Immune Globulin (IVIG and SCIG)

Policy Number: CS2022D0035JJ
Effective Date: October 1, 2022

Instructions for Use

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Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Immune Globulin (IVIG and SCIG) (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Immune Globulin (IVIG and SCIG) (for Louisiana Only)
Mississippi	Immune Globulin (IVIG and SCIG) (for Mississippi Only)
North Carolina	None
Pennsylvania	Immune Globulin (IVIG and SCIG) (for Pennsylvania Only)

For the state of Florida: This Medical Benefit Drug Policy only applies to Panzyga (immune globulin intravenous); for all other products, refer to the state's Medicaid clinical policy.

Coverage Rationale

This policy refers to FDA-approved intravenous (IV) and subcutaneous (SC) immune globulin (IG) products including but not limited to the following (list not all inclusive):

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

The intravenous (IVIG) and subcutaneous immune globulin (SCIG) Preferred Product Criteria in this section applies to the following states: AZ, CA, FL, HI, KY, MD, MI, MN, MS, NE, NJ, NY, OH, RI, TN, VA, and WA. For all other states, coverage will be provided contingent on the coverage criteria in the Diagnosis-Specific Criteria section.

Coverage for SCIG products: Cuvitru®, Hizentra®, HyQvia®, and Xembify® is contingent on criteria in the Diagnosis-Specific Criteria section.

Coverage for IVIG products, except for Asceniv™ and Panzyga®, is contingent on criteria in the Diagnosis-Specific Criteria section.

Subcutaneous Immune Globulin Preferred Product Criteria

Cutaquig® is a non-preferred SCIG product. Coverage for Cutaquig® is contingent on Preferred Product Criteria and Diagnosis-Specific Criteria.

Treatment with Cutaquig® is medically necessary for the indications specified in this policy when one of the criteria below are met:

- Both of the following:
  - History of a trial of adequate dose and duration of at least one of the following preferred SCIG products, resulting in minimal clinical response (provider must submit information regarding drug, dose, and duration of therapy):
    - Cuvitru®
    - Hizentra®
    - HyQvia®
    - Xembify®

    and
  - Physician attests that, in their clinical opinion, the clinical response with Cutaquig® would be expected to be superior than experienced with the preferred SCIG products;

  or
- Both of the following:
  - History of contraindication, intolerance, or severe adverse event to all preferred SCIG products not previously tried (provider must submit information regarding drug, dose, and duration of therapy):
    - Cuvitru®
    - Hizentra®
    - HyQvia®
    - Xembify®

    and
  - Physician attests that, in their clinical opinion, the same contraindication, intolerance, or severe adverse event would not be expected to occur with Cutaquig®

Intravenous Immune Globulin Preferred Product Criteria

Panzyga® and Asceniv™ are non-preferred IVIG products. Coverage for Panzyga® and Asceniv™ are contingent on Preferred Product Criteria and Diagnosis-Specific Criteria.

Treatment with Panzyga® or Asceniv™ is medically necessary for the indications specified in this policy when one of the criteria below are met:

- Both of the following:
  - History of a trial of adequate dose and duration of at least two other IVIG products, resulting in minimal clinical response. Alternative IVIG options are, but not limited to: Bivigam®, Gammagard®, Gamunex®, Privigen®, etc. (provider must submit information regarding drug, dose, and duration of therapy); and
  - Physician attests that, in their clinical opinion, the clinical response with Panzyga® or Asceniv™ would be expected to be superior than experienced with other IVIG products;

  or
- Both of the following:
  - History of contraindication, intolerance, or severe adverse event to all other IVIG products not previously tried. Alternative IVIG options are, but not limited to: Bivigam®, Gammagard®, Gamunex®, Privigen®, etc. (provider must submit information regarding drug, dose, and duration of therapy); and
  - Physician attests that, in their clinical opinion, the same contraindication, intolerance, or severe adverse event would not be expected to occur with Panzyga® or Asceniv™

Diagnosis-Specific Criteria

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		
Asthma (severe, persistent, high-dose steroid-dependent)	Autoimmune bullous diseases	Autoimmune uveitis
Bone marrow transplantation (BMT)	Chronic inflammatory demyelinating polyneuropathy	Chronic lymphocytic leukemia (CLL), prevention of infection in B-cell CLL
Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants	Dermatomyositis or polymyositis	Diabetes mellitus
Enteroviral meningoencephalitis	Feto-neonatal alloimmune thrombocytopenia	Graves' ophthalmopathy
Guillain-Barré syndrome (GBS)	HIV-infection, prevention of bacterial infection in pediatric HIV	Immune thrombocytopenia
IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy	Kawasaki disease	Lambert-Eaton myasthenic syndrome (LEMS)
Lennox Gastaut syndrome	Lymphoproliferative disease, treatment of bacterial infections	Monoclonal gammopathy
Multifocal motor neuropathy (MMN)	Multiple sclerosis, relapsing forms	Multiple myeloma, prevention of infection
Myasthenia gravis	Neuromyeltis optica	Paraproteinemic neuropathy
Posttransfusion purpura	Post B-cell targeted therapies	Primary immunodeficiency syndromes
Rasmussen syndrome	Renal transplantation, prevention of acute humoral rejection	Rheumatoid arthritis, severe
Rotaviral enterocolitis	Staphylococcal toxic shock	Stiff-person syndrome
Thrombocytopenia, secondary to HCV, HIV, or pregnancy	Toxic epidermal necrolysis or Stevens-Johnson syndrome	Urticaria, delayed pressure
Unproven uses		

The Following Information Pertains to Medical Necessity Review

General Requirements (Applicable to All Medical Necessity Requests)

- For initial therapy, both of the following:
  - Diagnosis; and
  - Medical records documenting both of the following:
    - History and physical examination documenting the severity of the condition, including frequency and severity of infections where applicable; and
    - Laboratory results or diagnostic evidence supporting the indication for which immune globulin is requested; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Documentation of positive clinical response to immune globulin therapy; and
  - Statement of expected frequency and duration of proposed immune globulin treatment; and
  - For long term treatment, documentation of titration to the minimum effective dose and frequency needed to maintain a sustained clinical response; and
  - Authorization will be for no more than 12 months

Diagnosis-Specific Requirements

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

Immune globulin is proven for:

- Asthma (severe, persistent, high-dose steroid-dependent)[64-66]
  Immune globulin is medically necessary for the treatment of severe, persistent, high-dose steroid-dependent asthma when all of the following criteria are met:
  - Patient is receiving optimal conventional asthma therapy (e.g., high-dose inhaled glucocorticoids, short- and long-acting inhaled β agonists); and
  - History of failure, contraindication, or intolerance to at least two the following:
    - Anti-IgE therapy [e.g., Xolair (omalizumab)]
    - Anti-interleukin 4 therapy [e.g., Dupixent (dupilumab)]
    - Anti-interleukin 5 therapy [e.g., Nucala (mepolizumab), Cinqair (resilizumab), Fasenra (benralizumab)];

    and
  - Patient has required continuous oral glucocorticoid therapy for a minimum of 2 months prior to the decision to initiate immune globulin therapy; and
  - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect; and
  - Prescribed by or in consultation with a pulmonologist or allergist/immunologist

