MEDICAL MUTUAL®

Drug Policy

Policy:	**201316**	**Initial Effective Date: 07/01/2013**
Code(s):	**HCPCS J1459, J1556, J1557, J1561, J1566, J1568, J1569, J1572, J1599**	**Annual Review Date: 08/16/2018**
SUBJECT:	**Immune globulin intravenous (IVIG)** **• Bivigam® (immune globulin intravenous – Biotest Pharmaceuticals);** **• Carimune® NF Nanofiltered (immune globulin intravenous – CSL Behring LLC [manufactured by CSL Behring AG]) DSC*;** **• Flebogamma® DIF (immune globulin intravenous – Grifols Biologicals [manufactured by Instituto Grifols, SA]);** **• Gammagard Liquid (immune globulin intravenous – Baxter Healthcare Corporation);** **• Gammagard® S/D (immune globulin intravenous – Baxter Healthcare Corporation);** **• Gammaked™ (immune globulin intravenous caprylate/chromatography purified – Kedrion Biopharma [manufactured by Talecris Biotherapeutics {Grifols Therapeutics Inc}]);** **• Gammaplex® (immune globulin intravenous – BPL Inc [manufactured by Bio Products Laboratory]);** **• Gamunex®-C (immune globulin intravenous caprylate/ chromatography purified – Grifols [manufactured by Grifols Therapeutics Inc]);** **• Octagam® (immune globulin intravenous – Octapharma USA [manufactured by Octapharma Pharmazeutika Produktionsges.m.b.H.]);** **• Panzyga (intravenous immunoglobulin 10%)** **• Privigen® Liquid (immune globulin intravenous – CSL Behring LLC [manufactured by CSL Behring AG])**	**Last Revised Date: 11/15/2018**

*Carimune NF- discontinued (DSC) by manufacturer in 2018

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

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.[1-11] 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.

All of the US licensed products (except Octagam 10%) are Food and Drug Administration (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).[1-10] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous (SC) infusion for primary immunodeficiency.[3,5,7] 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.[5,7-8,12]
2. B-cell chronic lymphocytic leukemia (CLL) for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections.[4]
3. Chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[5,7]
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.[1,4-5,7,9,11]
5. Kawasaki disease in pediatric patients for the prevention of coronary artery aneurysm.[4]
6. Multifocal motor neuropathy (MMN) in adults as maintenance therapy to improve muscle strength and disability.[3]

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 conditions of coverage in the **Criteria, Dosing (*applies to requests under the medical benefit only*), Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the criteria for coverage of the requested medication applies to patients not currently taking the requested medication. For patients already on the requested medication, follow the directions under the extended approval section. **Waste Management** applies for all covered conditions. **Exclusions** are listed following the recommended authorization criteria and Waste Management section.

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, initial approval requires IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is

required for continuation of therapy. The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.

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

FDA-Approved Indications

1. Immunodeficiency, Primary Humoral (Treatment).

Criteria. *The patient must meet the following criteria (A, B AND C):*

A) 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

B) The patient has ONE of the following primary humoral or combined immune deficiencies (i, ii, iii, iv, v, vi, or vii):

i. Common variable immunodeficiencies (CVID)[14-18] AND the patient meets the following criteria (a, b, c, d, and e):

a) The patient is at least 2 years of age;[17-18] AND

b) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present[14,17-18] according to the prescribing physician; AND

c) The total serum IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[17-18] AND

d) The IgA or IgM serum level is lower than the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[17] Note: Patients who do not have a low IgA or IgM level may be reviewed using criteria for Unspecified Hypogammaglobulinemia. AND

e) The patient has a markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus) [14,17-19,21-22] 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.[17] Note: In cases where impaired antibody testing would be deleterious to the patient's health, all other criteria for CVID in this section must be met.

OR

ii. X-linked agammaglobulinemia (XLA) [Bruton's agammaglobulinemia, congenital agammaglobulinemia];[14,18,23] OR

iii. Severe combined immunodeficiencies (SCID);[14,18,24] OR

iv. Wiskott-Aldrich syndrome;[14,18,25-26] OR

v. Hyper-Immunoglobulin M (IgM) syndromes, X-linked (e.g., CD40 L deficiency) OR autosomal recessive (e.g., activation-induced cytidine deaminase, uracil-DNA glycosylase, CD40 deficiency);[18,27-29] OR

vi. Other combined immunodeficiencies with significant hypogammaglobulinemia OR antibody production defect[14,18] (e.g., ataxia-telangiectasia,[14,18,30] hyper-Immunoglobulin E [IgE] syndrome,[18,53] STAT [signal transducer and activator of transcription]-3 deficiency,[18] STAT-1 deficiency,[18] DiGeorge syndrome,[14,27]

nuclear factor κB essential modifier [NEMO] deficiency,[14,18]) AND the patient has frequent and severe infections according to the prescribing physician; OR

vii. Unspecified hypogammaglobulinemia (or unspecified IgG deficiency)[17] AND the patient meets the following criteria (a, b, c, d, and e):

- **a)** The patient is at least 2 years of age;[17-18] AND
- **b)** Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present[14,17-18] according to the prescribing physician; AND
- **c)** The total serum IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[17-18] AND
- **d)** The IgA or IgM serum level is in the normal range or higher (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[17] AND
- **e)** The patient has a markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus); AND[14,17,19,21-22]

C) Site of care medical necessity is met.*

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.[14,18,31]

Patients with primary humoral immunodeficiency are at high risk of developing acute and chronic bacterial infections.[14] 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 controversial and 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.[14,18,19-22]

A new consensus document providing a definition of CVID was recently published.[17] 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 hypogamma-globulinemia. Their recommendations are as follows. Hypogammaglobulinemia should be defined according to age-adjusted reference range for the laboratory that performs the test. IgG levels must be repeatedly low in at least two measurements > 3 weeks apart in all patients. Repeated measurement may be omitted if the level is very low (< 100 to 300 mg/dL, depending on age), other characteristics are present, and it is considered in the best interest of the patient to start immune globulin (IG) therapy as soon as possible. IgA or IgM levels must be low. All patients with an IgG level > 100 mg/dL should be studied for responses to T cell dependent and T cell independent antigens whenever possible. In these patients there must be a demonstrated impairment of response to at least one type of antigen (i.e., T cell dependent or T cell independent). Certain exceptions can be made if all other criteria are met and if the delay caused by pre-vaccination and post-vaccination antibody measurement is deleterious to the patient's health. Other causes of hypogamma-globulinemia must be excluded (e.g., drug induced, single gene and other defects, chromosomal anomalies, infectious diseases,

malignancy, other systemic disorders). It is best to not confer the diagnosis of CVID before at least the age of 4 years. Some patients may not fulfill the diagnosis of CVID on initial evaluation because the serum IgA or IgM level is not low. In this case, the term unspecified hypogammaglobulinemia or unspecified IgG deficiency is used. Also the IgG and IgA levels may be low but the antigen response to vaccines appears normal. In either circumstance, patients should be assessed over time because Ig levels and antibody function may wane and the criteria for CVID will eventually be met.

Dosing in Primary Immune Deficiency in Adults, Children or Adolescents. *Dosing must meet ONE the following (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;[1-10,12,42] 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 prescribing physician; OR
d. Patients with primary immune deficiency and exposure to measles must meet one of the following (i or ii):
    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 ≥ 0.4 g per kg one time given just before the expected exposure to measles;
    ii. 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.[1-10,12,42] 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.[7,9-10] 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. 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.[13]

ACIP also recommends IVIG be given in the following persons: pregnant women without evidence of measles immunity who have been exposed to measles, and in severely immunocompromised patients (i.e., patients with bone marrow transplant, patients on treatment for acute lymphoblastic leukemia, patients with acquired immune deficiency syndrome [AIDS] or human immunodeficiency virus [HIV]-infected patients with severe immunosuppression who have not received measles, mumps, rubella (MMR) vaccination since receiving effective antiretroviral therapy).[13] Infants less than 12 months of age who are exposed to measles should receive intramuscular IG. In infants 6 through 11 months of age, MMR vaccine can be given in place of IG if given within 72 hours of exposure. Post-exposure prophylaxis with IVIG has also been recommended in infants if they have not been vaccinated for measles and who have been exposed to measles.[93]

In patients with primary immune deficiency, the dose and interval between infusions are adjusted according to clinical effectiveness. The dose of IVIG is increased/adjusted to improve clinical effectiveness (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). The trough (pre-dose) IgG levels may be used to determine the interval between doses. The interval between doses is determined by the prescribing physician. The trough IgG level alone is not used to determine the dosage (dose and interval). The interval between doses may be as often as every 2 weeks and is usually no longer than every 4 weeks.

The trough IgG level usually should be greater than or equal to 500 mg per dL (5 g per L) and varies depending on the assessment of the prescribing physician (allergist, immunologist, otolaryngologist, pulmonologist, infectious diseases physician or physician consulting with one of these specialists). The IgG trough level should be greater than 800 mg per dL in some patients with chronic lung and/or sinus disease to prevent serious bacterial infections. These higher trough levels may also be required to improve or prevent chronic lung disease, granulomatous infiltrative disease, or autoimmune disease in certain types of primary immune deficiency (such as CVID).

Background information. When starting IVIG therapy, a trough IgG level is usually measured at least every 3 months, mostly to assist with determining the interval to dose IVIG. Once therapy with IVIG is started, the IgG trough usually stabilizes after 3 to 4 months of therapy. As a general guideline, in growing children, the trough IgG level should be checked about every 3 to 6 months, and in adults, every 6 to 12 months. Once the patient is stabilized, a trough IgG level is usually measured once a year. The dose and interval between infusions are adjusted according to clinical effectiveness.

Initial Approval/Extended Approval.

A) Initial and maintenance therapy
- **i.** *Initial Approval*. 6 months for all indications.
- **ii.** *Extended Approval*.
  - **(1)** For common variable immunodeficiencies (CVID) [Criteria B) i above] or for other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect (conditions approved with Criteria B) vi above), approve for 12 months if the frequency and/or severity of infections has decreased according to the prescribing physician. Continue to approve every 12 months if the patient is responding with a decrease in frequency and/or severity of infections.
  - **(2)** For X-linked agammaglobulinemia (XLA); severe combined immunodeficiencies (SCID); hyper-IgM syndromes (X-linked or autosomal recessive); or Wiskott-Aldrich syndrome, approve for 12 months. Continue approving every 12 months.
  - **(3)** For unspecified hypogammaglobulinemia (or unspecified IgG deficiency), approve at 6-month intervals if the frequency and/or severity of infections has decreased according to the prescribing physician.

