IMMUNE GLOBULIN (IVIG AND SCIG)

Policy Number: 2018D0035X  Effective Date: November 1, 2018

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INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document, and in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.
COVERAGE RATIONALE

This policy refers to the following intravenous (IV) and subcutaneous (SC) immune globulin (IG) products (List not all inclusive):

- Bivigam™ (IV)
- Carimune® NF (IV)
- Cuvitru™ (SC)
- Flebogamma® DIF (IV)
- Gammagard® Liquid (IV, SC)
- Gammagard® S/D (IV)
- Gammaked™ (IV, SC)
- Gammaphor® (IV)
- Gammagard® (IV)
- Gammagard® S/D (IV)
- Gammaked™ (IV, SC)
- Gammaplex® (IV)
- Gamunex®-C (IV, SC)
- Hizentra® (SC)
- HyQvia® (SC)
- Octagam® (IV)
- Panzyga® (IV)
- Privigen® (IV)

In absence of a product listed, and in addition to applicable criteria outlined within the drug policy, prescribing and dosing information from the package insert is the clinical information used to determine benefit coverage.

Diagnoses Addressed in this Policy

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The Following Information Pertains to Medical Necessity Review

General Requirements (Applicable to All Medical Necessity Requests)

I. For initial therapy, both of the following:
   A. Diagnosis; and
   B. Medical records documenting both of the following:
      1. History and physical examination documenting the severity of the condition, including frequency and severity of infections where applicable; and
      2. Laboratory results or diagnostic evidence supporting the indication for which immune globulin is requested

II. For continuation of therapy, all of the following:
   A. Documentation of positive clinical response to immune globulin therapy; and
   B. For long term treatment, documentation of titration to the minimum effective dose and frequency needed to maintain a sustained clinical response.
**Diagnosis-Specific Requirements**

The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

I. **Immune globulin is proven for:**

A. **Asthma (severe, persistent, high-dose steroid-dependent)**[^59]

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of severe, persistent, high-dose steroid-dependent asthma when ALL of the following criteria are met:

1. Patient is receiving optimal conventional asthma therapy (e.g., high-dose inhaled glucocorticoids, short- and long-acting inhaled β agonists); **and**
2. Patient has required continuous oral glucocorticoid therapy for a minimum of 2 months prior to the decision to initiate immune globulin therapy; **and**
3. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

B. **Autoimmune bullous diseases** [pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane (cicatrical) pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, linear IgA bullous dermatosis][^13,24,59],

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of autoimmune bullous diseases when ALL of the following criteria are met:

1. Diagnosis of an autoimmune bullous disease; **and**
2. Extensive and debilitating disease; **and**
3. History of failure, contraindication, or intolerance to systemic corticosteroids **with concurrent** immunosuppressive treatment (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil); **and**
4. IVIG dose does not exceed 1,000 to 2,000 mg/kg per month divided into 3 equal doses each given over 3 consecutive days or 400 mg/kg per day given over 5 consecutive days per month. IVIG administration may be repeated monthly as needed for patients requiring maintenance therapy. Dosing interval may need to be adjusted in patients with severe comorbidities[^5]; **and**
5. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

C. **Autoimmune uveitis**[^59]

D. **Bone marrow transplantation (BMT)**[^9,14,59,37]

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary after allogeneic BMT when ALL of the following criteria are met:

1. **One** of the following uses:
   a. Prevention of acute graft vs. host disease (GVHD); **or**
   b. Prevention of infection **and**
2. Confirmed allogeneic bone marrow transplant within the last 100 days; **and**
3. Documented severe hypogammaglobulinemia (IgG < 400 mg/dL); **and**
4. IVIG dose does not exceed 500 mg/kg once weekly for the first 90 days of therapy, then monthly up to 360 days after transplantation.

E. **Chronic inflammatory demyelinating polyneuropathy**[^8,17,30,35,37,40,59]

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of chronic inflammatory demyelinating polyneuropathy when ALL of the following criteria are met:

1. **Initial treatment:**
   a. Diagnosis of chronic inflammatory demyelinating polyneuropathy as confirmed by **all** of the following:
      i. Progressive symptoms present for at least 2 months; **and**
      ii. Symptomatic polyradiculoneuropathy as indicated by progressive or relapsing motor or sensory impairment of more than one limb; **and**
      iii. Electrophysiologic findings when at least **three** of the following four criteria are present:
         1) Partial conduction block of ≥ 1 motor nerve
         2) Reduced conduction velocity of ≥ 2 motor nerves
         3) Prolonged distal latency of ≥ 2 motor nerves
         4) Prolonged F-wave latencies of ≥ 2 motor nerves or the absence of F waves

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b. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days administered in up to six monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.

2. **Continuation of treatment:**
   a. Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]; and
   b. For long-term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect; and
   c. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities.

F. **Chronic lymphocytic leukemia (CLL), prevention of infection in B-cell CLL**\(^{15,16,27,37}\)
   **Additional information to support medical necessity review where applicable:**
   Immune globulin is medically necessary for the prevention of infection in B-cell chronic lymphocytic leukemia when **ALL** of the following criteria are met:
   1. Diagnosis of B-cell chronic lymphocytic leukemia (CLL); and
   2. **One** of the following:
      a. Documented hypogammaglobulinemia (IgG < 500 mg/dL)
      b. History of bacterial infection(s) associated with B-cell CLL
   and
   3. IVIG dose does not exceed 400 mg/kg every 3 to 4 weeks.

G. **Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants**

H. **Dermatomyositis or polymyositis**\(^{8,9,30,59,62}\)
   **Additional information to support medical necessity review where applicable:**
   Immune globulin is medically necessary for the treatment of dermatomyositis or polymyositis when **ALL** of the following criteria are met:
   1. Diagnosis of dermatomyositis or polymyositis; and
   2. History of failure, contraindication, or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids, cyclophosphamide, methotrexate); and
   3. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days administered as monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities; and
   4. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

I. **Diabetes mellitus**\(^{59}\)
   **Additional information to support medical necessity review where applicable:**
   Immune globulin is medically necessary for the treatment of autoimmune diabetes mellitus when **BOTH** of the following criteria are met:
   1. Patient is newly diagnosed with insulin dependent (type 1) diabetes mellitus; and
   2. Patient is not a candidate for or is refractory to insulin therapy.

