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.
Review for medical necessity of select intravenous (IV) and injectable therapy services when the patient is aged 13 years or older will include:

- **Determination of medical necessity for the appropriate place of service of service**
  (where the drug will be given to the patient: in a hospital-based outpatient setting or in an alternate site, eg, infusion center, physician’s office, in the patient’s 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
- 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

<table>
<thead>
<tr>
<th>Site of Service Administration</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically necessary sites of service</td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</td>
</tr>
<tr>
<td>Physician’s Office</td>
<td></td>
</tr>
<tr>
<td>Infusion Center</td>
<td></td>
</tr>
<tr>
<td>Home Infusion</td>
<td></td>
</tr>
<tr>
<td>Hospital-based outpatient</td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</td>
</tr>
<tr>
<td>These are the preferred medically necessary sites of service for specified drugs.</td>
<td></td>
</tr>
<tr>
<td>Site of Service Administration</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>setting</strong></td>
<td>be covered in the most appropriate, safe and cost effective site:</td>
</tr>
<tr>
<td>• Outpatient hospital IV infusion department</td>
<td>• This site is considered <strong>medically necessary</strong> only when the following criteria are met:</td>
</tr>
<tr>
<td>• Hospital-based outpatient clinical level of care</td>
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<tr>
<td><strong>Hospital-based outpatient setting</strong></td>
<td>These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the above criteria are not met.</td>
</tr>
<tr>
<td>• Outpatient hospital IV infusion department</td>
<td></td>
</tr>
<tr>
<td>• Hospital-based outpatient clinical level of care</td>
<td></td>
</tr>
</tbody>
</table>
# Intravenous Immune Globulin (IVIg) Therapy

## Condition
### Medical Necessity

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

### Primary immunodeficiency states:
- Ataxia telangiectasia
- Common variable immunodeficiency
- Congenital agammaglobulinemia
- Hypogammaglobulinemia
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- X-linked agammaglobulinemia
- X-linked hyperimmunoglobulinemia M syndrome

**IVIg therapy may be considered medically necessary when items 1, 2, and 3 are present:**

1. Laboratory evidence of immunoglobulin deficiency indicated by:
   - Agammaglobulinemia (total immunoglobulin G [IgG] <200 mg/dL)
   - Persistent hypogammaglobulinemia (total IgG <400 mg/dL, or at least 2 standard deviations below normal, on at least 2 occasions)
   - Absence of B lymphocytes

2. Documented inability to mount an adequate immunologic response to inciting antigens as indicated by:
   - Lack of appropriate rise in antibody titer following a polysaccharide antigen
   - Lack of appropriate rise in antibody titer following a protein antigen

3. Persistent and severe infections, despite treatment with prophylactic antibiotics

### Individual with hematopoietic cell transplantation

**IVIg therapy may be considered medically necessary when IgG levels 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
  - Transplant (ABO) incompatible organ