- Autoimmune bullous diseases [pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, linear IgA bullous dermatosis][3,24,59]
  Immune globulin is medically necessary for the treatment of autoimmune bullous diseases when all of the following criteria are met:
  - Diagnosis of an autoimmune bullous disease; and
  - Extensive and debilitating disease; and
  - History of failure, contraindication, or intolerance to systemic corticosteroids with concurrent immunosuppressive treatment (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil); and
  - 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;[3] and
  - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- Autoimmune uveitis[59]

- Bone marrow transplantation (BMT)[9,14,59,37]
  Immune globulin is medically necessary after allogeneic BMT when all of the following criteria are met:
  - One of the following uses:
    - Prevention of acute graft vs. host disease (GVHD); or
    - Prevention of infection;

    and
  - Confirmed allogeneic bone marrow transplant within the last 100 days; and
  - Documented severe hypogammaglobulinemia (IgG < 400 mg/dL); and
  - 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

- Chronic inflammatory demyelinating polyneuropathy[8,17,30,35,37,40,59]
  Immune globulin is medically necessary for the treatment of chronic inflammatory demyelinating polyneuropathy when all of the following criteria are met:
  - Initial treatment:

        - Diagnosis of chronic inflammatory demyelinating polyneuropathy as confirmed by all of the following:
            - Progressive symptoms present for at least 2 months; and
            - Symptomatic polyradiculoneuropathy as indicated by progressive or relapsing motor or sensory impairment of more than one limb; and
            - Electrodiagnostic findings (consistent with EFNS/PNS guidelines for definite CIDP) indicating at least one of the following criteria are present:[68]
                - Motor distal latency prolongation in 2 nerves
                - Reduction of motor conduction velocity in 2 nerves
                - Prolongation of F-wave latency in 2 nerves
                - Absence of F-waves in at least 1 nerve
                - Partial motor conduction block of at least 1 motor nerve
                - Abnormal temporal dispersion in at least 2 nerves
                - Distal CMAP duration increase in at least 1 nerve;

            and
        - Prescribed by or in consultation with a neurologist; and
        - 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.
    - Continuation of treatment:
        - Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]; and
        - For long-term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect; and
        - Prescribed by or in consultation with a neurologist; and
        - 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

- Chronic lymphocytic leukemia (CLL), prevention of infection in B-cell CLL[15,16,27,37]
  Immune globulin is medically necessary for the prevention of infection in B-cell chronic lymphocytic leukemia when all of the following criteria are met:
    - Diagnosis of B-cell chronic lymphocytic leukemia (CLL); and
    - One of the following:
        - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
        - History of bacterial infection(s) associated with B-cell CLL;

      and
    - IVIG dose does not exceed 400 mg/kg every 3 to 4 weeks

- Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants

- Dermatomyositis or polymyositis[8,9,30,59,62]
  Immune globulin is medically necessary for the treatment of dermatomyositis or polymyositis when all of the following criteria are met:
    - Diagnosis of dermatomyositis or polymyositis; and
    - History of failure, contraindication, or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids, cyclophosphamide, methotrexate); and
    - 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
    - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- Diabetes mellitus[66-67]
  Immune globulin is medically necessary for the treatment of autoimmune diabetes mellitus when both of the following criteria are met:
    - Patient is newly diagnosed with insulin dependent (type 1) diabetes mellitus; and
    - Patient is not a candidate for or is refractory to insulin therapy

- Enteroviral meningoencephalitis[59]

- Feto-neonatal alloimmune thrombocytopenia (AIT)[1,32,79]
  Immune globulin is medically necessary for the treatment of feto-neonatal alloimmune thrombocytopenia when all of the following criteria are met:
  - For pregnant women:
    - Diagnosis of feto-neonatal alloimmune thrombocytopenia (AIT); and
    - One or more of the following:
      - Previously affected pregnancy
      - Family history of the disease
      - Platelet alloantibodies found on screening;

      and
    - One of the following:
      - IVIG dose does not exceed 1,000 mg/kg once weekly until delivery; or
      - Both of the following:
        - Fetus or newborn is considered to be at high risk for developing intracranial hemorrhage or other severe complication of AIT; and
        - IVIG dose does not exceed 2,000 mg/kg once weekly until delivery;

    or
  - For newborns:
    - Diagnosis of feto-neonatal alloimmune thrombocytopenia; and
    - Thrombocytopenia that persists after transfusion of antigen-negative compatible platelets

- Graves' ophthalmopathy[59]

- Guillain-Barré syndrome (GBS)[8,30,40,59,62]
  Immune globulin is medically necessary for the treatment of Guillain-Barré syndrome when all of the following criteria are met:
  - Diagnosis of Guillain-Barré Syndrome; and
  - Severe disease requiring aid to walk; and
  - Onset of neuropathic symptoms within the last four weeks; and
  - Prescribed by or in consultation with a neurologist; and
  - 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
  - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- HIV-infection, prevention of bacterial infection in pediatric HIV[14,23,37]
  Immune globulin is medically necessary for the prevention of bacterial infection in pediatric HIV when all of the following criteria are met:
  - Diagnosis of HIV disease; and
  - Patient age ≤ 13 years; and
  - One of the following criteria:
    - Documented hypogammaglobulinemia (IgG < 400 mg/dL); or
    - Functional antibody deficiency as demonstrated by either poor specific antibody titers or recurrent bacterial infections;

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

- Immune thrombocytopenia [Idiopathic thrombocytopenic purpura (ITP)][6,14,16,17,31,36,37,59]
  Immune globulin is medically necessary for the treatment of idiopathic thrombocytopenic purpura when at least one of the following criteria is met:
  - All of the following:
    - Diagnosis of acute thrombocytopenic purpura (ITP); and

        - Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days);[36] and
        - IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days;

      or
    - All of the following:
        - Diagnosis of chronic thrombocytopenic purpura (ITP); and
        - History of failure, contraindication, or intolerance to at least one of the following:
            - Corticosteroids
            - Splenectomy;

          and
        - 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

- IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy[8,59]

- Kawasaki disease[16,37,59]
  Immune globulin is medically necessary for the treatment of Kawasaki disease when both of the following criteria are met:
    - Diagnosis of Kawasaki disease; and
    - IVIG dose does not exceed 400 mg/kg for five consecutive days or a single dose of 2,000 mg/kg