J. **Enteroviral meningoencephalitis**\(^{59}\)

K. **Feto-neonatal alloimmune thrombocytopenia**\(^{1,32}\)
   **Additional information to support medical necessity review where applicable:**
   Immune globulin is medically necessary for the treatment of feto-neonatal alloimmune thrombocytopenia when **ALL** of the following criteria are met:
   1. For pregnant women:
      a. Diagnosis of feto-neonatal alloimmune thrombocytopenia; and
      b. **One** or more of the following:
         i. Previously affected pregnancy
         ii. Family history of the disease
         iii. Platelet alloantibodies found on screening
      and
   c. IVIG dose does not exceed 1,000 mg/kg once weekly until delivery or
   2. For newborns:
      a. Diagnosis of feto-neonatal alloimmune thrombocytopenia; and
      b. Thrombocytopenia that persists after transfusion of antigen-negative compatible platelets.
L. **Graves’ ophthalmopathy**

M. **Guillain-Barré syndrome (GBS)**

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of Guillain-Barré syndrome when **ALL of the following criteria are met:**

1. Diagnosis of Guillain-Barré Syndrome; **and**
2. Severe disease requiring aid to walk; **and**
3. Onset of neuropathic symptoms within the last four weeks; **and**
4. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated in up to three monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities; **and**
5. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

N. **HIV-infection, prevention of bacterial infection in pediatric HIV**

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the prevention of bacterial infection in pediatric HIV when **ALL of the following criteria are met:**

1. Diagnosis of HIV disease; **and**
2. Patient age ≤ 13 years; **and**
3. **One** of the following criteria:
   a. Documented hypogammaglobulinemia (IgG < 400 mg/dL); **or**
   b. Functional antibody deficiency as demonstrated by either poor specific antibody titers or recurrent bacterial infections

and
4. IVIG dose does not exceed 400 mg/kg every 28 days.

O. **Immune thrombocytopenia [Idiopathic thrombocytopenic purpura (ITP)]**

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of idiopathic thrombocytopenic purpura when at least **ONE of the following criteria is met:**

1. **All** of the following:
   a. Diagnosis of **acute** thrombocytopenic purpura (ITP); **and**
   b. Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days); **and**
   c. IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days.
   **or**

2. **All** of the following:
   a. Diagnosis of **chronic** thrombocytopenic purpura (ITP); **and**
   b. **History of failure, contraindication, or intolerance to at least one of the following:**
      i. Corticosteroids
      ii. Splenectomy
   **and**
   c. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.

P. **IgM antmyelin-associated glycoprotein paraprotein-associated peripheral neuropathy**

Q. **Kawasaki disease**

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of Kawasaki disease when **BOTH of the following criteria are met:**

1. Diagnosis of Kawasaki disease; **and**
2. IVIG dose does not exceed 400 mg/kg for five consecutive days or a single dose of 2,000 mg/kg.

R. **Lambert-Eaton myasthenic syndrome (LEMS)**

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of Lambert-Eaton myasthenic syndrome when **ALL of the following criteria are met:**

1. Diagnosis of Lambert-Eaton myasthenic syndrome (LEMS); **and**
2. History of failure, contraindication, or intolerance to immunomodulator monotherapy (e.g., azathioprine, corticosteroids); and
3. Concomitant immunomodulator therapy (e.g., azathioprine, corticosteroids), unless contraindicated, will be used for long-term management of LEMS; and
4. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities; and
5. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

S. Lennox Gastaut syndrome

Additional information to support medical necessity review where applicable:
Immune globulin is medically necessary for the treatment of Lennox Gastaut syndrome when ALL of the following criteria are met:
1. History of failure, contraindication or intolerance to initial treatment with traditional anti-epileptic pharmacotherapy (e.g., lamotrigine, phenytoin, valproic acid); and
2. IVIG dose does not exceed 400 mg/kg/day given for 4 to 5 consecutive days. IVIG administration may be repeated monthly as needed in patients requiring maintenance therapy. Dosing interval may need to be adjusted in patients with severe comorbidities; and
3. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

T. Lymphoproliferative disease, treatment of bacterial infections

U. Monoclonal gammopathy

V. Multifocal motor neuropathy (MMN)

Additional information to support medical necessity review where applicable:
Immune globulin is medically necessary for the treatment of multifocal motor neuropathy when both of the following criteria are met:
1. Initial treatment:
   a. Diagnosis of multifocal motor neuropathy as confirmed by all of the following;48
      i. Weakness with slowly progressive or stepwise progressive course over at least one month; and
      ii. Asymmetric involvement of two or more nerves; and
      iii. Absence of motor neuron signs and bulbar signs
      and
   b. IVIG dose does not exceed 2,400 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities.8,9,48,62
2. Continuation of treatment:
   a. Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]; and
   b. IVIG dose does not exceed 2,400 mg/kg per month given over 2 to 5 consecutive days. Dosing interval may need to be adjusted in patients with severe comorbidities.8,9,48,62; and
   c. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

W. Multiple sclerosis, relapsing forms

Note: Treatment of any other type of multiple sclerosis with immune globulin is not supported by clinical evidence.

Additional information to support medical necessity review where applicable:
Immune globulin is medically necessary for the treatment of relapsing remitting forms of multiple sclerosis when ALL of the following criteria are met:
1. Initial treatment:
   a. Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses); and
   b. Documentation of an MS exacerbation or progression (worsening) of the patient’s clinical status from the visit prior to the one prompting the decision to initiate immune globulin therapy; and
   c. History of failure, contraindication, or intolerance to at least two of the following agents:
      i. Aubagio (teriflunomide)
      ii. Avonex (interferon beta-1a)
      iii. Betaseron (interferon beta-1b)
      iv. Copaxone/Glatopa (glatiramer acetate)
v. Extavia (interferon beta-1b)
vi. Gilenya (fingolimod)

vii. Lemtrada (alemtuzumab)

viii. Ocrevus (ocrelizumab)

ix. Plegridy (peginterferon beta-1a)

x. Rebif (interferon beta-1a)

xi. Tecfidera (dimethyl fumarate)

xii. Tysabri (natalizumab)

and

d. Induction, when indicated, does not exceed a dose of 400 mg/kg daily for up to five days.

2. **Continuation of treatment:**
   a. Medical records, including findings of interval examination including neurological deficits incurred and assessment of disability [e.g., Expanded Disability Status Scale (EDSS), Functional Systems Score (FSS), Multiple Sclerosis Functional Composite (MSFC), Disease Steps (DS)]; and
   b. Stable or improved disability score (e.g., EDSS, FSS, MSFC, DS); and
   c. Documentation of decreased number of relapses since starting immune globulin therapy; and
   d. Diagnosis continues to be the relapsing-remitting form of MS (RRMS); and
   e. IVIG dose does not exceed 1,000 mg/kg monthly; and
   f. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

X. **Myasthenic exacerbation**

   **Note:** Evidence does not support the use of immune globulin maintenance therapy for generalized myasthenia gravis or for ocular myasthenia.

   **Additional information to support medical necessity review where applicable:**

   **Immune globulin is medically necessary for the treatment of myasthenic exacerbation when ALL of the following criteria are met:**

   1. Diagnosis of generalized myasthenia gravis; and
   2. Evidence of myasthenic exacerbation, defined by at least one of the following symptoms in the last month:
      a. Difficulty swallowing
      b. Acute respiratory failure
      c. Major functional disability responsible for the discontinuation of physical activity
      d. Recent immunotherapy treatment with a checkpoint inhibitor [e.g., Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab)].

   and

   3. **One** of the following:
      a. History of failure, contraindication, or intolerance to immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine) for long-term management of myasthenia gravis.
      b. Currently receiving immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine) for long-term management of myasthenia gravis.

   and

   4. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days administered in up to three monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.