### Infections

**Chronic lymphocytic leukemia**

**IVIg therapy may be considered medically necessary**
<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><strong>diagnosis and persistent bacterial infection</strong></td>
<td><strong>when:</strong></td>
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<tr>
<td></td>
<td>• the IgG level is less than 400 mg/dL</td>
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<tr>
<td></td>
<td><strong>AND</strong></td>
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<td></td>
<td>• There are persistent infections</td>
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<tr>
<td><strong>Children with HIV to prevent opportunistic infections</strong></td>
<td><strong>IVIg therapy may be considered medically necessary when the IgG level is less</strong></td>
</tr>
<tr>
<td></td>
<td><strong>than 400 mg/dL</strong></td>
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<tr>
<td><strong>Severe anemia due to human parvovirus B19</strong></td>
<td><strong>IVIg therapy may be considered medically necessary with documented diagnosis.</strong></td>
</tr>
<tr>
<td><strong>Toxic Shock Syndrome</strong></td>
<td><strong>IVIg therapy may be considered medically necessary with documented diagnosis.</strong></td>
</tr>
<tr>
<td><strong>Autoimmune / Inflammatory Conditions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Autoimmune mucocutaneous blistering diseases</strong></td>
<td><strong>IVIg therapy may be considered medically necessary for severe progressive</strong></td>
</tr>
<tr>
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<td><strong>disease, and the patient has failed treatment with conventional</strong></td>
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<tr>
<td></td>
<td><strong>agents such as corticosteroids, azathioprine, and cyclophosphamide.</strong></td>
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<tr>
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<td><strong>IVIG therapy is considered not medically necessary for patients with any type</strong></td>
</tr>
<tr>
<td></td>
<td><strong>of multiple sclerosis.</strong></td>
</tr>
<tr>
<td><strong>Idiopathic thrombocytopenic purpura (ITP)- Adults</strong></td>
<td><strong>Platelet count is &lt;30,000/ mm3 and any of the following medically necessary</strong></td>
</tr>
<tr>
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<td><strong>situations present:</strong></td>
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<td>• Need to rapidly increase platelets due to bleeding, major surgery planned, or</td>
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<td></td>
<td><strong>risk of cerebral bleeding</strong></td>
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<td></td>
<td><strong>OR</strong></td>
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<td></td>
<td>• Not a candidate for splenectomy, or experienced relapse post splenectomy</td>
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<td><strong>AND</strong></td>
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<td></td>
<td>• Failure, contraindication, or intolerance to corticosteroids*</td>
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<tr>
<td></td>
<td>*<strong>Note:</strong>  See 5.01.566- Pharmacotherapy of Thrombocytopenia for more details</td>
</tr>
<tr>
<td><strong>Idiopathic thrombocytopenic purpura (ITP)- Pediatric</strong></td>
<td><strong>Platelet count is &lt;30,000/mm3 and any of the following medically necessary</strong></td>
</tr>
<tr>
<td></td>
<td><strong>situations are present:</strong></td>
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<tr>
<td></td>
<td>• Need to rapidly increase platelets due to bleeding, major surgery planned, or</td>
</tr>
<tr>
<td></td>
<td><strong>risk of cerebral bleeding</strong></td>
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<td></td>
<td><strong>OR</strong></td>
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<tr>
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<td>• Not a candidate for splenectomy, or experienced relapse post splenectomy</td>
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<td><strong>AND</strong></td>
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<td></td>
<td>• Failure, contraindication, or intolerance to corticosteroids*</td>
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<td>*<strong>Note:</strong>  See 5.01.566- Pharmacotherapy of Thrombocytopenia for more details</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
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<tr>
<td>----------------------------------------------------</td>
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</tr>
<tr>
<td>IVIg therapy is subject to review for site of service administration.</td>
<td>major surgery planned, or risk of cerebral bleeding</td>
</tr>
<tr>
<td></td>
<td>• Prevention of bleeding in first 12 months after diagnosis</td>
</tr>
<tr>
<td>Adults with Guillain-Barré syndrome</td>
<td>IVIg therapy may be considered medically necessary as an equivalent alternative to plasma exchange</td>
</tr>
<tr>
<td>Kawasaki syndrome</td>
<td>IVIg therapy may be considered medically necessary with documented diagnosis.</td>
</tr>
<tr>
<td>Wegener granulomatosis (GPA)</td>
<td>IVIg therapy may be considered medically necessary with documented diagnosis.</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy with progressive symptoms for at least 2 months</td>
<td>IVIg therapy may be considered medically necessary with diagnosis based on:</td>
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<tr>
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<td>• 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</td>
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<td>• Electrophysiologic findings indicate demyelinating neuropathy (3 of the following 4 criteria are met per the American Academy of Neurology):</td>
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<tr>
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<td>o Partial conduction block* of ≥ 1 motor nerve</td>
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<td>o Reduced conduction velocity* of ≥ 2 motor nerves</td>
</tr>
<tr>
<td></td>
<td>o Prolonged distal latency* of ≥ 2 motor nerves</td>
</tr>
<tr>
<td></td>
<td>o Prolonged F-wave latencies* of ≥ 2 motor nerves or the absence of F waves</td>
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<tr>
<td></td>
<td>• Other causes of demyelinating neuropathy have been excluded (Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin, hereditary demyelinating neuropathy. Prominent sphincter disturbance, MMN, IgM monoclonal gammopathy, and others</td>
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<td>• If available, results of other testing to support diagnosis should be provided.</td>
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<td>o Cerebrospinal fluid (CSF) examination demonstrating elevated CSF protein with leukocyte count &lt;10/mm3</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
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<td>-----------------------------------------------</td>
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</tbody>
</table>
| IVIg therapy is subject to review for site of service administration. | o MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses  
 o Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis |
<p>| Multifocal motor neuropathy                   | IVIg therapy may be considered medically necessary with documented diagnosis, and symptoms present for one month.                                |
| Eaton-Lambert myasthenic syndrome             | IVIg therapy may be considered medically necessary when the patient fails to respond to anticholinesterase medications (mestinon), corticosteroids, and/or azathioprine. |
| Neuromyelitis optica                         | IVIg therapy may be considered medically necessary when there is contraindication to, or lack of response to first-line treatment, such as steroids or plasma exchange. |
| Severe refractory myasthenia gravis          | 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. |
| Myasthenic exacerbation (ie, acute episode of respiratory muscle weakness) | IVIg therapy may be considered medically necessary when plasma exchange is contraindicated or as an alternative. |
| Dermatomyositis or polymyositis              | IVIg therapy may be considered medically necessary when:                                                                                         |
|                                               | • The disease is refractory to treatment with corticosteroids                                                                                   |
|                                               | <strong>AND</strong>                                                                                                                                         |
|                                               | • IVIG used in combination with other immunosuppressive agents                                                                               |
| Warm antibody hemolytic anemia                | IVIg therapy may be considered medically necessary when the disease is refractory to other therapies:                                            |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
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</thead>
<tbody>
<tr>
<td>IVIg therapy is subject to review for site of service administration.</td>
<td>azathioprine, cyclophosphamide, prednisone, plasmapheresis, or splenectomy.</td>
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<tr>
<td>Antiphospholipid syndrome</td>
<td>IVIg therapy may be considered medically necessary with documented diagnosis.</td>
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<tr>
<td>Alloimune Processes</td>
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<tr>
<td>Neonatal alloimmune thrombocytopenia</td>
<td>IVIg therapy may be considered medically necessary with documented diagnosis.</td>
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<tr>
<td>Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis)</td>
<td>IVIg therapy may be considered medically necessary with documented diagnosis.</td>
</tr>
<tr>
<td>Miscellaneous</td>
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<tr>
<td>Stiff person syndrome</td>
<td>IVIg therapy may be considered medically necessary when all of the following are present:</td>
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<td>- The diagnosis is based on history and positive antibody tests for anti- GAD, or anti- amphiphysin, and EMG test AND</td>
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<td>- The patient has significant disability (uses walker or cane) AND</td>
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<tr>
<td></td>
<td>- The patient has not improved with diazepam or baclofen</td>
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<tr>
<td>Immunodeficiency states</td>
<td>IVIG therapy is considered investigational for patients who have received a solid organ transplant for:</td>
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<tr>
<td></td>
<td>- Prophylaxis or treatment of acute antibody mediated rejection</td>
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<tr>
<td>Infections</td>
<td>IVIG therapy is considered investigational for:</td>
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<tr>
<td></td>
<td>- Patients with neonatal sepsis (prophylaxis or treatment)</td>
</tr>
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<td></td>
<td>- Patients (adults) with sepsis</td>
</tr>
<tr>
<td>Autoimmune / inflammatory conditions</td>
<td>IVIG therapy is considered investigational for:</td>
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<tr>
<td></td>
<td>- Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
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<td>- Patients with inclusion body myositis</td>
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<td></td>
<td>- Patients with systemic lupus erythematosus</td>
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<tr>
<td>Condition</td>
<td>Investigational</td>
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<tr>
<td>• Patients with immune optic neuritis</td>
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<tr>
<td>• Patients with Crohn disease</td>
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<tr>
<td>• Patients with hemophagocytic lymphohistiocytosis</td>
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<tr>
<td>Alloimmune processes</td>
<td><strong>IVIG therapy is considered investigational for:</strong></td>
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<td>• Patients with recurrent spontaneous abortion</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td><strong>IVIG therapy is considered investigational for:</strong></td>
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<tr>
<td></td>
<td>• Patients with pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS)</td>
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<td></td>
<td>• Patients with autism spectrum disorder</td>
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<td></td>
<td>• Patients with complex regional pain syndrome</td>
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<td>• Patients with Alzheimer disease</td>
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<td>• Patients with paraproteinemic neuropathy</td>
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<td></td>
<td>• Patients with chronic fatigue syndrome</td>
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<td>• Patients with acute myocarditis</td>
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<td>• Patients with refractory recurrent pericarditis</td>
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<td>• Patients with noninfectious uveitis</td>
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<td></td>
<td>• Patients with postpolio syndrome</td>
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<tr>
<td></td>
<td>• Miscellaneous conditions: thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, paraneoplastic syndromes, epilepsy, chronic sinusitis, asthma, aplastic anemia, Diamond-Blackfan anemia, red cell aplasia, acquired factor VIII inhibitors, acute lymphoblastic leukemia, multiple myeloma, immune-mediated neutropenia, nonimmune thrombocytopenia, cystic fibrosis, recurrent otitis media, diabetes mellitus, Behçet syndrome, adrenoleukodystrophy, organ transplant rejection, Fisher syndrome, IGG subclass deficiency, opsoclonus-myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy), other vasculitides besides Kawasaki disease, including polyarteritis nodosa, Goodpasture syndrome, and vasculitis associated with other connective tissue diseases</td>
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</table>
Subcutaneous Immune Globulin (SC Ig) Therapy