- Lambert-Eaton myasthenic syndrome (LEMS)[8,9,30,47,59,62]
  Immune globulin is medically necessary for the treatment of Lambert-Eaton myasthenic syndrome when all of the following criteria are met:
    - Diagnosis of Lambert-Eaton myasthenic syndrome (LEMS); and
    - History of failure, contraindication, or intolerance to immunomodulator monotherapy (e.g., azathioprine, corticosteroids)*;* and
    - Concomitant immunomodulator therapy (e.g., azathioprine, corticosteroids), unless contraindicated, will be used for long-term management of LEMS; and
    - Prescribed by or in consultation with a neurologist; and
    - IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days.[62] IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities; and
    - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- Lennox Gastaut syndrome[9,62]
  Immune globulin is medically necessary for the treatment of Lennox Gastaut syndrome when all of the following criteria are met:
    - History of failure, contraindication or intolerance to initial treatment with traditional anti-epileptic pharmacotherapy (e.g., lamotrigine, phenytoin, valproic acid); and
    - Prescribed by or in consultation with a neurologist; and
    - 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
    - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- Lymphoproliferative disease, treatment of bacterial infections[59]

- Monoclonal gammopathy[59]

- Multifocal motor neuropathy (MMN)[8,9,15,30,48,59,62]
  Immune globulin is medically necessary for the treatment of multifocal motor neuropathy when both of the following criteria are met:
  - Initial treatment:
    - Diagnosis of multifocal motor neuropathy as confirmed by all of the following:[48]
      - Weakness with slowly progressive or stepwise progressive course over at least one month; and
      - Asymmetric involvement of two or more nerves; and
      - Absence of motor neuron signs and bulbar signs;

      and
    - Prescribed by or in consultation with a neurologist; and
    - 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]
  - Continuation of treatment:
    - Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]; and
    - Prescribed by or in consultation with a neurologist; and
    - 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
    - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- Multiple myeloma, prevention of infection in multiple myeloma[75,77]
  Additional information to support medical necessity review where applicable:
  Immune globulin is medically necessary for the prevention of infection in multiple myeloma when all of the following criteria are met:
  - Diagnosis of multiple myeloma; and
  - One of the following:
    - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
    - History of bacterial infection(s) associated with multiple myeloma;

    and
  - IVIG dose does not exceed 400 mg/kg every 3 to 4 weeks

- Multiple sclerosis, relapsing forms[9,11,18,59,62]
  (Note: Treatment of any other type of multiple sclerosis with immune globulin is not supported by clinical evidence.)
  Immune globulin is medically necessary for the treatment of relapsing forms of multiple sclerosis when all of the following criteria are met:
  - Initial treatment:
    - Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses); and
    - 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
    - History of failure, contraindication, or intolerance to at least two of the following agents:
      - Aubagio (teriflunomide)
      - Avonex (interferon beta-1a)
      - Bafiertam (monomethyl fumarate)
      - Betaseron (interferon beta-1b)
      - Copaxone/Glatopa (glatiramer acetate)
      - Extavia (interferon beta-1b)
      - Gilenya (fingolimod)
      - Lemtrada (alemtuzumab)
      - Mavenclad (cladribine)
      - Mayzent (siponimod)
      - Ocrevus (ocrelizumab)
      - Plegridy (peginterferon beta-1a)

- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)
- Tysabri (natalizumab)
- Vumerity (diroximel fumarate);

and

- Prescribed by or in consultation with a neurologist; and
- Induction, when indicated, does not exceed a dose of 400 mg/kg daily for up to five days

- Continuation of treatment:
  - 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
  - Stable or improved disability score (e.g., EDSS, FSS, MSFC, DS); and
  - Documentation of decreased number of relapses since starting immune globulin therapy; and
  - Diagnosis continues to be the relapsing forms of MS; and
  - Prescribed by or in consultation with a neurologist; and
  - IVIG dose does not exceed 1,000 mg/kg monthly; and
  - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

- Myasthenia Gravis[8,9,13,20,30,59,62,69]
  (Note: Evidence does not support the use of immune globulin maintenance therapy for ocular myasthenia.)
  - Myasthenia Exacerbation
    Immune globulin is medically necessary for the treatment of myasthenic exacerbation when all of the following criteria are met:
    - Diagnosis of generalized myasthenia gravis; and
    - Evidence of myasthenic exacerbation, defined by at least one of the following symptoms in the last month:
      - Difficulty swallowing
      - Acute respiratory failure
      - Major functional disability responsible for the discontinuation of physical activity
      - Recent immunotherapy treatment with a checkpoint inhibitor [e.g., Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab)];

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

      and
    - Prescribed by or in consultation with a neurologist; and
    - 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
  - Refractory Myasthenia Gravis
    Immune globulin is medically necessary for the treatment of refractory myasthenia gravis when all of the following criteria are met:
    - Diagnosis of refractory generalized myasthenia gravis by or in consultation with a physician or center with expertise in management of myasthenia gravis; and
    - Documentation that the disease status is unchanged or worsening (persistent or worsening symptoms that limit functioning) despite failure, contraindication, or intolerance to both of the following (used in adequate doses and duration):
      - Corticosteroids; and
      - Two immunomodulator therapies (e.g., azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus);

      and

- Currently receiving immunomodulator therapy (e.g., corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus), used in adequate doses, for long-term management of myasthenia gravis; and
- Prescribed by or in consultation with a neurologist; and
- IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days. Dosing interval may need to be adjusted in patients with severe comorbidities

- Neuromyelitis optica[22,55,56]
  Immune globulin is medically necessary for the treatment of neuromyelitis optica when all of the following criteria are met:
  - Initial therapy:
    - Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming all of the following:
      - Serologic testing for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies has been performed; and
      - Past medical history of (if AQP4-IgG/NMO-IgG positive one of the following, if negative two of the following):[25]
        - Optic neuritis
        - Acute myelitis
        - Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
        - Acute brainstem syndrome
        - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
        - Symptomatic cerebral syndrome with NMOSD-typical brain lesions;

        and
      - Diagnosis of multiple sclerosis or other diagnoses have been ruled out;

      and
    - History of failure, contraindication, or intolerance to at least three of the following:
      - Azathioprine
      - Corticosteroids
      - Mycophenolate mofetil
      - Complement inhibitors [e.g., Soliris (eculizumab)]
      - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab-mwge)]
      - Anti-CD19 therapy [e.g., Uplizna (inebilizumab-cdon)]
      - Anti-CD20 therapy (e.g., rituximab);

      and
    - Patient is not receiving immune globulin in combination with any of the following:
      - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
      - Complement inhibitors [e.g., Soliris (eculizumab)]
      - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab-mwge)]
      - Anti-CD19 therapy [e.g., Uplizna (inebilizumab-cdon)]
      - Anti-CD20 therapy (e.g., rituximab);

