Introduction

Immune globulins are proteins made by special cells that help the body fight infections. The proteins are in the blood stream, and are concentrated in plasma, the fluid that is left after removing red and white blood cells from whole blood. Advances in medical technology have made it possible to collect, store and infuse these proteins into other people who have immune system problems. This process is called immune globulin therapy. Some people lack some or all of the cells that make immune globulins. Providing them with intravenous immune globulin therapy can be life-saving. Other conditions also may improve with immune globulin therapy. This policy describes when the health plan covers the use of immune globulin therapy. For some diseases, the use of immune globulins is still under study. Generally, the use of immune globulin (IVIG) treatment requires pre-approval of the health plan.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.
We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician’s office, or at home.

**Drugs subject to site of service review addressed in this policy are:**

- Bivigam®
- Carmiune® NF
- Flebogamma® DIF
- GammaSTAN® S/D
- Gammagard
- Gammaked™
- Gammaplex®
- Gamunex®-C
- Hizentra®
- Octagam®
- Privigen®

Click on the links below to be directed to the related medical necessity criteria:

**Alloimmune Processes**

**Autoimmune / Inflammatory Conditions**

**Hematopoietic Cell Transplantation**

**Infections**

**Miscellaneous**

**Primary Immunodeficiency States**

**Prior to solid organ transplant**

**Site of Service**

### Site of Service Administration

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</strong></td>
</tr>
<tr>
<td>- These are the preferred <strong>medically necessary</strong> sites of service for specified drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital-based outpatient setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medically necessary sites of service</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physician’s office</strong></td>
</tr>
<tr>
<td><strong>Infusion center</strong></td>
</tr>
<tr>
<td><strong>Home infusion</strong></td>
</tr>
<tr>
<td>Site of Service Administration</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>infusion department</td>
</tr>
<tr>
<td>• Hospital-based outpatient clinical level of care</td>
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</tr>
<tr>
<td>Hospital-based outpatient</td>
</tr>
</tbody>
</table>
### Site of Service Administration |
**Medical Necessity**
| setting | and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met. |
| Outpatient hospital IV infusion department | |
| Hospital-based outpatient clinical level of care | |

## Intravenous Immune Globulin (IVIG) Therapy

### Condition |
**Medical Necessity**

IVIg therapy is subject to review for site of service administration.

<table>
<thead>
<tr>
<th>Primary immunodeficiency states:</th>
<th>IVIG therapy may be considered medically necessary when items 1, 2, and 3 are present:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia telangiectasia</td>
<td>1. Laboratory evidence of immunoglobulin deficiency indicated by:</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>o Agammaglobulinemia (total immunoglobulin G [IgG] &lt;200 mg/dl)</td>
</tr>
<tr>
<td>Congenital agammaglobulinemia</td>
<td>OR</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>o Persistent hypogammaglobulinemia (total IgG &lt;400 mg/dl, or at least 2 standard deviations below normal, on at least 2 occasions)</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>OR</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>o Absence of B lymphocytes</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>2. Documented inability to mount an adequate immunologic response to inciting antigens as indicated by:</td>
</tr>
<tr>
<td>X-linked hyperimmunoglobulinemia M syndrome</td>
<td>o Lack of appropriate rise in antibody titer following a polysaccharide antigen</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>o Lack of appropriate rise in antibody titer following a protein antigen</td>
</tr>
<tr>
<td></td>
<td>3. Persistent and severe infections, despite treatment with prophylactic antibiotics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific antibody deficiency (SAD)</th>
<th>IVIG therapy may be considered medically necessary when ALL of the following criteria are met:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Immunological evaluation with documented normal</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
</tbody>
</table>
| IVIg therapy is subject to review for site of service administration. | serum IgG, IgG subclass, IgA, and IgM  
- Normal responses to protein antigens (eg tetanus and diphtheria toxoid) measured 4 weeks after immunization  
- Inadequate responsiveness to pneumococcal polysaccharide vaccine (eg, Pneumovax®23) 4-8 weeks after vaccination as demonstrated by either of the following:  
  o Age < 6 years, <50% of serotypes are protective (ie, ≥1.3 mcg/ml per serotype), or  
  o Age ≥ 6 years, <70% of serotypes are protective (ie, ≥1.3 mcg/ml per serotype)  
- Recurrent infections as demonstrated by the following:  
  o History of recurrent, severe bacterial sinopulmonary infections despite treatment with:  
    ▪ Prevnar 7 or Prevnar 13 vaccination, and  
    ▪ Failure or inadequate response to prophylactic antibiotic therapy  
  o Documented management of underlying asthma or allergic rhinitis (eg, treatment with nasal or inhaled glucocorticoids, bronchodilators, or antihistamines) |

| Individual who is undergoing/undergone hematopoietic cell transplantation or CAR T-cell therapy | IVIG therapy may be considered medically necessary when IgG levels are less than 400 mg/dl. |
| Prior to solid organ transplant | IVIG therapy may be considered medically necessary when there is high risk of antibody-mediated rejection as indicated by either:  
- Highly sensitized patients (PRA >20%) panel reactive antibody test  
OR  
- Transplant (ABO) incompatible organ |

**Infections**
<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVIg therapy is subject to review for site of service administration.</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL) diagnosis and persistent bacterial</td>
<td>IVIG therapy may be considered medically necessary when:</td>
</tr>
<tr>
<td>infection</td>
<td>• The IgG level is less than 400 mg/dl AND • There are persistent bacterial infections</td>
</tr>
<tr>
<td>Children with HIV to prevent opportunistic infections</td>
<td>IVIG therapy may be considered medically necessary when the IgG level is less than 400 mg/dl.</td>
</tr>
<tr>
<td>Severe anemia due to human parvovirus B19</td>
<td>IVIG therapy may be considered medically necessary with this documented diagnosis.</td>
</tr>
<tr>
<td>Toxic Shock Syndrome (TSS)</td>
<td>IVIG therapy may be considered medically necessary with this documented diagnosis.</td>
</tr>
<tr>
<td><strong>Autoimmune / Inflammatory Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Autoimmune mucocutaneous blistering diseases</td>
<td>IVIG therapy may be considered medically necessary for severe progressive disease, and the patient has failed treatment with conventional agents such as corticosteroids, azathioprine, and cyclophosphamide</td>
</tr>
<tr>
<td>• pemphigus, pemphigoid, pemphigus vulgaris, and pemphigus foliaceus</td>
<td></td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura (ITP)- Adults</td>
<td>IVIG therapy may be considered medically necessary when:</td>
</tr>
<tr>
<td></td>
<td>• Platelet count is &lt;10,000/mm³ and individual is considered at risk for severe bleeding or cerebral bleeding OR • Platelet count is &lt;30,000/mm³ and ONE of the following medically necessary situations is present:</td>
</tr>
<tr>
<td></td>
<td>o Need to rapidly increase platelets due to bleeding, major surgery planned, or risk of cerebral bleeding OR o Not a candidate for splenectomy, or experienced relapse post splenectomy AND o Failure, contraindication, or intolerance to corticosteroids*</td>
</tr>
</tbody>
</table>

*Note: See 5.01.566 - Pharmacotherapy of Thrombocytopenia
<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Idiopathic thrombocytopenic purpura (ITP)- Pediatric**                  | **IVIG therapy may be considered medically necessary when:**  
  - Platelet count is <30,000/mm$^3$ and **ONE** of the following medically necessary situations is present:  
    - Need to rapidly increase platelets due to bleeding, major surgery planned, or risk of cerebral bleeding  
    - **OR**  
      - Prevention of bleeding in first 12 months after diagnosis                                                                                                                                                                                                                     |
| **Adults with Guillain-Barré syndrome**                                   | **IVIG therapy may be considered medically necessary as an equivalent alternative to plasma exchange.**                                                                                                                                                                                                                                         |
| **Kawasaki syndrome**                                                     | **IVIG therapy may be considered medically necessary with this documented diagnosis.**                                                                                                                                                                                                                                                              |
| **Wegener granulomatosis (GPA)**                                         | **IVIG therapy may be considered medically necessary with this documented diagnosis.**                                                                                                                                                                                                                                                              |
| **Chronic inflammatory demyelinating polyneuropathy (CIDP) with progressive symptoms for at least 2 months** | **IVIG therapy may be considered medically necessary with diagnosis based on:**  
  - Progressive or relapsing motor and/or sensory symptoms of more than one limb **AND** hyporeflexia or areflexia in affected limbs present for at least 2 months  
  - Electrophysiologic findings indicate demyelinating neuropathy (3 of the following 4 criteria are met per the American Academy of Neurology):  
    - Partial conduction block of ≥ 1 motor nerve  
    - Reduced conduction velocity of ≥ 2 motor nerves  
    - Prolonged distal latency of ≥ 2 motor nerves  
    - Prolonged F-wave latencies of ≥ 2 motor nerves or the absence of F waves  
  - Other causes of demyelinating neuropathy have been excluded (Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure, hereditary demyelinating neuropathy, prominent**
<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIg therapy is subject to review for site of service administration.</td>
<td>sphincter disturbance, multifocal motor neuropathy (MMN), IgM monoclonal gammopathy, and others</td>
</tr>
</tbody>
</table>