B) Measles exposure in primary immune deficiency
- **i.** *Initial Approval.* One dose.
- **ii.** *Extended Approval.* Not recommended.

Duration of Therapy in Primary Immune Deficiency or Other Immunodeficiency States. Indefinite or until definitive correction of the underlying disorder (such as hematopoietic cell transplant [HCT], gene therapy). Some patients continue to require IG supplementation after HCT because of failure of B-cell engraftment.[14,18]

Labs/Diagnostics. In CVID or unspecified hypogammaglobulinemia total IgG levels**,** and either IgA and/or IgM levels AND antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus) are required as part of the diagnosis.

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2. <u>B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Bacterial Infections</u>.

Criteria. *<u>The patient must meet the following criteria (A or B, AND C AND D)</u>:*
A) The patient has an immunoglobulin G (IgG) level < 500 mg/dL (5.0 g/L);[32] OR
B) The patient has a history of recurrent bacterial infections; AND
C) IVIG is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician; AND
D) Site of care medical necessity is met.*

CLL is a secondary humoral immunodeficiency.[18] The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on chronic lymphocytic leukemia/small lymphocytic lymphoma (version 5.2018) recommend evaluation of serum IgG if < 500 mg/dL in patients with CLL who have recurrent sinopulmonary infections requiring antibiotics or hospitalization.[32] IVIG has been associated with a significant decrease in infections, but no improvement in survival. According to a Canadian expert panel of hematologists, IVIG is recommended for infection prophylaxis in these adults who have either a recent episode of a life-threatening infection thought to be caused by low levels of polyclonal immunoglobulins or recurrent episodes of clinically significant infections (e.g., pneumonia) that are caused by low levels of polyclonal immunoglobulins.[33] IVIG is an option for acute life-threatening infections in these patients. This panel of hematologists recommended re-evaluation every 4 to 6 months when used for prophylaxis but there was no consensus on specific criteria to use for duration of treatment with IVIG.

Dosing in Patients with B-Cell Chronic Lymphocytic Leukemia (CLL). *<u>Dosing must meet ONE of the following (A, B, OR C)</u>:*
a) 0.4 g per kg intravenous infusion every 3 to 4 weeks;[6] OR
b) 0.3 to 0.5 g per kg intravenous infusion once monthly;[32] OR
c) The dose and interval have been adjusted to maintain a trough (pre-dose) IgG level of about 500 mg/dL[32] 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.[6] 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.[32] These guidelines recommend monthly IVIG for supportive care.

Initial Approval/Extended Approval.
<u>Initial Approval</u>: Initial approval is for 4 months of therapy.
<u>Extended Approval</u>: Approve at additional 4-month intervals if the patient is maintaining an IgG trough (pre-dose) level of about 500 mg/dL and up to 700 mg/dL.

Duration of Therapy in Chronic Lymphocytic Leukemia (CLL). Continue to maintain IgG trough of about 500 mg/dL and up to 700 mg/dL to prevent bacterial infections.

In the pivotal trial that established IVIG efficacy for prevention of bacterial infections in patients with B-cell CLL, seventeen infusions of IVIG were given.[6]

Labs/Diagnostics. Baseline IgG is required. Dose and interval are adjusted to maintain trough (pre-dose) IgG levels of about 500 mg/dL and up to 700 mg/dL.

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

Criteria. Approve if IVIG is prescribed by or in consultation with a neurologist and Site of care medical necessity is met.*

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IVIG is recommended as an equivalent alternative to plasma exchange in children and adults with CIDP.[36-38] IVIG has been effective at improving certain motor functions for up to 48 weeks after initial therapy.[35-36,39] In short-term, controlled trials, IVIG improved disability more than prednisolone and the quality of life was better with IVIG because adverse effects were less.[37] The goal is to prevent or decrease the frequency of relapses and stabilize the disease.[34]

Dosing in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Adults. *Dosing must meet ONE of the following (A, B, OR C)*:[7,9]

a) An initial loading dose of 2 g per kg as an IV infusion given in divided doses over 2 to 4 consecutive days.[7,9]

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.[7,9] Either regimen is given every 3 weeks.

c) If the patient has an inadequate response (not a full response) after ≥ 3 months of therapy, the dose and/or interval may be adjusted:

- **i.** The maximum dose per treatment course is 2 g per kg.[36]
- **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.[34]

The initial dose is a total loading dose of 2 g per kg given in divided doses over 2 to 4 consecutive days.[7,9] 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.[34] Corticosteroids, plasmapheresis, or other immunosuppressant therapy can be used with IVIG in patients with an inadequate response.

Initial Approval/Extended Approval.

a) *Initial Approval*. Approve for 3 months (which is for the loading dose and four additional 1 g per kg doses given every 3 weeks).

b) *Extended Approval*. Approve for an additional 6 months of therapy if the patient has a clinically significant improvement in neurologic symptoms (e.g., improvement in disability; nerve conduction study results improved or stabilized; physical examination shows improvement in neurological symptoms, strength, and sensation) as

determined by the prescribing physician (a neurologist or in consultation with a neurologist). The patient may not have a full response after 3 months, but there should be some response. Continue approving at 6-month intervals in patients who are responding.

Duration of Therapy in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Indefinite in patients who are responding and who cannot discontinue IVIG without relapse.

It is well accepted that therapy should be continuous in patients who respond and who cannot discontinue therapy without relapsing.

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet ONE of the following criteria (A, B, OR C AND D):*

A) Adults and adolescents (> 17 years of age) with ITP/IT. Approve for ONE of the following (i, ii, or iii):
- **i.** *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 if the patient meets the following criteria (a, b and c):
  - **a)** IVIG is prescribed by or in consultation with a hematologist; AND
  - **b)** One of the following applies:
    - **(1)** The patient has tried a systemic corticosteroid (e.g., prednisone) for ITP/IT;[40] OR
    - **(2)** There is an urgent need to increase the platelet count quickly AND IVIG will be started with a systemic corticosteroid;[41] OR
    - **(3)** A corticosteroid is contraindicated according to the prescribing physician; AND
  - **c)** The platelet count is < 30,000 per mm^3 (microliter). OR
- **ii.** To increase platelet counts before surgical procedures (e.g., splenectomy) or dental procedures, approve IVIG if the patient meets the following criteria (a and b):
  - **a)** IVIG is prescribed by or in consultation with a hematologist; AND
  - **b)** The platelet count is < 50,000 per mm^3 OR if the patient is undergoing major surgery (e.g., central nervous system or cardiac surgery) and the platelet count is < 75,000 per mm^3. OR
- **iii.** The patient has *persistent* (3 to 12 months duration) or *chronic* (≥ 12 months duration) ITP/IT. Approve IVIG if the patient meets the following criteria (a, b, and c):
  - **a)** IVIG is prescribed by or in consultation with a hematologist; AND
  - **b)** One of the following applies:
    - **(1)** The patient has tried a systemic corticosteroid (e.g., prednisone) for ITP/IT; OR
    - **(2)** There is an urgent need to increase the platelet count quickly AND IVIG will be started with a systemic corticosteroid;[41] OR
    - **(3)** A corticosteroid is contraindicated according to the prescribing physician; AND
  - **c)** IVIG is required to prevent bleeding.

B) Children and adolescents (≤ 17 years of age) with ITP/IT. Approve for one of the following (i, ii, iii, or iv):

i. 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 if the patient meets the following criteria (a and b):
  a) IVIG is prescribed by or in consultation with a hematologist; AND
  b) There is significant acute mucous membrane bleeding or other noncutaneous bleeding; OR

ii. The patient has *persistent* (3 to 12 months) or *chronic* (≥ 12 months) ITP/IT. Approve if the patient meets the following criteria (a and b):
  a) IVIG is prescribed by or in consultation with a hematologist; AND
  b) IVIG is required to prevent bleeding; OR

iii. Inaccessibility (such as travel, distance from hospital), activity level of the patient, or noncompliance is a concern with the prescribing physician.[41] Approve if the patient meets the following criteria (a and b):
  a) IVIG is prescribed by or in consultation with a hematologist; AND
  b) Child/adolescent is at risk of bleeding; OR

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. Approve if IVIG is prescribed by or in consultation with a hematologist.

C) Pregnant patient with ITP/IT. Approve for one of the following (i or ii):

i. Before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia.[40] Approve if IVIG is prescribed by or in consultation with a hematologist; OR

ii. Pregnant patient in any trimester.[41] Approve 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.); AND

D) Site of care medical necessity is met.*

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

Dosing in Idiopathic Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia (IT). *Dosing must meet ONE of the following (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.[2,7,9,42]

ii. Maintenance therapy for persistent or chronic ITP/IT:
  (1) IVIG ≤ 1 g per kg daily for 2 consecutive days as an IV infusion;[4,11] 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.[7,9] The total maximum dose is 2 g per kg.

Note: Some patients with acute bleeding may have an adequate response with the first 1 g per kg dose and not require the second dose.[7,9]

In patients with acute bleeding who do not respond to IVIG (increased platelet count and/or decreased bleeding), further therapy with IVIG is not recommended unless the patient will be using IVIG in combination with another therapy such as a corticosteroid.

For persistent or chronic ITP/IT, the dose and interval between doses is adjusted according to the platelet count and/or to prevent significant bleeding. The dose is adjusted to the minimum effective dose that can be given at maximum intervals. In patients who do not have a durable response for a minimum of 2 to 3 weeks, other therapies besides IVIG should be considered[33] or other therapies should be used in addition to IVIG.

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.[9,33,43] 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* (≥ 12 months) ITP/IT:

(1) 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).[33] Another recommended dose is 1 g per kg daily for 2 consecutive days.[4,9,42] 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.

(2) The dose and interval between doses has been adjusted according to the platelet count and/or to prevent significant bleeding[4] as determined by the prescribing physician 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 prescribing physician: 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.

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.

In children or adolescents with *persistent or chronic ITP/IT*, the dose is adjusted according to the response (the platelet count and/or to prevent significant bleeding) as determined by the prescribing physician and is adjusted to the minimum effective dose that can be given at maximum intervals. The IVIG dose is also adjusted according to body weight changes in children or adolescents who are growing.

