

**POLICY:**

Immune Globulin Intravenous (IVIG)

- Asceniv™ (immune globulin intravenous [human] liquid – sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous – Biotest Pharmaceuticals); not available
- Carimune® NF Nanofiltered (immune globulin intravenous – CSL Behring LLC [manufactured by CSL Behring AG]);
- Flebogamma® DIF (immune globulin intravenous – Grifols USA LLC [manufactured by Instituto Grifols, SA]);
- 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 [manufactured by Grifols Therapeutics Inc]);
- Gammaplex® (immune globulin intravenous – BPL Inc [manufactured by Bio Products Laboratory]);
- Gamunex®-C (immune globulin intravenous caprylate/ chromatography purified – Grifols USA LLC [manufactured by Grifols Therapeutics Inc]);
- Octagam® (immune globulin intravenous – Octapharma USA [manufactured by Octapharma Pharmazeutika Produktionsges.m.b.H.]);
- Panzyga® (immune globulin intravenous, human - ifas – Octapharma USA, Inc. [manufactured by Octapharma Pharmazeutika Produktionsges.m.b.H]);
- Privigen® Liquid (immune globulin intravenous – CSL Behring LLC [manufactured by CSL Behring AG])

**APPROVAL DATE:** 7/31/2019

**OVERVIEW**

Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are 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 primary immunodeficiencies (PID), it also has elevated levels of respiratory syncytial virus (RSV) antibodies.<sup>19</sup> It is manufactured using a unique plasma donor screening method which uses both normal source plasma and tailored plasma using a proprietary assay. Plasma donors with naturally occurring high circulating levels of anti-RSV antibodies are selected as the source for manufacturing the product; each lot of the product includes sufficient plasma from these selected donors to meet a standardized RSV antibody value.

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. Individual products are indicated for use in other conditions. The following indications are FDA-approved:

1. Replacement therapy for primary humoral immune deficiency (PID), 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).<sup>1-10,12,15,16,25</sup> Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous (SC) infusion for primary 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>7,10,13,25,47</sup>

2. B-cell chronic lymphocytic leukemia (CLL) for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections.<sup>6</sup>
3. Chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.<sup>7,9,12</sup>
4. 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>2,4,6-9,11-12,15,25</sup>
5. Kawasaki disease in pediatric patients for the prevention of coronary artery aneurysm.<sup>6</sup>
6. Multifocal motor neuropathy (MMN) in adults as maintenance therapy to improve muscle strength and disability.<sup>5</sup>

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

IVIG is given IV and is available as a lyophilized powder that requires reconstitution or as a solution in single-dose vials. The products are available in various strengths.

### **POLICY STATEMENT**

This policy involves the use of IVIG products. Prior authorization is recommended for medical benefit coverage of IVIG products. Coverage is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Extended approvals are allowed if the patient continues to meet the criteria and dosing.

Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG products as well as the monitoring required for adverse events and long-term efficacy, select approvals require IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

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

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of IVIG products is recommended in those who meet one of the following criteria.

#### **FDA-Approved Indications**

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##### **1. Primary Immunodeficiencies (PID).**

**Criteria.** Approve for the duration noted if the patient meets ONE of the following (A or B):

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- A) Initial Therapy:** Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
- i.** IVIG is prescribed by or in consultation with one of the following physician specialists: an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies; AND
  - ii.** 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 produce antibodies to specific antigens); OR
      - (3)** The patient has recurrent infections; OR
    - c)** The patient has an IgG subclass deficiency or a diagnosis of selective antibody deficiency (SAD) and meets the following criteria (1 and 2):
      - (1)** The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
      - (2)** The patient has recurrent infections.
- B) Patients Currently Receiving IVIG:** Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product (e.g., increased IgG levels, preventing or controlling infections).

IVIG is used for replacement in primary immunodeficiency disorders where antibody production is absent or deficient to increase IgG levels and most of the time to prevent or control recurrent or unusually severe bacterial infections.<sup>14,18</sup>

Patients with primary humoral immunodeficiency are at high risk of developing acute and chronic bacterial infections.<sup>14</sup> IVIG provides a broad spectrum of IgG antibodies that help prevent or attenuate infectious diseases. The use of IVIG in IgG subclass deficiencies (e.g., deficiencies of immunoglobulin A [IgA] or immunoglobulin E [IgE] in association with reduced IgG2 or IgG4) is recommended only in those patients who also demonstrate a deficiency in the ability to form antibodies against a variety of polysaccharide and protein antigens.<sup>14,18</sup>

A consensus document providing a definition of CVID was published in 2016.<sup>17</sup> The American Academy of Allergy, Asthma & Immunology (AAAAI), the European Academy of Allergy and Clinical Immunology, the World Allergy Organization, and the American College of Allergy, Asthma & Immunology (ACAAI) on common variable immunodeficiency developed this document. CVID is a group of heterogeneous primary antibody failure syndromes that are characterized by hypogammaglobulinemia.

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**Dosing in Primary Immune Deficiency in Adults, Children or Adolescents.** Approve the following dosing regimens (A, B, C, OR D):

- A) An initial loading dose of 1 g per kg as an IV infusion may be given one time; OR
- B) 0.2 to 0.8 g per kg IV infusion once every 3 to 4 weeks; OR
- C) The dose and interval between doses has been adjusted based on clinical response (e.g., frequency or severity of infections, hospitalization, days of school or work missed, failure to thrive, or to treat/prevent complications such as chronic lung disease, granulomatous infiltrative disease, or autoimmune diseases) as determined by the prescriber; OR
- D) Patients with primary immune deficiency and exposure to measles to meet one of the following (i, ii, or iii):
  - i. In patients routinely receiving less than 0.4 g of IVIG per kg every 3 to 4 weeks who are at risk of measles exposure, the dose of IVIG is  $\geq 0.4$  g per kg one time given just before the expected exposure to measles; OR
  - ii. In patients at risk for future measles exposure and receives a dose of less than 0.53 g of IVIG per kg every 3 to 4 weeks, the dose can be increased to at least 0.53 g per kg.; OR
  - iii. In patients who are already exposed to measles, the dose of IVIG is 0.4 g per kg given one time as soon as possible after exposure.

The approved dosing of IVIG in primary humoral immune deficiency is 0.2 to 0.8 g/kg once every 3 to 4 weeks.<sup>1-10,12,15,25</sup> The dose is adjusted according to clinical response. In patients at risk of *measles exposure* (i.e., traveling to a measles endemic area) who are routinely receiving an IVIG dose less than 0.4 g/kg every 3 to 4 weeks, a single IVIG dose of at least 0.4 g/kg is administered just prior to expected measles exposure.<sup>7,9</sup> If a patient has been exposed to measles, a single dose of IVIG 0.4 g/kg should be given as soon as possible after exposure. For certain IVIG products, in patients at risk for future measles exposure and receives a dose of less than 0.53 g of IVIG per kg every 3-4 weeks, the dose should be increase to at least 0.53 g per kg.<sup>8,10,25</sup> The Advisory Committee on Immunization Practices (ACIP) recommends that patients with severe primary immunodeficiency who are already receiving IVIG, receive at least 0.4 g/kg within 3 weeks before measles exposure.<sup>13</sup>

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## 2. B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Bacterial Infections.

**Criteria.** Approve for the duration noted if the patient meets ONE of the following (A or B):

- A) Initial Therapy: Approve for 4 months if the patient meets the following 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. IVIG is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.
- B) Patients Currently Receiving IVIG: Approve for 1 year if the patient is maintaining an IgG trough (pre-dose) level of about 500 mg/dL and up to 700 mg/dL to prevent bacterial infections.

CLL is a secondary humoral immunodeficiency.<sup>18</sup> The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on chronic lymphocytic leukemia/small lymphocytic lymphoma (version 5.2019) recommend evaluation of serum IgG if < 500 mg/dL in patients with CLL who have recurrent sinopulmonary infections requiring antibiotics or hospitalization.<sup>21</sup> IVIG has been associated with a significant decrease in infections, but no improvement in survival.

**Dosing in Patients with B-Cell Chronic Lymphocytic Leukemia (CLL).** Approve the following dosing regimens (A, B, OR C):

- A) 0.4 g per kg intravenous infusion every 3 to 4 weeks; OR
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- B) 0.3 to 0.5 g per kg intravenous infusion once monthly; OR
- C) The dose and interval have been adjusted to maintain a trough (pre-dose) IgG level of about 500 mg/dL and up to 700 mg/dL.

The approved dose of IVIG is 400 mg per kg as an IV infusion every 3 to 4 weeks.<sup>6</sup> The NCCN guidelines recommend evaluation of serum IgG if < 500 mg/dL in patients with CLL who have recurrent sinopulmonary infections requiring antibiotics or hospitalization.<sup>21</sup> These guidelines recommend monthly IVIG for supportive care.