- **If available**, results of other testing to support diagnosis should be provided. Such as:
  - Cerebrospinal fluid (CSF) examination demonstrating elevated CSF protein with leukocyte count <10/mm³
  - MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses
  - Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis

<table>
<thead>
<tr>
<th>Multifocal motor neuropathy</th>
<th>IVIg therapy may be considered medically necessary with this documented diagnosis, and symptoms have been present for one month or longer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eaton-Lambert myasthenic syndrome</td>
<td>IVIg therapy may be considered medically necessary when the patient fails to respond to anticholinesterase medications (Mestinon), corticosteroids, and/or azathioprine.</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>IVIg therapy may be considered medically necessary when there is a contraindication to, or lack of response to first-line treatment, such as steroids or plasma exchange.</td>
</tr>
<tr>
<td>Severe refractory myasthenia gravis</td>
<td>IVIg therapy may be considered medically necessary when the patient has chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.</td>
</tr>
<tr>
<td>Myasthenic exacerbation (ie, acute episode of respiratory muscle weakness)</td>
<td>IVIg therapy may be considered medically necessary when plasma exchange is contraindicated or as an alternative.</td>
</tr>
<tr>
<td>Dermatomyositis or polymyositis</td>
<td>IVIg therapy may be considered medically necessary when:</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>IVIg therapy is subject to review for site of service administration.</td>
<td>• The disease is refractory to treatment with corticosteroids</td>
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<td></td>
<td>AND</td>
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<td></td>
<td>• IVIG is used in combination with other immunosuppressive agents</td>
</tr>
<tr>
<td>Warm antibody hemolytic anemia</td>
<td>IVIG therapy may be considered medically necessary when the disease is refractory to other therapies: azathioprine, cyclophosphamide, prednisone, plasmapheresis, or splenectomy.</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>IVIG therapy may be considered medically necessary with this documented diagnosis.</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>IVIG therapy is considered not medically necessary for patients with any type of multiple sclerosis</td>
</tr>
<tr>
<td>Alloimmune Processes</td>
<td></td>
</tr>
<tr>
<td>Neonatal alloimmune thrombocytopenia</td>
<td>IVIG therapy may be considered medically necessary with this documented diagnosis.</td>
</tr>
<tr>
<td>Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis)</td>
<td>IVIG therapy may be considered medically necessary with this documented diagnosis.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Stiff person syndrome</td>
<td>IVIG therapy may be considered medically necessary when All of the following are present:</td>
</tr>
<tr>
<td></td>
<td>• The diagnosis is based on clinical findings and positive anti-GAD antibodies, or anti-amphiphysin antibodies, and EMG test</td>
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<tr>
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<td>AND</td>
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<td></td>
<td>• The patient has significant disability (uses walker or cane)</td>
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<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>• The patient has not improved with diazepam or baclofen</td>
</tr>
<tr>
<td>Immunodeficiency states</td>
<td>IVIG therapy is considered investigational for patients who have received a solid organ transplant for:</td>
</tr>
<tr>
<td>Condition</td>
<td>Investigational</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td><strong>IVIG therapy is considered investigational for:</strong></td>
</tr>
<tr>
<td>• Prophylaxis or treatment of acute antibody</td>
<td>• Patients with neonatal sepsis (prophylaxis or treatment)</td>
</tr>
<tr>
<td>mediated rejection</td>
<td>• Adult patients with sepsis</td>
</tr>
<tr>
<td><strong>Autoimmune / inflammatory conditions</strong></td>
<td><strong>IVIG therapy is considered investigational for:</strong></td>
</tr>
<tr>
<td>• Patients with Stevens-Johnson syndrome and</td>
<td>• Patients with inclusion body myositis</td>
</tr>
<tr>
<td>toxic epidermal necrolysis</td>
<td>• Patients with systemic lupus erythematosus</td>
</tr>
<tr>
<td>• Patients with inclusion body myositis</td>
<td>• Patients with immune optic neuritis</td>
</tr>
<tr>
<td>• Patients with inclusion body myositis</td>
<td>• Patients with Crohn disease</td>
</tr>
<tr>
<td>• Patients with hemophagocytic lymphohistiocytosis</td>
<td>• Patients with Crohn disease</td>
</tr>
<tr>
<td><strong>Alloimmune processes</strong></td>
<td><strong>IVIG therapy is considered investigational for:</strong></td>
</tr>
<tr>
<td>• Patients with recurrent spontaneous abortion</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td><strong>IVIG therapy is considered investigational for patients with:</strong></td>
</tr>
<tr>
<td>• Acquired factor VIII inhibitors</td>
<td>• Autism spectrum disorder</td>
</tr>
<tr>
<td>• Acute lymphoblastic leukemia</td>
<td>• Behçet syndrome</td>
</tr>
<tr>
<td>• Acute myocarditis</td>
<td>• Birdshot retinopathy</td>
</tr>
<tr>
<td>• Adrenoleukodystrophy</td>
<td>• Chronic fatigue syndrome</td>
</tr>
<tr>
<td>• Alzheimer disease</td>
<td>• Chronic sinusitis</td>
</tr>
<tr>
<td>• Aplastic anemia</td>
<td>• Complex regional pain syndrome</td>
</tr>
<tr>
<td>• Asthma</td>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td>• Autism spectrum disorder</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Behçet syndrome</td>
<td>• Diamond-Blackfan anemia</td>
</tr>
<tr>
<td>• Birdshot retinopathy</td>
<td>• Epidermolysis bullosa acquisita</td>
</tr>
<tr>
<td>• Chronic fatigue syndrome</td>
<td>• Epilepsy</td>
</tr>
<tr>
<td>• Chronic sinusitis</td>
<td>• Fisher syndrome</td>
</tr>
<tr>
<td>• Complex regional pain syndrome</td>
<td>• Goodpasture syndrome</td>
</tr>
<tr>
<td>• Cystic fibrosis</td>
<td>• Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>• IGG subclass deficiency</td>
</tr>
</tbody>
</table>
## Condition

### Investigational

- Immune-mediated neutropenia
- Multiple myeloma
- Necrotizing fasciitis
- Nonimmune thrombocytopenia
- Noninfectious uveitis
- Opsoclonus-myoclonus
- Organ transplant rejection
- Other vasculitides besides Kawasaki disease, including polyarteritis nodosa
- Otitis media, recurrent
- Paraneoplastic syndromes
- Paraproteinemic neuropathy
- Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS)
- Pericarditis, refractory recurrent
- Polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy [CIDP])
- Post-polio syndrome
- Red cell aplasia
- Rheumatoid arthritis, refractory
- Thrombotic thrombocytopenic purpura (TTP)
- Vasculitis associated with other connective tissue diseases

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### Subcutaneous Immune Globulin (SCIG) Therapy

#### Condition

**Medical Necessity**

**Conditions where SCIG is covered**

Subcutaneous immune globulin (SCIG) therapy may be considered medically necessary for any condition where IVIG would otherwise be covered.

#### Condition

**Investigational**

**All other diagnoses**

Other applications of SCIG therapy are considered investigational.
Approval | Criteria
---|---
**Initial authorization** | The initial authorization will be for 6 months unless otherwise indicated (eg, in bone marrow transplant).

**Re-authorization** | At the time of re-authorization for ongoing care, it is expected that there will be clinical documentation of objective measures of response (eg, reduction in the incidence of infections). Re-authorization will be provided for 12 months unless otherwise indicated.

**Documentation Requirements**
The medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:
- Diagnosis/condition
- History and physical examination documenting the severity of the condition, including frequency and severity of infections if applicable
- Laboratory results or diagnostic evidence supporting the indication for immune globulin

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
</tr>
<tr>
<td>90284</td>
<td>Immune globulin (SCig), human, for use in subcutaneous infusions, 100 mg, each</td>
</tr>
<tr>
<td><strong>HCPCS</strong></td>
<td></td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, nonlyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>J1555</td>
<td>Injection, immune globulin (Cuvitru), 100 mg</td>
</tr>
<tr>
<td>J1556</td>
<td>Injection, immune globulin (Bivigam), 500 mg</td>
</tr>
<tr>
<td>J1557</td>
<td>Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Hizentra), 100 mg</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), non-lyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>J1562</td>
<td>Injection, immune globulin (Vivaglobin), 100 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (eg, powder), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin (Octagam) intravenous, non-lyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin (Gammagard) intravenous, non-lyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>J1572</td>
<td>Injection, immune globulin (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>J1575</td>
<td>Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immune globulin</td>
</tr>
<tr>
<td>J1599</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (eg, liquid), not otherwise specified, 500 mg</td>
</tr>
</tbody>
</table>

**Related Information**

This policy only addresses nonspecific pooled preparations of immunoglobulin (IG); it does **not** address IG preparations that are specifically used as passive immunization to prevent or reduce infection that may occur with specific viral diseases that include but may not be limited to:

- Cytomegalovirus (CMV)
- Hepatitis A
- Hepatitis B
- Measles
- Respiratory syncytial virus (RSV)
- Rubella
- Varicella/chickenpox

**Black Box Warnings and Precautions for IVIG:**

- Thrombosis may occur with immunoglobulin products. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial
thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

- For individuals at risk of thrombosis, administer immunoglobulin products at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in individuals at risk for hyperviscosity.

- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of human IVIG products in predisposed individuals. Individuals predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes, age greater than 65, volume depletion, sepsis, paraproteinemia, or individuals receiving known nephrotoxic drugs.

- Renal dysfunction and acute renal failure occur more commonly in individuals receiving IVIG products that contain sucrose.

- For individuals at risk of renal dysfunction or renal failure, administer IVIG at the minimum infusion rate practicable.

Additional warnings and precautions include:

- Immunoglobulin A (IgA)-deficient individuals with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.

- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output, in individuals at risk of developing acute renal failure.

- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in individuals receiving IVIG therapy.

- Thrombosis may occur. Monitor individuals with known risk factors for thrombosis and consider baseline assessment of blood viscosity for those at risk of hyperviscosity.

- Aseptic meningitis syndrome may occur in individuals receiving IVIG therapy, especially with high doses or rapid infusion.

- Hemolytic anemia can develop subsequent to IVIG treatment. Monitor individuals for signs and symptoms of hemolysis and hemolytic anemia.

- Monitor individuals for pulmonary adverse reactions (transfusion-related acute lung injury).
• Individuals receiving IVIG for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for developing fever, chills, nausea, and vomiting.

• IVIG is made from human plasma and may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent).

• Passive transfer of antibodies may confound serologic testing.

The subcutaneous immunoglobulin (SCIG) product information labels note that reactions similar to other immunoglobulin products may occur. The most common adverse events with subcutaneous injections include local reactions (ie, swelling, redness, heat, pain, and itching at the injection site).

**Chronic inflammatory demyelinating polyneuropathy (CIDP)**

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) should have an established diagnosis of CIDP such as criteria established by the American Academy of Neurology in 1991 or those described in a guideline from the European Federation of Neurological Societies and the Peripheral Nerve Society, published in 2006 and updated in 2010. There is currently no criterion standard set of clinical or electrophysiologic criteria for the diagnosis of CIDP and its variants.

IVIG treatment in CIDP should be limited to patients who do not respond to initial therapy with prednisone and are experiencing serious clinical worsening. In patients treated for chronic diseases (eg, CIDP, multifocal motor neuropathy, dermatomyositis), the effect of IVIG is transitory and therefore periodic infusions of IVIG are needed to maintain treatment effect. The frequency of transfusions is titrated to the treatment response; typically, biweekly or monthly infusions are needed.

**Consideration of Age**

In relation to infusion place of service, the age described in this policy for medical necessity of select intravenous and injectable therapy services is 13 years of age or older. The age criteria are based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and
age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to patients above the age of 13.

The ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for this drug.

**Benefit Application**

Based on benefits or contract language, IVIG may be considered either a pharmacy or medical benefit.

**Evidence Review**

**Description**

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immune deficiency states and various autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G antibodies against a wide variety of bacterial and viral antigens. This policy addresses the use of human immunoglobulin therapy for preventing and/or treating disorders in the outpatient setting. Both intravenous immunoglobulin (IVIG) infusion and subcutaneous immunoglobulin (SCIG) infusion are addressed. However, the policy only considers nonspecific pooled preparations of IVIG; it does not consider other preparations used for passive immunization to specific antigens.

**Background**

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immunodeficiency states and various autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Two formulations of human IgG are available: intravenous
immunoglobulin (IVIG) and subcutaneous immunoglobulin. Intramuscular immunoglobulin depot injections have been largely abandoned.

IVIG is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIG has been used to correct immunodeficiencies in patients with inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIG products are available for clinical use in the United States. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (eg, Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

This policy only addresses nonspecific pooled preparations of IVIG; it does not address other immunoglobulin preparations specifically used for passive immunization to prevent or attenuate infection with specific viral diseases (eg, respiratory syncytial virus, cytomegalovirus, hepatitis B).

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.

Summary of Evidence

**Immunodeficiency States**

**Primary Humoral Immune Deficiencies**

Primary humoral immunodeficiency deficiencies refer to diseases resulting from impaired antibody production because of a molecular defect intrinsic to B cells or a failure of interactions between B and T cells. Antibody deficiency characteristically leads to recurrent, often severe upper and lower respiratory tract infections. Findings associated with severe primary humoral immunodeficiencies include failure to thrive, chronic diarrhea, recurrent fever, nodular lymphoid hyperplasia in the gut, and hepatosplenomegaly.

For individuals who have primary humoral immunodeficiency who receive IVIG or SCIG therapy, the evidence includes multiple RCTs and noncomparative studies. Relevant outcomes are overall survival, symptoms, change in disease status, morbid events, functional outcomes, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG and SCIG therapy improved disease-related outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Hematopoietic Cell Transplantation (Prophylaxis)

Hematopoietic cell transplantation (HCT) is the intravenous infusion of hematopoietic stem and progenitor cells designed to establish marrow and immune function in patients with various acquired and inherited malignant and nonmalignant disorders.

For individuals who are undergoing HCT who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs, systematic reviews, and a meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbidity events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for routine prophylaxis of infection in patients undergoing HCT was not associated with survival benefit or reduction in infection. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Acute Antibody-Mediated Rejection After Solid Organ Transplant

Acute rejection after transplant can be broadly divided into 2 categories: the more common acute cellular rejection related to activation of T cells, and the less common acute antibody-mediated rejection (ABMR) related to the presence of anti-donor antibodies. Acute ABMR is an entity now better defined and often detected earlier in the clinical course, based on the recognition of characteristic histologic findings, positive C4d staining, and the detection of donor-specific antibodies.

For individuals who are at risk of acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes multiple RCTs, noncomparative observational studies, systematic reviews, and meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbidity events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for prophylaxis of infection in patients with high panel reactive antibody levels was not associated with a survival benefit or reduction in infection. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbidity events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG treatment for ABMR has shown potential benefit in retrospective or small prospective
studies. Larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Infections**

**Chronic Lymphocytic Leukemia**

Chronic lymphocytic leukemia (CLL) is a disorder characterized by progressive accumulation of functionally incompetent lymphocytes and most patients develop hypogammaglobulinemia at some point in the course of their disease. Patients experiencing recurrent bacterial infections associated with hypogammaglobulinemia (less than 400mg/dl) are likely to benefit from monthly infusions of IVIG.

For individuals who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for recurrent bacterial infections associated with hypogammaglobulinemia in CLL patients has shown reductions in minor and moderate infections without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**HIV-Infected Children**

Prevention of opportunistic infections remains a critical component of care for HIV-infected children even though availability of combination antiretroviral therapies has substantially and dramatically decreased AIDS-related opportunistic infections and deaths.

For individuals who are HIV-infected children with recurrent bacterial infections associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes a single RCT. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prevention of opportunistic infections in HIV-infected children has shown reductions in minor and serious infections without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
**Neonatal Sepsis**

Preterm and low birth weight infants are prone to infection because of an immature immune system as well as increased exposure to nosocomial pathogens.

For individuals who are preterm and low birth weight infants with sepsis who receive IVIG therapy (treatment), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for neonatal sepsis did not differ significantly in the rates of death or major disability. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

**Prophylaxis of Neonatal Sepsis**

For individuals who are preterm and low birth weight infants and at risk for sepsis who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

**Treatment of Sepsis in Adults**

For individuals who are adults with sepsis who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for adult sepsis showed reductions in mortality in the meta-analysis. However, multiple factors preclude recommending routine use of IVIG to treat sepsis. They include the preponderance of small low-quality studies, use of heterogeneous dosing regimens, types of IVIG preparations used, and changes over time in the management of sepsis. The evidence is insufficient to determine the effects of the technology on health outcomes.
Severe Anemia Associated with Human Parvovirus B19

Human parvovirus B19 is a common single-stranded DNA virus. Infections are usually mild or asymptomatic, and do not require treatment. In some cases, infection can lead to sufficiently severe complications such as transient aplastic crisis in which case treatment is indicated and may be lifesaving.