C) Pregnant Patients. *Dosing must meet one ONE of the following (i OR ii):*

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.

The dose is adjusted to the minimum effective dose that can be given at maximum intervals. In patients who do not have a durable response for a minimum of 2 to 3 weeks, other therapies besides IVIG should be considered or other therapies should be used in addition to IVIG.

Initial Approval/Extended Approval.

a. In adults (non-pregnant), adolescents, and children with ITP/IT:
   - **i.** *Initial Approval*. Approve one course of therapy with a total maximum dose of 2 g per kg for the following conditions:
     - **a)** Acute bleeding (newly diagnosed or requiring therapy for the first time); OR
     - **b)** Acute bleeding in patients with persistent or chronic ITP/IT; OR
     - **c)** Before there is predictable bleeding from surgery or dental procedures.
   - **ii.** *Extended Approval*. Approve additional therapy with IVIG for up to 6 months in patients with persistent or chronic ITP/IT, if the patient responded (platelet count increased and/or significant bleeding is absent), and the patient requires additional therapy with IVIG to prevent bleeding according to the prescribing physician.

   In patients who have a response and who require additional therapy with IVIG to prevent bleeding, should be evaluated every 3 to 6 months for continued response. In patients who do not have an adequate response to IVIG, other drug therapies may be added to IVIG. IVIG should be discontinued in patients who do not respond.

b. Pregnant patients before normal vaginal delivery cesarean section or spinal or epidural anesthesia:
   - **i.** *Initial Approval:* Approve IVIG for 2 weeks.
   - **ii.** *Extended Approval:* Not recommended.

c. Pregnant patients in first, second or third trimester:
   - **i.** *Initial Approval.* Approve for 3 months of IVIG.
   - **ii.** *Extended Approval.* Approve for 3 months if the patient responded (platelet count increased and/or significant bleeding is absent). Evaluate every 3 months for response.

Duration of Therapy in Idiopathic Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia (IT). IVIG therapy is continued to maintain platelet count ≥ 30,000 per mm^3 [41] and/or to prevent bleeding or bleeding symptoms.[40]

IVIG is rarely indicated to maintain platelet counts greater than 30,000 per mm^3 unless bleeding is due to platelet dysfunction or another hemostatic defect, trauma, or surgery.

Labs/Diagnostics. None required.

5. **Kawasaki Disease.**

Criteria. *The patient must meet the following criteria (A, B AND C)*:

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 recrudescent (recurring) fever or signs of inflammation at least 36 hours after completing the initial IVIG infusion(s), AND

C) Site of care medical necessity is met.*

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.[46] 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 10th 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 recrudescent fever that is present 36 hours after the end of the first IVIG infusion can be retreated with IVIG one time.[45] 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.[46]

Dosing in Kawasaki Disease. *Dosing must meet the following:* 2 g per kg IV infusion usually given over 10 to 12 hours for persistent or recrudescent fever or signs of inflammation.[45-46]

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.[45-46] For persistent or recrudescent 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.[6]

Initial Approval/Extended Approval.

A) *Initial Approval*: One dose for persistent or recrudescent fever after completing the initial IVIG infusion that was given in the hospital.[45-46]

B) *Extended Approval*: Not recommended.

Duration of Therapy in Kawasaki Disease. One dose is given for persistent or recrudescent fever after an initial dose given in a hospital. Additional doses of IVIG are not recommended.

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria:* IVIG is prescribed by or in consultation with a neurologist and Site of care medical necessity is met.*

In several placebo-controlled trials, IVIG improved muscle strength and neurological disability scores.[5,36-38,47] IVIG is the only proven effective treatment and is considered first-line treatment. Plasma exchange and corticosteroids are not effective. IVIG is beneficial in maintenance treatment but the disease continues to progress over many years.

Dosing in Multifocal Motor Neuropathy (MMN). *Dosing must meet ONE of the following (A OR B)*:

a) Therapy is initiated with 2 g per kg IV infusion given in divided doses over 2 to 5 consecutive days;[47] 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;[5] OR
- **ii.** 1 g per kg IV infusion every 2 to 4 weeks;[47] OR
- **iii.** 2 g per kg IV infusion every 1 to 2 months.[47]

The approved dosage range is 0.5 to 2.4 g per kg per month.[5] The dose is adjusted to achieve the desired clinical response. In the pivotal trial that established efficacy and safety of IVIG, adults who were receiving maintenance IVIG 0.5 to 2.0 g/kg/month prior to enrollment were included. The results from this trial cannot be generalized to naïve patients. Many regimens have been used for initiating therapy and for maintenance therapy. The European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society Guideline on management of MMN recommends initial therapy with IVIG 2 g/kg given over 2 to 5 days.[47] Typical maintenance treatment regimens are 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks. In general the IVIG infusion needs to be repeated frequently, every 4 to 12 weeks.[36-37,47]

Repeated treatment with IVIG should be considered if the initial infusion of IVIG is effective. In patients who do not improve after Cycle 2 of IVIG treatment, the dose can be increased or decreased and/or the interval can be increased or decreased. In patients who respond, dosing should be aimed at maintaining optimal function. In patients who respond, the interval between doses can be increased to every 4 to 8 weeks, depending on response. Dosing must be individualized and is very variable; increasing the dose vs. increasing the interval may provide differing results and therefore is individualized. Note: alternate dosing will be assessed individually on a case-by-case basis.

Initial Approval/Extended Approval.

a) *Initial Approval*. Approve for 6 months.

b) *Extended Approval*. Approve for an additional 6 months of therapy if the patient has improvement in neurologic symptoms as determined by the prescribing physician (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. Continue approving at 6-month intervals in patients who are responding (that is, maintaining optimal function) according to the prescribing physician.

Duration of Therapy in Multifocal Motor Neuropathy (MMN). Indefinite for patients who are responding, according to the prescribing physician.

It is well accepted that therapy should be continuous in patients who respond. The frequency of the treatment courses will vary and may shorten over time. Despite IVIG therapy, weakness continues to increase.[37-38,47]

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence

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

Criteria. Approve IVIG if prescribed by or in consultation with a physician affiliated with a transplant center and Site of care medical necessity is met.*

Current strategies for a treatment of antibody-mediated rejection include plasmapheresis, intravenous immunoglobulin and T-cell or B-cell-depleting agents.[157] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,158] 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.[158,159] 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[160-162] 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.[68]

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.

Initial Approval/Extended Approval.
Initial and Extended Approval. Approve for 1 year.

Duration of Therapy for Antibody-Mediated Rejection. ABMR can be diagnosed within the first year post-transplant OR after the first year (late-onset or chronic).

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A, B AND C):*
A) IVIG is prescribed by or in consultation with a dermatologist; AND
B) The patient meets ONE of the following (i, ii or iii):[48-50]
- **i.** The patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescribing physician, 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

ii. The patient has rapid, debilitating, progressive disease, that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent; OR

iii. The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect; AND

C) Site of care medical necessity is met.*

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.[48,50] The total duration of treatment with IVIG can be at least 2 years or longer.[48] The interval between infusions is increased gradually and prolonged clinical remission has been reported with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, and mucous membrane pemphigoid (cicatricial pemphigoid).

Dosing for the Autoimmune Mucocutaneous Blistering Diseases. *Dosing must meet ONE of the following (A, B, OR C):*

a) 2 g per kg IV infusion per cycle administered every 3 to 4 weeks initially.[48-49] This dose is divided over 2, 3, or 5 consecutive days;[48] 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;[48] OR

c) The frequency of IVIG is gradually being slowly decreased as the lesions resolve and heal.[48-49]

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.

Initial Approval/Extended Approval.

A) *Initial Approval*. Approve for 6 months.[49]

B) *Extended Approval*. Approve for 6 months if the patient has responded (previous lesions are healing and there are fewer new lesions) according to the prescribing physician.

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.

Duration of Therapy for Autoimmune Mucocutaneous Blistering Diseases. The total duration of treatment with IVIG can be ≥ 2 years.[48]

Labs/Diagnostics. None required.

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

Criteria. Approve if IVIG is prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician and Site of care medical necessity is met.*

For CMV pneumonia, therapy consists of ganciclovir IV injection (or foscarnet IV injection if CMV is ganciclovir-resistant) and IVIG in combination.[51] Whether adding IVIG adds efficacy is controversial,[52,54] and there are no data to support adding IVIG for the treatment of any manifestation of CMV disease other than pneumonia.[52] Cytogam® (CMV immune globulin IV injection) may be preferred instead of IVIG for interstitial pneumonia. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) recommends the combination of ganciclovir and IVIG for the therapy of CMV pneumonia.[52] For other types of CMV disease, the EBMT recommends ganciclovir or foscarnet without IVIG. These recommendations are consistent with the NCCN guidelines on prevention and treatment of cancer-related infections (version 1.2018) that say IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.[51] IVIG is not indicated for CMV prophylaxis. (See Conditions Not Recommended for Approval.)

Dosing in CMV Interstitial Pneumonia. *Dosing must meet the following:* 400 mg per kg IV infusion every other day for 3 to 5 doses.[51]

Dosing recommended in the NCCN guidelines is 400 mg/kg every other day for three to five doses.[51] The optimal dosing schedule has not been defined.

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 2 months.
b) *Extended Approval*. Not recommended.

IVIG is given with ganciclovir (or foscarnet) which is given for 4 to 6 weeks.[51]

Duration of Therapy in CMV Interstitial Pneumonia. The duration of therapy is a maximum of 2 months.

Labs/Diagnostics. None required.

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10. Dermatomyositis or Polymyositis.

Criteria. *The patient must meet the following criteria (A, B, C AND D):*
A) IVIG is prescribed by or in consultation with a neurologist or a rheumatologist; AND
B) The patient has tried a systemic corticosteroid[36,38,55-56] OR a corticosteroid is contraindicated according to the prescribing physician; AND
C) The patient has tried an immunosuppressive agent (e.g., azathioprine, MTX, cyclosporine, cyclophosphamide, mycophenolate mofetil)[36,55-56] OR an immunosuppressive agent is contraindicated according to the prescribing physician; AND
D) Site of care medical necessity is met*

IVIG may be used in patients with dermatomyositis with severe active illness for whom other interventions have been unsuccessful or intolerable.[55-56] In one double-blind, placebo-controlled crossover trial, patients with treatment resistant dermatomyositis who received IVIG for 3 months had significant improvement in muscle strength, neuromuscular symptoms, and rash.[57] IVIG has been used to maintain response in dermatomyositis.