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**3. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy.**

**Criteria.** Approve for the duration noted if the patient meets ONE of the following (A or B):

- A) Initial Therapy: Approve for 3 months if the patient meets the following (i and ii):
  - i. IVIG is prescribed by or in consultation with a neurologist; AND
  - ii. Electrodiagnostic studies support the diagnosis of CIDP.
- B) Patients Currently Receiving IVIG: Approve for 1 year of therapy if the patient has a clinically significant improvement in neurologic symptoms (for example, improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation) as determined by the prescriber (a neurologist or in consultation with a neurologist). The patient may not have a full response after the initial 3 months, but there should be some response.

**Dosing in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Adults.** Approve the following dosing regimens (A, B, OR C):

- A) An initial loading dose of 2 g per kg as an IV infusion given in divided doses over 2 to 4 consecutive days; OR
- B) A maintenance dose of 1 g per kg as an IV infusion over one day or divided into two doses of 0.5 g per kg given on 2 consecutive days. Either regimen is given every 3 weeks. OR
- C) The dose and interval are adjusted according to clinical response:
  - i. The maximum dose per treatment course is 2 g per kg.
  - ii. Examples of other regimens that have been used for maintenance are 0.5 g per kg every 2 weeks or 2 g per kg every 4 weeks.

The initial dose is a total loading dose of 2 g per kg given in divided doses over 2 to 4 consecutive days.<sup>7,9</sup> For maintenance, 1 g per kg is given as an infusion over 1 day or divided into 2 doses of 0.5 g per kg given on 2 consecutive days. Dose(s) are given every 3 weeks for maintenance. The dose and interval are adjusted according to clinical response. Dosing should be aimed at maintaining optimal function.

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**4. Idiopathic (Immune) Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia [IT] Acute and Chronic.**

**Criteria.** Approve for the duration noted if the patient meets ONE of the following (A or B):

- A) Initial Therapy: Various approval durations apply.
  - i. Adults and adolescents (> 17 years of age) with ITP/IT. Approve for ONE of the following (a, b, or c):

- a) *Acute* bleeding in a patient who is newly diagnosed or requiring therapy for the first time OR in patients with persistent or chronic ITP. Approve IVIG for 1 month if the patient meets the following criteria (1, 2, and 3):
    - (1) IVIG is prescribed by or in consultation with a hematologist; AND
    - (2) One of the following applies:
      - The patient has tried a systemic corticosteroid (e.g., prednisone) for ITP/IT; OR
      - There is an urgent need to increase the platelet count quickly AND IVIG will be started with a systemic corticosteroid; OR
      - A corticosteroid is contraindicated according to the prescriber; AND
    - (3) The platelet count is  $< 30 \times 10^9/L$  or  $30,000/\mu L$ . OR
  - b) To increase platelet counts before surgical procedures (e.g., splenectomy) or dental procedures, approve IVIG for 1 month if the patient meets the following criteria (1 and 2):
    - (1) IVIG is prescribed by or in consultation with a hematologist; AND
    - (2) The platelet count is  $< 50 \times 10^9/L$  or  $50,000/\mu L$  OR if the patient is undergoing major surgery (e.g., central nervous system or cardiac surgery) and the platelet count is  $< 75 \times 10^9/L$  or  $75,000/\mu L$ . OR
  - c) The patient has *persistent* (3 to 12 months duration) or *chronic* ( $\geq 12$  months duration) ITP/IT. Approve for 1 year if the patient meets the following criteria (1, 2, and 3):
    - (1) IVIG is prescribed by or in consultation with a hematologist; AND
    - (2) One of the following applies:
      - The patient has tried a systemic corticosteroid (e.g., prednisone) for ITP/IT; OR
      - There is an urgent need to increase the platelet count quickly AND IVIG will be started with a systemic corticosteroid;<sup>41</sup> OR
      - A corticosteroid is contraindicated according to the prescriber; AND
    - (3) IVIG is required to prevent bleeding.
- ii. Children and adolescents ( $\leq 17$  years of age) with ITP/IT. Approve for one of the following (a, b, c, or d):
- a) Acute bleeding in a patient who is newly diagnosed or requiring therapy for the first time OR in patients with persistent or chronic ITP. Approve for 1 month if the patient meets the following criteria (1 and 2):
    - (1) IVIG is prescribed by or in consultation with a hematologist; AND
    - (2) There is significant acute mucous membrane bleeding or other noncutaneous bleeding; OR
  - b) The patient has *persistent* (3 to 12 months) or *chronic* ( $\geq 12$  months) ITP/IT. Approve for 1 year if the patient meets the following criteria (1 and 2):
    - (1) IVIG is prescribed by or in consultation with a hematologist; AND
    - (2) IVIG is required to prevent bleeding; OR
  - c) Inaccessibility (such as travel, distance from hospital), activity level of the patient, or noncompliance is a concern with the prescriber. Approve for 1 year if the patient meets the following criteria (1 and 2):
    - (1) IVIG is prescribed by or in consultation with a hematologist; AND
    - (2) Child/adolescent is at risk of bleeding; OR
  - d) To increase the platelet count before major surgery such as splenectomy, or before other surgery, dental extraction(s), or other procedures likely to cause blood loss. Approve for 1 month if IVIG is prescribed by or in consultation with a hematologist.
- iii. Pregnant patient with ITP/IT. Approve for one of the following (a or b):
- a) Before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia. Approve for 2 weeks if IVIG is prescribed by or in consultation with a hematologist; OR
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- b)** Pregnant patient in any trimester. Approve for 3 months if IVIG is prescribed by or in consultation with a hematologist. (This does not include before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia.)
- B) Patients Currently Receiving IVIG:** Approve for 1 year in children, adolescents, and adults with persistent or chronic ITP/IT, if the patient responded with increased platelet count and/or absence of significant bleeding and the patient requires additional therapy with IVIG to prevent bleeding, according to the prescriber.

Use the Initial Therapy criteria above in A) for patients who require additional therapy for one of the following: 1) acute bleeding, 2) to increase platelet counts before surgical or dental procedures, or 3) pregnant patients.

See Appendix A for more information on IVIG use in ITP.

**Dosing in Idiopathic Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia (IT).**  
Approve the following dosing regimens *(A, B, OR C)*:

**A) Adults (Non-Pregnant) and Adolescents Greater Than 17 Years of Age.**

- i.** Acute bleeding requiring therapy for the first time OR in patients with persistent or chronic ITP: IVIG 1 g per kg on 2 consecutive days OR 0.4 g per kg given on 5 consecutive days as an IV infusion.<sup>2,7,9,16,25</sup>
- ii.** Maintenance therapy for persistent or chronic ITP/IT:
  - (1)** IVIG  $\leq$  1 g per kg daily for 2 consecutive days as an IV infusion;<sup>4,11</sup> OR
  - (2)** The dose and interval between doses has been adjusted according to the platelet count and/or to prevent significant bleeding.
- iii.** To increase the platelet count before major surgery such as splenectomy, or before other surgery, dental extraction(s), or other procedures likely to cause blood loss: The dose is 1 g per kg on 2 consecutive days or 0.4 g per kg given on 5 consecutive days given one time as an IV infusion.<sup>7,9</sup> The total maximum dose is 2 g per kg.

**B) Children or Adolescents Less Than or Equal to 17 Years of Age.**

- i.** Acute bleeding requiring therapy for the first time OR in patients with persistent or chronic ITP: The dose is 0.8 to 1 g per kg IV infusion given one time.<sup>9</sup> This dose can be repeated one time within 48 hours if there is not an adequate response (increased platelet count and/or decreased bleeding). Lower doses such as 0.25, 0.4, or 0.5 g per kg per day may be used for 2 days. The total maximum dose is 2 g per kg.
  - ii.** Maintenance therapy for persistent (3 to 12 months duration) or chronic ( $\geq$  12 months) ITP/IT:
    - a)** The initial dose is 0.8 to 1 g per kg IV infusion given one time. This dose can be repeated one time within 48 hours if there is not an adequate response (increased platelet count and/or decreased bleeding). Another recommended dose is 1 g per kg daily for 2 consecutive days.<sup>4,9,16</sup> Lower doses such as 0.25, 0.4, or 0.5 g per kg per day may be used for 2 days. The total maximum dose is 2 g per kg.
    - b)** The dose and interval between doses has been adjusted according to the platelet count and/or to prevent significant bleeding<sup>4</sup> as determined by the prescriber and is adjusted to the minimum effective dose that can be given at maximum intervals.
  - iii.** Inaccessibility (such as travel, distance from hospital), activity level of the patient, or noncompliance is a concern with the prescriber: the dose is 0.8 to 1 g per kg IV infusion given one time. This dose can be repeated one time within 48 hours if there is an inadequate response (response is increased platelet count and/or decreased bleeding). Lower doses such as 0.25, 0.4, or 0.5 g per kg per day may be used for 2 days. The total maximum dose is 2 g per kg.
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- iv. To increase the platelet count before major surgery such as splenectomy, or before other surgery, dental extraction(s), or other procedures likely to cause blood loss: The dose is 0.8 to 1 g per kg IV infusion given one time. This dose can be repeated one time within 48 hours if there is not an adequate response (adequate response is increased platelet count and/or decreased bleeding). Lower doses such as 0.25, 0.4, or 0.5 g per kg per day may be used for 2 days. The total maximum dose is 2 g per kg.