Y. **Neuromyelitis optica**

   **Additional information to support medical necessity review where applicable:**

   **Immune globulin is medically necessary for the treatment of neuromyelitis optica when all of the following criteria are met:**

   1. Diagnosis of neuromyelitis optica; and
   2. History of failure, contraindication, or intolerance to at least two of the following:
      a. Azathioprine
      b. Corticosteroids
      c. Mycophenolate mofetil
      d. Rituximab

   and

   3. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days administered in up to six monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.

Z. **Paraproteinemic neuropathy**
AA. **Posttransfusion purpura**\(^3,59\)

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of posttransfusion purpura when BOTH of the following criteria are met:
1. Diagnosis of posttransfusion purpura; and
2. IVIG dose does not exceed 1,000 mg/kg for 2 days.

BB. **Post B-cell targeted therapies**

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the prevention of infection secondary to B-cell targeted therapy when ALL of the following criteria are met:
1. Documentation confirming previous treatment of B-cell targeted therapy within the last 100 days [e.g., CAR-T (e.g., Kymriah), Rituxan (rituximab), Besponsa (inotuzumab ozogamicin)]; and
2. **Both** of the following:
   a. Documented hypogammaglobulinemia (IgG < 500 mg/dL)
   b. History of bacterial infection(s) associated with B-cell depletion

   and
3. IVIG dose does not exceed 400 mg/kg every 4 weeks, up to 360 days after discontinuation of B-cell depleting therapy

CC. **Primary immunodeficiency syndromes**\(^3,6,12,14-17,21,28,31,37,42,43,48-54,59\) (See disease list linked to below)

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of primary immunodeficiency syndromes when ALL of the following criteria are met:
1. Diagnosis of primary immunodeficiency; and
2. Clinically significant functional deficiency of humoral immunity as evidenced by **one** of the following:
   a. Documented failure to produce antibodies to specific antigens; or
   b. History of significant recurrent infections

   and
3. Initial IVIG dose is 300 to 600 mg/kg every 3 to 4 weeks and titrated based upon patient response\(^28,51-2,57-61,76,118,133\) (For SCIG products, FDA-labeled dosing and conversion guidelines will used to determine benefit coverage.)

DD. **Rasmussen syndrome**\(^59,62\)

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of Rasmussen syndrome when BOTH of the following criteria are met:
1. Documentation that short term amelioration of encephalitis is needed prior to definitive surgical therapy; and
2. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days. IVIG is not recommended for long-term therapy for Rasmussen’s encephalitis as surgical treatment is the current standard of care.\(^62\)

EE. **Renal transplantation, prevention or treatment of acute humoral rejection**\(^59\)

FF. **Rheumatoid arthritis, severe**\(^59\)

GG. **Rotaviral enterocolitis**\(^59\)

HH. **Staphylococcal toxic shock**\(^59\)

II. **Stiff-person syndrome**\(^8,9,46,59,62\)

Additional information to support medical necessity review where applicable:

Immune globulin is medically necessary for the treatment of stiff-person syndrome when ALL of the following criteria are met:
1. Diagnosis of stiff-person syndrome; and
2. History of failure, contraindication or intolerance to GABAergic medication (e.g., baclofen, benzodiazepines)\(^59,62;\) and
3. History of failure, contraindication or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids)\(^59\); and
4. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days. IVIG administration may be repeated monthly as needed for patients requiring maintenance therapy. Dosing interval may need to be adjusted in patients with severe comorbidities\(^62\); and
5. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect.

JJ. **Thrombocytopenia, Secondary to Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), or pregnancy**

*Additional information to support medical necessity review where applicable:*

**Immune globulin is medically necessary for the treatment of thrombocytopenia when ONE of the following criteria is met:**

1. For initial therapy, **all** of the following:
   a. **One** of the following:
      i. **Both** of the following:
         1) Diagnosis of thrombocytopenia secondary to HCV infection
         2) **Patient is receiving concurrent antiviral therapy, unless contraindicated.**
         or
      ii. **Both** of the following:
         1) Diagnosis of thrombocytopenia secondary HIV infection
         2) **Patient is receiving concurrent antiviral therapy, unless contraindicated.**
         or
      iii. Diagnosis of thrombocytopenia secondary to pregnancy.
      and
   b. Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days); and
   c. IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days.
   or

2. For continuation of therapy, **both** of the following:
   a. **One** of the following:
      i. **Both** of the following:
         1) Diagnosis of thrombocytopenia secondary to HCV infection
         2) **Patient is receiving concurrent antiviral therapy, unless contraindicated.**
         or
      ii. **Both** of the following:
         1) Diagnosis of thrombocytopenia secondary HIV infection
         2) **Patient is receiving concurrent antiviral therapy, unless contraindicated.**
         or
      iii. Diagnosis of thrombocytopenia secondary to pregnancy.
      and
   b. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.

KK. **Toxic epidermal necrolysis or Stevens-Johnson syndrome**

LL. **Urticaria, delayed pressure**

II. **Immune globulin is unproven and not medically necessary for:**

- Acquired hemophilia
- Acute disseminated encephalomyelitis (ADEM)
- Adrenoleukodystrophy
- Alzheimer’s disease
- Amyotrophic lateral sclerosis (ALS)
- Antiphospholipid antibody syndrome (APS) in pregnancy
- Asthma, non-steroid dependent
- Atopic dermatitis
- Autism spectrum disorders
- Autoimmune hemolytic anemia
- Autoimmune liver disease
- Autoimmune neutropenia
- Bone marrow transplantation (BMT), prevention of acute graft vs. host disease (GVHD) after autologous BMT
- Bone marrow transplantation (BMT), prevention of chronic graft vs. host disease (GVHD) after autologous BMT
- Bone marrow transplantation (BMT), prevention of infection after autologous BMT
- *Campylobacter* species-induced enteritis
- Cerebral infarctions with antiphospholipid antibodies
- Chronic fatigue syndrome
- Demyelinative brain stem encephalitis
- Demyelinating neuropathy associated with monoclonal IgM
- Dilated cardiomyopathy
- HIV infection, to reduce viral load
- HTLV-1-associated myelopathy
- Idiopathic dysautonomia, acute
- Inclusion body myositis
- Isolated IgA deficiency
- Isolated IgG4 deficiency
- Lumbosacral or brachial plexitis
- Myocarditis, acute
- Neonatal isoimmune hemolytic jaundice
- Neonatal sepsis, prevention
- Neonatal sepsis, treatment
- Ocular myasthenia
- Opsonolus myclonous
- Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- POEMS syndrome
- Postinfectious cerebellar ataxia
- Postoperative sepsis
- Pseudomembranous colitis
- Rheumatic fever, acute
- Sjogren's syndrome
- Spontaneous recurrent abortions, prevention
- Systemic lupus erythematous
- Urticaria, chronic
- Vasculitides and antineutrophil antibody syndromes

Efficacy for these conditions has not been described in adequately designed studies. The available evidence is limited to case reports or case series, anecdotal reports, and open-label trials, or the available studies have failed to demonstrate a positive treatment effect. Further well-designed studies are needed to establish the role of immune globulin in these conditions.