IVIG may be considered among the treatment options for patients with polymyositis not responding to first-line immunosuppressive treatment.[38,55] In uncontrolled series, IVIG has been effective in polymyositis.

Dosing in Dermatomyositis or Polymyositis. *Dosing must meet ONE of the following (A OR B):*
a) 2 g per kg IV infusion given in divided doses over 2 to 5 consecutive days once monthly;[36,38,57] OR
b) 2 g per kg IV infusion given in divided doses over 2 to 5 consecutive days every 2 to 3 weeks.[38]

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 3 months of therapy.[38,57]
b) *Extended Approval*. Approve at 6-month intervals if the patient has responded (such as improved muscle strength, improved neuromuscular symptoms, improved functional ability) according to the prescribing physician.

Duration of Approval in Dermatomyositis or Polymyositis. Indefinite in patients who are responding.[56]

Labs/Diagnostics. None required.

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

Criteria. Approve IVIG if prescribed by or in consultation with a physician affiliated with a transplant center and Site of care medical necessity is met.*
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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.[58-59] Current protocols include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletions with Rituxan® (rituximab injection for IV infusion).[18]

Kidney. IVIG has been used in highly sensitized patients to reduce allosensitization, ischemia-reperfusion injuries, and acute antibody-mediated rejection (ABMR) episodes in renal allograft recipients.[18,58,60-63] IVIG has been used alone or after plasmapheresis. IVIG is also used in combination with Rituxan.® In one Phase III double-blind trial in patients with end stage renal disease (ESRD), IVIG was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients.[60]

Heart. IVIG has been used as a desensitization agent in patients undergoing cardiac transplantation.[62-63] Randomized trials are not available and many of the studies have not defined response. The studies have not shown that IVIG alone reduced antibody and results concerning survival after transplant are conflicting. In one study in sensitized patients with a left ventricular assist device who were awaiting cardiac transplant, treatment with IVIG reduced serum reactivity to HLA class I antigens, decreased the risk of positive cross-match reactions, and shortened the waiting time for cardiac transplantation.[64] In another study, in 35 sensitized patients who had orthotopic heart transplantation, IVIG was used with plasmapheresis pre-transplant to allow successful cardiac transplantation and to improve survival.[65]

Lung or Liver. The role of IVIG or any other desensitization therapy in patients prior to *lung* transplantation who are sensitized to HLA is not known.[62] There is insufficient evidence to recommend for or against use of IVIG in these patients for desensitization or for treatment of rejection.[62-63] Regarding *liver* transplantation, ABMR after transplantation is rare and patients are not routinely evaluated for HLA antibody formation.[62] According to guidelines from the Canadian Blood Services and the National Advisory Committee on Blood and Blood Products of Canada[62] there is insufficient evidence to make a recommendation for or against routine use of IVIG in preparation for liver transplantation or for treatment of rejection/ABO-incompatible liver transplantation. Use of IVIG in combination with other therapies in patients undergoing lung or liver transplantation requires further study.

Small intestine. Limited published information is available in sensitized recipients of small intestine transplants.[66-67] In a pilot study, highly sensitized patients (n = 6) with intestinal failure (short gut syndrome) who were awaiting isolated small bowel transplant received IVIG and immunosuppressive therapy pre-transplant.[66] Four of the six patients had reduction in high panel peak reactive antibody (PRA) and received intestinal transplantation. Patients continued on IVIG post-transplant at Days 1, 7 and 21. The waiting time for transplant and mortality was similar to non-sensitized patients.

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

a) 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;[59-61] OR

b) The IVIG dosage is based on a transplant center's protocol.[58]

In one Phase III trial in adults with ESRD, 2 g of IVIG/kg (maximum dose 180 g) was given monthly for 4 months.[60] Additional infusions of IVIG were given at 12 and 24 months after entering the study in patients who had not received a transplant. In patients who were transplanted, additional 2g/kg infusions of IVIG were given monthly for 4 months. In one guideline, a single IVIG dose of 2 g/kg is recommended in the first week after transplantation.[62] Low dose IVIG (e.g., 100 mg/kg) has been used with plasmapheresis.[59,62-63]

Initial Approval/Extended Approval.

a) *Initial Approval*. Approve for 4 months of therapy.

b) *Extended Approval*. Approve at 4-month intervals before transplantation OR for one time post-transplantation.

Duration of Approval for Desensitization Therapy Prior to and Immediately after Solid Organ Transplantation. Indefinite in patients who are awaiting transplantation.

Labs/Diagnostics. None required.

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12. <u>Guillain Barrè Syndrome (GBS)</u>.

Criteria. *<u>The patient must meet the following criteria (A , B and C)</u>:*

A) IVIG is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with GBS; AND

B) The patient meets one of the following criteria (i <u>or</u> ii):

i. 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

ii. The patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG; AND

C) Site of care medical necessity is met*

IVIG is recommended as an equivalent alternative to plasma exchange in children and adults with GBS.[34,36,69] IVIG is the treatment of choice, since plasmapheresis is not always readily available.[70] In controlled trials, IVIG was as effective or more effective than plasmapheresis in improving strength, time to unaided walking, or discontinuation of ventilation.[36] The effects of IVIG and plasma exchange are equivalent in hastening recovery, and multiple complications are less frequent with IVIG than with plasma exchange.[69] 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.[70] Treatment with IVIG after 4 weeks from onset is indicated since some patients may deteriorate after initial improvement and the relapse may be severe enough to warrant a repeat course of IVIG.[36-37] The first course of IVIG therapy may have been given in a hospital.

Patients who receive IVIG for GBS are usually hospitalized. Patients with severe GBS, that is, patients with bulbar or respiratory weakness, muscle weakness, inability to stand or walk and whose symptoms are progressing over 7 to 10 days or who have symptoms that interfere with eating or breathing are hospitalized for treatment with IVIG or plasma exchange. In children symptoms are different and usually are leg or back pain and with progression being more rapid than in adults.[34] Many patients with GBS recover fully without therapy. 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.[71] IVIG is not indicated or proven to be effective in mildly affected GBS patients.[55,71]

The EFNS task force on the use of IVIG in the treatment of neurological diseases states that no recommendation can be made as to whether patients with Miller Fisher syndrome (a variant of GBS) should be treated with IVIG, because this has not been well-studied.[55] In a retrospective review of 92 patients with Miller Fisher syndrome, the authors concluded that IVIG and plasmapheresis did <u>not</u> seem to have influenced patients' outcomes. The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) consensus statement on the use of IVIG in neuromuscular conditions notes, on the basis of a single retrospective analysis and case reports, it is difficult to clearly

define the role of IVIG in treating Miller Fischer syndrome.[38] Further, the literature suggests that best medical management may suffice for many patients.

Dosing for Guillain Barrè Syndrome (GBS). *Dosing must meet the following:* 2 g per kg IV infusion in divided doses over 2 to 5 days.[34,36,38,55,71]

This is one course and the first course may have been given in a hospital.

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve one course of treatment (2 g/kg in divided doses over 2 to 5 days).
b) *Extended Approval*. A second course of treatment may be given about 3 weeks after the first course.

Duration of Therapy for Guillain Barrè Syndrome (GBS). Two courses of therapy maximum.

Note: The first course may have been given in a hospital.

Labs/Diagnostics. None required.

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13. Hematologic Neoplasm-Associated Hypogammaglobulinemia (Secondary Immunodeficiency [SID]).

(See B-Cell Chronic Lymphocytic Leukemia [CLL] for Prevention of Bacterial Infections and Multiple Myeloma for these diagnosis-specific criteria)

Criteria. *The patient must meet the following criteria (A, B, C AND D):*
A) The patient has an immunoglobulin G (IgG) level of < 500 mg/dL (excluding paraprotein);[163] AND
B) The patient has recurrent or severe bacterial infections[163] or there is a high risk of infection, according to the prescribing physician; AND
C) IVIG is being prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician; AND
D) Site of care medical necessity is met*

Dosing for Hematologic Neoplasm-Associated Hypogammaglobulinemia. Various dosing regimens have been used for this diagnosis. Typical dosing is 400-500 mg/kg monthly.[163, 164]

Initial Approval/Extended Approval.
a) *Initial Approval.* Approve for 6 months.
b) *Extended Approval.* Approve for additional 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 prescribing physician.

Duration of Therapy in Hematologic Neoplasm-Associated Hypogammaglobulinemia. There is no consensus on duration of therapy. IgG levels and resolution of infections should be monitored to guide duration of therapy.[164]

Labs/Diagnostics. IgG level is required as part of the diagnosis.

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

Criteria. *The patient must meet the following criteria (A, B, C,D AND E):*

A) IVIG is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician; AND

B) The patient has had a HCT within the previous year: AND

C) The patient has an immunoglobulin G (IgG) level < 500 mg/dL OR the patient has multiple myeloma or malignant macroglobulinemia (In the professional opinion of a specialist physician, we have adopted this criterion for immunoglobulin G (IgG) level < 500 mg/dL); AND

D) According to the prescribing physician the patient has a significant risk of having frequent and/or severe bacterial infections; AND

E) site of care medical necessity is met*

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).[72] With regard to IVIG, guidelines recommend the following for prevention or preemptive treatment of specific infections in HCT recipients.[72] 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.[72] 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.

In a randomized trial where IVIG or no IVIG prophylaxis were given from Day 90 to Day 360 post-bone marrow transplant (with patients receiving MTX plus cyclosporine for GVHD prophylaxis), the incidence of bacteremia, sepsis, localized infection, survival, obliterative bronchiolitis, or the incidence or mortality of chronic GVHD were not reduced with IVIG.[73] Patients with severe demonstrable hypogammaglobulinemia (e.g., IgG levels < 400 mg/dL) can continue receiving IVIG.[72-74] IVIG supplementation is often used in patients with severe infections and IgG levels < 400 mg/dL to maintain levels until infections resolve.[74]

Gamimune® 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 infections, interstitial pneumonia

of infectious or idiopathic etiologies, and acute GVHD in the first 100 days post-transplant.[75] Currently marketed IVIG products do not carry this indication.