### Condition

<table>
<thead>
<tr>
<th>Medical Necessity</th>
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</thead>
<tbody>
<tr>
<td><strong>Conditions where IVIG is covered</strong></td>
</tr>
<tr>
<td>Subcutaneous immune globulin (SC Ig) therapy may be considered medically necessary for any condition where IVIG would otherwise be covered.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigational</th>
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</thead>
<tbody>
<tr>
<td><strong>All others diagnoses</strong></td>
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<tr>
<td>Other applications of SC Ig therapy are considered investigational.</td>
</tr>
</tbody>
</table>

### Approval

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>Initial authorization</strong></td>
</tr>
<tr>
<td>The initial authorization will be for 6 months unless otherwise indicated (eg, in bone marrow transplant).</td>
</tr>
<tr>
<td><strong>Re-authorization</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

### 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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<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>90284</td>
<td>Immune globulin (SCig), human, for use in subcutaneous infusions, 100 mg, each</td>
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<tr>
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<td><strong>HCPCS</strong></td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, non-lyophilized (eg, liquid), 500 mg</td>
</tr>
<tr>
<td>J1555</td>
<td>Injection, immune globulin (Cuvitru), 100 mg (new code effective 1/1/18)</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>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

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

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 criterion is 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, this policy is limited to patients above the age of 13.
Benefit Application

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

Evidence Review

Background

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immunodeficiency states and a variety of 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 either 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.
Review of Evidence

This current literature search update is through August 2017. A summary of the identified literature is presented next.

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.

