

## PRIOR AUTHORIZATION POLICY

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

**REVIEW DATE:** 10/12/2022

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### 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 bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections.<sup>6,18,21</sup>
- **Chronic inflammatory demyelinating polyneuropathy**, to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.<sup>7,9,12,67</sup>
- **Dermatomyositis (or polymyositis)**. Octagam 10% is indicated for the treatment of dermatomyositis in adults.<sup>11</sup> 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.<sup>33</sup> IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.<sup>32</sup>
- **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.<sup>2,4,6-9,11,12,15,23-25</sup>
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.<sup>6,26</sup>
- **Multifocal motor neuropathy** in adults as maintenance therapy to improve muscle strength and disability.<sup>5</sup>
- **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.<sup>1-10,12,15,16,25</sup> Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous infusion for primary

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immunodeficiency.<sup>5,7,9</sup> 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.<sup>3,4,7-10,12,13,17,25,45</sup>

IVIG is prepared from pooled plasma collected from a large number of human donors.<sup>1-12,15,16,25</sup> 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 PID, it also has elevated levels of respiratory syncytial virus (RSV) antibodies.<sup>19</sup>

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.<sup>75</sup> 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.<sup>18,76</sup> 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.<sup>76,77</sup> As in desensitization therapy, much of the information for 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<sup>20,44,80</sup>, 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.<sup>36</sup>
- **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.<sup>28-30</sup> 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.<sup>2</sup>
- **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 2.2022 – August 19, 2022) note IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.<sup>31</sup>
- **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.<sup>34,35</sup> 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.<sup>18</sup>
- **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.<sup>37</sup> 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.<sup>38</sup> IVIG is not indicated or proven to be effective in patients mildly affected with GBS.<sup>32,38</sup>

- **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 hypogammaglobulinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.<sup>27</sup> NCCN guidelines regarding management of immunotherapy-related toxicities (version 1.2022 – February 28, 2022) recommends that after anti-CD19 chimeric antigen receptor (CAR)-T cell therapy, IVIG replacement should be considered for patients with serum IgG levels < 400 to 600 mg/dL and serious or recurrent infections.<sup>73</sup>
- **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.<sup>39</sup> 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). NCCN guidelines on prevention and treatment of cancer-related infections discussed similar recommendations.<sup>31</sup>
- **Human Immunodeficiency virus (HIV)- or Hepatitis C-associated thrombocytopenia:** Secondary ITP can occur in patients with HIV infection.<sup>23,24</sup> It can also occur in patients with Hepatitis C. The American Society of Hematology (ASH) guidelines for ITP recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV. ASH also recommends IVIG for secondary ITP associated with Hepatitis C.<sup>23,24</sup>
- **HIV-infected infants and children to prevent recurrent infections:** IVIG is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (immunoglobulin G < 400 mg/dL).<sup>40</sup> 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] 4 and 5) and to use the pediatric guideline for guidance on the care of adolescents at SMR 3 or lower.<sup>40</sup>
- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy:** NCCN guidelines for the management of immunotherapy-related toxicities (version 1.2022 – February 28, 2022) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy; as treatment for severe myasthenia gravis; encephalitis; cardiovascular adverse events; musculoskeletal adverse events; moderate or severe GBS; transverse myelitis; bullous dermatitis; and Stevens-Johnson syndrome/toxic epidermal necrolysis.<sup>73</sup> 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.<sup>74</sup> These practice guidelines address the above mentioned indications along with other conditions (e.g., severe cutaneous skin adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome:** 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.<sup>18</sup>

- **Multiple myeloma:** Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.<sup>31</sup> The NCCN guidelines on multiple myeloma (version 1.2023 – September 14, 2022) notes that IVIG should be considered in the setting of recurrent, serious infections and/or hypogammaglobulinemia (immunoglobulin G  $\leq$  400 mg/dL).<sup>42</sup>
- **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.<sup>43</sup> 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.<sup>43</sup>
- **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.<sup>65</sup> 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.
- **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.<sup>13</sup> IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at  $\geq$  12 months, unless the patient is severely immunocompromised. The Advisory Committee on Immunization Practices 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.<sup>13</sup> 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.
- **Post-exposure prophylaxis for varicella OR treatment or post-exposure prophylaxis for tetanus:** Children infected with HIV 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 after close contact with a person who has chickenpox or shingles.<sup>41,46</sup> 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.<sup>47</sup> Per the CDC, if tetanus immune globulin is not available, clinicians can use immune globulin at a dose of 200 to 400 mg/kg.<sup>48</sup>
- **Parvovirus B19 infection and pure red blood cell aplasia, immunologic subtype:** In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment

of persistent B19 infection.<sup>49</sup> The guidelines from the American Society of Transplantation Infectious Diseases Community of Practice state that IVIG is frequently used for the treatment of solid organ transplant recipients with symptomatic parvovirus B19 infection.<sup>66</sup> 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.<sup>22</sup> 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.<sup>32</sup>
- **Thrombocytopenia, feto-neonatal alloimmune:** Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.<sup>50,51</sup> 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 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 one of the following criteria:

### FDA-Approved Indications

- 1. Primary Immunodeficiencies.** Approve for 1 year if the patient meets ONE of the following (A or B):
  - A) Initial Therapy.** Approve for 1 year 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 BOTH of the following (1 and 2):
        - (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 meets ONE of the following [(a) or (b)]:
      - (a) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR  
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.
      - (b) 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 produce 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 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, 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.
2. **B-Cell Chronic Lymphocytic Leukemia for Prevention of 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 BOTH of the following (i and ii):
    - i. Patient meets ONE of the following (a or b):
      - a) Patient has an immunoglobulin G (IgG) level < 600 mg/dL (6.0 g/L); OR
      - b) Patient has a history of recurrent infections; AND
    - ii. 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.
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 BOTH of 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 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.
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 ALL of 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 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.
- 5. Immune Thrombocytopenia.** 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  $\geq$  18 Years of Age.** Approve for 1 year if the patient meets BOTH of 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.
- 6. Kawasaki Disease.** Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.
- 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 BOTH of 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 probably 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.