Dosing in Hematopoietic Cell Transplantation (HCT). *Dosing must meet ONE of the following (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;[72] 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;[72]

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.[72]

Guidelines from the American Society for Blood and Marrow Transplantation (ASBMT) recommend the following dosing in HCT recipients to prevent infectious complication.[72] 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.

Initial Approval/Extended Approval.

a) *Initial Approval*. Approve for 3 months.

b) *Extended Approval*. Approve at 3-month intervals if the patient requires IVIG to maintain trough IgG levels > 400 to 500 mg/dL AND who according to the prescribing physician have significant risk of having frequent and/or severe bacterial infections.
Note: Most patients who receive IVIG require a maximum of 6 doses.

Duration of Therapy in Hematopoietic Cell Transplantation (HCT). Up to 12 months.

Generally IVIG is given for 6 months in patients with hypogammaglobulinemia and who have significant risk of frequent and/or severe bacterial infections despite antibiotic therapy. Some patients with recurrent infections may require therapy for one year and rarely longer.

Labs/Diagnostics. IgG level at baseline (< 500 mg/dL) and IgG trough (pre-dose) level every 2 weeks.[72]

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

Criteria. *The patient must meet the following criteria (A, B AND C):*

A) IVIG is prescribed by or in consultation with an infectious diseases specialist[41] 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[41] according to the prescribing physician; AND

C) site of care medical necessity is met*

Secondary ITP can occur in patients with HIV infection.[41] 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_0(D) immune globulin (IV or intramuscular [IM] injection) [Rhophylac®/WinRho® 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.

Evidence for IVIG use in HIV-associated thrombocytopenia is mostly based on case reports and cohort studies and most studies predate the current standard practices for treatment of HIV.[76-77] Rh_0(D) immune globulin is FDA-approved in non-splenectomized, Rh_0(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).[78] The safety and efficacy of Rh_0(D) immune globulin have not been evaluated in patients who are splenectomized or in patients who are Rh_0(D) negative. The American Society of Hematology (ASH) guidelines for immune thrombocytopenia recommend initial treatment with corticosteroids, IVIG, or Rh_0(D) immune globulin for patients with secondary ITP due to HIV (no preference for initial therapy is expressed).[41] In symptomatic patients who fail one of these therapies, splenectomy is recommended. No platelet count cut-offs are addressed in this patient population. A Canadian expert panel of hematologists recommends IVIG as a treatment option when platelet counts are < 10,000/mm^3 or when there is active bleeding.[33] Their recommendations do not discuss use of Rh_0(D) immune globulin.

Dosing in Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia. *Dosing must meet ONE of the following (A OR B):*

a) 2 g per kg given as an IV infusion in divided doses over 2 to 5 days;[33,77] OR
b) 1 g per kg one time as an IV infusion for platelet counts less than 20,000 to 30,000 per mm^3 and this dose is repeated once weekly if needed.[76]

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.

Initial Approval/Extended Approval.

a) *Initial Approval*. Approve for one month.
b) *Extended Approval*. Not recommended.

Duration of Therapy in Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia. One month.

Labs/Diagnostics. None required.

16. <u>Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections</u>.

Criteria. *<u>The patient must meet the following criteria (A, B, C, D AND E)</u>:*

A) IVIG is prescribed by or in consultation with an infectious diseases specialist or an immunologist; AND

B) The patient is < 18 years of age; AND

C) The patient is receiving combination antiretroviral therapy (cART); AND

D) The patient has ONE of the following (i, ii <u>or</u> iii):

i. Hypogammaglobulinemia (i.e., IgG < 400 mg/dL);[79] OR

ii. 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

iii. 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 cART and appropriate antimicrobial prophylaxis; AND[79,81]

E) Site of care medical necessity is met*

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.[79] 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.[79] 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.[75,82] 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.[79]

Dosing in Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections. *<u>Dosing must meet the following:</u>* 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.[79,82]

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).

Initial Approval/Extended Approval.

a) *<u>Initial Approval.</u>* Approve for up to 6 months.

b) *Extended Approval.* Continue to approve at 6-month intervals if the frequency and/**or** severity of infections has decreased according to the prescribing physician.

Duration of Therapy for Prevention of Recurrent Bacterial Infections. Continue as long as frequent, serious, recurrent bacterial infections cannot be controlled with antibiotic therapy.

Patients with frequent, serious, recurrent bacterial infections that cannot be controlled with antibiotic therapy can continue with IVIG. The duration of therapy will be determined by efficacy and should continue as long as it is working. Children who are stabilized on cART and improve on IG therapy can safely stop IG once T cells have been reconstituted with cART.[18]

Labs/Diagnostics. See Criteria 14 D) above: IgG level or testing for antibody response to protein and polysaccharide antigens before starting therapy.

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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. *The patient must meet the following criteria (A or B AND C):*
A) The patient has tried a systemic corticosteroid (e.g., prednisone, methylprednisolone) and has not adequately responded to therapy, according to the prescribing physician; OR
B) A corticosteroid is contraindicated, per the prescribing physician; AND
C) site of care medical necessity is met*

NCCN has guidelines in partnership with the American Society of Clinical Oncology (ASCO) [version 1.2018-February 14,2018] for Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities).[155] The guidelines recommend considering 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 Gillian-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.[156] 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.[155]

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 1 month.

b) *Extended Approval*. Approve at 6-month intervals if the patient is having a positive response to therapy, as determined by the prescribing physician, and the physician has determined extended therapy is required.

Duration of Therapy for Immunetherapy-Related Toxcities Associated with Checkpoint Inhibitor Therapy. Most IVIG use is short-term for severe (grade 3 or 4) toxicities.

Labs/Diagnostics. None required.

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18. Lambert-Eaton Myasthenic Syndrome (LEMS), Treatment.

Criteria. *The patient must meet the following criteria (A, B AND C):*
A) IVIG is prescribed by or in consultation with a neurologist; AND
B) The patient meets ONE of the following conditions (i or ii):
- **i.** The patient has paraneoplastic LEMS; OR
- **ii.** The patient has non-paraneoplastic LEMS AND meets ONE of the following criteria (a or b):
  - **a)** The patient has tried at least one of the following: a systemic corticosteroid OR azathioprine OR another immunosuppressive agent (e.g., cyclosporine, mycophenolate mofetil); OR
  - **b)** The patient has a contraindication to BOTH a corticosteroid AND azathioprine and other immunosuppressive agents[36] according to the prescribing physician; AND

C) Site of care medical necessity is met*

In one placebo-controlled crossover trial, a single dose of IVIG produced significant improvement in muscle strength and reduced serum calcium channel antibody titers in patients with LEMS.[83] There have been only five randomized controlled trials of treatment for LEMS: four with 3,4-diaminopyridine (amifampridine tablets) [available in the US through an expanded access use program][84] and one with IVIG. Plasma exchange, steroids, and immunosuppressive agents have not been studied in randomized controlled trials. IVIG may be useful as adjunctive therapy in difficult to treat patients.[36] IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies for LEMS.[18]

Dosing for Lambert-Eaton Myasthenic Syndrome (LEMS). *Dosing must meet ONE of the following (A OR B):*
a) 2 g per kg given as an IV infusion in divided doses over 2 to 5 consecutive days;[36] OR
b) Maintenance therapy every 4 weeks with IVIG ≤ 2 g per kg with the dose being adjusted based on clinical symptoms.[36]

Initial Approval/Extended Approval.
A) *Initial Approval*. Approve for one month.
B) *Extended Approval*. Approve at 6-month intervals if the patient has a response (e.g., improved muscle strength, other clinical response) or continued effectiveness, according to the prescribing physician.

Duration of Therapy for Lambert-Eaton Myasthenic Syndrome (LEMS). IVIG therapy may continue as long as there is continuing objective clinical improvement or maintenance of improvement as determined by the prescribing physician.

Labs/Diagnostics. None required.

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19. Multiple Myeloma.

Criteria. *The patient must meet the following criteria (A, B, C AND D):*
A. The patient has stable (plateau phase) disease (> 3 months from diagnosis); AND
B. The patient has severe recurrent bacterial infections according to the prescribing physician; AND
C. IVIG is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases specialist; AND
D. Site of care medical necessity is met*

Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated but the repertoire of antibody production restricted.[51] The NCCN clinical practice guidelines on multiple myeloma (version 4.2018) recommend that IVIG prophylaxis be considered in the setting of recurrent, life-threatening infections.[85] Prophylactic IVIG replacement therapy has reduced infection rates in patients in the plateau phase, but no effect has been demonstrated in newly diagnosed patients.[86] In one randomized placebo-controlled trial, prophylactic use of IVIG reduced serious and life-threatening infections in immunosuppressed patients with multiple myeloma.[33] According to a Canadian expert panel of hematologists, IVIG is recommended for infection prophylaxis in these adults who have either a recent episode of a life-threatening infection thought to be caused by low levels of polyclonal immunoglobulins or recurrent episodes of clinically significant infections (e.g., pneumonia) that are caused by low levels of polyclonal immunoglobulins.[33] IVIG is an option for acute life-threatening infections in these patients. This panel of hematologists recommended re-evaluation every 4 to 6 months when used for prophylaxis but there was no consensus on specific criteria to use for duration of treatment with IVIG. In another guideline from the British Committee for Standards in Haematology and UK Myeloma Forum, therapy for up to 6 months was recommended.[86]

Dosing in Multiple Myeloma. *Dosing must meet the following:* 0.4 to 0.5 g per kg as an IV infusion every 3 to 4 weeks.[33,86]

Initial Approval/Extended Approval.
A) *Initial Approval.* Approve for 6 months.[86]
B) *Extended Approval.* Approve for additional 6 months.

Duration of Therapy in Multiple Myeloma. 12 months.[33]

There is no consensus on duration of therapy.[33]

Labs/Diagnostics. None required.

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20. Multiple Sclerosis (MS), Acute Severe Exacerbation.

Criteria. *The patient must meet the following criteria (A, B AND C):*

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 AND is continuing to deteriorate despite therapy with one of the following (a, b, or c):
  - **a)** Oral or IV corticosteroids (e.g., methylprednisolone sodium succinate); OR
  - **b)** Plasma exchange; OR
  - **c)** Acthar® H.P. gel (Acthar) [repository corticotropin injection; adrenocorticotropic hormone {ACTH}]; OR
- **ii.** A systemic corticosteroid or Acthar is contraindicated AND the patient is not a candidate for plasma exchange according to the prescribing physician. (In the professional opinion of a specialist physician, we have adopted this criterion.)