In 2010, the National Advisory Committee on Blood and Blood Products (NAC) and Canadian Blood Services (CBS) published a guideline on use of immunoglobulin therapy for patients with primary immune deficiency; recommendations were based on a systematic review of evidence by a panel of experts. The search identified 3 RCTs, several cohort studies, and numerous case series.

Clinical immunologists have questioned whether having a low serum immunoglobulin G (IgG) subclass is a true immunodeficiency disease. The rationale is that low serum IgG subclass levels may be found with more sensitive assays available today, and these individuals may be otherwise healthy.

For individuals with immunodeficiencies, both intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) are effective. Use of SCIG for the treatment of primary immunodeficiencies was approved by the Food and Drug Administration (FDA) based on an open-label, nonrandomized, prospective, multicenter study. Generally, many 10% IVIG solutions can be administered subcutaneous or intravenous but more concentrated products (eg, 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse effects and provides more stable serum IgG levels. In contrast, SCIG have not been studied as extensively in autoimmune/inflammatory disorders. This is a covered indication.
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.

The initial use of immunoglobulin for prophylaxis in HCT was based on the randomized controlled trial (RCT) by Sullivan et al in 369 patients undergoing HCT. The trial showed that neither survival nor risk of relapse was altered by IVIG. However, IVIG treatment was associated with a reduction in the incidence of acute graft-versus-host disease (GVHD) compared to controls (51% vs 34%) and deaths due to transplant-related causes after transplantation of human leukocyte antigen (HLA)-identical marrow (46% vs 30%). There were many methodologic flaws in the trial, including lack of control for type 1 error for multiple comparisons, inclusion of a heterogeneous group of patients, and lack of a placebo control. Subsequent to this pivotal trial, multiple trials have been conducted and systematic reviews have assessed the efficacy of immunoglobulin prophylaxis in HCT to prevent infection and prolong survival. The most recent systematic review and meta-analysis (2009) included 30 trials with 4223 patients undergoing HCT. There was no difference in all-cause mortality between IVIG and cytomegalovirus-IVIG compared to controls (relative risk [RR], 0.99; 95% confidence interval [CI], 0.88 to 1.12; RR=0.86; 95% CI, 0.63 to 1.16, respectively). There was no difference in clinically documented infections with IVIG compared to control (RR=1.00; 95% CI, 0.90 to 1.10). Reviewers concluded that routine IVIG prophylaxis in patients undergoing HCT was not associated with survival benefit or reduction in infection and therefore routine use of IVIG prophylaxis in patients undergoing HCT is not recommended. This is a non-covered indication.

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.
**Prophylaxis**

The risk of ABMR is related to the presence of preformed alloantibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of alloantibodies is assessed using a panel reactive antibody (PRA) screen. Those with a PRA screen greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Recipients of ABO mismatched donor organs are also at risk of ABMR.

In the National Institutes of Health-sponsored IG02 study, 101 adults with a PRA screen of 50% or higher were randomized to IVIG 2 g/kg monthly for 4 months or placebo. If transplanted, additional infusions were given at 12 and 24 months. Treatment with IVIG therapy resulted in significant reduction in PRA levels compared to placebo (35% vs 17%). Seven graft failures occurred (4 IVIG, 3 placebo) among adherent patients with similar 2-year graft survival rates (80% IVIG, 75% placebo). The investigators concluded that IVIG therapy was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients with end-stage renal disease. In a follow-up study, the combination of high-dose IVIG and B-cell depletion therapy reduced PRA from 77% to 44% at the time of transplantation. However, more recent studies have failed to show reduction in PRA levels, specifically in patients with PRA greater than 80%. Nonrandomized clinical observations have suggested that a combination of plasmapheresis and low-dose IVIG combined with interleukin-2 blockade or rATG for induction was associated with improved patient survival compared with chronic dialysis for the treatment of sensitized patients. This is a covered indication.

**Treatment**

Most studies of IVIG treatment for ABMR are retrospective case series from single institutions. A 2012 systematic review by Roberts et al of treatments for acute ABMR in renal allografts found 10,388 citations but only 5 small RCTs, none of which addressed use of IVIG in the treatment of ABMR. An RCT has demonstrated that IVIG therapy is effective for the treatment of steroid-resistant rejection, however, it was ineligible for inclusion in the systematic review by Roberts et al because 83% of the patients had Banff 1 (pure cellular) rejection on biopsy. According to Roberts et al, the evidence to support the use of IVIG to treat ABMR is very low (GRADE criteria). This is a non-covered indication.

**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.

Multiple trials and a meta-analysis comparing IVIG to placebo have shown decreased bacterial infections but not decreased mortality.\textsuperscript{18-23} IVIG has not been directly compared with the use of prophylactic antimicrobials. The randomized trials of prophylactic IVIG found that patients who receive IVIG have a decreased incidence of minor and moderate, but not major, bacterial infections. Treatment with IVIG has not been shown to increase quality of life or survival. The largest study was a multicenter randomized trial in 84 patients with CLL who were at increased risk of bacterial infection due to hypogammaglobulinemia, a history of infection, or both.\textsuperscript{18} Although minor or moderate bacterial infections were significantly less common in patients receiving IVIG, there was no impact on the incidence of major infections, mortality, or nonbacterial infections. This is a \textit{covered} indication.

