses over 2 to 5 consecutive days) if the patient meets the following (i and ii):

i. The patient meets ONE of the following conditions (a, b, c, or d):

a) The patient has an exacerbation of myasthenia gravis; OR

b) The patient requires stabilization of myasthenia gravis before surgery; OR

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

i. The patient has refractory myasthenia gravis; AND

ii. The patient has tried pyridostigmine; AND

iii. The 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.

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

23. 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 criteria (A or B):

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

A) The patient is pregnant and meets the following criteria (i and ii):
- **i.** The patient has been exposed to measles and the medication will be given within 6 days of exposure; AND
- **ii.** The 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) The patient meets ALL of the following criteria (i, ii, and iii):
- **i.** The patient is severely immunocompromised; AND
  Note: Examples of severe immunocompromised status include patients with bone marrow transplant, graft-versus-host disease (GVHD), acute lymphoblastic leukemia (ALL), acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV)-infected patients.
- **ii.** The patient has been exposed to measles; AND
- **iii.** The medication will be given within 6 days of exposure.

24. 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 criteria (A or B):

A) The patient is human immunodeficiency virus (HIV)-infected and meets ALL of the following criteria (i, ii, and iii):
- **i.** VariZIG® (varicella zoster immune globulin [human] IM injection) is not available; AND
- **ii.** The 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) The patient is not HIV-infected and meets ALL of the following criteria (i, ii, iii, and iv):
- **i.** VariZIG (varicella zoster immune globulin [human] IM injection is not available; AND
- **ii.** The patient does not have evidence of immunity to varicella (i.e., the patient does not have a history of the disease or age-appropriate vaccination); AND
- **iii.** The patient meets ONE of the following criteria (a or b):
  - **a)** The patient is immune compromised; OR
  - **b)** The patient is pregnant; AND
- **iv.** The medication is prescribed by or in consultation with an infectious diseases specialist or immunologist.

25. 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 criteria (i, ii and iii):
- **i.** The 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.** The 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 in patients who 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.

26. 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 criteria (i, ii, and iii):

i. The patient has tried a systemic corticosteroid (e.g., prednisone); AND

ii. The 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 reticulocytosis, according to the prescriber.

27. 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 criteria (i and ii):

i. The patient meets ONE of the following criteria (a or b):

a) The patient has tried a benzodiazepine (e.g., diazepam) or baclofen; OR

b) The 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 as responded to therapy according to the prescriber.

Note: Examples of response to therapy includes reduced stiffness or frequency of spasms, ability to walk unassisted.

28. 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.

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 to placebo (mean 7.4 in the 400 mg/kg group; 8.9 in the 200 mg/kg group; 8.4 in the placebo group). There was not a statistically significant change in functional ability when compared to placebo (mean of -11.4 in the 400 mg/kg group; -12.4 in the 200 mg/kg group; -11.4 in the placebo group). Large placebo-controlled trials with a longer observation period are needed to established efficacy, determine the optimal dose regimen, and to confirm the safety of IVIG in the general AD poputation.[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 rituximab, omalizumab, intravenous immunoglobulin, and oral calcineurin inhibitors 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 significance between group differences 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). Spontaneous remissions cannot be excluded. 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. These patients were not diagnosed with CIPD. 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. Post-polio syndrome is characterized by new muscle weakness, atrophy, fatigue, and pain developing several years after the acute polio. A 2015 Cochrane Review concluded there was moderate- and low-quality evidence that IVIG has no beneficial effect of 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 Antiphospholipid Antibody-Positive Patients].** 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 (70% vs. 63%; P =0.76; odds ratio [OR]: 1.37 [95% CI: 0.41, 4.61]).[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.

REFERENCES

1. Bivigam® 10% liquid [prescribing information]. Boca Raton, FL: ADMA Biologics, Inc.; July 2019.
2. Carimune® NF lyophilized [prescribing information]. Kankakee, IL: CSL Behring LLC; May 2018.
3. Flebogamma® 5% DIF solution [prescribing information]. Los Angeles, CA: Grifols USA, LLC; September 2019.
4. Flebogamma DIF 10% solution [prescribing information]. Los Angeles, CA: Grifols USA LLC; September 2019.
5. Gammagard Liquid 10% solution [prescribing information]. Lexington, MA: Baxalta US Inc.; July 2017.
6. Gammagard S/D IgA < 1 mcg/mL in a 5% solution [prescribing information]. Lexington, MA: Baxalta US Inc.; August 2017.
7. Gammaked™ 10% solution [prescribing information]. Fort Lee, NJ: Kedrion Biopharma, Inc.; January 2020.
8. Gammaplex® 5% solution [prescribing information]. Durham, NC: BPL USA Inc.; September 2019.
9. Gamunex®-C 10% liquid [prescribing information]. Los Angles, CA: Grifols USA, LLC; January 2020.
10. Octagam® 5% liquid [prescribing information]. Hoboken, NJ: Octapharma USA, Inc.; September 2019.
11. Octagam® 10% liquid [prescribing information]. Hoboken, NJ: Octapharma USA, Inc.; August 2018.
12. Privigen® 10% liquid [prescribing information]. Kankakee, IL: CSL Behring LLC; March 2019.

13. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62:1-34.
14. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015;136(5):1186-205.
15. Panzyga 10% liquid [prescribing information]. New York, NY: Pfizer Laboratories; April 2019.
16. Asceniv 10% liquid [prescribing information]. Boca Raton, FL: ADMA Biologics; April 2019.
17. Bonilla FA, Barlan I, Chapel H, et al. International Consensus Document (ICON): Common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract.* 2016;4(1):38-59.
18. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. Available at: http://www.jacionline.org/article/S0091-6749(16)31141-1/pdf. Accessed on June 30, 2020.
19. Wasserman RL, Lumry W, Harris J, et al. Efficacy, safety, and pharmacokinetics of a new 10% liquid intravenous immunoglobulin containing high titer neutralizing antibody to RSV and other respiratory viruses in subjects with primary immunodeficiency disease. *J Clin Immunol.* 2016;36:590-599.
20. Otani S, Davis AK, Cantwell L, et al. Evolving experience of treating antibody-mediated rejection following lung transplantation. *Transpl Immunol.* 2014;31(2):75-80.
21. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 4.2020 – December 20, 2019) 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 30, 2020.
22. Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. *Transfus Med Rev.* 2007;21(2 Suppl 1):s9-56.
23. Neunert C, Terrell DR. Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv.* 2019;3(23):3829-3866.
24. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidenced-based practice guideline for immune thrombocytopenia. *Blood.* 2011;117:4190-4207.
25. Gammaplex 10% liquid [prescribing information]. Durham, NC: BPL USA, Inc.; October 2019.
26. American Academy of Pediatrics. Kawasaki disease. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book; 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics;2018:490-497.
27. UK National Health Service. Clinical Guidelines for Immunoglobulin Use. November 2019. http://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf. Accessed June 25, 2020.
28. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol.* 2006;6(4):557-578.
29. Enk A and the European Dermatology Forum Guideline Subcommittee. Guidelines of the use of high-dose intravenous immunoglobulin in dermatology. *Eur J Dermatol.* 2009;19:90-98.
30. Gurean HM, Jeph S, Ahmed AR. Intravenous immunoglobulin therapy in autoimmune mucocutaneous blistering diseases: a review of the evidence for its efficacy and safety. *Am J Clin Dermatol.* 2010;11:315-326.
31. The NCCN Prevention and Treatment of Cancer-Related Infections Clinical Practice Guidelines in Oncology (version 2.2020 – June 5, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on June 30, 2020.
32. Elovaara I, Apostolski S, Van Doorn P, et al. EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. *Eur J Neurol.* 2008;15:893-908.
33. Dalakas MC. The role of high-dose immune globulin intravenous in the treatment of dermatomyositis. *Int Immunopharmacol.* 2006;6:550-556.
34. Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. *Clin J Am Soc Nephrol.* 2011;6:922-936.
35. Zachary AA, Leffell MS. Desensitization for solid organ and hematopoietic stem cell transplantation. *Immunol Rev.* 2014;258:183-207.
36. Colvin MM, Cook JL, Chang P, et al; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; American Heart Association Heart Failure and Transplantation Committee of the Council on Cardiopulmonary Critical Care, Perioperative and Resuscitation, et al. Antibody-mediated rejection in cardiac transplantation emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. *Circulation.* 2015;131:1608-1639.
37. Hughes RA, Wijdicks EF, Barohn R, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2003;61:736-740. Guideline Reaffirmed April 19, 2016.
38. Van Doorn P, Kuitwaard K, Walgaard C. et al. IVIG treatment and prognosis in Guillain-Barre Syndrome. *J Clin Immunol.* 2010;30 Suppl 1:s74-78.
39. Tomblyn M, Chiller T, Einsele H, et al; Center for International Blood and Marrow Research; National Marrow Donor program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention.

Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: A global perspective. *Biol Blood Marrow Transplant.* 2009;1:1143-1238.
40. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Department of Health and Human Services. Last review February 8, 2019. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed on July 7, 2020.
41. American Academy of Pediatrics. Human Immunodeficiency Virus Infection. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, ede. Redbook®: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018:459-476.
42. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 4.2020 – May 8,2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 8, 2020.
43. National Multiple Sclerosis Society. Relapse management. Available at: http://www.nationalmssociety.org/For-Professionals/Clinical-Care/Managing-MS/Relapse-Management. Accessed on July 8, 2020.
44. Drugs and lactation database of the National Library of Medicine (Immune Globulin in Lactmed). Available at: https://www.ncbi.nlm.nih.gov/books/NBK501437/. Accessed on July 8, 2020.
45. Lejeune A, Martin L, Santibanez S, et al. Postexposure prophylaxis with intravenous immunoglobulin G prevents infants from getting measles. *Acta Paediatr.* 2017;106(1):174-177.
46. American Academy of Pediatrics. Varicella-Zoster Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book®: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018:869-883.
47. VariZIG® for intramuscular injection [prescribing information]. Roswell, GA: Saol Therapeutics, Inc.; June 2018.
48. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG – United States, 2013. *MMWR.* 2013;62:574-576.
49. Broliden K, Tolfyenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *J Intern Med.* 2006;260:285-304.
50. Symington A, Paes B. Fetal and neonatal alloimmune thrombocytopenia: harvesting the evidence to develop a clinical approach to management. *Am J Perinatal.* 2011;28:137-144.
51. Townsley DM. Hematologic complications of pregnancy. *Semin Hematol.* 2013;50:222-231.
52. Fillit H, Hess G, Hill J, et al. IV immunoglobulin is associated with a reduced risk of Alzheimer disease and related disorders. *Neurology.* 2009;73:180-185.
53. Dodel R, Rominger A, Bartenstein P, et al. Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, rancomised, double-blind, placebo-controlled, dose-finding trial. *Lancet Neurol.* 2013;12:233-243.
54. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2020. Available at http://www.ginaasthma.org/. Accessed on July 13, 2020.
55. Eichenfield LF, Ahluwalia J, Waldman A, et al. Current guidelines for the evaluation and management of atopic dermatitis: A comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology Guidelines. *J Allergy Clin Immunol.* 2017;139(4S):S49-S57.
56. Vollmer-Conna U, Hickie I, Hadzi-Paylovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med.* 1997;103:38-43.
57. Goebel A, Baranowski A, Maurer K, et al. Intravenous immunoglobulin treatment of the complex regional pain syndrome: A randomized trial. *Ann Intern Med.* 2010;152:152-158.
58. Goebel A, Bisla J, Carganillo R, et al. Low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome: A randomized trial. *Ann Intern Med.* 2017;167(7):476-483.
59. Chrissafidou A, Malek M, Musch E. Experimental study on the use of intravenous immunoglobulin in patients with steroid-resistant Crohn's disease. *Z Gastroenterol.* 2007;45:605-608.
60. Balfour-Lynn IM, Mohan U, Bush A, Rosenthal M. Intravenous immunoglobulin for cystic fibrosis lung disease: a case series of 16 children. *Arch Dis Child.* 2004;89:315-319.
61. Relkin NR, Thomas RG, Rissman RA, et al. A phase 3 trial of IV immunoglobulin for Alzheimer disease. *Neurology.* 2017;88(18):1768-1775.
62. Colagiuri S, Leong GM, Thayer Z, et al. Intravenous immunoglobulin therapy for autoimmune diabetes mellitus. *Clin Exp Rheumatol.* 1996;14 Suppl 15:S93-97.
63. Heinze E. Immunoglobulins in children with autoimmune diabetes mellitus. *Clin Exp Rheumatol.* 1996;14 Suppl 15:S99-102.
64. Caro XJ, Winter EF, Dumas AJ. A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIG. *Rheumatology (Oxford).* 2008;47:208-211.
65. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology.* 2016;87(4):419-425.
66. Aukrust P, Yndestad A, Ueland T, et al. The role of intravenous immunoglobulin in the treatment of chronic heart failure. *Int J Cardiol.* 2006;112:40-45.
67. Kuhar DT, Henderson DK, Struble KA, et al; US Public Health Service Working Group. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. Published 9/25/2013. Updated May 23, 2018. Available at: http://stacks.cdc.gov/view/cdc/20711. Accessed on July 13, 2020.

68. Practice Committee of the American Society for Reproductive Medicine. The role of immunotherapy in in vitro fertilization: a guideline. *Fertil Steril.* 2018;110:387-400. Available at: www.asrm.org. Accessed on July 13, 2020.
69. Koopman FS, Beelen A, Gilfus NE, et al. Treatment for postpolio syndrome. *Cochrane Database of Systematic Reviews.* 2015 May 18;5:CD007818.
70. Branch DW, Peaceman AM, Druzin M, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. *Am J Obstet Gynecol.* 2000;182(1 Pt 1):122-127.
71. Stephenson MD, Kutteh WH, Purkiss S, et al. Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered, randomized, placebo-controlled trial. *Hum Reprod.* 2010;25:2203-2209.
72. Ata B, Lin Tan S, Shehata F, et al. A systematic review of intravenous immunoglobulin for treatment of unexplained recurrent miscarriage. *Fertil Steril.* 2011;95:1080-1085.
73. The Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril.* 2012;95:1103-1111.
74. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (Version 1.2020 – December 16, 2019). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 13, 2020.
75. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2018;36:1714-1768.
76. Garces JC, Biusti S, Giusti S, et al. Antibody-mediated rejection: A review. *Ochsner J.* 2017;17(1):46-55.
77. Wan SS, Ying TD, Wyburn K, et al. The treatment of antibody-mediated rejection in kidney transplantation: An updated systematic review and meta-analysis. *Transplantation.* 2018;102(4):557-568.
78. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9Suppl3:S1
79. Witt CA, Gaut JP, Yusen RD, et al. Acute antibody-mediated rejection after lung transplantation. *J Heart Lung Transplant.* 2013;32:1034.
80. Hachem RR, Yusen RD, Meyers BF, et al. Anti-human leukocyte antigen antibodies and preemptive antibody-directed therapy after lung transplantation. *J Heart Lung Transplant.* 2010:29:973.