      and
    - Prescribed by or in consultation with a neurologist; and
    - 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
  - Continuation therapy:
    - Patient has previously been treated with immune globulin; and
    - Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by at least both of the following:
      - Reduction in the number and/or severity of relapses or signs and symptoms of NMOSD
      - Maintenance, reduction, or discontinuation of dose(s) of any baseline immunosuppressive therapy (IST) prior to starting immune globulin. Note: Add on, dose escalation of IST, or additional rescue therapy from baseline to treat NMOSD or exacerbation of symptoms while on immune globulin therapy will be considered as treatment failure;

      and

- Patient is not receiving immune globulin in combination with any of the following:
  - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
  - Complement inhibitors [e.g., Soliris (eculizumab)]
  - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab-mwge)]
  - Anti-CD19 therapy [e.g., Uplizna (inebilizumab-cdon)]
  - Anti-CD20 therapy (e.g., rituximab);

  and
- Prescribed by or in consultation with a neurologist; and
- 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

- Paraproteinemic neuropathy[59]

- Posttransfusion purpura[3,59]
  Immune globulin is medically necessary for the treatment of posttransfusion purpura when both of the following criteria are met:
  - Diagnosis of posttransfusion purpura; and
  - IVIG dose does not exceed 1,000 mg/kg for 2 days

- Post B-Cell Targeted Therapies
  Immune globulin is medically necessary for the prevention of infection secondary to B-cell targeted therapy when all of the following criteria are met:
  - 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
  - Both of the following:
    - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
    - History of bacterial infection(s) associated with B-cell depletion;

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

- Primary immunodeficiency syndromes[3,6,12,14-17,21,28,31,37,42,43,48-54,59] (Refer to the disease list linked below.)
  Immune globulin is medically necessary for the treatment of primary immunodeficiency syndromes when all of the following criteria are met:
  - Diagnosis of primary immunodeficiency; and
  - Clinically significant functional deficiency of humoral immunity as evidenced by one of the following:
    - Documented failure to produce antibodies to specific antigens; or
    - History of significant recurrent infections;

    and
  - Initial IVIG dose is 200 to 800 mg/kg every 3 to 4 weeks, based on product prescribing information, and titrated based upon patient response[28,51-52,57-61,76,118,133] (For SCIG products, FDA-labeled dosing and conversion guidelines will used to determine benefit coverage.)

- Rasmussen syndrome[59,62,80]
  Immune globulin is medically necessary for the treatment of Rasmussen syndrome when both of the following criteria are met:
  - Documentation of one of the following demonstrating that:
    - Short term amelioration of encephalitis is needed prior to definitive surgical therapy
    - Disease symptoms (e.g., seizures) persist despite surgical treatment
    - The patient is not a candidate for surgical treatment;

    and
  - IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days

- Renal transplantation, prevention or treatment of acute humoral rejection[59]

- Rheumatoid arthritis, severe[59]
- Rotaviral enterocolitis[59]
- Staphylococcal toxic shock[59]
- Stiff-person syndrome[8,9,46,59,62]
  Immune globulin is medically necessary for the treatment of stiff-person syndrome when all of the following criteria are met:
  - Initial treatment:
    - Diagnosis of stiff-person syndrome; and
    - History of failure, contraindication or intolerance to GABAergic medication (e.g., baclofen, benzodiazepines);[9,59,62] and
    - Prescribed by or in consultation with a neurologist; and
    - 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]
  - Continuation of treatment:
    - Documentation of a positive clinical improvement from baseline; and
    - Prescribed by or in consultation with a neurologist; and
    - 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
    - For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect
- Thrombocytopenia, secondary to Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), or pregnancy[57]
  Immune globulin is medically necessary for the treatment of thrombocytopenia when one of the following criteria is met:
  - For initial therapy, all of the following:
    - One of the following:
      - Both of the following:
        - Diagnosis of thrombocytopenia secondary to HCV infection
        - Patient is receiving concurrent antiviral therapy, unless contraindicated;

        or
      - Both of the following:
        - Diagnosis of thrombocytopenia secondary HIV infection
        - Patient is receiving concurrent antiviral therapy, unless contraindicated;

        or
      - Diagnosis of thrombocytopenia secondary to pregnancy;

      and
    - Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days);[36] and
    - IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days;

    or
  - For continuation of therapy, both of the following:
    - One of the following:
      - Both of the following:
        - Diagnosis of thrombocytopenia secondary to HCV infection
        - Patient is receiving concurrent antiviral therapy, unless contraindicated;

        or
      - Both of the following:
        - Diagnosis of thrombocytopenia secondary to HIV infection
        - Patient is receiving concurrent antiviral therapy, unless contraindicated;

        or
      - Diagnosis of thrombocytopenia secondary to pregnancy;

      and

    - 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

- Toxic epidermal necrolysis or Stevens-Johnson syndrome[59]

- Urticaria, delayed pressure[59]

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 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 IgE deficiency
- Isolated IgG4 deficiency
- Isolated IgM deficiency
- Lumbosacral or brachial plexitis
- Myocarditis, acute
- Neonatal isoimmune hemolytic jaundice
- Neonatal sepsis, prevention
- Ocular myasthenia
- Opsoclonus myoclonus
- 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
- 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.

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 federal, state, or contractual requirements 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 Guidelines may apply.

CPT Code	Description
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each

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HCPCS Code	Description
J1459	Injection, immune globulin (Privigen®), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1554	Injection, immune globulin (Asceniv™), 500 mg
J1555	Injection, immune globulin (Cuvitru®), 100mg
J1556	Injection, immune globulin (Bivigam®), 500 mg
J1557	Injection, immune globulin, (Gammaplex®), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (Xembify®), 100 mg
J1559	Injection, immune globulin (Hizentra®), 100 mg
J1561	Injection, immune globulin, (Gamunex®-C/Gammaked™), intravenous, nonlyophilized (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, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard® liquid), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma®/Flebogamma® DIF), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (Hyqvia®), 100 mg immune globulin
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg

Diagnosis Code	Description
A08.0	Rotaviral enteritis
A48.3	Toxic shock syndrome
A49.9	Bacterial infection, unspecified
A87.0	Enteroviral meningitis
A87.8	Other viral meningitis
A87.9	Viral meningitis, unspecified
A88.0	Enteroviral exanthematous fever [Boston exanthem]
A88.8	Other specified viral infections of central nervous system
B20	Human immunodeficiency virus [HIV] disease
B25.0	Cytomegaloviral pneumonitis