\textbf{HIV-Infected Children}

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

A double-blind RCT published in 1991 allocated 372 HIV-infected children to IVIG or placebo every 28 days.\textsuperscript{24} Median length of follow-up was 17 months. Results were stratified data by CD4+ counts (\(\geq 0.2\times10^9/L\) or <\(0.2\times10^9/L\)). After 24 months, for children with CD4+ counts of \(0.2\times10^9/L\) or greater, IVIG treatment compared to placebo significantly increased infection-free rates (67\% vs 48\% respectively; \(p<0.05\)); reduced overall the number of serious and minor bacterial infections (RR=0.68; \(p<0.05\)); and reduced the number of hospitalizations for acute care (RR=0.65; \(p<0.05\)). The effect was less marked in children with CD4+ counts of less than \(0.2\times10^9/L\). Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children have recommended IVIG to prevent serious bacterial infections in HIV-infected children who have IgG levels less than 400 mg/dL.\textsuperscript{25} The guidelines for the prevention and treatment of serious opportunistic infections in HIV-infected adults and adolescents do not give such recommendations.\textsuperscript{26} This is a \textit{covered} indication.

\textbf{Neonatal Sepsis}
Preterm and low birth weight infants are prone to infection because of immature immune system as well as increased exposure to nosocomial pathogens.

**Prophylaxis of Neonatal Sepsis**

A 2013 Cochrane review addressed IVIG for the prevention of infection in preterm and/or low birth weight infants.\(^{27}\) Investigators identified 19 RCTs that compared IVIG to placebo or no intervention for approximately 5000 preterm (<37 weeks of gestational age) and/or low birth weight (<2500 g) infants. Five of the 19 studies were considered to be high quality; the remaining studies had potential biases (eg, lack of caregiver blinding in 10 studies). In meta-analysis of 10 studies, IVIG was associated with a statistically significant reduction in sepsis (>1 episodes; RR=0.85; 95% CI, 0.75 to 0.98). Moreover, meta-analysis of 16 studies showed a significant reduction in serious infection (>1 episodes) with IVIG (RR=0.82; 95% CI, 0.74 to 0.92). However, IVIG was not associated with a significant reduction in mortality. Meta-analysis of 15 studies that reported all-cause mortality found a relative risk of 0.89 (95% CI, 0.75 to 1.05), and meta-analysis of 10 studies that reported mortality due to infection found a relative risk of 0.83 (95% CI, 0.56 to 1.22). Reviewers noted that 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, were of marginal clinical importance. No major adverse effects related to IVIG administration were reported. This is a **non-covered** indication.

**Treatment of Neonatal Sepsis**

A 2015 Cochrane review identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or proven infection.\(^{28}\) Studies included a total of 3973 infants; the largest trial had a sample size of 3493 and contributed 90% of the data. Meta-analysis of all 9 trials found no statistically significant difference in mortality rate with IVIG versus control (RR=0.95; 95% CI, 0.80 to 1.13). Meta-analysis of 3 trials found that IVIG significantly reduced the length of the hospital stay compared with a control intervention (mean difference [MD], -4.08; 95% CI, -6.47 to -1.69). Results were not pooled for other outcomes.

The trial with the large sample size was published by the International Neonatal Immunotherapy Study group in 2011; it was conducted in 9 countries.\(^{29}\) Infants receiving antibiotics for suspected or confirmed serious infection were randomly assigned to receive 2 infusions of IVIG at a dose of 500 mg/kg of body weight (n=1759) or a matching volume of placebo (n=1734). Infusions were given 48 hours apart. The primary study outcome was the rate of death or major disability (according to predefined criteria) at age 2 years. By age 2, 686 (39%) of 1759 children
in the IVIG group had died or had major disability compared with 677 (39%) of 1734 children in
the placebo group (RR=1.00; 95% CI, 0.92 to 1.08). There were also no statistically significant
differences in the primary outcome when prespecified subgroups (eg, birthweight, gestational
age at birth, sex) were examined. Moreover, there were no statistically significant differences
between groups in secondary outcomes, including rates of subsequent sepsis episodes. The
number of reported adverse events was 12 in the IVIG group (including 2 deaths) versus 10 in
the placebo group (including 4 deaths). This is a non-covered indication.

**Treatment of Sepsis in Adults**

A 2016 published meta-analysis that pooled 18 RCTs showed that use of IVIG reduced the
mortality risk of septic patients by half (odds ratio [OR], 0.50; 95% CI, 0.34 to 0.71). However,
there was a preponderance of small low quality studies in the evidence base, which was further
complicated by heterogeneous dosing regimens and types of IVIG preparations used across
studies that were conducted over a long time horizon. Reviewers concluded that the evidence
did not support widespread use of IVIG as adjunctive therapy for sepsis in adults. This is a non-
covered indication.