**C) Pregnant Patients.**

- i. 0.4 g per kg per day for 5 days or 1 g per kg per day for two doses as an IV infusion; OR (Infusions may be repeated to prevent hemorrhage and assure an adequate platelet count for delivery.)
- ii. The dose and interval between doses is adjusted according to the platelet count and/or to prevent significant bleeding.

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5. **Kawasaki Disease.**

**Criteria.** Approve a single dose if the patient meets the following criteria (A and B):

- A) IVIG is prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician; AND
- B) The patient has persistent or recrudescing (recurring) fever or signs of inflammation at least 36 hours after completing the initial IVIG infusion(s).

**Note:** These criteria assume that the first dose was given in a hospital within 7 to 10 days of onset.

The efficacy of IVIG in reducing the prevalence of coronary artery abnormalities is well-established when given in conjunction with aspirin in the acute phase of Kawasaki disease.<sup>27</sup> Patients should receive a single dose of IVIG together with aspirin as soon as possible within the first 10 days of illness onset. About 10% to 20% of patients do not respond to initial IVIG therapy. IVIG can also be given in children presenting after the 10<sup>th</sup> day of illness (i.e., the diagnosis was missed earlier) if they have ongoing systemic inflammation as manifested by increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) plus either persistent fever without other explanation or coronary artery aneurysms. Patients with persistent or recrudescing fever that is present 36 hours after the end of the first IVIG infusion can be retreated with IVIG one time.<sup>26</sup> Patients with recurrent Kawasaki disease defined as a repeat episode of complete or incomplete Kawasaki disease after complete resolution of the previous episode, should receive standard therapy with IVIG and aspirin.<sup>27</sup>

**Dosing in Kawasaki Disease.** Approve the following dosing regimen: 2 g per kg IV infusion usually given over 10 to 12 hours for persistent or recrudescing fever or signs of inflammation.

The American Heart Association (AHA) and American Academy of Pediatrics (AAP) recommend initial therapy within 10 days of onset of fever (the acute phase) with 2 g of IVIG per kg as a single IV dose given over 10 to 12 hours.<sup>26,27</sup> For persistent or recrudescing fever that is present 36 hours after the end of the IVIG infusion, retreatment with IVIG (2 g per kg) and high-dose aspirin is recommended. The IVIG prescribing information recommends a single 1 g per kg dose or 400 mg per kg for four consecutive days beginning within 7 days of onset of fever with aspirin therapy.<sup>6</sup>

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6. **Multifocal Motor Neuropathy (MMN) [Treatment].**

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**Criteria.** Approve for 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) **Patients Currently Receiving IVIG:** Approve for 1 year if the patient has improvement in neurologic symptoms as determined by the prescriber (a neurologist or in consultation with a neurologist). IVIG should be discontinued in patients who do not respond after the first 6 months of therapy. Approve for 1 year in patients who are responding (that is, maintaining optimal function) according to the prescriber.

**Dosing in Multifocal Motor Neuropathy (MMN).** Approve the following dosing regimens (A OR B):

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

The approved dosage range is 0.5 to 2.4 g per kg per month.<sup>5</sup> The dose is adjusted to achieve the desired clinical response.

#### **Other Uses with Supportive Evidence**

#### **7. Antibody-Mediated Rejection (ABMR) in Solid Organ Transplant (e.g., Kidney, Heart, Lung, Liver).**

**Criteria.** Approve for 1 year if IVIG is prescribed by or in consultation with a physician affiliated with a transplant center.

Current strategies for a treatment of antibody-mediated rejection include plasmapheresis, intravenous immunoglobulin and T-cell or B-cell-depleting agents.<sup>79</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>18,80</sup> Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes [KDIGO]) recommends a combination of corticosteroids, plasmapheresis, IVIG, anti-CD-20 antibody and lymphocyte-depleting antibody for antibody-mediated rejection.<sup>80,81</sup> As in desensitization therapy with solid organ transplants, much of the information on 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>20,82,83</sup> and a scientific statement from the AHA 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> ABMR can be diagnosed within the first year post-transplant OR after the first year (late-onset or chronic).

**Dosing for Antibody-Mediated Rejection.** Various dosing regimens have been used for this diagnosis and dosing regimens will be evaluated on a case-by-case basis.

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#### **8. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita).**

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**Criteria.** 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. IVIG is prescribed by or in consultation with a dermatologist; AND
  - ii. 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 (e.g., azathioprine, cyclophosphamide, dapsone, methotrexate [MTX], cyclosporine, mycophenolate mofetil, tacrolimus) OR an immunosuppressive agent is contraindicated according to the prescribing physician; OR
    - 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.
- B) Patients Currently Receiving IVIG: Approve for 1 year if the patient has responded (previous lesions are healing and there are fewer new lesions) according to the prescriber.

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>

**Dosing for the Autoimmune Mucocutaneous Blistering Diseases.** Approve the following dosing regimens (A, B, OR C):

- A) 2 g per kg IV infusion per cycle administered every 3 to 4 weeks initially. This dose is divided over 2, 3, or 5 consecutive days; OR
- B) In patients with aggressive ocular disease such as ocular cicatricial pemphigoid, 2 g per kg IV infusions may be given every 2 weeks in divided doses over 2, 3, or 5 consecutive days; OR
- C) The frequency of IVIG is gradually being slowly decreased as the lesions resolve and heal.

When the disease is stable, IVIG is continued about every 4 weeks. Once previous lesions are healed and there have been no new lesions for several weeks, the frequency of IVIG treatments can be slowly decreased with the dose remaining the same. Some patients can be gradually tapered off IVIG. Patients who respond to IVIG may be tapered off corticosteroids and have immunosuppressive therapy discontinued. Then if disease is controlled, may try to taper off IVIG.

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**9. Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Cancer or Transplant-Related Infection.**

**Criteria.** Approve for 2 months if IVIG is prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

For CMV pneumonia, therapy consists of ganciclovir IV injection (or foscarnet IV injection if CMV is ganciclovir-resistant) and IVIG in combination.<sup>31</sup> The NCCN guidelines on prevention and treatment of cancer-related infections (version 1.2019) show IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.<sup>51</sup>

**Dosing in CMV Interstitial Pneumonia.** Approve the following dosing regimen: 400 mg per kg IV infusion every other day for 3 to 5 doses.

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Dosing recommended in the NCCN guidelines is 400 mg/kg every other day for three to five doses.<sup>31</sup> The optimal dosing schedule has not been defined. IVIG is given with ganciclovir (or foscarnet) which is given for 4 to 6 weeks.<sup>51</sup>

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#### **10. Dermatomyositis or Polymyositis.**

**Criteria.** 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. IVIG is prescribed by or in consultation with a neurologist or a rheumatologist; AND
  - ii. The patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND
  - iii. The patient has tried an immunosuppressive agent (e.g., azathioprine, MTX, cyclosporine, cyclophosphamide, mycophenolate mofetil) OR an immunosuppressive agent is contraindicated according to the prescriber.
- B) **Patients Currently Receiving IVIG:** Approve for 1 year if the patient has responded (such as improved muscle strength, improved neuromuscular symptoms, improved functional ability) according to the prescriber.

IVIG may be used in patients with dermatomyositis with severe active illness for whom other interventions have been unsuccessful or intolerable.<sup>32,33</sup>

IVIG may be considered among the treatment options for patients with polymyositis not responding to first-line immunosuppressive treatment.<sup>32</sup> In uncontrolled series, IVIG has been effective in polymyositis.

**Dosing in Dermatomyositis or Polymyositis.** Approve the following dosing regimens (A OR B):

- A) 2 g per kg IV infusion given in divided doses over 2 to 5 consecutive days once monthly; OR  
B) 2 g per kg IV infusion given in divided doses over 2 to 5 consecutive days every 2 to 3 weeks.