For individuals who have severe anemia associated with human parvovirus B19 who receive IVIG therapy, the evidence includes case series. Relevant outcomes are change in disease status, treatment-related mortality, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy, data are retrospective. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Toxic Shock Syndrome

Toxic shock syndrome is also called Streptococcal toxic shock syndrome. Streptococcal toxins induce the release of inflammatory cytokines, which cause capillary leakage and tissue damage resulting in shock, multiorgan failure, and death.

For individuals who have toxic shock syndrome who receive IVIG therapy, the evidence includes a small RCT and multiple observational studies. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for toxic shock syndrome in adult women has shown reductions in mortality in the small RCT and in multiple observational studies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Autoimmune / Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenia, is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. It is a more common cause of thrombocytopenia in otherwise asymptomatic adults.

For individuals who have ITP who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, a meta-analysis, and noncomparative studies. Relevant outcomes are disease-specific survival, change in disease status, morbid events, and treatment-related mortality and
morbidity. Compared with corticosteroids, IVIG therapy improved platelet counts. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a heterogeneous condition with several variant forms and encapsulates many acute immune-mediated polyneuropathies. It is characterized by a rapid-onset of muscle weakness caused by the immune system damaging the peripheral nervous system.

For individuals who have Guillain-Barré syndrome who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with plasma exchange or combination therapy with plasma exchange, IVIG therapy showed similar outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Kawasaki Disease

Kawasaki disease is among the most common vasculitides of childhood; it is characterized by fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. It is typically self-limiting but may cause cardiovascular complications, particularly coronary artery aneurysms, which can lead to coronary occlusion and cardiac ischemia ultimately leading to significant morbidity and even death. Therefore, early treatment is essential. Although the mechanism of action of IVIG is not understood, its use early in the course of the disease has reduced the prevalence of coronary artery abnormalities.

For individuals who have Kawasaki disease who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown significant decreases in new coronary artery abnormalities. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Granulomatosis with Polyangiitis (Wegener Granulomatosis)

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes systematic reviews and an RCT. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. The success of IVIG in Kawasaki disease has led to the investigation of IVIG therapy for other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This small trial found significantly more responders in the IVIG treatment group at 3 months—but no significant differences after 3 months, or in the frequency of relapse or use of other medications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired neurologic disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder is caused by damage to the myelin sheath of the peripheral nerves. CIDP is difficult to diagnose due to its heterogeneous presentation (both clinical and electrophysiological).

For individuals who have CIDP who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CIDP who receive SCIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (eg, 45% of patients withdrew from the trial). The other RCT demonstrated that the use of SCIG for the maintenance of CIDP might be effective, with relatively low adverse events, but this trial also had a number of limitations (eg, small sample, 30% dropout rate). The evidence is insufficient to determine the effects of the technology on health outcomes.
**Multifocal Motor Neuropathy**

Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities, a presentation similar to that of motor neuron disease.

For individuals who have MMN who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Eaton-Lambert Myasthenic Syndrome**

Eaton-Lambert myasthenic syndrome is an autoimmune disease with antibodies directed against the neuromuscular junction. Patients have muscle weakness of the lower extremities, autonomic dysfunction, and extra-ocular muscle impairment. This is a paraneoplastic syndrome associated most commonly with small-cell lung cancer.

For individuals who have Eaton-Lambert myasthenic syndrome who receive IVIG therapy, the evidence includes an RCT and multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in outcomes assessing muscle strength and activity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Neuromyelitis Optica**

Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Previously considered a variant of multiple sclerosis, it is now recognized as a distinct clinical entity.

For individuals who have NMO who receive IVIG therapy, the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. Studies have shown that IVIG treatment may
benefit patients who are refractory to first-line treatment with steroids or plasma exchange, particularly children. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation**

Myasthenia gravis (MG) is a relatively rare autoimmune disorder in which antibodies form against acetylcholine nicotinic postsynaptic receptors at the neuromuscular junction of skeletal muscles resulting in characteristic patterns of progressively reduced muscle strength with repeated use and recovery of muscle strength after a period of rest.

For individuals who have severe refractory myasthenia gravis or myasthenic exacerbation who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. Compared with plasma exchange, IVIG therapy did not show significantly improved outcomes but was better tolerated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Relapsing-Remitting Multiple Sclerosis**

Relapsing-remitting multiple sclerosis (RRMS) is an immune-mediated inflammatory disease that attacks and destroys myelinated axons in the central nervous system, resulting in variable degrees of physical disability characterized by symptomatic episodes that occur months or years apart and affect different anatomic locations.

For individuals who have RRMS who receive IVIG therapy, the evidence includes multiple RCTs and technology assessments. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. According to technology assessments, IVIG therapy is no longer considered a treatment of choice for RRMS. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Hayes concluded, “Evidence regarding the efficacy of IVIG as a treatment for MS is conflicting. There is some evidence from published studies that IVIG may reduce the frequency of acute exacerbations and provide symptomatic relief in patients with relapsing-remitting forms of MS and may lessen the pregnancy-related exacerbations of MS. However, the evidence is relatively
weak, and the effects reported are variable, measured by subjective parameters, and of small magnitude. In addition, there is no information regarding the benefits of IVIG compared with other available therapies. Moreover, the largest placebo-controlled study found no treatment effect of IVIG in patients with secondary progressive disease, and there was no evidence of benefit in patients with MS-related syndromes, including muscle group weakness and optic neuritis. There were no randomized, placebo-controlled studies of IVIG in patients with primary progressive MS.\textsuperscript{155}

**Autoimmune Mucocutaneous Blistering Diseases**

Autoimmune mucocutaneous blistering diseases are a group of conditions that manifest with blisters on the skin or mucous membranes and include pemphigus vulgaris, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, and linear IgA dermatosis.

For individuals who have autoimmune mucocutaneous blistering diseases who receive IVIG therapy, the evidence includes 2 RCTs, a systematic review, and multiple uncontrolled studies. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. A systematic review found improvements in over 90% of patients. RCTs have reported benefit in disease activity in the population as a whole (1 trial) or subgroup of patients with severe disease (1 trial). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Toxic Epidermal Necrosis and Stevens-Johnson Syndrome**

For individuals who have TEN or SJS who receive IVIG therapy, the evidence includes systematic reviews of observational studies. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. No RCTs have evaluated IVIG for TEN or SJS; most trials that have, have been uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.
**Idiopathic Inflammatory Myopathies**

Idiopathic inflammatory myopathies are a group of disorders characterized by inflammation of skeletal muscles and include dermatomyositis, polymyositis and inclusion body myositis. Polymyositis and dermatomyositis involve weakness of the proximal muscles such as the muscles of the hips and thighs, upper arms, and neck. Dermatomyositis is associated with various characteristic skin manifestations. In inclusion body myositis, the muscles most affected are those of the wrists and fingers and the front of the thigh.

**Dermatomyositis and Polymyositis**

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes 2 RCTs, multiple noncomparative observational studies, and a systematic review. Relevant outcomes are change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. In one of the RCTs, compared with placebo, IVIG therapy showed improvements in muscle strength. A large case series also noted improvements in most patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Inclusion Body Myositis**

For individuals who have inclusion body myositis who receive IVIG therapy, the evidence includes multiple RCTs. Relevant outcomes are change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy failed to show improvements in muscle strength. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

**Systemic Lupus Erythematosus**

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has protean manifestations and follows a relapsing and remitting course. It is characterized by an autoantibody response to nuclear and cytoplasmic antigens. SLE can affect any organ system, but it mainly attacks the skin, joints, kidneys, blood cells, and nervous system.
For individuals who have SLE who receive IVIG therapy, the evidence includes an RCT, multiple observational studies, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy for surrogate outcomes, data are retrospective. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Immune Optic Neuritis**

Optic neuritis is an inflammatory demyelinating condition that causes acute, usually monocular, visual loss. It is associated with multiple sclerosis, occurring in 50% of individuals with MS at some time during the course of their illness.

For individuals who have immune optic neuritis who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show improvements in vision-related outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

**Crohn Disease**

Crohn disease is an inflammatory condition of unknown etiology that can affect any portion of the gastrointestinal tract, from the mouth to the perianal area, with a wide spectrum of clinical presentations.

For individuals who have Crohn disease who receive IVIG therapy, the evidence includes multiple case reports of single patients summarized in a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.
**Hemophagocytic Lymphohistiocytosis**

Hemophagocytic lymphohistiocytosis is an uncommon but potentially fatal syndrome of excessive immune activation resulting from overactive histiocytes and lymphocytes. It may be inherited or acquired.

For individuals who have hemophagocytic lymphohistiocytosis who receive IVIG therapy, the evidence includes multiple case reports summarized in a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related mortality and morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Warm Antibody Autoimmune Hemolytic Anemia**

Also known as autoimmune hemolytic anemia, warm antibody autoimmune hemolytic anemia occurs commonly due to IgG antibodies that react with protein antigens on the red blood cell surface at body temperature.