C) Site of care medical necessity is met*

High dose corticosteroids, usually methylprednisolone, are first-line treatment of MS relapses in patients with acute optic neuritis, if needed.[87] Acthar is an option in patients with poor venous access or who prefer to self-inject medication. Second-line therapy with plasmapheresis (plasma exchange) is recommended for steroid-resistant exacerbations in relapsing forms of MS.[69,87] Two studies showed that IVIG had no effect on recovery from acute relapse when given either concomitantly with, or immediately before therapy with IV methylprednisolone.[36,55] According to an expert panel of neurologists guidelines, IVIG is only recommended for acute exacerbations of MS in patients with severe refractory optic neuritis who have had no recovery of vision after 3 months of standard steroid therapy or in patients who have a contraindication to corticosteroid therapy.[36] For other MS uses (relapsing remitting MS [RRMS]), this panel has recommended either a single 1 g/kg dose or 0.4 g/kg daily for 5 days.

Dosing for Acute Exacerbation of Multiple Sclerosis (MS). *Dosing must meet ONE of the following (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.

Initial Approval/Extended Approval.

a) *Initial Approval.* Approve for one course of therapy as listed in dosing.

b) *Extended Approval.* Not recommended.

Duration of Therapy in Multiple Sclerosis (MS). One course.

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A, B AND C):*

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 is not currently receiving disease modifying therapy (DMT) for MS (e.g., 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], Tecfidera® [dimethyl fumarate capsules], Tysabri® [natalizumab IV injection], Novantrone® [mitoxantrone injection]) to prevent relapses; AND
C) site of care medical necessity is met*

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.[88]

There is an increase in relapse rates in women with MS during the initial 3 months after birth which may continue for up to 6 months (in patients not receiving therapy).[89-91] In one randomized, confirmatory, multicenter, double-blinded-placebo-period (Days 1 through 3 post-partum) trial, women with clinically confirmed RRMS and at least one relapse within the 2 years prior to pregnancy received treatment with one of the following IVIG regimens: IVIG 150 mg/kg Day 1 post-partum followed by placebo injections on Days 2 and 3 (Group I) or IVIG 900 mg/kg over a 3-day period (Group II).[91] Initial IVIG treatment was followed by an open phase in which both groups received five doses of IVIG 150 mg/kg at monthly (every 4 weeks) intervals. Prior to pregnancy the number of relapses per women per year in the 2 years prior to pregnancy was 1.0 ± 0.7 and 1.0 ± 0.6 in Group I and Group II, respectively. In Groups I and II, 75.6% and 81.5% of patients respectively, remained relapse-free during the 3-month post-partum period (primary efficacy endpoint). The difference between the groups (6%) at 3 months was not statistically significant (P = 0.2353). Numerically more patients in Group II remained relapse-free compared with Group I between Months 4 to 6 (82.3% vs. 70.9%) and within the total observation period of 6 months (69.1% vs. 57.5%); none of these differences reached statistical significance between groups.

Steroids may be used to treat acute relapses during pregnancy and in the post-partum period in nursing women (see Multiple Sclerosis, Acute Severe Exacerbation).

IVIG is not recommended for maintenance treatment to prevent relapses. (See Conditions Not Recommended for Approval.)

Dosing in Multiple Sclerosis (MS), Post-partum. *Dosing must meet ONE of the following (A, B, OR C):*
a) IVIG 0.15 g per kg as an IV infusion on Day 1 post-partum;[91] 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);[91] 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).[91]

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 6 months.
b) *Extended Approval*. Patients may receive a second 6-month course of therapy if they are not taking a DMT for MS.

Duration of Therapy in Multiple Sclerosis (MS), Post-partum. Maximum duration is up to 12 months.

Most patients require 6 months of therapy. Rarely patients may continue for a total of 12 months.

Labs/Diagnostics. None required.

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22. Myasthenia Gravis.

Criteria. *The patient must meet the following criteria (A, B AND C):*
A) IVIG is prescribed by or in consultation with a neurologist; AND
B) One of the following applies (i or ii):
- **i.** Short-term therapy. Approve IVIG for ONE of the following (a, b, c, or d):
  - **a)** The patient has an exacerbation of myasthenia gravis;[36] OR
  - **b)** The patient requires stabilization of myasthenia gravis before surgery;[36] OR
  - **c)** The patient has been started on an immunosuppressive drug (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, MTX, tacrolimus)[92,127] 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.[127] OR
- **ii.** Maintenance therapy. Approve IVIG if the patient meets the following criteria (a, b, and c):[127]
  - **a)** The patient has refractory myasthenia gravis; AND
  - **b)** The patient has tried pyridostigmine; AND
  - **c)** The patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, MTX, or tacrolimus AND has had an inadequate response; AND

C) Site of care medical necessity is met*

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.[127] 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. 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.

IVIG is used as short-term therapy until more effective long-term immunosuppression can be achieved for patients with severe myasthenic exacerbations or in preparation for surgery.[36] In one randomized study, IVIG 0.4 g/kg for either 3 or 5 days was similar in efficacy to plasma exchange in patients with severe exacerbations of myasthenia gravis.[94] IVIG may be considered in patients with severe myasthenia gravis to treat acute severe decompensation when other treatments have been unsuccessful or are contraindicated.[36] In one randomized, double-blind, placebo-controlled trial in 51 patients (not hospitalized) with myasthenia gravis and worsening weakness, IVIG-treated patients had a clinically meaningful improvement in the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity at Day 14 and Day 28.[95] The greatest improvement occurred in patients with more severe disease (QMG Score for Disease Severity > 10.5).

Dosing in Myasthenia Gravis. *Dosing must meet ONE of the following (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;[36,95,127] OR

b) Maintenance therapy: 0.4 to 1 g per kg every 4 weeks.[127]

The international consensus guidance statement for management of adult or juvenile myasthenia gravis[127] 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.

Initial Approval/Extended Approval.

a) *Initial Approval*.
For short-term use for severe exacerbations and as a short-term measure, approve for one treatment course of 2 g per kg divided over 2 to 5 consecutive days.
For maintenance therapy, approve for 1 year.

b) *Extended Approval.*
For short-term use, extended approval is not recommended. The patient may relapse and require an additional short-term therapy.

For maintenance therapy, approve for 1 year if the patient is responding according to the prescribing physician.

IVIG is usually used for severe exacerbations and as a short-term measure.[36,127] For short-term (acute use), the maximum dose per course is 2 g per kg given in divided doses.

Duration of Therapy in Myasthenia Gravis:
A) For short-term use, up to 5 days (as above in dosing).
B) For maintenance therapy, as long as the patient continues to respond according to the prescribing physician.

Some patients may require additional doses for treatment of severe exacerbations.

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A OR B and C):*
A. The patient is pregnant and meets the following criteria (i and ii); OR
   i. The patient has been exposed to measles and IVIG will be given within 6 days of exposure;
   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).
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 prescribing physician, AND the patient has been exposed to measles and IVIG will be given within 6 days of exposure; AND
C. Site of care medical necessity is met

Note: For patients with primary immune deficiency, see criteria for Immunodeficiency, Primary Humoral: Dosing.

When administered within 6 days of exposure, IG can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at age ≥ 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.

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.[13] 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^3 [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. *Dosing must meet the following:* 0.4 g per kg IV infusion administered one time as soon as possible after exposure.[13]

The ACIP recommends 400 mg/kg as an IV infusion.[13]

Initial Approval/Extended Approval.
a) *Initial approval*. 1 day (one dose).
b) *Extended approval*. Not recommended.

Duration of Therapy for Passive Immunization of Measles: 1 day (one dose).

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A OR B and C):*
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® (varicella zoster immune globulin [human] for IM injection) is not available;[96] 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; AND

C) site of care medical necessity is met*

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.[80] Post-exposure prophylaxis with VariZIG, or if VariZIG is not available, IVIG should be considered for HIV-infected children with moderate-to-severe immune compromise even if they have been immunized with varicella vaccine. Children who have received IVIG within 3 weeks of exposure do not require additional passive immunization.[79-80]

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.[79,96-98] 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.[98] 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 ≥ 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 ≤ 1,000 g at birth, regardless of their mothers' evidence of immunity to varicella; and 5) pregnant women without evidence of immunity.[98] 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[96] (and ideally within 96 hours after exposure).[79] The dose is 400 mg/kg given once.[79,96] Patients who have received IVIG 400 mg/kg within the prior 3 weeks should be protected.[79] 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.[96]

Dosing for Passive Immunization for Varicella. *Dosing must meet the following:* 0.4 g per kg IV infusion administered one time.[79-80,96]

Initial Approval/Extended Approval.
a) *Initial Approval.* 1 day (one dose).[79-80,96]
b) *Extended Approval.* Not recommended.

Duration of Therapy for Passive Immunization for Varicella. 1 day (one dose).

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A, B, C AND D):*

A) IVIG is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist; AND
B) The patient has a chronic immunodeficiency condition (e.g., patients with HIV infection, solid organ transplants [e.g., renal, liver], chemotherapy for hematologic malignancy);[92,99] AND
C) The patient has clinically significant anemia as determined by the prescribing physician OR the patient is transfusion dependent.[92] ; AND
D) site of care medical necessity is met*

In *immunosuppressed* patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[33,100] 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 hemoglobin level, and is often curative in that B19 is cleared from the body.[92,100] Persistent B19 infection in apparently *immunocompetent* individuals who possess neutralizing antibodies does not respond well to IVIG.[100] In immunocompetent children, adolescents and adults, parvovirus B19 is self limiting and does not require treatment with IVIG.[99] PRCA and the underlying persistent parvovirus B19 infection may be terminated rapidly by discontinuing immunosuppressive therapy or by instituting antiretroviral therapy in patients with AIDS. IVIG has been curative in patients with congenital immunodeficiency, but in patients with AIDS, parvovirus often persists at lower levels; relapses of anemia may require repeated administration of immunoglobulin. Maintenance therapy has been used in patients who relapse.[92]

Dosing for Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic Parvovirus B19. *Dosing must meet the following (A OR B):*
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;[92,99-100] OR
b) 0.4 to 0.5 g per kg daily for 5 days.[51]

A second course of IVIG may be required based on hemoglobin response. More than 2 courses of IVIG are rarely indicated. Response is measured by increase in hemoglobin and reticulocytosis.