U.S. FOOD AND DRUG ADMINISTRATION

There are currently eight clinical indications for which IVIG has been licensed by the United States Food and Drug Administration (FDA). The indications can be summarized as follows:

- Treatment of primary immunodeficiencies such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies
- Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia
- Prevention of coronary artery aneurysms in Kawasaki disease (KD)
- Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation
- Reduction of serious bacterial infection in children with human immunodeficiency virus (HIV)
- Increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding
- Improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in chronic inflammatory demyelinating polyneuropathy (CIDP)
- Maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy

Subcutaneous human immune globulin products are FDA approved for the treatment of patients with primary immune deficiency. This includes, but not is limited to diagnoses such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

BACKGROUND

Immune globulin, whether intravenous (IV) or subcutaneous (SC), is a sterile, purified preparation of human immunoglobulin derived from pooled human plasma from thousands of donors. Consisting primarily of immunoglobulin G, one of 5 classes of immunoglobulin (Ig), each batch of immune globulin (typically referred to as IVIG) provides immunomodulating peptides and antibodies against most exogenous antigens, many normal human proteins, and Fab,
the antigen-binding region of autoantibodies.\textsuperscript{20} All currently available products contain high concentrations of IgG with subclass distribution corresponding to that of normal serum.\textsuperscript{6,12,14-17,21,28,31,42,43,58}

IVIG is considered a mainstay of treatment for immunodeficiency conditions and bullous skin disorders. It has been prescribed off-label to treat a wide variety of autoimmune and inflammatory neurologic conditions.\textsuperscript{20}

### APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
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<td>90284</td>
<td>Immune globulin (SCIG), human, for use in subcutaneous infusions, 100 mg, each</td>
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<td>Injection, immune globulin (Cuvitru), 100 mg</td>
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<td>J1556</td>
<td>Injection, immune globulin (Bivigam), 500 mg</td>
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<td>J1557</td>
<td>Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g. liquid), 500 mg</td>
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<td>Injection, immune globulin (Hizentra), 100 mg</td>
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<td>Injection, immune globulin, (Gamunex-C/Gammaked), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
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<td>Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
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<td>Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immunoglobulin</td>
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### ICD-10 Diagnosis Codes

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<td>IVIG and SCIG ICD-10</td>
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### CLINICAL EVIDENCE

**Proven**

**Autoimmune Diseases**

IVIG is beneficial for treatment of a number of autoimmune diseases based upon US Food and Drug Administration (FDA) approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include immune thrombocytopenic purpura,\textsuperscript{6,14,16,17,31,36,37,59} Graves’ ophthalmopathy,\textsuperscript{59} autoimmune uveitis,\textsuperscript{59} dermatomyositis and polymyositis,\textsuperscript{6,9,30,59,62} severe rheumatoid arthritis,\textsuperscript{59} and autoimmune diabetes mellitus.\textsuperscript{59}

IVIG is a first-line therapy for fetomaternal alloimmune thrombocytopenia.\textsuperscript{32}
An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for hematologic conditions. Response rates in available reports of post-transfusion purpura, a rare and life-threatening condition were high.\(^8\)

**Infectious and Infection-related Diseases**

IVIG is beneficial for a number of infectious and infection-related diseases based upon FDA approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include prevention of coronary artery aneurysms associated with Kawasaki syndrome,\(^1,6,17,37,59\) treatment of CMV-induced pneumonitis in solid organ transplants,\(^8\) treatment of rotaoviral enterocolitis,\(^59\) treatment of staphylococcal toxic shock,\(^59\) treatment of enteroviral meningoencephalitis,\(^59\) treatment of bacterial infections in lymphoproliferative diseases,\(^59\) prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL).\(^1,6,17,37\)

**Neuroimmunologic Disorders**

IVIG is beneficial for treatment of a number of neuroimmunologic diseases based upon FDA approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include chronic inflammatory demyelinating polyneuropathy,\(^8,17,30,37,40,59\) Guillain-Barré syndrome,\(^8,30,41,59,62\) multifocal motor neuropathy,\(^8,9,15,30,59,62\) Lambert-Eaton myasthenic syndrome,\(^8,9,30,59,62\) IgM antimiylelin-associated glycoprotein paraprotein-associated peripheral neuropathy,\(^8,9,13,20,59,62\) paraproteinemic neuropathy,\(^8,9,59\) myasthenia gravis,\(^8,9,13,20,59,62\) Lennox-Gastaut,\(^9,62\) Rasmussen syndrome,\(^59,62\) and monoclonal gammopathy.

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions states that IVIG should be reserved as an option for patients with relapsing-remitting MS who fail, decline, or are not able to take standard immunomodulatory therapies. Based on consensus by the expert panel, IVIG is not recommended for treatment of primary or secondary progressive MS or for acute exacerbations of MS.\(^62\)

In their Guidelines for the Use of Intravenous Immunoglobulin in the Treatment of Neurological Diseases, the European Federation of Neurological Associations (EFNA) states that IVIG could be considered as a second or third-line therapy in RRMS if conventional immunomodulatory therapies are not tolerated because of side effects or concomitant diseases, and in particular in pregnancy where other therapies may not be used. IVIG cannot be recommended for treatment in secondary progressive MS. IVIG does not seem to have any valuable effect as add-on therapy to methylprednisolone for acute exacerbations and cannot be recommended as treatment for chronic symptoms in MS. In clinically isolated syndromes and in primary progressive MS, the EFNS Task Force concluded that there is not sufficient evidence to make any recommendations.\(^9\)

Similar findings were reported in a review of evidence by members of the Primary Immunodeficiency Committee of the AAAAI. The Committee concluded that IVIG might provide benefit for relapsing-remitting multiple sclerosis.\(^59\) A meta-analysis and a review of multiple sclerosis clinical trials also found that evidence supports the use of IVIG for reduction of relapses in relapsing-remitting MS.\(^18\) The use of IVIG in relapsing-remitting MS should only be considered when other established therapies have failed or cannot be utilized.

In their review of relapse therapy and intermittent long-term therapy, the Neuromyelitis Optica Study Group (NEMOS) suggests IVIG therapy as an alternative for patients with contraindication to one of the other treatments (azathioprine and rituximab) or, particularly, in children.\(^22\)

The use of intravenous immunoglobulin (IVIG) as treatment for acute relapses in NMO was reported in a retrospective review of 10 patients.\(^55\) In the majority of cases, IVIG was used due to lack of response to steroids with/without plasma exchange. Improvement was noted in five of 11 (45.5%) events; the remaining had no further worsening.