**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.

No controlled trials have evaluated IVIG for severe anemia associated with parvovirus B19. Only
case reports and small case series are available. One of the larger case series, published in
2013 by Crabol et al, retrospectively reported on 10 patients with documented human
parvovirus B19 and pure red cell aplasia. Following a mean of 2.7 courses of IVIG treatment,
hemoglobin level was corrected in 9 of 10 patients. Four patients had adverse effects associated
with IVIG (2 cases of acute reversible renal failure, 2 cases of pulmonary edema). In the same
article, Crabol et al reported on findings of a literature search in which they identified 123 cases
of pure red cell aplasia treated with IVIG (other than the 10 patients in their series). Among 86
(70%) of 123 patients available at 12-month follow-up, hemoglobin was corrected in 36 (42%)
patients, and the remaining 50 (58%) patients had persistent anemia. This is a covered
indication based on clinical vetting, in severe disease.
**Toxic Shock Syndrome**

Toxic shock syndrome is also called as 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.

The evidence for use of IVIG treatment for toxic shock syndrome is limited and includes 1 small RCT and multiple observational studies. IVIG is used for treatment of septic shock syndrome to boost antibody levels via passive immunity. The 2003 RCT allocated 21 adults with toxic shock syndrome to IVIG or to placebo. Mortality rates were 10% and 36%, respectively, but the difference in mortality rates was not statistically significant. However, the study was originally planned to enroll 120 patients, so was likely underpowered to detect any significant differences. In a 2014 prospective observational study, 23 patients receiving IVIG therapy were compared 44 patients who received placebo. The odds ratio for survival was 5.6 for IVIG versus placebo (p=0.03). The proportion of patients alive at 28 days by treatment was 87% and 50%, respectively. In 2 retrospective studies, 27 patients with toxic shock syndrome treated with IVIG were compared with historical controls. While the mortality rate was lower with IVIG than with historical controls, lack of randomization or statistical adjustment of the 2 groups pose difficulties when interpreting the results. A 2009 retrospective study including 192 children with toxic shock syndrome failed to show improvement in outcomes with IVIG. This is a covered indication, as most studies show a beneficial effect on treatment.

**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.

In 2007, NAC and CBS issued guidelines on the use of IVIG for hematologic conditions, including ITP, based on 6 RCTs and 1 nonrandomized trial of IVIG for adult ITP. Three of the trials compared IVIG with corticosteroids, and 4 trials evaluated different doses of IVIG. None compared IVIG with no therapy. The largest trial that compared IVIG with corticosteroids included 122 patients with severe acute ITP. The primary outcome, mean number of days with platelet count greater than 50x10^9/L at day 21, was significantly greater in the IVIG group than in the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIG vs
corticosteroids)\textsuperscript{42} and 1 randomized (IVIG alone vs oral prednisone alone vs IVIG plus oral prednisone)\textsuperscript{43} found no difference in platelet counts greater than 50x10\textsuperscript{9}/L at 48 hours or in response rates between groups, respectively. This is a \textbf{covered} indication when standard treatment has failed.

**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. This is a \textbf{covered} indication. Treatment appears to be equivalent to other options.

A Cochrane review by Hughes et al, updated in 2014, reviewed the results of randomized trials of immunotherapy for GBS.\textsuperscript{44} Reviewers identified 12 randomized trials; none was placebo-controlled. Seven trials compared IVIG with plasma exchange, 3 trials compared IVIG with supportive treatment only, 2 trials compared plasma exchange, and 2 compared IVIG with immunoabsorption (1 compared of IVIG plus immunoabsorption to immunoabsorption only). Four trials included adults only, 5 included children only, 1 included both, and 2 included adults and possibly children. The primary outcome of the review was change in disability level (using a 7-grade disability scale) after 4 weeks. A pooled analysis of 7 trials comparing IVIG with plasma exchange did not find significant differences between groups in change in the number of disability grades at 4 weeks (MD = -0.02; 95% CI, -0.25 to 0.20). There were also no significant differences in other outcome measures for IVIG versus plasma exchange (eg, number of patients who improved by \textgeq 1 grades). There were insufficient data to pool results for comparisons of IVIG with other types of alternative interventions or for a subgroup analysis by age. However, patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to plasma exchange (RR=0.14; 95% CI, 0.05 to 0.36).

Most trials had small sample sizes. The largest was a 1997 multicenter, randomized trial of 383 adults that compared IVIG, plasma exchange, and combination IVIG plus plasma exchange.\textsuperscript{45} The objectives of the trial were to establish that IVIG is equivalent or superior to plasma exchange and to establish that plasma exchange followed by IVIG is superior to a single treatment. Noninferiority was defined as no more than a 0.5-grade difference in change in disability grade at 4 weeks. At 4 weeks, the difference in improvement between the IVIG group and plasma exchange group was 0.09 grade (95% CI, -0.23 to 0.42); this met the predefined criterion for equivalence of these treatments. Differences were 0.29 grade (95% CI, -0.04 to 0.63) between the IVIG plus plasma exchange group and the IVIG only group, and 0.20 grade (95% CI, -0.14 to
0.54) between the IVIG plus plasma exchange group and the plasma exchange only group. Thus, neither combined treatment groups was superior to either treatment alone.

Miller Fisher syndrome is a variant of GBS characterized by impairment of eye movements (ophthalmoplegia), incoordination (ataxia), and loss of tendon reflexes (areflexia). A 2007 Cochrane systematic review evaluated acute immunomodulatory therapies in Fisher syndrome or its variants.\textsuperscript{46} No RCTs were identified.