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#### **11. Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation.**

**Criteria.** Approve for the duration noted if the patient meets ONE of the following (A or B):

- A) **Initial Therapy:** Approve for 4 months if prescribed by or in consultation with a physician affiliated with a transplant center.
- B) **Patients Currently Receiving IVIG:** Approve for 1 year if given before transplantation OR approve for one dose if given post-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 solid organ 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.<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 Rituxan<sup>®</sup> (rituximab injection for IV infusion).<sup>18</sup>

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**Dosing for Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation.** Approve the following dosing regimens (A OR B):

- A) Up to 2 g per kg as an IV infusion (as a single dose or divided in smaller doses [e.g., 400 mg per kg daily for 5 days]) monthly; OR
- B) The IVIG dosage is based on a transplant center's protocol.

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**12. Guillain Barrè Syndrome (GBS).**

**Criteria.** 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. IVIG is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with GBS; AND
  - ii. The patient meets one of the following criteria (a or b):
    - a) IVIG is initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms (weakness, inability to stand or walk without assistance, respiratory or bulbar weakness); OR
    - b) The patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG.
- B) Patients Currently Receiving IVIG: 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.

The American Academy of Neurology (AAN) 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 mildly affected GBS patients.<sup>32,38</sup>

**Dosing for Guillain Barrè Syndrome (GBS).** Approve the following dosing regimen: 2 g per kg IV infusion in divided doses over 2 to 5 days.<sup>32,38</sup>

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**13. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]).**

*(See B-Cell Chronic Lymphocytic Leukemia [CLL] for Prevention of Bacterial Infections and Multiple Myeloma for these diagnosis-specific criteria) (Some examples of B-cell targeted therapy are chimeric antigen receptor [CAR]-T cell therapy [e.g., Kymriah], a rituximab product, Besponsa [inotuzumab ozogamicin].)*

**Criteria.** 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 an immunoglobulin G (IgG) level of < 500 mg/dL (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.

- iii. IVIG is being prescribed by or in consultation with an oncologist, hematologist, infectious disease physician, or immunologist.
- B) Patients Currently Receiving IVIG:** Approve for 6 months if the patient is maintaining an IgG level of over 400 mg/dL and having a positive response to therapy (e.g., decrease in infections), according to the prescriber.

**Dosing for Hematologic Neoplasm-Associated Hypogammaglobulinemia.** Various dosing regimens have been used for this diagnosis. Approve the following dosing regimen: 0.4 to 0.5 g per kg monthly. Other regimens will be reviewed on a case-by-case basis.

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#### **14. Hematopoietic Cell Transplantation (HCT) to Prevent Bacterial Infection.**

**Criteria.** 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. IVIG is prescribed by or in consultation with a hematologist, oncologist or infectious diseases physician; AND
  - ii. The patient has had a HCT within the previous year; AND
  - iii. The patient has an immunoglobulin G (IgG) level < 500 mg/dL OR the patient has multiple myeloma or malignant macroglobulinemia; AND
  - iv. According to the prescriber the patient has a significant risk of having frequent and/or severe bacterial infections.
- B) Patients Currently Receiving IVIG:** Approve for 6 months if the patient requires IVIG to maintain trough IgG levels greater than 400 to 500 mg/dL AND who according to the prescriber have significant risk of having frequent and/or severe bacterial 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).<sup>39</sup> With regard to IVIG, guidelines recommend the following 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 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).

Although IVIG has been recommended for use in producing immune system modulation for the prevention of graft-versus-host disease (GVHD), routine administration of IVIG to HCT recipients for prophylaxis of bacterial infection within the first 100 days after transplantation is not recommended.<sup>39</sup> Some centers check total IgG levels in high-risk HCT recipients (e.g., those with unrelated marrow grafts). For patients with severe hypogammaglobulinemia (i.e., IgG < 400 mg/dL) IVIG prophylaxis may be considered to maintain a trough serum IgG concentration > 400 mg/dL. Also, in preventing late disease (> 100 days after HCT), routine use of IVIG monthly is not recommended unless the IgG level is < 400 mg/dL to prevent bacterial infections. These reduced levels may be associated with bacteremia or recurrent sinopulmonary infections.

Gamimune<sup>®</sup> N, a brand of IVIG that has been discontinued, was FDA-approved for the treatment of bone marrow transplant in patients ≥ 20 years of age to decrease the risk of septicemia and other

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infections, interstitial pneumonia of infectious or idiopathic etiologies, and acute GVHD in the first 100 days post-transplant.<sup>40</sup> Currently marketed IVIG products do not carry this indication.

**Dosing in Hematopoietic Cell Transplantation (HCT).** Approve the following dosing regimens (A OR B):

- A) During the first 100 days after HCT, the patient meets ONE of the following (i or ii):
- i. Adults and adolescents: 0.5 g per kg per week as an IV infusion and the dose is adjusted to maintain trough (pre-dose) serum IgG greater than 400 to 500 mg per dL; OR
  - ii. Pediatric patient with allogeneic HCT: 0.4 g per kg per month as an IV infusion and the dose is adjusted to keep IgG greater than 400 mg/dL;
- B) Greater than 100 days post-HCT, the dose is 0.5 g per kg IV infusion every 3 to 4 weeks, and the dose is adjusted to keep IgG greater than 400 mg/dL.

Guidelines from the American Society for Blood and Marrow Transplantation (ASBMT) recommend the following dosing in HCT recipients to prevent infectious complication.<sup>39</sup> During the first 100 days after HCT, the dose in adults and adolescents is 0.5 g/kg per week. The IVIG dose should be individualized to maintain trough (pre-dose) serum IgG greater than 400 to 500 mg/dL. The dose in allogeneic pediatric HCT patients is 0.4 g/kg per month, adjusted to keep IgG > 400 mg/dL. Higher and more frequent dosing may be necessary in patients for prevention of early disease after HCT because the half-life of IVIG is reduced to 1 to 10 days in this population. Dosing for > 100 days post-HCT is 0.5 g/kg every 3 to 4 weeks. The dose is not adjusted using serum IgG level in patients with multiple myeloma or malignant macroglobulinemia.

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#### **15. Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia.**

**Criteria.** Approve for 1 month if the patient meets the following criteria (A and B):

- A) IVIG is prescribed by or in consultation with an infectious diseases specialist or a physician who specializes in the treatment of HIV infection; AND
- B) The patient meets one of the following criteria (i or ii):
- i. The patient is receiving combination antiretroviral therapy (cART) for their HIV infection; OR
  - ii. The patient has clinically significant bleeding complications according to the prescriber.

Secondary ITP can occur in patients with HIV infection.<sup>24</sup> 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. IVIG and Rh<sub>0</sub>(D) immune globulin (IV or intramuscular [IM] injection) [Rhophylac<sup>®</sup>/WinRho<sup>®</sup> SDF] have been reported to increase the platelet count. Splenectomy is an effective option for patients who fail to respond to corticosteroid or IVIG therapy.

Rh<sub>0</sub>(D) immune globulin is FDA-approved in non-splenectomized, Rh<sub>0</sub>(D) positive patients for the treatment of childhood acute or chronic ITP, chronic ITP in adults, and ITP secondary to HIV infection (adults and children).<sup>41</sup> The safety and efficacy of Rh<sub>0</sub>(D) immune globulin have not been evaluated in patients who are splenectomized or in patients who are Rh<sub>0</sub>(D) negative. The American Society of Hematology (ASH) guidelines for immune thrombocytopenia recommend initial treatment with corticosteroids, IVIG, or Rh<sub>0</sub>(D) immune globulin for patients with secondary ITP due to HIV (no preference for initial therapy is expressed).<sup>24</sup> In symptomatic patients who fail one of these therapies, splenectomy is recommended. No platelet count cut-offs are addressed in this patient population.

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**Dosing in Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia.** Approve the following dosing regimens (*A OR B*):

- A) 2 g per kg given as an IV infusion in divided doses over 2 to 5 days; OR
- B) 1 g per kg one time as an IV infusion for platelet counts less than  $20 \times 10^9/L$  or  $20,000/\mu L$  to  $30 \times 10^9/L$  or  $30,000/\mu L$  per  $mm^3$  and this dose is repeated once weekly if needed.

Very limited information is available on dosing because this condition is not common and most studies predate the most current standard of practice for treatment of HIV infection.

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**16. Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections.**

**Criteria.** 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. IVIG is prescribed by or in consultation with an infectious diseases specialist or an immunologist; AND
  - ii. The patient is < 18 years of age; AND
  - iii. The patient is receiving combination antiretroviral therapy (cART); AND
  - iv. The patient has ONE of the following (a, b, or c):
    - a) Hypogammaglobulinemia (i.e., IgG < 400 mg/dL); 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 (cART) and appropriate antimicrobial prophylaxis.
- B) **Patients Currently Receiving IVIG:** Approve for 1 year if the frequency and/or severity of infections have decreased according to the prescriber.