In a case series of eight Spanish patients with neuromyelitis optica (NMO), positive results were observed from bimonthly IVIG treatment (0.7 g/kg body weight/day for 3 days).\(^58\) The primary outcome measure in the study was the occurrence of serious adverse effects. Secondary outcome measures were changes in the yearly rate of attacks and in the degree of neurological disability measured with the Expanded Disability Status Scale (EDSS). All 8 patients were treated with IVIG; 5 had relapsing optic neuritis with or without myelitis and 3 had recurrent longitudinally extensive transverse myelitis (LETM). The mean age of onset was 20.5 years (range, 7-31 years) and 87.5% were female. The mean duration of the disease before beginning treatment was 9.0 years (range, 3-17 years). Following 83 infusions (range, 4-21 per patient) and a mean follow-up time of 19.3 months (range, 6-39 months), minor adverse events had occurred (headache in 3 patients and a mild cutaneous eruption in a single patient). The relapse rate decreased from 1.8 in the previous year to 0.006 during follow-up (z = −2.5, p=0.01). The EDSS score fell from 3.3 [SD 1.3] to 2.6 [SD 1.5] (z = −2.0, p=0.04). The investigators concluded that treatment with IVIG is safe and well-tolerated, and it may be used as a treatment alternative for NMO spectrum disorders.
Primary and Secondary Immune Deficiencies
IVIG is indicated as replacement therapy in primary immune deficiencies.5,12,14-17,21,28,31,37,42,43,59

IVIG is also beneficial in chronic lymphocytic leukemia with reduced IgG and history of infections3,15,16,27,37 and prevention of bacterial infection in HIV-infected children.14,23,37 IVIG is also beneficial in patients with reduced IgG and history of infections for the prevention of infection following B-cell targeted therapies.38,45

Miscellaneous Categories
Evidence supports IVIG for autoimmune bullous diseases,3,24,27,59 toxic epidermal necrolysis and Stevens-Johnson syndrome;3,59 severe, persistent, high-dose, steroid-dependent asthma;39 delayed-pressure urticaria;59 prevention of infection and acute GVHD after allogeneic bone marrow transplantation;14,37,59 and prevention and treatment of acute humoral rejection in renal transplantation.59

Unproven
Acquired Hemophilia
An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for hematologic conditions. In the opinion of the expert panel, there is no convincing evidence of clinical benefit of IVIG in this disorder, and routine use is not recommended.3

Adrenoleukodystrophy (ALD)
This is one of a group of genetic disorders called the leukodystrophies that cause damage to the myelin sheath surrounding nerve cells in the brain and progressive dysfunction of the adrenal gland. In one very small randomized trial 6 patients received IVIG in addition to the dietary therapy while 6 received dietary therapy alone. No treatment effect of IVIG was demonstrated in this study. MRI findings and clinical status deteriorated in both groups.27 The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions stated that IVIG should not be used for ALD.62

Alzheimer’s Disease
An open label dose-ranging study was conducted in 8 mild Alzheimer’s disease (AD) patients. IVIG was added to approved AD therapies for 6 months, discontinued, and then resumed for another 9 months. Anti-Aβ antibodies in the serum from AD patients increased in proportion to IVIG dose and had a shorter half-life than anti-hepatitis antibodies and total IgG. Plasma Aβ levels increased transiently after each infusion. Cerebrospinal fluid Aβ decreased significantly at 6 months, returned to baseline after washout and decreased again after IVIG was re-administered for an additional 9 months. Mini-mental state scores increased an average of 2.5 points after 6 months, returned to baseline during washout and remained stable during subsequent IVIG treatment. This study did not include an adequate number of AD patients to establish whether IVIG altered cognitive status.33

Devi et al. reported on a retrospective investigation of patients (n=10) with Alzheimer’s disease treated with IVIG. Eight of the patients completed 6 months of treatment; two completed 3.5 months of treatment. Two patients developed a pruritic, maculopapular, generalized rash, resolving with appropriate treatment, but both continued with IVIG. Patients showed stability on neurocognitive scores overall, with trends toward decline on their WAIS information subtest and the BNT (p=0.1). Patients showed trends toward improvement on the WMS logical memory II recall (p=0.1), WMS verbal paired associates (p=0.15), and the WMS auditory delayed memory test (p=0.1). It was found that IVIG was well tolerated and effective in this sample, with patients showing stability on neurocognitive test scores and trends toward improvement in some areas.7

Further studies are needed to establish efficacy, to determine the optimal dosing regimen and to confirm the safety of IVIG in the general population of AD patients.

Amyotrophic Lateral Sclerosis (ALS)
This is a disease characterized by progressive motor neuron degeneration, which manifests as weakness, spasticity, and muscle atrophy, usually beginning with the upper limbs. Two small-scale, uncontrolled studies (n=7,9) examined the use of IVIG for treatment of ALS; neither of these studies found a positive treatment effect. During and after treatment, all patients showed progressive deterioration at a pace similar to that observed before treatment or faster.35,109 The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions stated that there is no role for IVIG in the treatment of ALS.62
**Antiphospholipid Antibody Syndrome (APS) in Pregnancy**

In their guideline for the treatment of recurrent first-trimester and second-trimester miscarriage, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends against the use of IVIG. There are several reports supporting a role for IVIG in the treatment of antiphospholipid antibody syndrome (APS), including in patients with APS undergoing in vitro fertilization. However, a meta-analysis of several modes of therapy (heparin, aspirin, glucocorticosteroids, and IVIG) in this clinical setting did not support any improved outcome with IVIG and a possible association with pregnancy loss or premature birth. A small randomized controlled study (n=16) demonstrated no greater benefit from IVIG (plus heparin and aspirin) than from heparin and aspirin alone. Because the efficacy of IVIG has not been proved in appropriately designed studies, its use is not recommended for APS in pregnancy.

**Asthma, Non-Steroid Dependent**

While there have been studies done on the effect of IVIG on steroid-dependent asthma patients with efficacy shown in a trial with a subgroup that required relatively high doses of daily oral steroids, there are no clinical trials or studies to support the effect on non-steroid dependent patients.

**Atopic Dermatitis**

IVIG treatment has shown success in small, open, uncontrolled trials of patients not responding to standard therapies. A small, randomized, evaluator-blinded trial (n = 10) did not support the routine use of IVIG in patients with atopic dermatitis.

**Autism Spectrum Disorders**

According to the review of evidence by members of the Primary Immunodeficiency Committee of the AAAAI, there are no formal randomized studies to evaluate the use of IVIG in autism. They found that two small, open-trial reports of autistic children placed on IVIG for 6 months showed no benefit. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions stated that the available evidence does not support the use of IVIG in the treatment of autism.

**Autoimmune Hemolytic Anemia**

Multiple anecdotal reports demonstrate benefit from the use of IVIG in the treatment of autoimmune hemolytic anemia (AIHA), but the use of IVIG should be considered only when other therapeutic modalities fail. An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for hematologic conditions. They found “sparse evidence” on the use of IVIG in AIHA and despite a literal definition of response rates, those with IVIG were substantially less than accepted published response rates with other treatment alternatives. Therefore, they agreed the overall role of IVIG in AIHA is very limited.

**Autoimmune Neutropenia**

Improvement in neutrophil counts has been described in several small series of patients with autoimmune neutropenia treated with IVIG, and anecdotal reports also suggest utility for IVIG in post- bone marrow transplantation neutropenia, which might be autoimmune in nature. It is unclear whether IVIG offers any advantage over corticosteroid therapy for the treatment of autoimmune neutropenia. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts evidence-based practice guideline on the use of IVIG for hematologic conditions found that “the evidence to support treatment with IVIG is sparse and of poor quality. However, there was some discussion regarding its use in rare circumstances when other options (e.g. intravenous antibiotics and G-CSF) have failed.