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 2 months.
b) *Extended Approval*.
- **i.** Approve additional single courses of IVIG 2 g per kg given in divided doses over 2 to 5 consecutive days if the patient responded with an increase in hemoglobin to a previous course of IVIG, but relapses when off IVIG;[92] OR
- **ii.** Approve maintenance therapy with IVIG 0.4 g per kg every 4 week to prevent relapse in patients who continue to be immunocompromised[92] and who have responded with an increase in hemoglobin to previous courses of IVIG.

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.

Duration of Therapy for Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic Parvovirus B19: IVIG therapy may continue in patients who relapse, or maintenance therapy can continue to prevent relapse in patients who are still infected with parvovirus and who are immunosuppressed.

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.

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A, B, C AND D):*

A. IVIG is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist; AND
B. The patient has tried a systemic corticosteroid (e.g., prednisone);[33] AND
C. The patient has tried either cyclophosphamide OR cyclosporine.[33] ; AND
D. Site of care medical necessity if met*

The Canadian expert panel of hematologists recommends prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type PRCA.[33] 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. *Dosing must meet the following:* 0.5 g per kg IV infusion every week for 4 weeks.[33]

Very limited information is available because this condition is uncommon.

Initial Approval/Extended Approval.

a) *Initial Approval.* Approve for 4 weeks of therapy.
b) *Extended Approval.* Approve a second 4-week course if the patient has responded with an increase in hemoglobin and reticulocytosis, according to the prescribing physician.

Duration of therapy in Pure Red Cell Aplasia (PRCA), Immunologic Subtype. Up to 2 months.

Labs/Diagnostics. None required.

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

Criteria. *The patient must meet the following criteria (A, B AND C):*
A) IVIG is prescribed by or in consultation with a neurologist; AND
B) The patient meets one of the following criteria (i or ii):
i. The patient has tried a benzodiazepine (e.g., diazepam) OR baclofen; OR
ii. The patient has contraindications to both a benzodiazepine AND baclofen according to the prescribing physician; AND
C) Site of care medical necessity is met*.

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.[36,55,101]

Dosing for Stiff-Person Syndrome. *Dosing must meet the following (A OR B):*
a) 2 g per kg IV infusion given over a period of 2 to 5 consecutive days every month;[36,55,101] 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.

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for 3 months.
b) *Extended Approval*. Approve for 12 months, if the patient has responded (such as reduced stiffness or frequency of spasms, ability to walk unassisted) according to the prescribing physician.

Duration of Therapy for Stiff-Person Syndrome. IVIG therapy may continue as long as there is continuing objective clinical improvement as determined by the prescribing physician.

Labs/Diagnostics. None required.

28. Thrombocytopenia, Fetal Alloimmune.

Criteria. *The patient must meet the following criteria (A, B AND C)*:[33,102]
A) The patient is pregnant and receiving antenatal therapy; AND
B) IVIG is prescribed by or in consultation with a hematologist or an obstetrician; AND
C) Site of care medical necessity is met*.

Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia (NAIT).[102-105] IVIG reduces the risk of intracranial hemorrhage (ICH) and increases the fetal platelet count. In one prospective, multicenter study, 73 women with alloimmune thrombocytopenia who had *not* delivered an infant with an ICH in a prior pregnancy were randomized to receive either IVIG 2 g/kg/week (group A) or IVIG 1 g/kg/week plus prednisone 0.5 mg/kg/day (group B), starting at about 20 weeks of gestation.[103] Fetal blood sampling was performed at about 32 weeks of gestation and, if the fetal platelet count was < 30,000 per

mm^3 or cordocentesis could not be done, salvage therapy was given. Salvage therapy in patients in group A was addition of prednisone 0.5 mg/kg/day and in patients in group B was increasing IVIG to 2 g/kg/week in addition to the prednisone they were already taking. One neonate in each group suffered an ICH (primary outcome variable) during the neonatal period and neither was due to treatment failure. At the time of fetal blood sampling, the average platelet counts were 121,600 per mm^3 in group A and 116,100 per mm^3 in group B. The average birth platelet counts were 169,400 per mm^3 in group A and 134,000 per mm^3 in group B. In all, 27% of patients in group A and 17% of patients in group B received salvage therapy. Randomized controlled trials comparing IVIG or steroids vs. no treatment alone have not been done because of the known risk of ICH.[104]

First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive.[33]

Dosing in Antepartum Treatment of Fetal Alloimmune Thrombocytopenia. *Dosing must meet ONE of the following (A OR B):*
a) IVIG 1 g per kg as an IV infusion every week;[33,102-103] OR
b) IVIG 2 g per kg IV infusion every week or 1 g per kg twice weekly.[102-103]

Initial Approval/Extended Approval.
a) *Initial Approval*. Approve for up to 6 months.
b) *Extended Approval*. Not recommended.

Duration of Approval in Antepartum Treatment of Fetal Alloimmune Thrombocytopenia. Up to 6 months.

Antenatal therapy usually consists of IVIG and prednisone started between 12 and 20 weeks gestation, and then elective delivery at 37 to 38 weeks gestation.[105]

Lab/Diagnostics. None required.

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29. Hypogammaglobulinemia after CAR-T infusion.

Approve in patients who meeting the following criteria (A, B, and C):
A) Patient is diagnosed with Hypogammaglobulinemia or IgG agammaglobulinemia after infusion with CAR-T Therapy [examples of Car-T therapy are as follows: Kymriah (tisagenlecleucel)]; AND
B) IVIG is prescribed by or in consultation with an infectious diseases physician, hematologist or an oncologist; AND
C) site of care medical necessity is met*.

Hypogammaglobulinemia and IgG agammaglobulinemia may occur in patients with a complete remission (CR) after tisagenlecleucel infusion. Because B-cell aplasia is an on-target effect of tisagenlecleucel, hypogammaglobulinemia may persist as long as tisagenlecleucel persists. Monitor immunoglobulin levels after tisagenlecleucel treatment. Manage hypogammaglobulinemia with infection precautions, antibiotic prophylaxis and immunoglobulin treatment

(per standard replacement guidelines). Pregnant women who have received tisagenlecleucel may have hypogammaglobulinemia; assess immunoglobulin levels in newborns of mothers treated with tisagenlecleucel.

Dosing in Hypogammaglobulinemia after Car-T infusion. *Dosing must meet the following:* 0.3- 0.4 g per kg IV infusion every 3- 4 weeks.

Initial Approval/Extended Approval.
Initial Approval: Initial approval is for 6 months of therapy.
Extended Approval: Approve at additional 6-month intervals.

Duration of Therapy in Hypogammaglobulinemia after Car-T infusion. Continue to maintain IgG to prevent bacterial infections.

Labs/Diagnostics. Baseline IgG is required. Dose and interval are adjusted to maintain trough (pre-dose) IgG levels.

Waste Management for All Indications. Vials of IVIG are available in many sizes and concentrations. The dose should be calculated and the number of vials needed assessed.

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.[18,36,92] Only one small study (n = 12) is available; IVIG did not arrest disease progression.[106]

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.[107,120] 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.[108-109]

3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG.[18,36,110-111] Only case series are available; no improvement in muscle strength was observed.[110-111]

4. **Anemia, Aplastic.** Evidence does not support IVIG use.[33,92]

5. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[112]

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.[113] 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. In one randomized, placebo-controlled study, children (n = 40) with moderate to severe atopic dermatitis received three injections of IVIG 2 g/kg or placebo every month over a 12-week period.[114] The disease severity index was significantly decreased 3 months after completing treatments compared with baseline values ($P < 0.05$), but improvement had decreased by 6 months after therapy. 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.[115] 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.[18,36,92] In case series, IVIG has not demonstrated consistent efficacy in the majority of patients.[36] Well-controlled, double-blind trials are needed.

8. **Chronic Fatigue Syndrome.** Evidence does not support IVIG use.[116] One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.[116] 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.[117] 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.[121] 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.[118] 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.[119] Well- designed, controlled trials are needed.[18]

12. **Cytomegalovirus (CMV) Disease Prophylaxis in Hematopoietic Cell Transplantation (HCT) Recipients or in Solid Organ Transplantation.** IVIG is not recommended.[52,72] IVIG has been used in the past for CMV prophylaxis,

but CMV prophylaxis is currently based on using seronegative blood in seronegative recipients, screening for CMV antigenemia, and prophylaxis with antiviral therapy. However, IVIG is recommended for other indications in these patients. See Other Uses with Supportive Evidence.

13. **Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use.[18,122-123] In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.[122] 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.

14. **Epilepsy, Pediatric Intractable.** Only one randomized controlled trial is available in a small (n = 61) number of patients (n = 4 with Lennox Gastaut syndrome; n = 49 with partial epilepsy; and n = 8 with generalized epilepsy).[124] In this study, there was no statistically significant difference between IVIG and placebo for the primary endpoint (a 50% or greater reduction in seizure frequency). Additional controlled trials are needed in well-defined populations. The EFNS recognizes IVIG may have a favorable effect in childhood refractory epilepsy and rated it as a good practice point which indicates the lowest level of evidence.[55] An American Epilepsy Society evidence-based guideline does not address the use of IVIG in status epilepticus in children and adults.[125] A recent review of the evidence concluded that due to the scarcity of reliable studies showing substantial efficacy of IVIG in intractable childhood epilepsy, routine use cannot be recommended.[18] However, the poor prognosis and quality of life of children who do not improve with antiepileptic drug therapy and corticosteroids might justify a trial of IVIG therapy, especially in patients who are not candidates for surgical resection.

15. **Fibromyalgia Syndrome.** There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy received IVIG 400 mg/kg given daily for 5 days.[126] 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.

16. **Graft-Versus-Host Disease (GVHD), Acute (Within First 100 days After Hematopoietic Cell Transplantation [HCT]).** IVIG is not recommended unless the patient has severe hypogammaglobulinemia.[72] Current guidelines do not include using IVIG for this indication unless the patient has severe hypogammaglobulinemia defined as IgG < 400 mg/dL.[72] IVIG is recommended in patients with severe hypogammaglobulinemia after transplantation to prevent bacterial infection. (See HCT to Prevent Bacterial Infections above under Other Uses with Supportive Evidence.)