Diagnosis Code	Description
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D47.2	Monoclonal gammopathy
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D69.3	Immune thrombocytopenic purpura
D69.51	Posttransfusion purpura
D69.59	Other secondary thrombocytopenia
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.82	Activated Phosphoinositide 3-kinase Delta Syndrome [APDS]
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	Di George's syndrome
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
D84.81	Immunodeficiency due to conditions classified elsewhere
D84.821	Immunodeficiency due to drugs
D84.822	Immunodeficiency due to external causes
D84.89	Other immunodeficiencies
D89.2	Hypergammaglobulinemia, unspecified
D89.810	Acute graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.82	Autoimmune lymphoproliferative syndrome [ALPS]

Diagnosis Code	Description
D89.9	Disorder involving the immune mechanism, unspecified
E05.00	Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm
E05.01	Thyrotoxicosis with diffuse goiter with thyrotoxic crisis or storm
E10.10	Type 1 diabetes mellitus with ketoacidosis without coma
E10.11	Type 1 diabetes mellitus with ketoacidosis with coma
E10.21	Type 1 diabetes mellitus with diabetic nephropathy
E10.22	Type 1 diabetes mellitus with diabetic chronic kidney disease
E10.29	Type 1 diabetes mellitus with other diabetic kidney complication
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E10.3211	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E10.3212	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E10.3213	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.3291	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E10.3292	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E10.3293	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3299	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.3311	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E10.3312	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E10.3313	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.3391	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E10.3392	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E10.3393	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3399	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.3411	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E10.3412	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E10.3413	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.3491	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E10.3492	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye

Diagnosis Code	Description
E10.3493	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3499	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.3511	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E10.3512	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E10.3513	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E10.3521	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E10.3522	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E10.3523	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E10.3529	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E10.3531	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E10.3532	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E10.3533	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E10.3539	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E10.3541	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E10.3542	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E10.3543	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E10.3549	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E10.3551	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E10.3552	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E10.3553	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E10.3559	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E10.3591	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E10.3592	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E10.3593	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E10.36	Type 1 diabetes mellitus with diabetic cataract
E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E10.37X9	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye

Diagnosis Code	Description
E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E10.52	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E10.59	Type 1 diabetes mellitus with other circulatory complications
E10.610	Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E10.618	Type 1 diabetes mellitus with other diabetic arthropathy
E10.620	Type 1 diabetes mellitus with diabetic dermatitis
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E10.628	Type 1 diabetes mellitus with other skin complications
E10.630	Type 1 diabetes mellitus with periodontal disease
E10.638	Type 1 diabetes mellitus with other oral complications
E10.641	Type 1 diabetes mellitus with hypoglycemia with coma
E10.649	Type 1 diabetes mellitus with hypoglycemia without coma
E10.65	Type 1 diabetes mellitus with hyperglycemia
E10.69	Type 1 diabetes mellitus with other specified complication
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications
E31.0	Autoimmune polyglandular failure
G04.81	Other encephalitis and encephalomyelitis
G04.90	Encephalitis and encephalomyelitis, unspecified
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere
G05.4	Myelitis in diseases classified elsewhere
G11.3	Cerebellar ataxia with defective DNA repair
G25.82	Stiff-man syndrome
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
G40.811	Lennox-Gastaut syndrome, not intractable, with status epilepticus
G40.812	Lennox-Gastaut syndrome, not intractable, without status epilepticus
G40.813	Lennox-Gastaut syndrome, intractable, with status epilepticus
G40.814	Lennox-Gastaut syndrome, intractable, without status epilepticus
G61.0	Guillain-Barré syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.89	Other inflammatory polyneuropathies
G61.9	Inflammatory polyneuropathy, unspecified
G62.89	Other specified polyneuropathies

Diagnosis Code	Description
G62.9	Polyneuropathy, unspecified
G65.0	Sequelae of Guillain-Barré syndrome
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
G73.1	Lambert-Eaton syndrome in neoplastic disease
H20.00	Unspecified acute and subacute iridocyclitis
H20.011	Primary iridocyclitis, right eye
H20.012	Primary iridocyclitis, left eye
H20.013	Primary iridocyclitis, bilateral
H20.019	Primary iridocyclitis, unspecified eye
H20.021	Recurrent acute iridocyclitis, right eye
H20.022	Recurrent acute iridocyclitis, left eye
H20.023	Recurrent acute iridocyclitis, bilateral
H20.029	Recurrent acute iridocyclitis, unspecified eye
H20.041	Secondary noninfectious iridocyclitis, right eye
H20.042	Secondary noninfectious iridocyclitis, left eye
H20.043	Secondary noninfectious iridocyclitis, bilateral
H20.049	Secondary noninfectious iridocyclitis, unspecified eye
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
L10.0	Pemphigus vulgaris
L10.2	Pemphigus foliaceous
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.30	Acquired epidermolysis bullosa, unspecified
L12.35	Other acquired epidermolysis bullosa
L13.8	Other specified bullous disorders
L50.8	Other urticaria
L51.1	Stevens-Johnson syndrome
L51.2	Toxic epidermal necrolysis [Lyell]
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M05.00	Felty's syndrome, unspecified site
M05.011	Felty's syndrome, right shoulder
M05.012	Felty's syndrome, left shoulder
M05.019	Felty's syndrome, unspecified shoulder
M05.021	Felty's syndrome, right elbow
M05.022	Felty's syndrome, left elbow
M05.029	Felty's syndrome, unspecified elbow
M05.031	Felty's syndrome, right wrist
M05.032	Felty's syndrome, left wrist

Diagnosis Code	Description
M05.039	Felty's syndrome, unspecified wrist
M05.041	Felty's syndrome, right hand
M05.042	Felty's syndrome, left hand
M05.049	Felty's syndrome, unspecified hand
M05.051	Felty's syndrome, right hip
M05.052	Felty's syndrome, left hip
M05.059	Felty's syndrome, unspecified hip
M05.061	Felty's syndrome, right knee
M05.062	Felty's syndrome, left knee
M05.069	Felty's syndrome, unspecified knee
M05.071	Felty's syndrome, right ankle and foot
M05.072	Felty's syndrome, left ankle and foot
M05.079	Felty's syndrome, unspecified ankle and foot
M05.09	Felty's syndrome, multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder
M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow

Diagnosis Code	Description
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip
M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site

Diagnosis Code	Description
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems
M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems

Diagnosis Code	Description
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement
M05.7A	Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems involvement
M06.1	Adult-onset Still's disease
M08.00	Unspecified juvenile rheumatoid arthritis of unspecified site
M08.011	Unspecified juvenile rheumatoid arthritis, right shoulder
M08.012	Unspecified juvenile rheumatoid arthritis, left shoulder
M08.019	Unspecified juvenile rheumatoid arthritis, unspecified shoulder
M08.021	Unspecified juvenile rheumatoid arthritis, right elbow
M08.022	Unspecified juvenile rheumatoid arthritis, left elbow
M08.029	Unspecified juvenile rheumatoid arthritis, unspecified elbow
M08.031	Unspecified juvenile rheumatoid arthritis, right wrist
M08.032	Unspecified juvenile rheumatoid arthritis, left wrist
M08.039	Unspecified juvenile rheumatoid arthritis, unspecified wrist
M08.041	Unspecified juvenile rheumatoid arthritis, right hand
M08.042	Unspecified juvenile rheumatoid arthritis, left hand
M08.049	Unspecified juvenile rheumatoid arthritis, unspecified hand
M08.051	Unspecified juvenile rheumatoid arthritis, right hip
M08.052	Unspecified juvenile rheumatoid arthritis, left hip
M08.059	Unspecified juvenile rheumatoid arthritis, unspecified hip
M08.061	Unspecified juvenile rheumatoid arthritis, right knee
M08.062	Unspecified juvenile rheumatoid arthritis, left knee
M08.069	Unspecified juvenile rheumatoid arthritis, unspecified knee
M08.071	Unspecified juvenile rheumatoid arthritis, right ankle and foot
M08.072	Unspecified juvenile rheumatoid arthritis, left ankle and foot
M08.079	Unspecified juvenile rheumatoid arthritis, unspecified ankle and foot
M08.08	Unspecified juvenile rheumatoid arthritis, vertebrae
M08.09	Unspecified juvenile rheumatoid arthritis, multiple sites
M08.0A	Unspecified juvenile rheumatoid arthritis, other specified site
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site
M08.211	Juvenile rheumatoid arthritis with systemic onset, right shoulder
M08.212	Juvenile rheumatoid arthritis with systemic onset, left shoulder
M08.219	Juvenile rheumatoid arthritis with systemic onset, unspecified shoulder
M08.221	Juvenile rheumatoid arthritis with systemic onset, right elbow
M08.222	Juvenile rheumatoid arthritis with systemic onset, left elbow
M08.229	Juvenile rheumatoid arthritis with systemic onset, unspecified elbow

Diagnosis Code	Description
M08.231	Juvenile rheumatoid arthritis with systemic onset, right wrist
M08.232	Juvenile rheumatoid arthritis with systemic onset, left wrist
M08.239	Juvenile rheumatoid arthritis with systemic onset, unspecified wrist
M08.241	Juvenile rheumatoid arthritis with systemic onset, right hand
M08.242	Juvenile rheumatoid arthritis with systemic onset, left hand
M08.249	Juvenile rheumatoid arthritis with systemic onset, unspecified hand
M08.251	Juvenile rheumatoid arthritis with systemic onset, right hip
M08.252	Juvenile rheumatoid arthritis with systemic onset, left hip
M08.259	Juvenile rheumatoid arthritis with systemic onset, unspecified hip
M08.261	Juvenile rheumatoid arthritis with systemic onset, right knee
M08.262	Juvenile rheumatoid arthritis with systemic onset, left knee
M08.269	Juvenile rheumatoid arthritis with systemic onset, unspecified knee
M08.271	Juvenile rheumatoid arthritis with systemic onset, right ankle and foot
M08.272	Juvenile rheumatoid arthritis with systemic onset, left ankle and foot
M08.279	Juvenile rheumatoid arthritis with systemic onset, unspecified ankle and foot
M08.28	Juvenile rheumatoid arthritis with systemic onset, vertebrae
M08.29	Juvenile rheumatoid arthritis with systemic onset, multiple sites
M08.2A	Juvenile rheumatoid arthritis with systemic onset, other specified site
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.40	Pauciarticular juvenile rheumatoid arthritis, unspecified site
M08.411	Pauciarticular juvenile rheumatoid arthritis, right shoulder
M08.412	Pauciarticular juvenile rheumatoid arthritis, left shoulder
M08.419	Pauciarticular juvenile rheumatoid arthritis, unspecified shoulder
M08.421	Pauciarticular juvenile rheumatoid arthritis, right elbow
M08.422	Pauciarticular juvenile rheumatoid arthritis, left elbow
M08.429	Pauciarticular juvenile rheumatoid arthritis, unspecified elbow
M08.431	Pauciarticular juvenile rheumatoid arthritis, right wrist
M08.432	Pauciarticular juvenile rheumatoid arthritis, left wrist
M08.439	Pauciarticular juvenile rheumatoid arthritis, unspecified wrist
M08.441	Pauciarticular juvenile rheumatoid arthritis, right hand
M08.442	Pauciarticular juvenile rheumatoid arthritis, left hand
M08.449	Pauciarticular juvenile rheumatoid arthritis, unspecified hand
M08.451	Pauciarticular juvenile rheumatoid arthritis, right hip
M08.452	Pauciarticular juvenile rheumatoid arthritis, left hip
M08.459	Pauciarticular juvenile rheumatoid arthritis, unspecified hip
M08.461	Pauciarticular juvenile rheumatoid arthritis, right knee
M08.462	Pauciarticular juvenile rheumatoid arthritis, left knee
M08.469	Pauciarticular juvenile rheumatoid arthritis, unspecified knee
M08.471	Pauciarticular juvenile rheumatoid arthritis, right ankle and foot
M08.472	Pauciarticular juvenile rheumatoid arthritis, left ankle and foot
M08.479	Pauciarticular juvenile rheumatoid arthritis, unspecified ankle and foot
M08.48	Pauciarticular juvenile rheumatoid arthritis, vertebrae