For individuals who have warm antibody autoimmune hemolytic anemia, refractory to prednisone and splenectomy, who receive IVIG therapy, the evidence includes pooled observational data. Relevant outcomes are change in disease status, quality of life, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential benefit with IVIG therapy in select patients. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Antiphospholipid Syndrome**

Antiphospholipid syndrome is an autoimmune disease that results from the development of antibodies against phospholipid proteins, which causes venous or arterial thromboses and/or pregnancy morbidity.

For individuals who have antiphospholipid syndrome who receive IVIG therapy, the evidence includes pooled data from a registry. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential mortality benefit with IVIG therapy. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.
**Alloimmune Processes**

**Neonatal Alloimmune Thrombocytopenia**

Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet-antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage (ICH) is identified in 10% to 30% of affected neonates. Currently, screening for this condition is unavailable and, thus, thrombocytopenia is only identified at birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia and the severity of thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIG.

For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple 2 RCTs and a systematic review. Relevant outcomes are disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Compared with combination use with corticosteroids, IVIG alone did not show any additional increases in platelet counts. Multiple trials have demonstrated increased platelet counts with IVIG therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Recurrent Spontaneous Abortion**

Recurrent spontaneous abortion (RSA) is defined as 3 or more pregnancies resulting in a spontaneous abortion before 16 to 20 weeks of gestational age. Women with recurrent spontaneous abortion frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss.

For individuals who have recurrent spontaneous abortion who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are disease-specific survival, treatment-related mortality, and treatment-related morbidity. In multiple RCTs, compared with placebo, IVIG therapy alone did not show any beneficial effects in preventing spontaneous abortions. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.
**Miscellaneous**

**Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections**

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a term used to describe a subset of children whose symptoms of obsessive-compulsive disorder (or tic disorders) are exacerbated by group A streptococcal infections. This syndrome is not well-understood and diagnosis of PANDAS requires expert consultation.

For individuals who have PANDAS who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related mortality and morbidity. The trials had mixed findings and both had small sample sizes and short intervention duration. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Autism Spectrum Disorder**

Autism spectrum disorder is a neurodevelopmental disorder characterized by deficits in social communication and social interaction and restricted repetitive patterns of behavior, interests, and activities.

For individuals who have autism spectrum disorder who receive IVIG therapy, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. Although improvements were observed in 1 case series, the other two reported negative findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Complex Regional Pain Syndrome**

Complex regional pain syndrome (CRPS) is defined as a disorder of the extremities characterized by regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion.

For individuals who have CRPS who receive IVIG therapy, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown improvements in pain scores.
However, methodologic limitations restrict the conclusions drawn from data on 12 patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Alzheimer Disease**

For individuals who have Alzheimer disease who receive IVIG therapy, the evidence includes 3 RCTs. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. With the exception of a few subgroup analyses using MCI status, IVIG therapy was not significantly better than placebo for outcomes such as brain atrophy, level of plasma amyloid β 1–40, or cognition and function. Studies differed by treatment protocols, outcomes assessed, and two of the three had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Paraproteinemic Neuropathy**

Paraproteinemic neuropathy is a heterogeneous set of neuropathies characterized by the presence of paraproteins, which are immunoglobulins produced in excess by an abnormal clonal proliferation of B lymphocytes or plasma cells. Paraproteinemic neuropathy may be caused by the interaction of antibodies with specific antigenic targets on peripheral nerves or by deposition of immunoglobulins or amyloid.

For individuals who have paraproteinemic neuropathy who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG showed mild and transitory improvements in 1 trial but failed to show any improvement in another. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Chronic Fatigue Syndrome**

Chronic fatigue syndrome, aka systemic exertion intolerance disease, is a complex and controversial disease with multiple definitions.

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes an RCT and anecdotal reports. Relevant outcomes are symptoms, quality of life, and
treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown no therapeutic benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Acute Myocarditis**

Acute myocarditis is a sudden inflammation of myocardium that can occur in individuals of all ages. It is presumed to start as a viral infection, although autoimmune and idiopathic forms also occur. It remains unclear whether the primary problem is most commonly ongoing damage from virus, a post-infectious inflammatory reaction, or a combination of the two.

For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes an RCT, a quasi-randomized trial, and multiple case reports. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy failed to show improvements in event-free survival in the RCT while it showed favorable effects on rates of event-free survival in a quasi-randomized study. However, both studies were rated as very low quality and at a high risk of bias. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Refractory Recurrent Pericarditis**

Refractory recurrent pericarditis is defined as recurrent pericarditis not responding to conventional anti-inflammatories such as aspirin, nonsteroidal inflammatory drugs, corticosteroids, and colchicine.

For individuals who have refractory recurrent pericarditis who receive IVIG therapy, the evidence includes multiple case reports and case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Although improvements were observed in some patients, controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Stiff Person Syndrome**

Stiff person syndrome is a rare acquired neurologic disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, resulting in severely impaired ambulation. It is caused by increased muscle activity due to decreased inhibition of the central
nervous system. If left untreated, it can progress to cause difficulty walking and significantly impact a person's ability to perform routine, daily tasks.

For individuals who have stiff person syndrome who receive IVIG therapy, the evidence includes an RCT and multiple case reports. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown decreases in stiffness score and improvements in functional outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Noninfectious Uveitis**

Noninfectious uveitis is the inflammation of eye that results from eye trauma, anomalous immune processes, or unknown etiology.

For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. The case series (total N=28 patients) reported measurable improvements in visual acuity after IVIG therapy, but controlled studies are needed to draw conclusions about the efficacy of IVIG for this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Post-polio Syndrome**

Although polio no longer poses a major public health threat in the United States, many patients live with the sequelae of paralytic polio. Many polio survivors experience a modest decline in function and muscle strength over many years that may reflect the natural history of polio.

For individuals who have post-polio syndrome who receive IVIG therapy, the evidence includes multiple RCTs, prospective studies, and a meta-analysis. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show reductions in the severity of pain and fatigue or improvements in muscle strength. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.
Necrotizing Fasciitis

For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes an RCT. Relevant outcomes are overall survival, symptoms, functional outcomes, and treatment-related mortality and morbidity. The RCT found that, compared with placebo, IVIG therapy did not significantly improve functional outcomes, mortality rates, or other outcomes (eg, the use of life support in the intensive care unit). Additional controlled studies are needed to draw conclusions about the efficacy of IVIG for treating necrotizing fasciitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 3 physician specialty societies and 5 academic medical centers in March 2013 after this policy was under review in 2012. Input focused on intravenous immunoglobulin (IVIG) treatment for 7 rare conditions. There was consensus, or near-consensus, that IVIG is investigational for 6 of these conditions: birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, opsoclonus myoclonus, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, and polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy). Clinical input was mixed overall on the seventh condition, IVIG for treating severe anemia associated with parvovirus B19.

Additional clinical input was obtained in June 2013, focusing on severe anemia due to parvovirus B19. Input was received from 3 reviewers (all hematologists), and there was consensus that IVIG is not investigational for this indication. There was a lack of consensus among the 3 reviewers on any specific clinical or patient characteristics that can be used to select patients with severe anemia due to parvovirus B19 for treatment with IVIG and on any treatments that should be used by these patients before IVIG.
Practice Guidelines and Position Statements

**Immunodeficiency States**

**Primary Humoral Immune Deficiencies**

*National Advisory Committee on Blood and Blood Products and Canadian Blood Services*

In 2010, the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services (CBS) published guidelines on use of immunoglobulin therapy for patients with primary immune deficiency. The guidelines reported that there was sufficient evidence that immunoglobulin therapy reduces the rate of infection and hospitalization in patients with primary immune deficiency, lowers mortality, and improves quality of life. Treatment should be started at a dose of 400 to 600 mg/kg per 4 weeks for intravenous immunoglobulin (IVIG) or 100 to 150 mg/kg per week for subcutaneous immunoglobulin infusion.

*American Academy of Allergy, Asthma, and Immunology*

In 2015, the American Academy of Allergy, Asthma, and Immunology published practice parameters for the diagnosis and management of primary immunodeficiency. The Academy advised that treatment of these conditions include antibiotic prophylaxis and immunoglobulin G (IgG) replacement.

*Hematopoietic Cell Transplantation (Prophylaxis)*

In 2007, NAC and CBS published guidelines on the use of IVIG for hematologic conditions. The guidelines stated that evidence does not support the use of IVIG after hematopoietic cell transplantation.