**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 disease has reduced the prevalence of coronary artery abnormalities. This is a covered indication.

Multiple RCTs and meta-analysis have demonstrated efficacy of IVIG in preventing cardiac consequences of Kawasaki disease in children. A 2003 systematic review of RCTs identified 59 trials in the initial search and included 16 trials for meta-analysis using relative risk for dichotomous data or weighted mean difference for continuous data.\textsuperscript{47} Results showed a significant decrease in new coronary artery abnormalities in favor of IVIG compared to placebo at 30 days (RR=0.74; 95% CI, 0.61 to 0.90). Reviewers concluded that children fulfilling the diagnostic criteria for Kawasaki disease should be treated with IVIG (2 gm/kg single dose) within 10 days of onset of symptoms.

**Granulomatosis with Polyangiitis (Wegener Granulomatosis)**

The success of IVIG therapy for Kawasaki disease led to investigation of IVIG therapy in other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis.\textsuperscript{48} This trial, published by Jayne et al, compared single course IVIG (n=17) with placebo (n=17) and 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.\textsuperscript{49}

A single crossover trial in Wegener granulomatosis demonstrated that IVIG treatment increased in response rates compared to placebo. This is a covered indication.
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). This is a covered indication.

In 2013, Eftimov et al published a Cochrane review of RCTs on IVIG for treating CIDP. Reviewers identified 8 RCTs that enrolled 332 patients with definite or probable CIDP and that compared IVIG with placebo, corticosteroid, or plasma exchange. Three trials compared IVIG with another active treatment, and the other 5 were placebo-controlled (n=235). The primary trial outcome was the proportion of participants with a significant improvement in disability within 6 weeks of starting treatment. Studies used a variety of disability measures. When possible, Cochrane reviewers transformed the data on disability to a modified 6-point Rankin Scale for disability. Data from the 5 placebo-controlled RCTs were pooled. The pooled relative risk for improvement in the IVIG group compared with the placebo group was 2.40 (95% CI, 1.72 to 3.36; p<0.001). When data were pooled from 3 studies on IVIG versus placebo in which the disability measures could be converted to the Rankin Scale, the relative risk was similar (2.40) but not statistically significant (95% CI, 0.98 to 5.83; p=0.054). Pooled analyses of data from these 3 placebo-controlled studies found a statistically higher rate of any adverse event with IVIG, but not serious adverse events. Data from studies comparing IVIG with an active treatment were not pooled due to differences in comparators. Limitations of the meta-analysis included the use of different disability scales and varying definitions of clinical response.

ICE, the largest trial included in the meta-analysis, was a double-blind multicenter trial that randomized 117 patients to IVIG or placebo. The primary outcome measure was proportion of patients showing clinically meaningful improvement in disability at week 24. Results showed that the proportion of patients meeting the primary end point was significantly greater with IVIG treatment (54%) than with placebo (21%), with an absolute difference of 33.5% (95% CI, 15.4% to 51.7%). In the 24-week extension phase, 57 patients who received IVIG in the randomized phase were rerandomized to IVIG or placebo. Relapse rates were significantly lower for patients treated with IVIG (13% vs 45%; hazard ratio [HR], 0.19; 95% CI, 0.05 to 0.70). Benefits of IVIG treatment extended to as long as 48 weeks with maintenance treatments of 1 g/kg every 3 weeks.
A 2012 evidence-based guideline on IVIG for treating neuromuscular disorders, prepared by a subcommittee of American Academy of Neurology, stated that IVIG should be offered for the long-term treatment of CIDP.59

**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. The benefit of IVIG for MMN has been demonstrated in 4 RCTs (total N=53 patients).61-64 The largest of the 4 RCTs randomized 19 patients with MMN with persistent conduction block to IVIG or placebo. Response to treatment was assessed by measuring Medical Research Council (MRC) score in 28 muscles; a responder was defined as at least 1 more MRC point in 2 affected muscles plus 1 point less in 2 activities of daily life compared with baseline. At 4 months, 7 of 9 patients who received IVIG responded compared with 2 of 9 patients treated with placebo. Von Schaik et al (2005) included 4 RCTs (total N=34 patients) in a meta-analysis to assess the efficacy and safety of IVIG in MMN.65 Strength improved in 78% of patients treated with IVIG versus 4% in placebo-treated patients. Disability improved in 39% and 11%, respectively (p=NS). Mild, transient side effects were reported in 71% of IVIG-treated patients. Serious side effects were not encountered. This is a covered indication.

**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.

One crossover RCT of 9 patients treated with IVIG therapy (1 g/kg/d for 2 days) or placebo showed statistically significant improvements in serial measurements of limb, respiratory, and bulbar muscle strength associated with IVIG treatment, and a nonsignificant improvement in the resting compound muscle action potential amplitude.66 A number of noncomparative studies have substantiated clinical benefits.67-70 This is a covered indication.
**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.