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.<sup>42</sup> In rare situations where cART and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, secondary prophylaxis with IVIG can be considered.<sup>42</sup> 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.

Gamimune N, a brand of IVIG that has been discontinued, was FDA-approved for pediatric HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalization and to increase the time free of serious bacterial infection.<sup>40</sup> Currently marketed IVIG products do not carry this indication.

Clinicians providing care for adolescents are advised to use the U.S. 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.<sup>42</sup>

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**Dosing in Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections.** Approve the following dosing regimen: IVIG 0.4 g per kg IV infusion every 2 to 4 weeks and the dose and interval between infusions are adjusted according to clinical effectiveness.<sup>42</sup>

The dose of IVIG may be increased to improve clinical effectiveness (frequency or severity of infections, hospitalization, days of school or work missed, failure to thrive).

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### **17. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy.**

*Note: Examples of checkpoint inhibitors are: Keytruda (pembrolizumab), Opdivo (nivolumab), Yervoy (ipilimumab), Tecentriq (atezolizumab), Bavencio (avelumab), Imfinzi (durvalumab).*

**Criteria.** 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 the following criteria (i or ii):
- i. The patient has tried a systemic corticosteroid (e.g., prednisone, methylprednisolone) and has not adequately responded to therapy, or IVIG is being started with a systemic corticosteroid; OR
  - ii. A corticosteroid is contraindicated, per the prescriber.
- B) **Patients Currently Receiving IVIG:** 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.

NCCN has guidelines in partnership with the American Society of Clinical Oncology (ASCO) [version 2.2019- April 8,2019] for Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities).<sup>77</sup> The guidelines recommend IVIG in the following circumstances: for the management of severe pneumonitis after 48 hours of methylprednisolone therapy; as treatment for severe myasthenia gravis with no improvement/worsening on high-dose corticosteroids or for severe symptoms; for moderate or severe Guillain-Barre Syndrome or severe peripheral neuropathy in combination with pulse-dose methylprednisolone; as treatment for encephalitis in combination with pulse-dose methylprednisolone; and severe transverse myelitis. ASCO has also issued practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.<sup>78</sup> 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).

**Dosing for Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy.** Dosing varies per toxicity; typical dosing regimens are 0.4 g/kg/day for 5 days or 2 g/kg over 2-5 days.<sup>77</sup>

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### **18. Lambert-Eaton Myasthenic Syndrome (LEMS).**

**Criteria.** 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. IVIG is prescribed by or in consultation with a neurologist; AND
  - ii. The patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND
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- iii. 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.
- B) Patients Currently Receiving IVIG: Approve for 1 year if the patient has a response (for example, improved muscle strength, other clinical response) or continued effectiveness, according to the prescriber.

IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies for LEMS.<sup>18</sup>

**Dosing for Lambert-Eaton Myasthenic Syndrome (LEMS).** Approve the following dosing regimens (*A OR B*):

- A) 2 g per kg given as an IV infusion in divided doses over 2 to 5 consecutive days; OR
- B) Maintenance therapy every 4 weeks with IVIG  $\leq$  2 g per kg with the dose being adjusted based on clinical symptoms.

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## 19. Multiple Myeloma.

**Criteria.** 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. IVIG is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.
- B) Patients Currently Receiving IVIG: Approve for 1 year.

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 clinical practice guidelines on multiple myeloma (version 3.2019) recommend that IVIG should be considered in the setting of recurrent, life-threatening infections.<sup>44</sup>

**Dosing in Multiple Myeloma.** Approve for the following dosing regimen: 0.4 to 0.5 g per kg as an IV infusion every 3 to 4 weeks.

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## 20. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses.

**Criteria.** 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) IVIG is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS; AND
  - B) 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
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(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.

Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotropic hormone (ACTH), plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.<sup>45</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>45</sup>

**Dosing for Acute Exacerbation of Multiple Sclerosis (MS).** Approve the following dosing regimens (A OR B):

- A) A single 1 g per kg dose as an IV infusion; OR
- B) 0.4 g per kg per day IV infusion for 5 consecutive days.

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## **21. Multiple Sclerosis (MS), Post-Partum to Prevent Relapses.**

**Criteria.** 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. IVIG is prescribed by or in consultation with, a neurologist or a physician who specializes in the treatment of MS; AND
  - ii. The patient is not currently receiving disease modifying therapy (DMT) for MS to prevent relapses.

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], Tysabri® [natalizumab injection], Novantrone® [mitoxantrone injection].

- B) **Patients Currently Receiving IVIG:** 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], Tysabri [natalizumab injection], Novantrone [mitoxantrone injection].

None of the DMTs 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.<sup>46</sup>

**Dosing in Multiple Sclerosis (MS), Post-partum.** Approve the following dosing regimens (A, B, OR C):

- A) IVIG 0.15 g per kg as an IV infusion on Day 1 post-partum; OR
  - B) IVIG 0.9 g per kg IV infusion given in 3 divided doses over 3 days (post-partum Day 1: 0.45 g per kg, Day 2: 0.3 g per kg, Day 3: 0.15 g per kg); OR
  - C) Initial IVIG doses given post-partum as in A) or B), and then 0.15 g per kg every 4 weeks for up to 5 doses (total 6 months of therapy).
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## 22. Myasthenia Gravis.

**Criteria.** 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 criteria (i and ii):
- i. IVIG is prescribed by or in consultation with a neurologist; AND
  - ii. 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 (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, MTX, or tacrolimus) and is waiting for full effect; OR
    - d) The patient is starting therapy with a corticosteroid and IVIG is being given to prevent or minimize exacerbations.
- B) Initial Therapy for Maintenance: Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv):
- i. IVIG is prescribed by or in consultation with a neurologist; AND
  - ii. The patient has refractory myasthenia gravis; AND
  - iii. The patient has tried pyridostigmine; AND
  - iv. The patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, MTX, tacrolimus AND has had an inadequate response.
- C) Patients Currently Receiving IVIG for Maintenance Therapy: Approve for 1 year if the patient is responding according to the prescriber.

Patients who require additional short-term (acute) therapy for exacerbations or relapses are reviewed using the Initial Therapy for Short-Term Use above in A).

Note: Patients with myasthenia gravis crisis are hospitalized. Crisis is defined by respiratory failure resulting from myasthenic weakness and necessitating assisted ventilation.

Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.<sup>68</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, MTX, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. A nonsteroidal immunosuppressive agent may be used initially in combination with corticosteroids in patients with a high risk of steroid adverse effects. Also, nonsteroidal immunosuppressive agents should be added to corticosteroids if steroid adverse effects are significant, if the response to steroids is inadequate, or if the dose of the corticosteroid cannot be reduced because symptoms recur. 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.

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The choice of PLEX or IVIG depends on patient factors and the availability of each. PLEX and IVIG are probably equally effective in the therapy of severe generalized myasthenia gravis. The efficacy of IVIG is less certain in milder cases of myasthenia gravis or in ocular myasthenia gravis. PLEX may be more effective than IVIG in muscle specific tyrosine kinase myasthenia gravis. 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. There are no randomized controlled trials regarding the value of using IVIG as maintenance therapy. PLEX and IVIG are used as short-term treatment for *impending and manifest myasthenic crisis and in patients with significant respiratory or bulbar dysfunction*. These patients are hospitalized. In pregnant patients, PLEX or IVIG is used when a prompt but temporary response is needed.

**Dosing in Myasthenia Gravis.** Approve the following dosing regimens (A OR B):

- A) Short-term use: 2 g per kg given in divided doses over 2 to 5 consecutive days as an IV infusion;  
OR
- B) Maintenance therapy: 0.4 to 1 g per kg every 4 weeks.

The international consensus guidance statement for management of adult or juvenile myasthenia gravis<sup>68</sup> recommends an initial dose of IVIG 2 g/kg given in divided doses over 2 to 5 days. For maintenance therapy, the recommended dose is 0.4 to 1 g/kg given every 4 weeks; an attempt to decrease frequency can be made over time. If additional treatment is required, the dose should be adjusted based on the response.

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### 23. Passive Immunization for Measles (Post-Exposure Prophylaxis).

**Criteria.** 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 pregnant and meets the following criteria (i and ii):
  - i. The patient has been exposed to measles and IVIG 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 is severely immunocompromised (e.g., patients with a bone marrow transplant, graft-versus-host disease [GVHD], acute lymphoblastic leukemia [ALL], acquired immunodeficiency syndrome [AIDS], human immunodeficiency virus [HIV]-infected patients) according to the prescriber, AND the patient has been exposed to measles and IVIG will be given within 6 days of exposure.