*Acute Antibody-Mediated Rejection After Solid Organ Transplant*

In 2010, CBS and NAC developed guidelines addressing the use of IVIG for sensitized individuals undergoing solid organ transplantation. The following conclusions were issued on non-kidney solid organ transplantation:
• For patients undergoing heart transplantation, to improve graft/overall survival or to treat rejection: insufficient evidence to recommend for or against the routine use of IVIG (however, other factors may influence decision-making)

• For desensitization for patients undergoing lung transplantation or for the treatment of rejection: insufficient evidence to make a recommendation for or against the routine use of IVIG (however, other factors may influence decision-making)

• For patients undergoing liver transplantation or for the treatment of rejection/ABO-incompatible liver transplantation: insufficient evidence to make a recommendation for or against the routine use of IVIG

• For the use of IVIG for solid organ transplantation: limited methodologically rigorous evidence

• Future studies are needed to delineate the effect of IVIG on desensitization using standardized methods for desensitization; the effect of IVIG on acute rejection rates, graft survival, and overall survival; the use of the combined modality IVIG and plasmapheresis compared either to plasmapheresis or IVIG alone; and the optimum dosage of IVIG.

Chronic Lymphocytic Leukemia

The National Comprehensive Cancer Network guidelines (v.1.2019) on chronic lymphocytic leukemia recommend IVIG as supportive care for patients with chronic lymphocytic leukemia: for the treatment of autoimmune cytopenias and recurrent sinopulmonary infections (IgG levels <500 mg/dL). The guidelines recommend monitoring IVIG levels and administering monthly IVIG (0.3-0.5 g/kg) to maintain levels of 500 mg/dl.

Infections

Infections in HIV-Infected Children

In 2013, updated joint guidelines on prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children were published. The guidelines, endorsed by the American Academy of Pediatrics, the Infectious Diseases Society of America, and other agencies and societies, included the following statement: “Intravenous immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia.”
Neonatal Sepsis

The American Academy of Pediatrics published guidelines in 2012 on the management of neonates with suspected or proven early-onset bacterial sepsis. The guidelines did not address the use of IVIG to treat neonatal sepsis.

Autoimmune / Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

In 2007, NAC and CBS issued guidelines on the use of IVIG for hematologic conditions, including idiopathic thrombocytopenic purpura (ITP). Recommendations for patients with ITP are as follows:

- Adult acute ITP with bleeding: IVIG strongly recommended as a part of multimodality therapy for major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding.
- Adult acute ITP with severe thrombocytopenia but no bleeding: IVIG not recommended as first-line therapy alone, except for patients with contraindications to corticosteroids.
- Adult ITP with no or slow response to adequate dose corticosteroids: IVIG may be considered as a possible adjunctive therapy.
- Adult chronic ITP post splenectomy: IVIG may be considered as a possible adjunctive therapy as a corticosteroid-sparing measure. The minimal dose of IVIG should be used that maintains a safe platelet count. Patients should be reevaluated every 3 to 6 months, and alternative therapies to IVIG should be considered for patients who do not achieve a durable response for a minimum of 2 to 3 weeks.

Guillain-Barré Syndrome

The 2012 American Academy of Neurology (AAN) guidelines on the treatment of neuromuscular disorders concluded that IVIG is as efficacious as plasmapheresis and should be offered as a treatment option to adults with Guillain-Barré syndrome (Level A). The guidelines indicated that there was insufficient evidence to support or refute the use of IVIG in children.
The European Federation of Neurological Societies (EFNS) issued guidelines in 2008 on the use of IVIG for the treatment of neurological disorders. The guidelines stated that the efficacy of IVIG treatment of Guillain-Barré syndrome is proven (level A).

**Kawasaki Syndrome and Other Vasculitides**

The American Academy of Family Physicians (2015) and the American Heart Association (2004) have supported the use of IVIG in the treatment of Kawasaki syndrome.

**Chronic Inflammatory Demyelinating Polyneuropathy**

The 2012 AAN guidelines on the treatment of neuromuscular disorders stated that IVIG is effective and should be offered in the long-term treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) (level A). The guidelines indicated that data are insufficient to compare the efficacy of prednisone and IVIG in the treatment of CIDP.

EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders. The guidelines indicated that the efficacy of IVIG for the treatment of CIDP has been established (level A).

**Multifocal Motor Neuropathy**

The 2012 AAN guidelines on the treatment of neuromuscular disorders have stated that IVIG is probably effective and should be considered for the treatment of multifocal motor neuropathy (level B). There were insufficient data to determine the optimal treatment interval, dosing, and duration.

EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders. The guidelines indicated that the efficacy of IVIG for the treatment of multifocal motor neuropathy has been established (level A).

**Eaton-Lambert Myasthenic Syndrome**

The 2012 AAN guidelines on the treatment of neuromuscular disorders stated that IVIG is possibly effective and may be considered for treating Lambert-Eaton myasthenic syndrome (level C).
Neuromyelitis Optica

According to the Neuromyelitis Optica’s 2014 updated guidelines, high-dose IVIG is potentially beneficial in long-term treatment of neuromyelitis optica and may be used as an alternative for patients with a contraindication to one of the other treatments or, particularly, in children.\textsuperscript{146}

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

The 2012 AAN guidelines on the treatment of neuromuscular disorders concluded that IVIG therapy is probably effective in treating patients with severe myasthenia gravis and should be considered in the treatment plan (level B).\textsuperscript{59} There was insufficient evidence to compare IVIG and plasmapheresis in treatment of these patients.

EFNS issued guidelines in 2008 on the use of IVIG to treat neurologic disorders.\textsuperscript{143} The guidelines indicated that the efficacy of IVIG for the treatment of acute exacerbations of myasthenia gravis and short-term treatment of severe myasthenia gravis has been established (level A).

Relapsing-Remitting Multiple Sclerosis

In 2002, AAN published a technology assessment on therapies for multiple sclerosis.\textsuperscript{79} The assessment was reviewed and reaffirmed in 2018. The assessment offered the following recommendations on IVIG:

- Studies of IVIG to date have generally involved small numbers of patients, have lacked complete data on clinical and MRI (magnetic resonance imaging) outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIG reduces the attack rate in relapsing-remitting multiple sclerosis (type C recommendation: possibly effective, ineffective, or harmful).

- Current evidence suggests that IVIG is of little benefit with regard to slowing disease progression (type C recommendation: possibly effective, ineffective, or harmful).

EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders.\textsuperscript{143} The guidelines recommended IVIG as second- or third-line therapy for relapsing-remitting multiple sclerosis, if conventional immunomodulatory therapies are not tolerated (level B).
**Autoimmune Mucocutaneous Blistering Diseases**

There are currently no guidelines specific to the treatment of autoimmune mucocutaneous blistering disease.

**Toxic Epidermal Necrosis and Stevens-Johnson Syndrome**

In 2016, the British Association of Dermatologists published guidelines on the management of toxic epidermal necrosis and Stevens-Johnson syndrome. These guidelines are accredited by the National Institute for Health and Care Excellence. The guidelines indicated that evidence for the use of IVIG for the treatment of toxic epidermal necrosis and Stevens-Johnson syndrome is not of sufficient quality or consistency.

**Idiopathic Inflammatory Myopathies**

The 2012 AAN guidelines on IVIG for treating neuromuscular disorders have stated that IVIG is possibly effective and may be considered as a treatment for nonresponsive dermatomyositis (an idiopathic inflammatory condition) in adults (level C).

EFNS issued guidelines in 2008 on the use of IVIG for treating neurologic disorders. The guidelines recommended IVIG in combination with prednisone as a second-line treatment for dermatomyositis (level B).

**Immune Optic Neuritis**

Optic neuritis presents as a manifestation of multiple sclerosis (see the **Relapsing-Remitting Multiple Sclerosis** section above).

**Alloimmune Processes**

**Neonatal Alloimmune Thrombocytopenia**

In 2007, NAC and CBS published guidelines on the use of IVIG for hematologic conditions.
• Treatment of fetus: Evidence is limited and weak but given that the condition is rare and the consequences are serious, IVIG was deemed an appropriate option and should be considered the standard of care.

• Treatment of newborn: First line therapy should be antigen-negative compatible platelets, with IVIG considered as adjunctive therapy.

**Recurrent Spontaneous Abortion**

In 2011, the Royal College of Obstetricians and Gynecologists issued guidelines on the treatment of recurrent first- and second-trimester miscarriages. The guidelines, accredited by the National Institute for Health and Care Excellence, concluded that IVIG does not improve the live birth rate in women with recurrent miscarriages (level A).

**Miscellaneous**

**Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections**

In 2007, NAC and CBS convened a panel of national experts to develop evidence-based practice guidelines on the use of IVIG for neurologic conditions. The panel recommended the use of IVIG for the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The optimal dose and duration of treatment is uncertain.

**Autism Spectrum Disorder**

The 2007 NAC and CBS guideline on neurologic conditions did not recommend IVIG for autism.

In 2014, the American Academy of Child and Adolescent Psychiatry published practice parameters on the assessment and treatment of autism spectrum disorder. The Academy parameters did not address the use of IVIG for the treatment of autism spectrum disorder.
**Chronic Fatigue Syndrome**

In 2007, the National Institute for Health and Care Excellence issued guidance on the diagnosis and management of chronic fatigue syndrome.\(^{151}\) The guidance was reviewed in 2014, and no changes to the recommendations were made at that time. The guidance indicated that there is no cure for chronic fatigue syndrome and that symptoms (pain, sleep disturbances, physical limitations, and debilitating fatigue) should be managed under supervision of a specialist. The use of IVIG was not addressed.