### Other Uses with Supportive Evidence

- 8. Antibody-Mediated Rejection in Transplantation.** Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.
- 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 meets BOTH of the following (1 and 2):
      - (1) Patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND
      - (2) Patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; ORNote: 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.
- 10. Cytomegalovirus 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.
- 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.** 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 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) 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.

**13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency).** 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 intravenous infusion], Abecma [idecabtagene vicleucel intravenous infusion], Breyanzi [lisocabtagene maraleucel intravenous infusion], Tecartus [brexucabtagene autoleucel intravenous infusion], Yescarta [axicabtagene ciloleucel intravenous infusion]), a rituximab product, Besponsa (inotuzumab ozogamicin intravenous infusion).

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 < 600 mg/dL (6.0 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 diseases 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.

**14. Hematopoietic Cell Transplantation (HCT) 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 < 600 mg/dL (6.0 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.

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

- A) Patient is receiving antiviral therapy; AND**

- B) The medication is prescribed by or in consultation with an infectious diseases specialist, a physician who specializes in the treatment of HIV infections, a gastroenterologist, hepatologist, or a liver transplant physician.

**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.

**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 intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), Libtayo (cemiplimab intravenous infusion), Jemperli (dostarlimab intravenous infusion).
- A) Initial Therapy. Approve for 1 month if the patient meets ONE of 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.

**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 ALL of 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.

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 BOTH of the following (i and ii):
- i. Patient has, or is at risk of, 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.

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 ALL of the following (A, B, and C):

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

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 BOTH of 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) Patient is Currently 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. 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.
  - 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 includes improvement in weakness (bulbar, limb, or respiratory), improvement with ocular symptoms.
- 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 BOTH of the following criteria (i and ii):
    - i. Patient has been exposed to measles; AND
    - ii. The patient does not have evidence of immunity to measles (i.e., the patient does not have a of the disease or age-appropriate vaccination); OR
  - B) Patient meets BOTH of the following criteria (i and ii):
    - i. Patient is immunocompromised; AND
    - ii. Patient has been exposed to measles.
- 23. **Post-Exposure Prophylaxis for Varicella OR Treatment or Post-Exposure Prophylaxis for Tetanus.** Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following (A or B):
  - A) For Varicella post-exposure, Varicella immune globulin is not available or cannot be administered within 10 days of exposure; OR
  - B) For Tetanus treatment or post-exposure, Tetanus Immune globulin is not available.
- 24. **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 BOTH of the following (i and ii):
    - i. Patient has an immunodeficiency condition; AND  
Note: Examples of an immunodeficiency condition include patients with HIV infection, solid organ transplants (e.g., renal, liver), chemotherapy for hematologic malignancy.
    - ii. 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 6 months.
- 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 reticulocytosis, according to the prescriber.
- 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 BOTH of 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 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.
- 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.

#### 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.<sup>18</sup>
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.<sup>61</sup> There was no statistically significant difference in the rate of cognitive decline when compared to 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 established efficacy, determine the optimal dose regimen, and to confirm the safety of IVIG in the general AD population.<sup>52,53</sup>
3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG.<sup>18</sup>
4. **Anemia, Aplastic.** Evidence does not support IVIG use.<sup>22</sup>
5. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.<sup>54</sup>
6. **Atopic Dermatitis.** Limited data exist to determine the utility of IVIG in the management of atopic dermatitis.<sup>55</sup>
7. **Autism.** Evidence does not support IVIG use.<sup>18</sup> Well-controlled, double-blind trials are needed.
8. **Chronic Fatigue Syndrome.** Evidence does not support IVIG use.<sup>56</sup> One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.<sup>56</sup>

Although scores were improved in IVIG and placebo treatment groups, no significant 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.<sup>57</sup> 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.<sup>58</sup> 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.<sup>59</sup> 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.<sup>60</sup> Well-designed, controlled trials are needed.<sup>18</sup>
- 12. Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use.<sup>18,62,63</sup> In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.<sup>62</sup> 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.<sup>64</sup> Pain, tenderness, and strength reportedly improved. Double-blind, placebo controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.
- 14. In Vitro Fertilization (IVF).** There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.<sup>68</sup>
- 15. Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.<sup>18</sup>
- 16. Recurrent Spontaneous Pregnancy Loss (RSPL) [Including a Patient with Antiphospholipid Antibody-Positive].** Evidence does not support IVIG use.<sup>69-72</sup> 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.<sup>69</sup> 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.<sup>70</sup> 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.<sup>72</sup>
- 17. Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of IVIG.<sup>14,18</sup> 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.<sup>14</sup> Selective IgA deficiency may co-exist in

some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.<sup>14,18</sup> Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

- 18.** 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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