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

When administered within 6 days of exposure, 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 age  $\geq$  12 months, unless they are severely immunocompromised. IG therapy should not be used to control measles outbreaks, but is used to reduce the risk of infection and complications in the person receiving it. IG therapy has not been shown to prevent rubella or mumps infection after exposure and is not recommended for that purpose.

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The 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 complications from measles: infants less than 12 months of age; pregnant women without evidence of measles immunity; and severely immunocompromised persons.<sup>13</sup> IM IG can be given to other persons who do not have evidence of measles immunity, but priority is given to persons exposed in settings with intense, prolonged, close contact. For patients exposed without evidence of measles immunity, a rapid IgG antibody test can be used to inform immune status, if administration of IG is not delayed. For *infants aged < 12 months* IM IG is used; infants aged 6 through 11 months can receive MMR vaccine instead of IG if given within 72 hours of exposure. *Pregnant women* without evidence of measles immunity who are exposed to measles should receive IVIG. *Severely Immunocompromised patients* who are exposed to measles should receive IVIG prophylaxis regardless of immunologic or vaccination status because they may not be protected by the vaccine. Severely immune compromised patients include patients with severe primary immunodeficiency; patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment or longer in patients with GVHD; patients on treatment for ALL within and until at least 6 months after completion of immunosuppressive chemotherapy; and patients with AIDS or HIV-infected persons with severe immunosuppression (defined as CD4 percent < 15% [all ages] or CD4 count < 200 lymphocytes/mm<sup>3</sup> [aged > 5 years]) and those who have not received MMR vaccine since receiving effective antiretroviral therapy. Some experts include HIV-infected persons who lack recent confirmation of immunologic status or measles immunity.

**Dosing for Passive Immunization for Measles.** Approve the following dosing regimen: 0.4 g per kg IV infusion administered one time as soon as possible after exposure.

The ACIP recommends 400 mg/kg as an IV infusion.<sup>13</sup>

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#### **24. Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis].**

**Criteria.** 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 HIV-infected and meets the following criteria (i, ii, and iii):
- i. IVIG is prescribed by or in consultation with an infectious diseases specialist or an immunologist; AND
  - ii. VariZIG<sup>®</sup> (varicella zoster immune globulin [human] for IM injection) is not available; AND
  - iii. 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); OR
- B) The patient is not HIV-infected and meets the following criteria (i, ii, iii and iv):
- i. IVIG is prescribed by or in consultation with an infectious diseases specialist or immunologist; AND
  - ii. VariZIG (varicella zoster immune globulin [human] for IM injection) is not available; AND
  - iii. 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
  - iv. The patient meets one of the following criteria (a or b):
    - a) The patient is immune compromised; OR
    - b) The patient is pregnant.

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.<sup>43</sup> Post-exposure prophylaxis with VariZIG, or if VariZIG is not available, IVIG should be considered for HIV-infected

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children with moderate-to-severe immune compromise even if they have been immunized with varicella vaccine. Children who have received IVIG within 3 weeks of exposure do not require additional passive immunization.<sup>42,43</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>42,48-50</sup> 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.<sup>50</sup> Patients without evidence of immunity to varicella who are at high risk for severe varicella and complications, who have been exposed to varicella or herpes zoster, and for whom varicella vaccine is contraindicated should receive VariZIG. The following patient groups are recommended by the Centers for Disease Control and Prevention (CDC) to receive VariZIG: 1) immunocompromised patients without evidence of immunity; 2) newborn infants whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after) [these babies are probably hospitalized]; 3) hospitalized premature infants born at  $\geq 28$  weeks of gestation whose mothers do not have evidence of immunity to varicella; 4) hospitalized premature infants born at  $< 28$  weeks gestation or who weigh  $\leq 1,000$  g at birth, regardless of their mothers' evidence of immunity to varicella; and 5) pregnant women without evidence of immunity.<sup>98</sup> In situations where administration of VariZIG does not appear possible within 10 days of exposure, IVIG is considered an alternative and should be given within 10 days of exposure<sup>48</sup> (and ideally within 96 hours after exposure).<sup>42</sup> The dose is 400 mg/kg given once.<sup>42,48</sup> Patients who have received IVIG 400 mg/kg within the prior 3 weeks should be protected.<sup>42</sup> 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.<sup>48</sup>

**Dosing for Passive Immunization for Varicella.** Approve the following dosing regimen: 0.4 g per kg IV infusion administered one time.

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## **25. Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic [Persistent] Parvovirus B19 Infection.**

**Criteria.** 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. IVIG is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist; AND
  - ii. The patient has a chronic immunodeficiency condition (e.g., patients with HIV infection, solid organ transplants [e.g., renal, liver], chemotherapy for hematologic malignancy); AND
  - iii. The patient has clinically significant anemia as determined by the prescriber OR the patient is transfusion dependent.
- B) **Patients Currently Receiving IVIG:** 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.

In *immunosuppressed* patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.<sup>51</sup> 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. Three to five days of IVIG induces an increase in reticulocyte count with an accompanied rise in the

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hemoglobin level, and is often curative in that B19 is cleared from the body.<sup>51</sup> Persistent B19 infection in apparently *immunocompetent* individuals who possess neutralizing antibodies does not respond well to IVIG.<sup>51</sup>

After 2 months (or two courses of IVIG), patients are evaluated for an increase in hemoglobin. If there is no improvement according to the prescribing physician, then further authorization is not recommended. IVIG is rarely indicated for more than 2 months in a row. If parvovirus becomes undetectable, IVIG should be discontinued. When/if the underlying immunosuppression is reversed (e.g., when immunosuppressive therapy is discontinued, tacrolimus is replaced with cyclosporine, or HIV-infected patients are treated with antiretroviral therapy), IVIG should be discontinued.

**Dosing for Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic Parvovirus B19.** Approve the following dosing regimens (A OR B OR C):

- A) 2 g per kg as an IV infusion given over a period of 2 to 5 consecutive days (one course) for up to two courses; OR
- B) 0.4 to 0.5 g per kg daily for 5 days.
- C) 0.4 g/kg every 4 weeks.

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## **26. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype.**

**Criteria.** 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. IVIG is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist; AND
  - ii. The patient has tried a systemic corticosteroid (e.g., prednisone); AND
  - iii. The patient has tried either cyclophosphamide OR cyclosporine.
- B) Patients Currently Receiving IVIG: Approve for 1 month if the patient has responded with an increase in hemoglobin and reticulocytosis, according to the prescriber.

The Canadian expert panel of hematologists recommends prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type PRCA.<sup>22</sup> Based on case reports about 50% of patients have an initial benefit with IVIG therapy. This panel considers IVIG a reasonable second-line option since this is a serious condition. The immunologic subtype mechanism may be humoral or cellular and can be caused by tumors, certain drugs (e.g., azathioprine, carbamazepine), connective tissue disorders, and incompatible bone marrow transplant.

**Dosing in Pure Red Cell Aplasia (PRCA), Immunologic Subtype.** Approve the following dosing regimen: 0.5 g per kg IV infusion every week for 4 weeks. Very limited information is available because this condition is uncommon.

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## **27. Stiff-Person Syndrome (Moersch-Woltman Syndrome).**

**Criteria.** 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. IVIG is prescribed by or in consultation with a neurologist; AND
  - ii. 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.
- B) Patients Currently Receiving IVIG: Approve for 1 year if the patient has responded (such as reduced stiffness or frequency of spasms, ability to walk unassisted) according to the prescriber.

In one double-blind, placebo-controlled crossover trial in 16 patients with stiff-person syndrome, IVIG 2 g/kg divided into two consecutive daily doses and given once monthly for 3 months, decreased stiffness scores significantly and decreased heightened sensitivity scores.<sup>32</sup>

**Dosing for Stiff-Person Syndrome.** Approve the following dosing regimens (*A OR B*):

- A) 2 g per kg IV infusion given over a period of 2 to 5 consecutive days every month; OR  
B) For maintenance therapy, the dose of IVIG is adjusted to provide the minimum effective dosage of IVIG. The maximum dose is 2 g per kg.

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## 28. Thrombocytopenia, Feto-neonatal Alloimmune.

**Criteria.** Approve for 6 months if the pregnant mother or newborn patient is prescribed IVIG by or in consultation with a hematologist or an obstetrician.

Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia (NAIT).<sup>52,53</sup>

First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive.

