

Immune Globulin (IVIG and SCIG) (for Louisiana Only)

Policy Number: CSLA2022D0035HHGG

Effective Date: ~~Jul~~TBA 1, 2022

 [Instructions for Use](#)

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Reviewed 8.16.22:

This does NOT appear more clinically restrictive than the state

Please submit to LDH for acceptance

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Application

This Medical Benefit Drug Policy only applies to the state of Louisiana.

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

Coverage for Cuvitru, Hizentra, ~~and HyQvia~~, and Xembify is contingent on criteria in the [Diagnosis Specific Criteria](#) section.

Coverage for IVIG products, except for Panzyga and Asceniv, is contingent on criteria in the [Diagnosis Specific Criteria](#) section.

Subcutaneous Immune Globulin Preferred Product Criteria

Cutaquig ~~and Xembify~~ are a non-preferred SCIG products. Coverage for Cutaquig ~~and Xembify~~ are contingent on Preferred Product Criteria and [Diagnosis Specific Criteria](#).

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

- **Both** of the following:

- o 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
 - o Physician attests that, in their clinical opinion, the clinical response with Cutaquig ~~or Xembify~~ would be expected to be superior than experienced with the preferred SCIG products
- or
- **Both** of the following:
 - o 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
 - o Physician attests that, in their clinical opinion, the same contraindication, intolerance, or severe adverse event would not be expected to occur with Cutaquig ~~or Xembify~~

Intravenous Immune Globulin Preferred Product Criteria

Panzyga and Asceniv ~~are~~ are a non-preferred IVIG products. Coverage for Panzyga and Asceniv ~~are~~ 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:
 - o 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**
 - o 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:
 - o 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**
 - o 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 |

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

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 **all** 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:

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

- o Diagnosis of an autoimmune bullous disease; **and**
- o Extensive and debilitating disease; **and**
- o History of failure, contraindication, or intolerance to systemic corticosteroids with concurrent immunosuppressive treatment (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil); **and**
- o 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**
- o 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:

- o **One** of the following uses:
 - Prevention of acute graft vs. host disease (GVHD); **or**
 - Prevention of infection
- and**
- o Confirmed allogeneic bone marrow transplant within the last 100 days; **and**
 - o Documented severe hypogammaglobulinemia (IgG < 400 mg/dL); **and**
 - o 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:

- o 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.
- o 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:
 - o Diagnosis of B-cell chronic lymphocytic leukemia (CLL); **and**
 - o **One** of the following:
 - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
 - History of bacterial infection(s) associated with B-cell CLL
 - and**
 - o 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:
 - o Diagnosis of dermatomyositis or polymyositis; **and**
 - o History of failure, contraindication, or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids, cyclophosphamide, methotrexate); **and**
 - o 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**
 - o 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:
 - o Patient is newly diagnosed with insulin dependent (type 1) diabetes mellitus; **and**
 - o 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:

- o 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
 - IVIG dose does not exceed 2,000 mg/kg once weekly until delivery
- or**
- o 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:

- o Diagnosis of Guillain-Barré Syndrome; **and**
- o Severe disease requiring aid to walk; **and**
- o Onset of neuropathic symptoms within the last four weeks; **and**
- o Prescribed by or in consultation with a neurologist; **and**
- o 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**
- o 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:

- o Diagnosis of HIV disease; **and**
- o Patient age ≤ 13 years; **and**
- o **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**
- o 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:

- o **All** of the following:
 - Diagnosis of acute thrombocytopenic purpura (ITP); **and**
 - Documented platelet count < 50 x 10⁹ / 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**
- o **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:

 - o Diagnosis of Kawasaki disease; **and**
 - o 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:

 - o Diagnosis of Lambert-Eaton myasthenic syndrome (LEMS); **and**
 - o History of failure, contraindication, or intolerance to immunomodulator monotherapy (e.g., azathioprine, corticosteroids); **and**
 - o Concomitant immunomodulator therapy (e.g., azathioprine, corticosteroids), unless contraindicated, will be used for long-term management of LEMS; **and**
 - o Prescribed by or in consultation with a neurologist; **and**
 - o 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**
 - o 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:

 - o History of failure, contraindication or intolerance to initial treatment with traditional anti-epileptic pharmacotherapy (e.g., lamotrigine, phenytoin, valproic acid); **and**
 - o Prescribed by or in consultation with a neurologist; **and**
 - o 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**
 - o 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:

 - o 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}
- o 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:
 - o Diagnosis of multiple myeloma; **and**
 - o **One** of the following:
 - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
 - History of bacterial infection(s) associated with multiple myeloma
 - and**
 - o 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:
 - o 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

o 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.)

o **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

o **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:

- o 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
- 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

- o 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:

- o Diagnosis of posttransfusion purpura; **and**
- o 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:

- o 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**
- o **Both** of the following:
 - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
 - History of bacterial infection(s) associated with B-cell depletion
- and**
- o 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} ([See disease list linked to below.](#))

Immune globulin is medically necessary for the treatment of primary immunodeficiency syndromes when **all** of the following criteria are met:

- o Diagnosis of primary immunodeficiency; **and**
- o 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**
- o 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^{28,51-2,57-61,76,118,133}

(For SCIG products, FDA-labeled dosing and conversion guidelines will be 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:

- o 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**
- o 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:

- o 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 comorbidities⁶²
- o 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:

- o 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 10⁹ / 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
- o 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, nonlyophilized (e.g., liquid), 500 mg |
| J1558 | Injection, immune globulin (Xembify), 100 mg |

| HCPSC Code | Description |
|------------|---|
| 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 xanthema] |
| A88.8 | Other specified viral infections of central nervous system |
| B20 | Human immunodeficiency virus [HIV] disease |
| B25.0 | Cytomegaloviral pneumonitis |
| 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 |

| Diagnosis Code | Description |
|----------------|--|
| 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 |
| D81.89 | 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] |
| 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 |

| Diagnosis Code | Description |
|----------------|---|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|---|
| 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 |
| G62.9 | Polyneuropathy, unspecified |

| Diagnosis Code | Description |
|----------------|--|
| 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 foliaceus |
| 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 |
| M05.039 | Felty's syndrome, unspecified wrist |
| M05.041 | Felty's syndrome, right hand |
| M05.042 | Felty's syndrome, left hand |

| Diagnosis Code | Description |
|----------------|---|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|--|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|---|
| 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 |

| Diagnosis Code | Description |
|----------------|--|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|---|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|--|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|---|
| 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 |
| 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 |

| Diagnosis Code | Description |
|----------------|---|
| 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 |
| 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 US Food and Drug Administration (FDA) approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include immune thrombocytopenic purpura,^{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 fetomaternal 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 $\geq 50\%$ above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
 - Reduction of motor conduction velocity $\geq 30\%$ below LLN in two nerves, or
 - Prolongation of F-wave latency $\geq 30\%$ above ULN in two nerves ($\geq 50\%$ if amplitude of distal negative peak CMAP $< 80\%$ of LLN values), or

- o Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes $\geq 20\%$ of LLN + ≥ 1 other demyelinating parameter in ≥ 1 other nerve, or
- o Partial motor conduction block: $\geq 50\%$ amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP $\geq 20\%$ of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parameter in ≥ 1 other nerve, or
- o Abnormal temporal dispersion ($>30\%$ duration increase between the proximal and distal negative peak CMAP) in ≥ 2 nerves, or
- o 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) + ≥ 1 other demyelinating parameter in ≥ 1 other nerve

Clinical Diagnostic Criteria

- Inclusion Criteria:
 - o 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
 - o 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), or
 - Pure motor, or
 - Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
- Exclusion Criteria:
 - o *Borrelia burgdorferi* infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
 - o Hereditary demyelinating neuropathy
 - o Prominent sphincter disturbance
 - o Diagnosis of multifocal motor neuropathy
 - o IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
 - o 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 anti-myelin-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} 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-A β 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 A β levels increased transiently after each infusion. Cerebrospinal fluid A β 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

Bone Marrow Transplantation (BMT), 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

Bone Marrow Transplantation (BMT), 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 is retrospective, but no prospective, data, which indicates 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 $\geq 30\%$ 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 $24\% \pm 31\%$ in the IVIG group (n=17) and $12\% \pm 27\%$ 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 $55\% \pm 33\%$ at week 12 and $62\% \pm 33\%$ 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.^{59,74} 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 ~~250~~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 leukemia¹⁶
- Prevention of coronary artery aneurysms in Kawasaki disease (KD)¹⁶
- Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation¹⁴
- 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 neuropathy¹⁵

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 |
|-------------------|---|
| <u>xx/01/2022</u> | <u>Xembify removed as non-preferred product. Asceniv moved to non-preferred product.</u> |
| 07/01/2022 | Applicable Codes <ul style="list-style-type: none">Updated list of applicable HCPCS codes to reflect quarterly edits; added J1551 Supporting Information <ul style="list-style-type: none">Archived previous policy version CSLA2021D0035FF |

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.

Archived Policy Versions

| Effective Date | Policy Number | Policy Title |
|-------------------------|-----------------|--|
| 12/01/2021 – 06/30/2022 | CSLA2021D0035FF | Immune Globulin (IVIG and SCIG) (for Louisiana Only) |
| 07/01/2021 – 11/30/2021 | CSLA2021D0035EE | Immune Globulin (IVIG and SCIG) (for Louisiana Only) |
| 04/01/2021 – 06/30/2021 | CSLA2021D0035DD | Immune Globulin (IVIG and SCIG) (for Louisiana Only) |
| 02/01/2021 – 03/31/2021 | CSLA2021D0035CC | Immune Globulin (IVIG and SCIG) (for Louisiana Only) |
| 11/01/2020 – 01/31/2021 | CSLA2020D0035BB | Immune Globulin (IVIG and SCIG) (for Louisiana Only) |
| 08/01/2019 – 10/31/2020 | CSLA2019D0035AA | Immune Globulin (IVIG and SCIG) (for Louisiana Only) |
| 03/01/2019 – 07/31/2019 | CS2019D0035Z | Immune Globulin (IVIG and SCIG) |
| 11/01/2018 – 02/28/2019 | CS2018D0035Y | Immune Globulin (IVIG and SCIG) |
| 03/01/2018 – 10/31/2018 | CS2018D0035X | Immune Globulin (IVIG and SCIG) |
| 01/01/2018 – 02/28/2018 | CS2018D0035W | Immune Globulin (IVIG and SCIG) |
| 10/01/2017 – 12/31/2017 | CS2017D0035V | Immune Globulin (IVIG and SCIG) |
| 02/01/2017 – 09/30/2017 | CS2017D0035U | Immune Globulin (IVIG and SCIG) |