17. **Graft-Versus-Host Disease (GVHD), Chronic, Prevention in Hematopoietic Cell Transplantation (HCT) Recipient.** IVIG is not recommended unless the patient has severe hypogammaglobulinemia.[72] In one randomized trial where IVIG or no IVIG prophylaxis were given from Day 90 to Day 360 post-transplantation, the incidence or mortality of chronic GVHD was not reduced with IVIG.[73] (See HCT to Prevent Bacterial Infections above under Other Uses with Supportive Evidence.)

18. **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%.[128] 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.

19. **Hematopoietic Cell Transplantation (HCT) in Allogeneic Recipients from Human Leukocyte Antigen (HLA)-Identical Sibling Donors.** IVIG is not recommended. In one placebo-controlled trial, prophylactic IVIG had no benefit over placebo for prophylaxis of infection, interstitial pneumonia, GVHD, transplantation-related mortality at 6 months, or survival at 24 months.[129] IVIG is recommended in patients with severe hypogammaglobulinemia after HCT to prevent bacterial infection and acute GVHD.[72] (See HCT to Prevent Bacterial Infections above under Other Uses with Supportive Evidence.)

20. **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.[130]

21. **Immune Globulin M (IgM) Paraproteinemic Demyelinating Neuropathy (or Other Paraproteinemic Demyelinating Neuropathies).** The Canadian expert panel of neurologists does not recommend IVIG for IgM paraproteinemic neuropathy because the available evidence is limited to small trials with variable quality and mixed results.[36] In one 4-week, placebo-controlled, cross-over trial comparing IVIG to placebo, IVIG produced a modest but statistically significant decrease in overall disability and a significant improvement in many secondary outcome measures (e.g., time to walk 10 meters, grip strength, and sensory symptom scores).[131] However, the short duration of follow-up makes it unclear whether this is clinically significant in a chronic condition.[36] A EFNS/Peripheral Nerve Society guideline recommends IVIG or plasma exchange be considered for initial therapy especially in patients with rapid worsening or clinically similar course to typical CIDP, although any benefit may be only short term.[132] This recommendation was rated as a good practice point which indicates the lowest level of evidence. Long-term studies are needed.

22. **In Vitro Fertilization (IVF).** Evidence does not support IVIG use.[133]

23. **Infantile Spasms (West Syndrome).** There is insufficient evidence to recommend IVIG.[134]

24. **Marburg Variant Multiple Sclerosis (MS).** The Canadian panel of expert neurologists guidelines agreed that other therapies besides IVIG have greater validity.[36] Marburg disease is an acute and often fatal, demyelinating phenotype that is characterized by fulminant demyelination and necrosis. The expert panel said that IVIG may be considered among the treatment options considering the life-threatening nature of this condition. Studies are not available using IVIG for this condition.

25. **Multiple Sclerosis (MS), Primary Progressive.** Evidence does not support IVIG use.[36] Clinical trials are needed.[36,135] Also see studies for MS, secondary progressive below.

26. **Multiple Sclerosis (MS), Secondary Progressive.** Evidence does not support IVIG use.[36] In one placebo-controlled trial, patients with advanced stage secondary progressive MS received IVIG for 27 months.[136] There was no beneficial effect on the primary outcome measure, time to confirmed Expanded Disability Status Scale (EDSS)

progression (hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 0.08, 1.53 for IVIG vs. placebo).[136] The annual relapse rate was 0.46 for both groups. No significant differences between the treatment groups were found in any of the other clinical outcome measures or in the change of T2-lesion load over time. In another placebo-controlled trial, patients with primary progressive (n = 34) or secondary progressive [n = 197] MS were randomized to IVIG once monthly or placebo for 2 years.[137] Mean duration of MS was 14 to 15 years and mean EDSS scores were about 5.5 at baseline. In the intent-to-treat population (both groups combined) IVIG delayed progression by 12 weeks compared with placebo and diminished the rate of patients with sustained progression by 15%. This effect was significant in patients with primary progressive disease. In all, 51% of patients withdrew from the study. The study was not powered to show differences between the primary and secondary progressive groups and the number of patients with primary progressive disease was too small to draw valid conclusions. EDSS scores were similar with IVIG and placebo. Treatment with IVIG cannot be recommended for patients with secondary or primary progressive MS.

27. **Multiple Sclerosis (MS), Relapsing Remitting for the Prevention of Relapses.** IVIG has been beneficial in controlled trials in preventing relapses in RRMS, but additional studies are needed.[18,36,135] In one Phase II, multicenter, double-blind, placebo-controlled trial, 127 patients with RRMS were randomized to therapy with IVIG 0.2 or 0.4 g/kg or to placebo (0.1% albumin) given every 4 weeks for 48 weeks.[138] After 1 year, there was no statistical difference in the percentage of relapse-free patients (IVIG 0.2 g/kg: 57% of patients [n = 25/44]; IVIG 0.4 g/kg: 60% of patients [n = 25/42]; placebo: 68% of patients [n = 28/41]). The P value for the treatment effect was 0.29. The studies of IVIG have usually involved small heterogeneous patient populations, have lacked complete data on clinical and magnetic resonance imaging (MRI) outcomes, or have used methods that have been questioned. In one retrospective analysis of pregnant women with RRMS, patients who received IVIG during pregnancy and post-partum or post-partum only had lower relapse rates than those who were untreated.[135] Randomized, double-blind trials are needed to confirm these findings, to determine the optimal dose, and to compare IVIG with interferon beta products (e.g., Betaseron, Rebif), Copaxone, and other DMTs. Current evidence suggests IVIG is of little benefit in slowing disease progression.[135]

28. **Nephropathy, Membranous.** Evidence does not support IVIG use.[139] IVIG has been used in several types of glomerulonephritis in cases resistant to conventional therapy, but no controlled studies supporting their use exist. IVIG may increase the likelihood of remission when used at an early stage, but it does not appear to have an impact on the long-term prognosis of membranous nephropathy. The dose and length of treatment remain to be defined.

29. **Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.[18,132,140]

30. **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.[141] The evidence for effectiveness of IVIG on muscle strength is inconsistent.

31. **Recurrent Spontaneous Pregnancy Loss (RSPL) [Including Antiphospholipid Antibody-Positive Patients].** Evidence does not support IVIG use.[142-145] 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.[142] 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]).[143] 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.[145]

32. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of IVIG.[14,18,27,146] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

33. **Systemic Lupus Erythematosus (SLE).** There is no role for IVIG as a first-line treatment in patients with SLE.[147] Well-controlled trials are needed to determine which subsets of patients will benefit the most from IVIG.[147-148]

34. **Systemic Sclerosis (Scleroderma).** Evidence does not support IVIG use. In one small open-label trial, IVIG reduced skin fibrosis in patients with systemic sclerosis.[149] Randomized, double-blind, placebo-controlled trials are needed. In the natural course of the disease, skin atrophy may develop which would affect the measurement of skin involvement. Well-designed, randomized trials are not available to assess how IVIG would affect the other manifestations of systemic sclerosis (blood vessels, visceral organs, joint disease).[150]

35. **Thrombocytopenia, Heparin-Induced (HIT).** IVIG is not recommended. HIT is a prothrombotic disorder; IVIG could potentially increase the risk of thrombosis and is not recommended.[33] Appropriate management alternatives such as supportive care and judicious use of blood products and plasma exchange (where indicated) are recommended.

36. **Uveitis, Noninfectious.** Evidence does not support use of IVIG. There are no controlled trials using IVIG to treat uveitis. For acute uveitis corticosteroids are used.[151] For chronic uveitis, immunosuppressive therapy (e.g., MTX, cyclosporine, mycophenolate mofetil, azathioprine) is used either to reduce the adverse effects of corticosteroids or to provide better control of ocular inflammation. In case series, IVIG has been effective in treating uveitis in patients who were refractory to corticosteroids and immunosuppressive agents.[151-154]

37. **Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS).** Evidence does not support IVIG use.[90,149] Patients should be in a formal research protocol. In one controlled trial, 29 children with new onset or severe exacerbations of obsessive compulsive disorder (OCD) or tic disorder after streptococcal infections were randomized to IVIG, plasma exchange, or placebo. Patients who received either IVIG or plasma exchange improved compared to placebo. However, there are many limitations to this study. Additional studies are needed to determine the role of immunomodulatory therapies and antibiotic prophylaxis in PANDAS.[150] A Phase III placebo-controlled clinical trial is underway to test the efficacy of IVIG in treating OCD symptoms related to PANDAS.[151]

38. 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.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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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].[41] An International Working Group (IWG) consensus panel defines primary ITP as a platelet count < 100,000 per mm^3 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 < 30,000/mm^3 initial therapy is systemic corticosteroids.[40-41] 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.[41] 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.[33,41] If there is an urgent need to increase the platelet count quickly, IVIG can be started with a corticosteroid.[41]

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.[41]

Systemic glucocorticoids have been the standard initial therapy for adults with moderate to severe thrombocytopenia and symptomatic purpura.[41,44] 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 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 < 20,000 or < 30,000 per mm^3, 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_0(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.[41] 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 > 30,000 per mm^3 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.[41] 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 ≤ 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.[40,43] In emergency situations, platelet transfusions given with IV corticosteroids and IVIG should be given for intracranial hemorrhaging or other life-threatening or serious bleeding.[33]

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.[41] 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.[41,43]

ASH recommends pregnant patients requiring treatment for ITP receive either a corticosteroid or IVIG.[41] 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.[41] 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.

FOR MEDICAL BENEFIT COVERAGE REQUESTS:

***MMO Site of Care Medical Necessity Criteria:**

- Medications in this policy will be administered in a place of service that is a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met†:

    1. Age less than 18* years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

No initial doses are allowed in a hospital based outpatient facility without other above criteria being met.
* Effective 01/01/2019, age criterion applies to 18 years of older. Age at original effective date (03/01/2016) was 21 years or older.

†This criterion does not apply to Medicare or Medicare Advantage members.

HCPCS Code(s):	
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (eg., liquid), 500 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex/Gamunex-c/Gammaked), non-lyophilized (e.g. liquid), 500 mg
J1566	Injection, immune globulin, intravenous lyophilized (e.g. powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, non-lyophilized, (e.g. liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma dif), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified 500 mg