**Bone Marrow Transplantation (BMT)**

**Prevention of Acute Graft-Versus-Host Disease (GVHD) After Autologous BMT**

According to the Centers for Disease Control and Prevention, routine use of IVIG among autologous recipients is not recommended.

**Prevention of Chronic Graft-Versus-Host Disease (GVHD) After Either Allogeneic or Autologous BMT**

The use of IVIG was studied in a randomized, double-blind, dose-effect, placebo-controlled, multicenter trial in related allogeneic marrow transplantation. The trial included 200 patients receiving HLA-identical sibling marrow. IVIG-treated patients experienced no benefit versus placebo in reduction of incidence of infection, interstitial pneumonia, GVHD, transplantation-related mortality, or overall survival. There was a statistically higher incidence of grade 3 (severe) veno-occlusive disease associated with high-dose IVIG. The patients given higher doses of IVIG also had more side effects, such as fever and chills. The data does not support a recommendation for IVIG in HLA-identical sibling bone marrow transplants.
Prevention of Infection After Autologous BMT
According to the Centers for Disease Control and Prevention, routine use of IVIG among autologous recipients is not recommended.61

Chronic Fatigue Syndrome
Numerous anecdotal reports have shown subjective benefits of IVIG for chronic fatigue syndrome. However, a double-blind, placebo-controlled trial demonstrated IVIG was not effective in the treatment of typical chronic fatigue syndrome.29

Dilated Cardiomyopathy
According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, “Case reports suggest that patients with acute myocarditis benefit from high-dose IVIG. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo. High-dose IVIG might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy.59

HIV Infection, to Reduce Viral Load
Although IVIG is FDA-approved for reducing the incidence of secondary infection in HIV-infected children, its use in treating HIV infection per se has not been as widely evaluated. A study examining the effect of a 2 g/kg IVIG dose on viral load found that p24 antigen levels and numbers of HIV RNA copies were significantly increased after treatment. Thus IVIG might be useful for preventing bacterial infections but should not be considered an antiviral therapy in the HIV-infected patient.59

Inclusion Body Myositis
The treatment of inclusion body myositis (IBM) with IVIG has been studied in two randomized, double-blind, placebo controlled trials. In the first study (n=19), no statistically significant treatment differences were noted between IVIG and placebo. In the second study (n=22), outcome measures showed a trend towards improvement with IVIG. Based on these studies, IVIG is not recommended as routine therapy for IBM due to the variability of response and expense of therapy.8

IVIG for inclusion body myositis was also assessed in open-label trials, but generalized conclusions or recommendations are not presently possible.59

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions stated that IVIG should not be used for the treatment of IBM.62

In their Guidelines for the Use of Intravenous Immunoglobulin in the Treatment of Neurological Diseases, the European Federation of Neurological Societies (EFNS) states that IVIG cannot be recommended for the treatment of sporadic IBM.9

In their evidence-based guideline on IVIG in the treatment of neuromuscular disorders, the American Academy of Neurology states that there is insufficient evidence to support the use of IVIG in IBM.30

Isolated IgA Deficiency
This is the most common immunodeficiency disorder characterized by a deficiency of IgA with normal levels of other immunoglobulin classes. Isolated IgA deficiency is marked by recurrent sinusitis, bronchitis, and pneumonia, and recurrent diarrhea, although many patients have no symptoms. Management of selective IgA deficiency is limited to treating associated infections. Some advocate prophylactic daily doses of antibiotics for patients with multiple, recurrent infections. No intervention is available to either replace IgA via infusion or increase production of native IgA.140 Selective IgA deficiency is not an indication for IVIG replacement therapy, although in some cases poor specific IgG antibody production, with or without IgG2 subclass deficiency, might coexist; in these patients IVIG might be required. Intravenous administration of IVIG can pose a risk of anaphylaxis for IgA-deficient patients who have IgE anti-IgA antibodies or reactions caused by complement activation if IgG anti-IgA antibodies are present.59

Isolated IgG4 Deficiency
IgG4 deficiency may be found in 10-15% of the general population. The significance of isolated, or selective, IgG4 deficiency is unclear.

Myocarditis, Acute
According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, “Case reports suggest that patients with acute myocarditis benefit from
high-dose IVIG. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo. High-dose IVIG might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy. 59

**Neonatal sepsis**

**Prevention**

A recent meta-analysis found that there is insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proved neonatal infection. 120 Despite encouraging trials of IVIG as an adjunct to enhance the antibacterial defenses of premature newborn infants, there are substantial contradictory data and insufficient overall evidence to support the routine administration of IVIG in infants at risk for neonatal infection. 59

**Treatment**

In a multi-center, international, double-blind controlled trial of 3,493 infants receiving antibiotics for suspected or proven infection, subjects were randomly assigned to receive two infusions of either polyvalent IgG immune globulin (500 mg/kg) or placebo 48 hours apart. The investigators found that there was no significant between-group difference in the rates of primary outcome which was death or major disability at the age of 2 years. The primary outcome was observed in 686 of 1,759 infants (39.0%) in the intravenous immune globulin group and in 677 of 1,734 infants (39.0%) in the placebo group (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). No significant differences in the rates of seven pre-specified secondary outcomes were observed, including the incidence of subsequent sepsis episodes and causative organisms. In follow-up of survivors at 2 years, there were no significant differences in the rates of major or non-major disability or of adverse events. The authors concluded that the use of immune globulin was not associated with significant differences in the risk of major complications or other adverse outcomes in neonates with suspected or proven sepsis. 5

A recent meta-analysis also found that there is insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proved neonatal infection. 29

**Ocular Myasthenia**

Myasthenia gravis is an autoimmune disorder in which the body’s own antibodies block the transmission of nerve impulses to muscles, causing fluctuating weakness and muscles that tire easily. Approximately half of patients present with purely ocular symptoms (ptosis, diplopia), so-called ocular myasthenia. Between 50% and 60% of people who have ocular myasthenia will progress to develop generalized myasthenia gravis (GMG) and weakness affecting other muscles. The aims of treatment for ocular myasthenia are to return the person to a state of clear vision and to prevent the development, or limit the severity of GMG. Treatments proposed for ocular myasthenia include drugs that suppress the immune system including corticosteroids and azathioprine, thymectomy, and acetylcholinesterase inhibitors. There are retrospective, but no prospective, data, which indicate that immunosuppressive treatment of ocular myasthenia may decrease the likelihood of developing GMG. It is not clear from these studies whether treatment actually reduces the incidence of GMG, delays its onset, or just masks its symptoms. Plasmapheresis and intravenous immune globulin are used for the short-term management of severe GMG, but available evidence does not indicate that either therapy has a role in patients with ocular myasthenia. 44

**Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS)**

Streptococcal infections induce exacerbation of symptoms in some children with obsessive-compulsive and tic disorders, possibly on an autoimmune basis. The syndrome of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection is referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, IVIG might provide benefit for PANDAS. However, it should be noted that those children who do not have the autoimmune feature do not benefit from IVIG. 29 The review cited only one case-controlled, single-dose study which showed benefit from plasmapheresis and IVIG therapy. Additional double-blind, placebo-controlled studies are needed before this becomes a standard of therapy.