**Viral Myocarditis**

In 2013, the American College of Cardiology Foundation and the American Heart Association issued joint guidelines on the management of heart failure.\(^{152}\) The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

**Stiff Person Syndrome**

The EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders.\(^{143}\) The guidelines indicated that IVIG seems to have a favorable effect in the treatment of stiff person syndrome (Level A).

**Post-polio Syndrome**

EFNS updated its guidelines on the definition and management of post-polio syndrome in 2011.\(^{153}\) The guidelines indicated that IVIG could have a modest therapeutic effect on post-polio syndrome, though there were limitations to the study evidence (small sample size, inadequate comparators, appropriate dosage). Due to these limitations, EFNS concluded that IVIG cannot be recommended as a standard treatment.

**Medicare National Coverage**

In 2002, the Centers for Medicare & Medicaid Services published a national coverage determination on IVIG for treatment of autoimmune mucocutaneous blistering diseases.\(^{154}\) IVIG is covered for patients with biopsy-proven disease who have failed conventional therapy or for
whom conventional therapy is contraindicated, and to supplement conventional therapy in patients with rapidly progressive disease.

No national coverage determinations on other uses of IVIG or subcutaneous immune globulin were identified.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in *Table 1*.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT00892112a</td>
<td>Intravenous Immunoglobulin (IVIg) for Parvovirus B19(PVB19) Mediated Cardiomyopathy</td>
<td>50</td>
<td>Jan 2019</td>
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<tr>
<td>NCT03065244</td>
<td>KIDCARE (Kawasaki Disease Comparative Effectiveness Trial) (KIDCARE)</td>
<td>250</td>
<td>Sep 2020</td>
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<tr>
<td>NCT02176863a</td>
<td>Study of the Efficacy and Safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in Patients With Post-polio Syndrome (FORCE)</td>
<td>210</td>
<td>Jun 2021</td>
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<tr>
<td>NCT03194815</td>
<td>IVIG and Rituximab in Antibody-associated Psychosis - SINAPPS2 (SINAPPS2)</td>
<td>80</td>
<td>Dec 2021</td>
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<tr>
<td>NCT02899702</td>
<td>Effectiveness of Intravenous Immunoglobulins (IVIG) in Toxic Shock Syndromes in Children (IGHN2)</td>
<td>156</td>
<td>Apr 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.  
*a* Denotes industry-sponsored or cosponsored trial.

**Regulatory Status**

Several IVIG products have been approved by the U.S. Food and Drug Administration (FDA). They include Bivigam® (Biotest) Carimune® (CSL Behring AG), Flebogamma DIF® (Instituto Grifols), GammaSTAN S/D® (Grifols Therapeutics), Gammagard Liquid® (Baxter), Gammagard
S/D® (Baxter), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), and Privigen® (CSL Behring).¹

Several subcutaneous immunoglobulin products have been approved by FDA. They include Gammagard Liquid® (Baxter), Gamunex-C® (Grifols Therapeutics), Cuvitru® (Baxalta), Hizentra® CSL (Behring AG), Hyqvia® (Baxter), and Vivaglobin® CSL (Behring GmbH).¹

At least 1 IVIG product is FDA-approved to treat the following conditions¹:

- Primary humoral immunodeficiency
- Multifocal motor neuropathy
- B-cell chronic lymphocytic leukemia
- Immune (aka idiopathic) thrombocytopenic purpura
- Kawasaki syndrome
- Chronic inflammatory demyelinating polyneuropathy

References


11. Kozlowski T, Andreoni K. Limitations of rituximab/IVIg desensitization protocol in kidney transplantation; is this better than a tincture of time? Ann Transplant. Apr-Jun 2011;16(2):19-25. PMID 21716181


<table>
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<tr>
<th>Date</th>
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<tr>
<td>09/01/98</td>
<td>Add to Therapy Section - New Policy</td>
</tr>
<tr>
<td>03/22/99</td>
<td>Replace Policy - Added myasthenia gravis to medically necessary indications</td>
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<tr>
<td>02/12/02</td>
<td>Replace Policy - Updated policy approved by P&amp;T committee January 2002. No change to policy statement, added reference.</td>
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<tr>
<td>02/11/03</td>
<td>Replace Policy - Updated policy approved by P&amp;T committee February 2003. No change to policy statement.</td>
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<tr>
<td>07/08/03</td>
<td>Replace Policy - Policy replaces CP.MP.PR.8.01.103. Policy updated; added 2 medically necessary myasthenia gravis indications and additional information in the rationale section on autoimmune mucocutaneous blistering diseases, stiff person syndrome, organ transplant rejection, non-infectious uveitis, and demyelinating optic neuritis.</td>
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<td>05/11/04</td>
<td>Replace Policy - Policy replaces CP.MP.BC.8.01.05. Policy reviewed and updated by P&amp;T committee 3/24/04; policy statements concerning medically necessary and investigational conditions significantly revised. Policy guidelines, rationale, and references updated.</td>
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<td>Replace Policy - Policy renumbered from PR.8.01.103. No changes to dates.</td>
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<td>Replace Policy - Scheduled review; policy reviewed and approved by P&amp;T 3/22/05; policy statement changed to remove autoimmune hemolytic anemia from investigational and add B-cell malignancy as medically necessary.</td>
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<td>04/11/06</td>
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<td>06/02/06</td>
<td>Disclaimer and Scope update - No other changes.</td>
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<td>12/21/06</td>
<td>Codes Updated - No other changes.</td>
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<td>05/08/07</td>
<td>Replace Policy - Policy updated with literature review; references added. Policy statement updated to include pure red cell aplasia as a medically necessary off-label indication for IVlg. Reviewed by P&amp;T on March 27, 2007.</td>
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<tr>
<td>08/23/07</td>
<td>Codes Updated - No other changes.</td>
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<td>03/11/08</td>
<td>Cross Reference Updated - No other changes.</td>
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<td>Replace Policy - Policy updated with literature search; no change to the policy statement. Reviewed by P&amp;T committee on March 25, 2008. Code Q4097 added.</td>
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<td>01/13/09</td>
<td>Code Updates - Code added, J1459; effective 1/1/09.</td>
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<td>06/09/09</td>
<td>Replace Policy - Policy updated with literature search. Policy updated to include b cell</td>
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05/08/07: Replace Policy - Policy updated with literature review; references added. Policy statement updated to include pure red cell aplasia as a medically necessary off-label indication for IVlg. Reviewed by P&T on March 27, 2007.

08/23/07: Codes Updated - No other changes.

03/11/08: Cross Reference Updated - No other changes.

05/13/08: Replace Policy - Policy updated with literature search; no change to the policy statement. Reviewed by P&T committee on March 25, 2008. Code Q4097 added.

01/13/09: Code Updates - Code added, J1459; effective 1/1/09.

06/09/09: Replace Policy - Policy updated with literature search. Policy updated to include b cell.
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<td>03/09/10</td>
<td>Replace Policy - Policy updated with literature search. Multiple Myeloma deleted from the Investigational criteria list in the policy statement. Reviewed by Pharmacy in January 2010.</td>
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<td>08/10/10</td>
<td>Replace Policy - Policy updated to include treatment of antibody-mediated rejection or high risk of antibody-mediated rejection of solid organ transplants is considered medically necessary. Codes added: 90284, 96365, 96366, 96369, 96370, 96371; J1567, J1572.</td>
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<td>05/10/11</td>
<td>Replace Policy - PANDAS added to the list of investigational applications within the Policy section; Rationale updated in support of this addition. References added.</td>
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<tr>
<td>07/12/11</td>
<td>Replace Policy - Policy updated policy statements for Hizentra: considered medically necessary for FDA-approved indication for txt of PIDD; considered medically necessary for subcutaneous administration as equal to any other IVIG drug as listed as medically necessary in this policy; and considered investigational for any other indication. Description and Rationale sections updated; reference added. Reviewed by P&amp;T in May 2011. Title changed; “Intravenous” removed, to leave the title as “Immune Globulin Therapy”.</td>
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<td>01/27/12</td>
<td>Codes updated; HCPCS codes J1557 and J7183 added.</td>
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<td>02/21/12</td>
<td>Code update; HCPCS code J1559 added to the policy.</td>
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<td>04/10/12</td>
<td>Replace policy. Policy rewritten and reorganized, merging content from 8.01.05 (not an active policy). Policy Guidelines updated to support new policy statements. Reviewed by P&amp;T on March 27, 2012. Codes added: J1599 and 90284; code J1567 removed. This policy was approved with a 90-day hold for provider notification and is effective September 1, 2012.</td>
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<td>Update Related Policies. Add 5.01.526.</td>
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<td>Replace policy. Policy updated with literature search through February 12, 2013. Clinical input added. References 30, 44, 83-86, 97 and 98 added; other references renumbered or removed. PANDAs moved to investigational from medically necessary; birdshot retinopathy added as investigational; laboratory testing section removed from policy. Rationale updated.</td>
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<td>Annual Review. Organ transplant rejection deleted from investigational list because it has been considered medically necessary since 2010.</td>
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<td>08/11/15</td>
<td>Interim Review. Policy tabled at August MPC meeting for further revisions and formatting changes.</td>
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<td>Annual Review. Diagnoses added to Medically Necessary statement: Hemolytic disease of the fetus and newborn (aka erythoblastosis fetalis), Stevens-Johnson syndrome, toxic epidermal necrolysis. Clarified B-Cell-like pathology indications under hematologic subheading. Postpolio syndrome added to Investigational policy</td>
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statement. Policy statement for treatment of relapsing/remitting multiple sclerosis changed from medically necessary to not medically necessary. Diagnostic criteria for CIDP and MMN moved from the Appendix to the Policy Guidelines section. Subheading for Initial and Ongoing Authorization of Coverage added to Policy Guidelines. All lists put in alphabetical order. Policy updated with literature review through April 20, 2015. References 26, 27, 53, 73-74, 80, 91 added. Policy statements revised as noted. Removed CPT codes 96360, 96361, 96365, 96366, 96399, 95370, 96371; all PX/DX ICD9/ICD10 codes; and HCPCS code J7183 – these are not reviewed in relationship to this policy.