**Dosing in Thrombocytopenia, Feto-neonatal Alloimmune in the mother.** Approve the following dosing regimens (*A OR B*):

- A) IVIG 1 g per kg as an IV infusion every week; OR  
B) IVIG 2 g per kg IV infusion every week or 1 g per kg twice weekly.

**Dosing in the newborn.** IVIG 1 to 2 g/kg can be administered. Other dosing regimens can be evaluated on a case-by-case basis.

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## CONDITIONS NOT RECOMMENDED FOR APPROVAL

IVIG has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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>63</sup> 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 establish efficacy, determine the optimal dosing regimen, and to confirm the safety of IVIG in the general AD population.<sup>54,55</sup>
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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>56</sup>
  6. **Atopic Dermatitis.** Evidence does not support IVIG use. According to a practice parameter endorsed by the AAAAI; the ACAAI; and the Joint Council of Allergy, Asthma and Immunology, use of IVIG to treat severe refractory atopic dermatitis has produced conflicting results.<sup>57</sup> Most studies are not controlled and included small numbers of patients. According to the practice parameter, although children appear to have a better response than adults, controlled studies are needed to answer the question of efficacy in a more definitive manner. Guidelines from the American Academy of Dermatology state that there is insufficient data to make a recommendation for the use of IVIG in the management of atopic dermatitis.<sup>58</sup> Double-blind, placebo-controlled trials that are at least 4 months long and that are powered to show whether IVIG is effective are needed.
  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>59</sup> One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.<sup>59</sup> Although scores were improved in IVIG and placebo treatment groups, no significant between group difference was demonstrated.
  9. **Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy).** There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g of IVIG per kg produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients.<sup>60</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>64</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>61</sup> 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.<sup>62</sup> Well- designed, controlled trials are needed.<sup>18</sup>
  12. **Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use.<sup>18,65,66</sup> In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.<sup>65</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
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received IVIG 400 mg/kg given daily for 5 days.<sup>67</sup> 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%.<sup>69</sup> 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.<sup>70</sup>
  16. **In Vitro Fertilization (IVF).** There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.<sup>71</sup>
  17. **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.<sup>18</sup>
  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 on activity limitations in the short term and long term, respectively.<sup>72</sup> 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.<sup>73-76</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>73</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 (70% vs. 63%; P = 0.76; odds ratio [OR]: 1.37 [95% CI: 0.41, 4.61]).<sup>74</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>76</sup>
  20. **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.
  21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. IVIG has been used in many conditions when multiple other therapies have failed or are not tolerated and for rare conditions. Many case reports and pilot studies have reported its use for various indications and data are preliminary. Well-designed studies are needed to assess safety and efficacy. For conditions that are rare more information is needed to assess IVIG's place in therapy. Criteria will be updated as new published data are available.
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### APPENDIX A

ITP can occur in isolation (primary) or in association with other disorders (secondary) [e.g., autoimmune diseases, viral infections such as hepatitis C and HIV, and certain drugs].<sup>41</sup> An International Working Group (IWG) consensus panel defines primary ITP as a platelet count < 100 x 10<sup>9</sup>/L or 100,000/μL in the absence of other causes or disorders associated with thrombocytopenia. ITP is also defined by time from diagnosis: newly diagnosed (diagnosis to 3 months), persistent (3 months to 12 months from diagnosis), or chronic {lasting for more than 12 months}. These definitions may not apply to patients with secondary forms of ITP.

In adults with ITP/IT who are acutely bleeding, American Society of Hematology (ASH) guidelines indicate that if the platelet count is < 30 x 10<sup>9</sup>/L or 30,000/μL initial therapy is systemic corticosteroids.<sup>40-41</sup> Longer courses of steroids over shorter courses of steroids or IVIG are preferred as first-line treatment in adults because they are associated with a longer time-to-loss of response.<sup>41</sup> IVIG may be used with corticosteroids when a more rapid increase in platelet count is required. IVIG may be added to corticosteroid therapy if thrombocytopenia persists or worsens after about 3 days of corticosteroid therapy.<sup>33,41</sup> If there is an urgent need to increase the platelet count quickly, IVIG can be started with a corticosteroid.<sup>41</sup>

Adults who are at risk for intracerebral bleeding will be hospitalized and treated with a high-dose corticosteroid, IVIG, and platelet transfusions or other modalities.<sup>41</sup>

Systemic glucocorticoids have been the standard initial therapy for adults with moderate to severe thrombocytopenia and symptomatic purpura.<sup>41,44</sup> Evidence for use of glucocorticoids is based on case series and on a small randomized trial that compared glucocorticoid therapy to IVIG and both in combination as

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initial treatment. According to the ASH guideline, there is limited evidence for basing treatment recommendations on a specific platelet count or age for all patients. Observational data of patients with ITP have suggested that bleeding risk is increased with platelet counts  $< 20 \times 10^9/L$  or  $20,000/\mu L$  or  $< 30 \times 10^9/L$  or  $30,000/\mu L$ , but it is unclear whether offering treatment to all patients with ITP at these levels will result in decreased bleeding. In patients with recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course with corticosteroids or with IVIG or Rh<sub>0</sub>(D) immune globulin, there is no evidence to guide a sequence of treatments.

Splenectomy remains the only treatment that provides sustained remission off all treatments at 1 year and beyond.<sup>41</sup> ASH recommends splenectomy for patients who have failed corticosteroids. Patients who do not achieve spontaneous remission or do not maintain a complete response following cessation of therapy are classified as having persistent (3 to 12 months from diagnosis) or chronic (lasting  $> 12$  months) ITP. Patients who have failed splenectomy or relapsed thereafter and have severe ITP or have a risk of bleeding that requires therapy are classified as having refractory ITP. ASH does not recommend therapy in patients with platelet counts  $> 30 \times 10^9/L$  or  $30,000/\mu L$  in the absence of bleeding after splenectomy.

ITP is usually chronic in *adults*. There is no clear age at which children should be treated in a manner more like adults.<sup>41</sup> Although data suggest that adolescents are more likely than younger children to develop persistent or chronic disease, there have been no studies investigating a benefit to altered treatment in this age group or the age at which point this effect is likely to be most present. Therefore the management of adolescents should follow the usual management for children. Children with no or mild bleeding are managed with observation alone regardless of platelet count.

In children and adolescents  $\leq 17$  years of age, use of IVIG is based on risk of bleeding and not on platelet counts. Most children do not require therapy with IVIG.<sup>40,43</sup> In emergency situations, platelet transfusions given with IV corticosteroids and IVIG should be given for intracranial hemorrhaging or other life-threatening or serious bleeding.<sup>33</sup>

Studies in children with ITP suggest the majority of children experience no bleeding or mild bleeding regardless of whether or not they initially receive drug therapy.<sup>41</sup> ASH notes the decision to manage with observation requires a detailed discussion between the healthcare provider, patient and family. Treatment may be appropriate if follow-up cannot be assured, if there are other societal concerns (e.g., travel, distance from hospital), if there are concerns attributed to activity level or risk of bleeding, or there is a need for upcoming procedures associated with a risk of bleeding. For pediatric patients requiring treatment, a single dose of IVIG or a short course of corticosteroids are recommended as first-line treatment (long-term use of corticosteroids should be avoided). IVIG can be used if a more rapid rise in platelet count is desired.<sup>41,43</sup>

ASH recommends pregnant patients requiring treatment for ITP receive either a corticosteroid or IVIG.<sup>41</sup> Newborns of mothers with ITP are hospitalized.

In pregnant women, corticosteroids and IVIG are considered safe with regard to teratogenicity but may have maternal side effects including exacerbation of gestational diabetes and post-partum psychiatric disorders.<sup>41</sup> The ASH guideline recommends IVIG or corticosteroids in pregnant patients requiring treatment with no recommendations for specific platelet counts at which patients should be treated. During labor and delivery, ITP management is based on assessment of maternal bleeding risks associated with delivery and epidural anesthesia, and the minimum platelet counts required to undergo these procedures.