Diagnosis Code	Description
M08.4A	Pauciarticular juvenile rheumatoid arthritis, other specified site
M08.80	Other juvenile arthritis, unspecified site
M08.811	Other juvenile arthritis, right shoulder
M08.812	Other juvenile arthritis, left shoulder
M08.819	Other juvenile arthritis, unspecified shoulder
M08.821	Other juvenile arthritis, right elbow
M08.822	Other juvenile arthritis, left elbow
M08.829	Other juvenile arthritis, unspecified elbow
M08.831	Other juvenile arthritis, right wrist
M08.832	Other juvenile arthritis, left wrist
M08.839	Other juvenile arthritis, unspecified wrist
M08.841	Other juvenile arthritis, right hand
M08.842	Other juvenile arthritis, left hand
M08.849	Other juvenile arthritis, unspecified hand
M08.851	Other juvenile arthritis, right hip
M08.852	Other juvenile arthritis, left hip
M08.859	Other juvenile arthritis, unspecified hip
M08.861	Other juvenile arthritis, right knee
M08.862	Other juvenile arthritis, left knee
M08.869	Other juvenile arthritis, unspecified knee
M08.871	Other juvenile arthritis, right ankle and foot
M08.872	Other juvenile arthritis, left ankle and foot
M08.879	Other juvenile arthritis, unspecified ankle and foot
M08.88	Other juvenile arthritis, vertebrae
M08.89	Other juvenile arthritis, multiple sites
M08.90	Juvenile arthritis, unspecified, unspecified site
M08.911	Juvenile arthritis, unspecified, right shoulder
M08.912	Juvenile arthritis, unspecified, left shoulder
M08.919	Juvenile arthritis, unspecified, unspecified shoulder
M08.921	Juvenile arthritis, unspecified, right elbow
M08.922	Juvenile arthritis, unspecified, left elbow
M08.929	Juvenile arthritis, unspecified, unspecified elbow
M08.931	Juvenile arthritis, unspecified, right wrist
M08.932	Juvenile arthritis, unspecified, left wrist
M08.939	Juvenile arthritis, unspecified, unspecified wrist
M08.941	Juvenile arthritis, unspecified, right hand
M08.942	Juvenile arthritis, unspecified, left hand
M08.949	Juvenile arthritis, unspecified, unspecified hand
M08.951	Juvenile arthritis, unspecified, right hip
M08.952	Juvenile arthritis, unspecified, left hip
M08.959	Juvenile arthritis, unspecified, unspecified hip
M08.961	Juvenile arthritis, unspecified, right knee

Diagnosis Code	Description
M08.962	Juvenile arthritis, unspecified, left knee
M08.969	Juvenile arthritis, unspecified, unspecified knee
M08.971	Juvenile arthritis, unspecified, right ankle and foot
M08.972	Juvenile arthritis, unspecified, left ankle and foot
M08.979	Juvenile arthritis, unspecified, unspecified ankle and foot
M08.98	Juvenile arthritis, unspecified, vertebrae
M08.99	Juvenile arthritis, unspecified, multiple sites
M08.9A	Juvenile arthritis, unspecified, other specified site
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.00	Juvenile dermatomyositis, organ involvement unspecified
M33.01	Juvenile dermatomyositis with respiratory involvement
M33.02	Juvenile dermatomyositis with myopathy
M33.03	Juvenile dermatomyositis without myopathy
M33.09	Juvenile dermatomyositis with other organ involvement
M33.10	Other dermatomyositis, organ involvement unspecified
M33.11	Other dermatomyositis with respiratory involvement
M33.12	Other dermatomyositis with myopathy
M33.13	Other dermatomyositis without myopathy
M33.19	Other dermatomyositis with other organ involvement
M33.20	Polymyositis, organ involvement unspecified
M33.21	Polymyositis with respiratory involvement
M33.22	Polymyositis with myopathy
M33.29	Polymyositis with other organ involvement
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.91	Dermatopolymyositis, unspecified with respiratory involvement
M33.92	Dermatopolymyositis, unspecified with myopathy
M33.93	Dermatopolymyositis, unspecified without myopathy
M33.99	Dermatopolymyositis, unspecified with other organ involvement
M36.0	Dermato(poly)myositis in neoplastic disease
O26.40	Herpes gestationis, unspecified trimester
O26.41	Herpes gestationis, first trimester
O26.42	Herpes gestationis, second trimester
O26.43	Herpes gestationis, third trimester
P61.0	Transient neonatal thrombocytopenia
T86.00	Unspecified complication of bone marrow transplant
T86.01	Bone marrow transplant rejection
T86.02	Bone marrow transplant failure
T86.03	Bone marrow transplant infection
T86.09	Other complications of bone marrow transplant
T86.10	Unspecified complication of kidney transplant
T86.11	Kidney transplant rejection
T86.12	Kidney transplant failure

Diagnosis Code	Description
T86.13	Kidney transplant infection
T86.19	Other complication of kidney transplant
Z29.8	Encounter for other specified prophylactic measures
Z29.9	Encounter for prophylactic measures, unspecified
Z48.290	Encounter for aftercare following bone marrow transplant
Z86.19	Personal history of other infectious and parasitic diseases
Z86.2	Personal history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Z92.22	Personal history of monoclonal drug therapy
Z92.29	Personal history of other drug therapy
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

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.[20] All currently available products contain high concentrations of IgG with subclass distribution corresponding to that of normal serum.[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.[20]

Clinical Evidence

Proven

Autoimmune Diseases

IVIG is beneficial for treatment of a number of autoimmune diseases based upon U.S. Food and Drug Administration (FDA) approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include immune thrombocytopenic purpura,[6,14,16,17,31,36,37,59] Graves' ophthalmopathy,[59] autoimmune uveitis,[59] dermatomyositis and polymyositis,[8,9,30,59,62] severe rheumatoid arthritis,[59] and autoimmune diabetes mellitus.[59]

IVIG is a first-line therapy for feto-maternal alloimmune thrombocytopenia.[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,[16,37,59] treatment of CMV-induced pneumonitis in solid organ transplants,[58] treatment of rotaviral 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).[16,27,37]

Neuroimmunologic Disorders

In 2016, the Myasthenia Gravis Foundation of America published consensus based guidance for the management of myasthenia gravis (MG).[69] Guidance statements were developed for symptomatic and immunosuppressive treatments, IV immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle-specific tyrosine kinase, and MG in pregnancy. In regard to the use of IVIG, the task force concluded:

- Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to immunosuppressant agents, chronic IVIG may also be used.
- IVIG is appropriately used as short-term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations.
- IVIG and PLEX are probably equally effective in the treatment of severe generalized MG.
- The efficacy of IVIG is less certain in milder MG or in ocular MG.
- PLEX may be more effective than IVIG in MuSK-MG.
- The use of IVIG as maintenance therapy can be considered for patients with refractory MG or for those in whom IS agents are relatively contraindicated.

In 2010, the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) published clinical guidelines for the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[68] In regard to the diagnosis and treatment of CIDP with IVIG, the task force concluded:

- For induction of treatment, IVIG should be considered in sensory and motor CIDP in the presence of disabling symptoms (level A recommendation).
- For maintenance treatment, there is no sufficient evidence to recommend any particular drug. If response to IVIG is inadequate or result in adverse events, then other first-line treatment alternatives should be considered before combination treatments.
- Electrodiagnostic criteria:
    - Definite: at least one of the following:
        - Motor distal latency prolongation ≥ 50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
        - Reduction of motor conduction velocity ≥ 30% below LLN in two nerves, or
        - Prolongation of F-wave latency ≥ 30% above ULN in two nerves (≥ 50% if amplitude of distal negative peak CMAP < 80% of LLN values), or
        - Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥ 20% of LLN + ≥ 1 other demyelinating parameter in ≥ 1 other nerve, or
        - Partial motor conduction block: ≥ 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parametera in ≥ 1 other nerve, or
        - Abnormal temporal dispersion (> 30% duration increase between the proximal and distal negative peak CMAP) in ≥ 2 nerves, or
        - Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥ 1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) b + ≥ 1 other demyelinating parametera in ≥ 1 other nerve
- Clinical diagnostic criteria:
    - Inclusion criteria:
        - *Typical CIDP*
          Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
          Absent or reduced tendon reflexes in all extremities
        - *Atypical CIDP* (still considered CIDP but with different features)
          One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
          Predominantly distal (distal acquired demyelinating symmetric, DADS) or
          Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or

Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
Pure motor or
Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

- *Exclusion criteria*
  Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
  Hereditary demyelinating neuropathy
  Prominent sphincter disturbance
  Diagnosis of multifocal motor neuropathy
  IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein
  Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

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,[8,17,30,35,37,40,59] 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 antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy,[59] paraproteinemic neuropathy,[59] stiff-person syndrome,[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).[56] 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.[6,12,14-17,21,28,31,37,42,43,59]

IVIG is also beneficial in chronic lymphocytic leukemia and multiple myeloma with reduced IgG and history of infections[3,15,16,27,37,75,77] 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;[59] severe, persistent, high-dose, steroid-dependent asthma;[59] 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 verbal scale and full-scale intelligence scores ($p < 0.1$), as well as on the WAIS information ($p < 0.1$) 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.[34] 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.[10] A small randomized controlled study (n = 16) demonstrated no greater benefit from IVIG (plus heparin and aspirin) than from heparin and aspirin alone.[20] Because the efficacy of IVIG has not been proved in appropriately designed studies, its use is not recommended for APS in pregnancy.[2]

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.[59]

Atopic Dermatitis

IVIG treatment has shown success in small, open, uncontrolled trials of patients not responding to standard therapies.[59] 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.[122] They found that two small, open-trial reports of autistic children placed on IVIG for 6 months showed no benefit.[131] 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.[62]

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.[60]

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.[61]

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.[32] 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.[60]

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.[59]

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]

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). Thirty-five children were enrolled in a small, randomized-entry, double-blind, placebo-controlled, 6-week trial of IVIG (1 g/kg/day on 2 consecutive days), followed by optional open-label treatment for nonresponders, with follow-up at 12 and 24 weeks. The primary outcome measures were the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and the Clinical Global Impressions-Improvement (CGI-I) rating. "Responders" were defined, a priori, by a ≥ 30% decrease in CY-BOCS total score, and a "much" or "very much" improved rating on CGI-I. During the double-blind phase, the mean decrease in

CY-BOCS score was 24% ±31% in the IVIG group (n = 17) and 12% ±27% in the placebo group (n = 18), with six responders in the IVIG group (35%) versus four (22%) in the placebo group; these differences were not statistically significant. Twenty-four participants met criteria for nonresponse to double-blind infusion and received open-label IVIG at week 6. Among all participants, the mean CY-BOCS improvement from baseline was 55% ±33% at week 12 and 62% ±33% at week 24. The authors concluded that IVIG was safe and well tolerated. Between-group differences were smaller than anticipated, and the double-blind comparison failed to demonstrate superiority of IVIG over placebo. The observed open-label improvements indicate that future trials would benefit from larger sample sizes designed in part to aid in the identification of biomarkers predictive of a positive response to immunotherapy. The study did not demonstrate an effect of IVIG versus placebo during the double-blind phase. In the subsequent open-label phase, the majority of patients improved on IVIG. These authors did not determine a factor that predicted favorable treatment response, but elevated baseline levels of serum calcium calmodulin-dependent protein kinase II (CaMKII) and anti-nuclear antibody (ANA) were associated with treatment response in a post hoc analysis.[76]

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.[74] 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]

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
  - Nijmegen breakage syndrome
  - WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome
  - Wiskott Aldrich syndrome
- Common variable immunodeficiency (CVID)
- Congenital hypogammaglobulinemia late onset, ICOS impaired
- 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

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

There are currently eight clinical indications for which IVIG has been licensed by the United States Food and Drug Administration (FDA).[37] 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[6,12,14-17,21,28,31,42,43,58,63,70-72]
- Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia[16]
- Prevention of coronary artery aneurysms in Kawasaki disease (KD)[16]
- Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation[14]
- Reduction of serious bacterial infection in children with human immunodeficiency virus (HIV)[14]
- Increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding[6,14,15,17,28,31]
- Improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in chronic inflammatory demyelinating polyneuropathy (CIDP)[17]
- Maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy[15]

Subcutaneous human immune globulin products are FDA approved for the treatment of patients with primary immune deficiency.[13,17,21,42,58] 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.

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Policy History/Revision Information

Date	Summary of Changes

10/01/2022	**Coverage Rationale**
	Xembify
	• Added language to indicate:
	  ○ Coverage for Xembify® is contingent on criteria in the *Diagnosis-Specific Criteria* section of the policy
	  ○ Removed language indicating:
	  ▪ Xembify is a non-preferred subcutaneous (SC) immune globulin (IG) product
	  ▪ Coverage for Xembify is contingent on the criteria in the *Preferred Product Criteria* and *Diagnosis-Specific Criteria* sections of the policy
	Cutaquig
	• Updated list of preferred SCIG products the individual must have a history of trial with minimal clinical response, contraindication, intolerance, or severe adverse event; added Xembify
	Asceniv
	• Added language to indicate:

Date	Summary of Changes
	○ Asceniv™ is a non-preferred IVIG product; coverage for Asceniv is contingent on the criteria in the *Preferred Product Criteria* and *Diagnosis-Specific Criteria* sections of the policy ○ Treatment with Asceniv is medically necessary for the indications specified in this policy when one of the criteria below are met: ▪ Both of the following: – History of a trial of adequate dose and duration of at least two other IVIG products, resulting in minimal clinical response; alternative IVIG options are, but not limited to: Bivigam®, Gammagard®, Gamunex®, Privigen®, etc. (provider must submit information regarding drug, dose, and duration of therapy); and – Physician attests that, in their clinical opinion, the clinical response with Asceniv would be expected to be superior than experienced with other IVIG products ▪ Both of the following: – History of contraindication, intolerance, or severe adverse event to all other IVIG products not previously tried; alternative IVIG options are, but not limited to: Bivigam®, Gammagard®, Gamunex®, Privigen®, etc. (provider must submit information regarding drug, dose, and duration of therapy); and – Physician attests that, in their clinical opinion, the same contraindication, intolerance, or severe adverse event would not be expected to occur with Asceniv **Applicable Codes** ● Updated list of ICD-10 diagnosis codes to reflect annual edits; added D81.82 **Supporting Information** ● Archived previous policy version CS2022D0035II

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit 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 InterQual® criteria , to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies 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.