**POEMS Syndrome**

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome also known as Crow-Fukase syndrome or osteosclerotic myeloma is a unique multisystem disorder strongly associated with plasma cell dyscrasia. Only anecdotal experience is available for assessing IVIG as treatment for POEMS syndrome. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions stated there is no role for IVIG in the treatment of POEMS syndrome. 62
Sjogren's Syndrome
IVIG has shown some efficacy in Sjogren's syndrome. Most of the reports have focused on associated dysautonomia or neuropathy although they have been very small case studies.19,26 One case study was of a 41 year old man with severe sympathetic and parasympathetic autonomic dysfunction as a consequence of acetylcholine receptor antibodies and Sjogren's syndrome who failed to respond to IVIG. Larger, blinded and controlled studies of IVIG are required regarding its efficacy for Sjogren's syndrome.

Spontaneous Recurrent Abortions, Prevention
Results of treatment with IVIG have been conflicting. While prospective studies have suggested that the use of IVIG in pregnant women with a history of recurrent abortions imparted a protective benefit, other studies suggested no benefit. The members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology assessed a review from a number of high-quality randomized, placebo-controlled, multicenter studies and found that, "Given the review of randomized trials, cumulative current evidence does not presently support the use of IVIG for the prevention of recurrent spontaneous abortions."60

Systemic Lupus Erythematosus
The use of IVIG in the treatment of systemic lupus erythematosus (SLE) has been studied in a few open label trials. In the first trial, 20 patients with severe thrombocytopenia associated with SLE received IVIG 2 g/kg for 5 consecutive days each month and patients received between 1-8 treatment courses. A beneficial response was noted in 17 out of 20 patients based on either the disappearance or marked clinical improvement of the main clinical manifestation. In 9 patients who had Systemic Lupus Activity Measure (SLAM) scores before and after IVIG, there was a significant reduction in SLAM scores (19.3 ± 4.7 to 4 ± 2.9; p<0.0001). The average daily dose of prednisolone was decreased (29.7 ± 18.2 mg/day to 13.8 ± 16.7 mg/day; p=0.02) and laboratory abnormalities improved after IVIG. Two other open label studies, with 12 patients each, showed similar results. In another trial, 14 patients with progressive lupus nephritis who had received cyclophosphamide 1 g/m2 monthly for 6 months with 0.5 mg/kg/d of prednisone were randomized to cyclophosphamide 1 g/m2 every 2 months for 6 months and then every 3 months for 1 year or to IVIG 400 mg/kg monthly for 18 months. The two groups were similar after randomization and at the end of follow-up.18 In a retrospective study of 59 SLE patients, 65% of the thirty-one subjects given IVIG had clinical improvement. However, responses were transient. In other case reports high-dose IVIG led to disease resolution in patients with lupus affecting specific organs. However, there is limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE.59

Vasculitides And Antineutrophil Antibody Syndromes
The efficacy of IVIG in the treatment of anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV) was assessed in a randomized, placebo-controlled trial. Thirty four patients (24 diagnosed with Wegener's granulomatosis, 10 diagnosed with microscopic polyangiitis) were randomized to a single course of either 400 mg/kg/day IVIG or placebo for 5 days. A therapeutic response was defined as a 50% decrease in the Birmingham Vasculitis Activity Score (BVAS) at 3 months. A therapeutic response was found in 14/17 patients who received IVIG and 6/17 patients who received placebo (OR = 8.56, 95% CI = 1.74 - 42.2, p=0.015). The C-reactive protein (CRP) level decrease was significantly greater at 2 weeks and one month in the IVIG group compared to the placebo group. After 3 months, there was no difference in disease activity or CRP level between the IVIG and placebo groups. In addition, small open label trials of IVIG found some clinical benefit as an alternative therapeutic agent.25 Results were reported as transient in several of these. Additional randomized controlled trials will need to be conducted to determine its place in therapy.

Professional Societies
Immune Deficiency Foundation (IDF)
There are more than 300 primary immunodeficiency diseases (PIDs) recognized by the World Health Organization. The following diseases are PIDs and thus are proven indications for immune globulin (list not all inclusive). Additional PID information can be found at the IDF website: primaryimmune.org. Back to criteria

- Autosomal recessive agammaglobulinemia
- Autosomal recessive hyperimmunoglobulin M syndrome (HIM)
- Bruton's disease
- Chronic mucocutaneous moniliasis (CMC or APCED),
- Combined immunodeficiency disorders
  - Ataxia-telangiectasia
  - DiGeorge syndrome
  - Nijmegan breakage syndrome
  - WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome
  - Wiskott Aldrich syndrome
- Common variable immunodeficiency (CVID)
- Congenital hypogammaglobulinemia late onset, ICOS impaired

Immune Globulin (IVIG and SCIG)
UnitedHealthcare Commercial Medical Benefit Drug Policy

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• Congenital / X-linked agammaglobulinemia
• Good syndrome (immunodeficiency with thymoma)
• Hyperimmunoglobulinemia E syndrome
• Hypogammaglobulinemia
• ICF syndrome
• Polyendocrinopathy and enteropathy (IPEX)
• Selective IgG subclass deficiencies (persistent absence of IgG1, IgG2, and/or IgG3)
• Selective IgM deficiency
• Severe combined immunodeficiency
• Specific antibody deficiency
• Transient hypogammaglobulinemia of infancy, short-term treatment of recurrent severe bacterial infections
• X-linked immunodeficiency with hyperimmunoglobulin M

CENTERS FOR MEDICARE AND MEDICAID SERVICES

National Coverage Determinations (NCDs) exist see the NCDs for Intravenous Immune Globulin for the Treatment of Autoimmune MucoCutaneous Blistering Diseases (250.3) and Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine) (260.7). Local Coverage Determinations (LCDs) exist; see the LCDs for and Immune Globulin Intravenous (IVIG), Immune Globulins, Intravenous Immune Globulin and Intravenous Immune Globulin (IVIG).


REFERENCES

Immune Globulin (IVIG and SCIG)

34. Royal College of Obstetricians and Gynaecologists (RCOG). The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Apr. 18 p. (Green-top guideline; no. 17).