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**HISTORY**

Type of Revision	Summary of Changes	Approval Date
Annual (early)	<ul style="list-style-type: none"> <li>• ITP – Dosing was revised slightly for children and adolescents ≤ 17 years of age. For maintenance therapy (persistent or chronic), another recommended dose was added (i.e., 1 g per kg daily for two consecutive days).</li> <li>• Conditions Not Recommended for Approval: The following conditions were removed: BK Virus Associated Nephropathy (BKVAN) in Kidney Transplant Patient, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS), and Urticaria, Chronic Autoimmune.</li> </ul>	03/09/2016
Selected	<ul style="list-style-type: none"> <li>• ITP or IT, Acute and Chronic: In the criteria referring to pregnant “woman” with ITP/IT and pregnant “woman” in any trimester, the word “woman” was changed to “patient” since gender is not needed to be specified.</li> <li>• Multiple Sclerosis, Post-Partum to Prevent Relapses: In the approval criteria the word “women” was changed to “patients” since gender is not needed to be specified.</li> <li>• Passive Immunization for Measles (Post-Exposure Prophylaxis): In the criterion referring to pregnant “woman”, the reference to woman was deleted since gender is not needed to be specified.</li> <li>• Thrombocytopenia, Fetal Alloimmune: The criterion “The patient is a pregnant woman receiving antenatal therapy” was changed to “The patient is pregnant and receiving antenatal therapy” since gender is not needed to be specified.</li> <li>• Conditions Not Recommended for Approval: For the condition of Recurrent Spontaneous Pregnancy Loss [Including Antiphospholipid Antibody-Positive Patients], the reference to “Women” was changed to “Patients” since gender is not needed to be specified.</li> </ul>	08/10/2016
Selected	Added Gammaplex 10%	03/07/2017
Annual	<ul style="list-style-type: none"> <li>• Immunodeficiencies, Primary Humoral, CVID: <b>a)</b> The requirement for a documented history of significant recurrent or persistent, severe bacterial infections and that infections are responding inadequately to treatment with antibiotics and/or appropriate prophylaxis with antibiotics or the patient has multiple antibiotic hypersensitivities were removed. <b>b)</b> The requirement that patient is ≥ 4 years of age was added. <b>c)</b> Previously the criteria required that at least one of three criteria be met. Of these, the option for reduced IgG1 and IgG3 subclass levels or IgG1 alone was deleted. The total IgG level was revised to add that it is below the normal range and measured at least two times more than 3 weeks apart (IgG level is age adjusted and according to the reference lab is still required). Criteria for an antibody response to protein antigen or polysaccharide antigen were revised to add an exception if the physician believes the delay for this testing would be deleterious. Criteria were added requiring that IgA or IgM serum level is lower than the normal range. See policy for details.</li> <li>• Immunodeficiencies, Primary Humoral, Unspecified Hypogammaglobulinemia: Similar revisions were made to the criteria as noted in Immunodeficiencies, Primary Humoral CVID above. One difference is that the IgA or IgM levels are in the normal range or higher.</li> <li>• Kawasaki disease: Criteria were revised to require that fever or signs of inflammation persisted for at least 36 hours after completing the initial IVIG infusion; previously it was listed to last at least 24 to 48 hours.</li> <li>• Guillain Barré syndrome: The word relapse was clarified to include treatment-related fluctuation.</li> <li>• Myasthenia gravis: Criteria were added for maintenance therapy based on new consensus guidelines. See policy for details. The criteria for short-term therapy were revised to remove that the patient has responded to a previous course of IVIG but relapsed and has no response to other medications. A criterion was added for patients who are starting a steroid allowing IVIG to be used to prevent or minimize exacerbations. Dosing, Initial and Extended Approval, and Duration of Therapy were added for maintenance therapy.</li> <li>• Conditions not Recommended for Approval: “Heart block, congenital” and “Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome” were removed.</li> </ul>	06/14/2017



Selected	<ul style="list-style-type: none"> <li>The Policy Statement was revised to add the following: The requirement that the patient meet the criteria for coverage of the requested medication applies to the initial authorization only.</li> </ul>	02/07/2018
Selected	<ul style="list-style-type: none"> <li>Immunodeficiencies, Primary Humoral: Age in patients with CVID or Unspecified hypogammaglobulinemia revised to be at least 2 years of age. Previously the age was at least 4 years.</li> </ul>	03/14/2018
Annual	<ul style="list-style-type: none"> <li>Criteria created for the following diagnoses: Antibody-Mediated Rejection (ABMR) in Solid Organ Transplant (e.g., Kidney, Heart, Lung, Liver), Hematologic Neoplasm-Associated Hypogammaglobulinemia (Secondary Immunodeficiency [SID]), and Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy.</li> <li>B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Bacterial Infections- updated criteria to IgG level below 500 mg/dL OR a history of recurrent bacterial infections. Previously both were required.</li> <li>Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Hematopoietic Cell Transplantation (HCT) updated to Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Cancer or Transplant-Related Infection.</li> <li>Removed the following conditions not recommended for approval: Cytomegalovirus (CMV) Infection, Preemptive Therapy for CMV Infection or Treatment of CMV Disease, in Allogeneic Hematopoietic Cell (HCT) Recipients and Cytomegalovirus (CMV) Infections, Prophylaxis or Treatment in Solid Organ Transplantation. Updated the condition not recommended for approval Cytomegalovirus (CMV) Disease Prophylaxis in Hematopoietic Cell Transplantation (HCT) Recipients to include Solid Organ Transplantation.</li> <li>Removed specific age limit in the following diagnosis: Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]</li> <li>Updated age to &lt; 18 years old (previously &lt; 13 years of age) in the following diagnosis: Human Immunodeficiency Virus (HIV) Infected Infants and Children to Prevent Recurrent Bacterial Infections.</li> </ul>	07/11/2018
Selected	<ul style="list-style-type: none"> <li>The Policy Statement was revised from, the requirement that the patient meet the criteria for coverage of the requested medication applies to the initial authorization only, to the requirement that the patient meet the criteria for coverage of the requested medication applies to patients not currently taking the requested medication. Also added: For patients already on the requested medication, follow the directions under the extended approval section.</li> </ul>	7/24/2018
Selected	<ul style="list-style-type: none"> <li>Added Panzyga to the policy.</li> </ul>	10/29/2018
Selected revision	<ul style="list-style-type: none"> <li>The duration of therapy was updated in the criteria section throughout the policy to align with the PA policy. Updated formatting of the policy by removing extended approval section and placing within the criteria (under patients already started on therapy) to align with the PA policy. Removed duration of therapy and labs/diagnostics section. The policy statement was updated.</li> <li>Immunodeficiency, Primary Humoral (Treatment): For the unspecified hypogammaglobulinemia diagnosis in the criterion that requires that the patient has markedly impaired antibody response to protein testing with polysaccharide antigen (pneumococcus), the option of "OR according to the prescribing physician the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health" was added.</li> </ul>	1/16/2019
Annual revision	<ul style="list-style-type: none"> <li>Asceniv was added to the policy with the same criteria as all other immune globulin products.</li> <li>Immunodeficiency, Primary Humoral (Treatment) was updated to Primary Immunodeficiencies (PID). Criteria for PID was updated to the following: approval if (along with prescribing by a physician specialist) 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) syndrome, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing. For a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant</li> </ul>	7/31/2019

	<p>hypogammaglobulinemia, approval if (along with prescribing physician specialist) the patients pretreatment IgG level is below the normal range AND either an impaired antibody response or recurrent infections. For a diagnosis of IgG subclass deficiency or selective antibody deficiency, approval if (along with prescribing physician specialist) the patient has an impaired antibody response and has recurrent infections.</p> <ul style="list-style-type: none"> <li>• Dosing criteria was added if the patient receives a dose of less than 0.53 g of IVIG per kg for measles prophylaxis in patients with PID.</li> <li>• Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP): the criterion, electrodiagnostic studies to support the diagnosis of CIDP, was added.</li> <li>• CIDP dosing- the wording was updated to “the dose and interval are adjusted according to clinical response.”</li> <li>• Desensitization Therapy Prior to and Immediately after Solid Organ Transplantation: added the wording “up to” in the dosing section.</li> <li>• Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy: added the criteria or IVIG is being started with a systemic corticosteroid for Initial Therapy.</li> <li>• Lambert-Eaton Myasthenic Syndrome (LEMS): criteria regarding the patient having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine was added. Criteria regarding non-paraneoplastic LEMS was updated to having 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.</li> <li>• Multiple Myeloma: the following criteria was removed “the patient has stable (plateau phase) disease (&gt; 3 months from diagnosis).</li> <li>• Multiple Sclerosis (MS), Acute Severe Exacerbation was updated to include the wording “or relapses.” Acthar HP gel was removed as one of the required alternatives. Criteria was updated as to only a corticosteroid would require to be contraindicated, according to the prescriber.</li> <li>• Multiple Sclerosis (MS), Post-Partum to Prevent Relapses: Mavenclad and Mayzent were added as disease modifying therapy.</li> <li>• Thrombocytopenia, Fetal Alloimmune, was updated to include not only the pregnant mother, but the newborn as well. Criteria that the patient is pregnant and receiving antenatal therapy was removed. Also added dosing for the newborn.</li> <li>• Wording in each applicable criteria that referenced “determined by the prescribing physician” was changed to “determined by the prescriber.”</li> </ul>	
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