01/20/16 Coding update. New HCPCS code J1575, effective 1/1/16, added to policy.

01/27/16 Minor edit. Reordered codes in coding table for numeric order.

02/01/16 Coding update. HCPCS code J1556 added to policy.

05/01/16 Annual Review, approved April 12, 2016. Policy updated with criteria for site of service for IV infusion of IVIG – considered medically necessary in hospital-based outpatient center only when criteria are met. Policy section reformatted for purposes of clarity and understandability.

05/17/16 Minor edit. Corrected typo related to INCAT sensory sum score.

07/01/16 Interim Review, approved June 14, 2016. Correction made to site of service administration criteria.

10/01/16 Interim update, approved September 13, 2016. Coding updated. Policy moved into new policy format.

11/01/16 Interim Review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages.

02/01/17 Annual Review, approved January 10, 2017. Content adopted from BCBSA most recent update, with literature review through October 2016. New covered indications include stiff-person syndrome, polymyositis, and Wegener’s granulomatosis, patients with CLL who meet criteria, and neuromyelitis optica. The following were changed from medically necessary to investigational: treatment of antibody mediated rejection following solid organ transplantation, patients with neonatal sepsis (prophylaxis or treatment), patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Coding update; removed 90281, 96365, 96366, 96369, 96370 and 96371.

04/01/17 Interim Review, approved March 14, 2017. Five indications, intended for inclusion in the January 2017 update, unintentionally omitted. These 5 indications: toxic shock syndrome (references 36-39 added), warm antibody autoimmune hemolytic anemia (reference 106 and 107 added), antiphospholipid syndrome (references 108 added), X-linked hyper-IgM syndrome, and ataxia telangiectasia. Section on dosing related to rituximab was deleted because it was a typographical error.
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<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/17</td>
<td>Formatting update; added hyperlinks to Medical Necessity sections.</td>
</tr>
<tr>
<td>09/12/17</td>
<td>Formatting updated for clarity in Policy Guidelines section.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Interim Review, approved October 10, 2017. Policy updated to address different therapy approach for ITP for Pediatrics versus Adults based on specialty input. Additional detail for alternative treatments added to policy. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the patient’s home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.</td>
</tr>
<tr>
<td>01/01/18</td>
<td>Coding update; added HCPCS code J1555 (new code effective 1/1/18).</td>
</tr>
<tr>
<td>02/14/18</td>
<td>Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.</td>
</tr>
<tr>
<td>02/20/18</td>
<td>Coding update; removed HCPCS code J1460.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 18, 2018. Clarified initial and ongoing authorization criteria. Policy updated with literature search. Medically necessary statement for neuromyelitis optica changed to state when there is contraindication to, or lack of response to, “first-line treatment (particularly in children)”. Removed references 95, 96, 122, and 159 as well as duplicate references. Added references 84, 118, 126, and 138. Policy statements otherwise unchanged.</td>
</tr>
<tr>
<td>06/01/18</td>
<td>Minor update. Removed IVIG bullet from adult ITP criteria that had been added incorrectly from a related pharmacy policy.</td>
</tr>
<tr>
<td>07/01/18</td>
<td>Interim Review, approved June 22, 2018. Reference 155 added. Policy statement updated to read “IVIG therapy is considered not medically necessary for patients with any type of multiple sclerosis.” The words relapsing-remitting were removed.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, the Site of Service criteria was updated for clarity.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>Interim Review, approved December 13, 2018. References 156, 157 added. Medically necessary indications added for those undergoing/undergone CAR-T cell therapy and for specific antibody deficiency (SAD) and ITP in an adult with a platelet count less than 10,000/mm³. Additional edit approved December 19, 2018. Multiple myeloma is considered investigational; this was inadvertently not reflected in previous policy history.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.
**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladiann. Avi sila a kapab genyen enfòmasyon enpòtan konsàn an apliaksiyon w fam osa konséna kouvètè asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pou an kòk aksyon avan sèten dat limit pou ka jenbe kouvètè asirans sante w la osa pou yo ka ède w avèk repson yo. Se dwa w pou resewwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou pèye ou pa sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaa ket naglaon iti Napagete nga Impormasion. Daytoy a pakdaa mabalin nga adda ket naglaon iti napagete nga impormasion maipanggep i apliaksiyon yowo coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a peta ini daytoy a pakdaa. Mabalin nga adda rampang nga aramideny nga adda sambay dagiti partikular a naituding nga adda napaw tapo napatgalaineyo ti coverage ti sal-anayo yowo tulog kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulog iti bakodyo a pagasaso nga awan ti bayadangon. Tunwagaw iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Japanese (Japanese): この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれています。この通知に記載されている情報は重要であることをご確認ください。健康保険や治療サポートを維持するには、定期的に行なうことをお勧めします。これにより、あなたの保険の詳細を検証し、必要に応じて更新することができます。


Punjabi (Punjabi): ਇਸ ਵਿਚ ਸੰਨਾਈ ਵਧੀ ਧਾਰਾਵਾਂ ਦੀ ਵਪਾਰ ਕਰਨ ਵਾਲੀਆਂ ਸੂਚਿਆਂ ਦੀ ਤਸਵੀਰ ਨਹੀਂ ਹੈ। ਇਸ ਵਿਚ ਛੋਟੀ ਸੂਚਿਆਂ ਦੀ ਵਪਾਰ ਕਰਨ ਵਾਲੀਆਂ ਸੂਚਿਆਂ ਦੀ ਤਸਵੀਰ ਨਹੀਂ ਹੈ। ਇਸ ਵਿਚ ਵਧੀ ਧਾਰਾਵਾਂ ਦੀ ਵਪਾਰ ਕਰਨ ਵਾਲੀਆਂ ਸੂਚਿਆਂ ਦੀ ਤਸਵੀਰ ਨਹੀਂ ਹੈ। ਇਸ ਵਿਚ ਵਧੀ ਧਾਰਾਵਾਂ ਦੀ ਵਪਾਰ ਕਰਨ ਵਾਲੀਆਂ ਸੂਚਿਆਂ ਦੀ ਤਸਵੀਰ ਨਹੀਂ ਹੈ। ਇਸ ਵਿਚ ਵਧੀ ਧਾਰਾਵਾਂ ਦੀ ਵਪਾਰ ਕਰਨ ਵਾਲੀਆਂ ਸੂਚਿਆਂ ਦੀ ਤਸਵੀਰ ਨਹੀਂ ਹੈ। 

Farsi (Farsi): ابن اعلامیه‌ای می‌شود. این اعلامیه می‌تواند علائمی را جایگزین کند که نتیجه‌ی آن در زنده‌مانده نیست. این اعلامیه تنها به‌طور کلی می‌تواند این اعلامیه را جایگزین کند که نتیجه‌ی آن در زنده‌مانده نیست. این اعلامیه تنها به‌طور کلی می‌تواند این اعلامیه را جایگزین کند که نتیجه‌ی آن در زنده‌مانده نیست. این اعلامیه تنها به‌طور کلی می‌تواند این اعلامیه را جایگزین کند که نتیجه‌ی آن در زنده‌مانده نیست. این اعلامیه تنها به‌طور کلی می‌تواند این اعلامیه را جایگزین کند که نتیجه‌ی آن در زنده‌مانده نیست. 