63. Panzyga [prescribing information]. Vienna, Austria: Octapharma; August 2018.
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<th>Date</th>
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| 10/01/2017 | - Updated list of applicable ICD-10 diagnosis codes to reflect annual code edits:  
  - Added M33.03, M33.13, and M33.93  
  - Revised description for M33.00, M33.01, M33.02, M33.09, M33.10, M33.11, M33.12, and M33.19  
  - Archived previous policy version 2017D0035U  
  
<p>| 02/01/2016 | Annual Review. Added titration to minimum effective dose to general requirements. Consolidated clinical criteria for bone marrow transplantation, renal transplantation, and secondary thrombocytopenia, Added J1575. Updated ICD9 &amp; ICD10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 11/18/2015. Policy 2015D0035R archived. |
| 10/01/2015 | Updated Applicable Codes for ICD-10 transition. Policy 2015D0035Q archived.                                                                                     |
| 03/01/2015 | Policy updated to include trial/failure language to myasthenia gravis. Updated Benefits Consideration. Removed J1562. Added codes 279.02 and D80.4. Approved by the National Pharmacy &amp; Therapeutics Committee on 02/18/2015. Policy 2015D0035P archived. |
| 01/01/2015 | Policy updated to include HyQvia and additional language supporting new products and SCIG dosing. Removed NJ language. Approved by the National Pharmacy &amp; Therapeutics Committee on 11/19/2014. Policy 2014D0035Q archived. |
| 09/01/2014 | Added NMO and secondary thrombocytopenia as proven uses. Updated medical necessity criteria for ITP. Clarified examples of PID subtypes. Updated clinical evidence and references. Updated list of ICD-9 codes (added 204.11, 287.49, 341.0, 647.60, 647.61, 647.63, and 647.64) and associated ICD-10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 07/08/2014. Policy 2014D0035N archived. |
| 04/01/2014 | Clarified General Criteria for Medical Necessity Review. Revised dosing criteria for ITP and PID. Added dose titration criterion to asthma, autoimmune bullous diseases, CIDP, dermatomyositis, polymyositis, Guillain-Barré syndrome, LEMS, Lennox Gastaut syndrome, MMN, MS, and stiff person syndrome. Removed concomitant immunomodulator requirement from continuation of therapy criteria for CIDP and MMN. Updated clinical evidence and references. Updated list of ICD-9 codes (added 334.8 and 448.0) and associated ICD-10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 02/18/2014. Policy 2013D0035M archived. |
| 01/01/2014 | Policy updated with code J1556, effective on 01/01/2014.                                                                                     |
| N/A        | Added product selection criteria. Approved by the National Pharmacy &amp; Therapeutics Committee on 11/12/2013.                                                                 |
| 12/01/2013 | Full policy review. Removed Gamunex from list of products. Changed &quot;myasthenia gravis, acute exacerbation&quot; to &quot;myasthenic exacerbation,&quot; and revised medical necessity criteria for this indication. Revised medical necessity criteria for CIDP, dermatomyositis and polymyositis, GBS, LEMS, MMN, MS, and stiff-person syndrome. Specified that IVIG is proven in allogeneic BMT. Added treatment of acute GVHD after autologous BMT, prevention of infection after autologous BMT, and ocular myasthenia to the list of unproven uses. Added FDA Safety Communication. Updated clinical evidence and references. Updated list of applicable ICD codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 02/18/2015. Policy 2015D0035S archived. |</p>
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<tr>
<td>06/01/2013</td>
<td>Revised dosing for prevention of infection and prevention of GVHD after BMT and for fetomaternal alloimmune thrombocytopenia. Approved by the National Pharmacy &amp; Therapeutics Committee on 04/09/2013. Policy 2013D0035K archived.</td>
</tr>
<tr>
<td>04/01/2013</td>
<td>Policy updated. Added Bivigam to list of products. Updated list of ICD-9 codes (added 242.00 and 242.01, and removed 242.0, 287.33, 337.00, 337.09, 356.9, 358.00, 714.4, and 776.7) and associated ICD-10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 02/19/2013.</td>
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<tr>
<td>04/01/2013</td>
<td>Annual policy review. Removed Vivaglobin from list of products. Added Alzheimer’s disease to the list of unproven uses. Revised paraproteinemic neuropathy from unproven to proven use. Reformatted list of proven and unproven uses to appear in alphabetical order. Added medical necessity criteria. Updated clinical evidence and references. Added FDA Safety Communication. Added CPT codes 90283 and 90284 to the policy. Updated list of ICD-9 codes (added 204.12, 279.11, 279.8, 279.9, 288.09, 288.1, 323.01, 323.02, 323.9, 357.9, 484.1, 646.80, 646.81, 646.82, 646.83, 646.84, 678.00, 678.03, 757.39, 776.8, and 776.9, and removed 038.10, 041.01, 279.02, 337.01, 694.0, 772.10, 772.11, 772.12, 772.13, 772.14, 995.91, and 995.92) and applicable ICD-10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 11/13/2012. Modifications to policy based upon societal input approved by the National Pharmacy &amp; Therapeutics Committee on 12/14/2012. Policy 2012D0035J archived.</td>
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<td>11/1/2012</td>
<td>Policy updated. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) revised to unproven use. Updated FDA section to list multifocal motor neuropathy as a new indication for Gammagard. Updated clinical evidence and references. Updated list of ICD-9 codes (added 337.00, 337.01, 337.09, 772.10, 772.11, 772.12, 772.13, 772.14, and 773.2, and removed 337.0, 493, 772.1, and 996.8) Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/2014. Approved by the National Pharmacy &amp; Therapeutics Committee. Policy 2012D0035J archived.</td>
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<td>03/01/2012</td>
<td>Policy updated. Added Gammaked to list of products. Approved by the National Pharmacy &amp; Therapeutics Committee on 01/10/2012. Policy 2012D0035H archived.</td>
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<td>01/01/2012</td>
<td>Policy updated with code J1557, effective on 01/01/2012. Policy 2011D0035F archived.</td>
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<tr>
<td>09/01/2011</td>
<td>Annual policy review. Added Flebogamma DIF and Gamunex-C to list of products. Autoimmune blistering skin diseases revised to proven use. Revised proven status and evidence for intractable childhood epilepsy to be specific to Lennox Gastaut syndrome. Updated list of proven ICD-9 codes (added 041.0, 238.79, 242.0, 273.1 279.51, 279.53, 323.81, 337.0, 345.00, 345.01, 345.10, 345.11, 493, 493.01, 493.11, 493.21, 694.0, 694.4, 694.5, 694.60, 694.61, 694.8, 695.13, 695.14, 695.15, 708.5, 708.8, 772.1, 776.7, 995.91, 995.92, 996.8, 996.81, and 996.85, and removed 204.00 and 446.6). Removed all unproven ICD-9 codes from the policy because standard policy format is to list only proven ICD-9 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 07/12/2011. Policy 2010D0035D archived.</td>
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<td>01/05/2011</td>
<td>Policy updated with addition of codes J1559 and J1599, which became effective on 01/01/2011.</td>
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<td>11/14/2010</td>
<td>Removed 287.4 from and added 287.41 to list of proven ICD-9 codes.</td>
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<tr>
<td>08/16/2010</td>
<td>Policy revised per annual review. Posttransfusion purpura revised to proven use. Clinical evidence and references revised. Switched ICD-9 287.4 to proven. Approved by the National Pharmacy &amp; Therapeutics Committee on 05/11/2010. Added Gammaplex to list of products and information to Background section regarding product IgG content. Approved by the National Pharmacy &amp; Therapeutics Committee on 08/11/2010. Policy 2009D0035C archived.</td>
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