There are no published clinical trials demonstrating efficacy of IVIG treatment in NMO. Published literature consists of case reports and case series. A retrospective review of 10 patients treated with IVIG for acute relapses after lack of response to steroids with or without plasma exchange showed improvement in about 50% of patients. A case series of 9 Spanish NMO patients showed positive results using bimonthly IVIG treatment (0.7 g/kg body weight per day for 3 days) for up to 2 years. This is a covered indication when standard therapy has failed (steroids or plasmapheresis).

**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. This is a covered indication when used for acute exacerbations of myasthenia gravis.

In 2012, a Cochrane systematic review was published on IVIG for treating acute exacerbations or for chronic long-term MG. Reviewers identified 7 RCTs including 1 unpublished trial, all of which investigated short-term benefit. The trials varied in inclusion criteria, comparator interventions, and outcome measures and, thus, study findings were not pooled. Five trials evaluated IVIG for treating MG worsening or exacerbation, and 2 evaluated IVIG for treatment of moderate or severe MG. Several trials were small, with insufficient statistical power. Reviewers concluded that there was some evidence for efficacy in exacerbations of MG, and that evidence for treating chronic MG was insufficient to form conclusions about efficacy.

Zinman et al (2007) is the only RCT that compared IVIG to placebo in 51 patients with MG with progressive weakness. The primary outcome measure was the difference between arms in the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity from baseline to days 14 and 28. In IVIG-treated patients, a clinically meaningful improvement in QMG Score for Disease Severity was observed at day 14 and persisted at day 28. The greatest improvement occurred in patients with more severe disease as defined by a QMG Score for Disease Severity greater than 10.5. Remaining RCTs either compared IVIG with plasma exchange or compared 2 doses of IVIG.
Gajdos et al (1997) compared IVIG with plasma exchange in 87 patients with MG exacerbations.\textsuperscript{77} The study did not find a statistically significant difference in the efficacy between the 2 treatments, but found that IVIG was better tolerated. Nine patients experienced adverse events (8 in the plasma exchange group, 1 in the IVIG group). Barth et al (2011) compared IVIG with plasma exchange in 84 patients with moderate-to-severe MG.\textsuperscript{78} The study also did not find a statistically significant difference in the efficacy between both treatments. Gajdos et al (2005) compared 2 doses of IVIG (1 g and 2 g/kg) in 170 patients with acute exacerbation of MG.\textsuperscript{79} Mean improvement in the myasthenic muscular scores did not differ significantly between doses after 2 weeks. The trial by Schuchardt (2002) was not published and therefore not summarized here.

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.

A 1998 TEC Assessment concluded that IVIG therapy for RRMS met TEC criteria.\textsuperscript{80} However, by 2002, AAN was recommending the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation). AAN suggested that IVIG was no longer considered a drug of choice for RRMS.\textsuperscript{81} This is a non-covered indication, and is considered not medically necessary as there are other agents shown to be more efficacious.

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. This is a covered indication.

A 2010 systematic review identified 23 studies evaluating IVIG for autoimmune mucocutaneous blistering diseases (22 case series, 1 RCT). The studies included a total of 260 patients treated with IVIG: 191 patients had pemphigus, and 69 patients had pemphigoid. Of the 260 patients, 245 (94%) improved after IVIG treatment.

The RCT, published in 2009 by Amagai et al, was multicenter, placebo-controlled and double-blind; it included adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥20 mg/d). Patients were randomized to a single cycle of IVIG 400 mg/kg/d for 5 days, IVIG 200 mg/kg/d for 5 days, or a placebo infusion for 5 days. The primary end point was the duration of time that patients could be maintained on the treatment protocol before symptoms required additional treatment (ie, time to escape protocol). Time to escape protocol was significantly longer for patients in the IVIG 400-mg group than for patients in the placebo group but not between the IVIG 200-mg group and the placebo group. Furthermore, a significant decrease in a pemphigus activity score was detected at all study observation points for patients in the IVIG 400-mg group and at all study observation points after day 15 in the IVIG 200-mg group. The pemphigus activity score did not decrease significantly at any time point in the placebo group.

Another RCT by the same research group was published in 2017 and evaluated IVIG for bullous pemphigoid. The trial was multicenter, double-blind and placebo-controlled randomized trial and included 56 patients, The IVIG group received an intravenous drip infusion of human IgG, 400 mg/kg/d for 5 days and the placebo group received an intravenous drip infusion of saline for 5 days. The primary end point was the Disease Activity Score (DAS) on day 15 (lower score is a better outcome). Mean scores were 19.8 in the IVIG group and 32.3 in the placebo group, but the difference between groups was not statistically significant (p=0.089). In a post hoc analysis using the DAS on day 1 as a covariate, the DAS was significantly lower in the IVIG group (19.7) than in the placebo group (32.4) at day 15 (p=0.041). In patients with severe disease, there were significantly lower DAS scores in the IVIG than in the placebo group on days 8, 15, and 22; between-group scores did not differ in patients with mild or moderate disease.
**Toxic Epidermal Necrosis and Stevens-Johnson Syndrome**

Data on the use of IVIG therapy for toxic epidermal necrosis (TEN) and Stevens-Johnson syndrome (SJS) are limited and conflicting. The use of IVIG was initially proposed based on the hypothesis that Fas ligand (FasL) was the main mediator of widespread keratinocyte apoptosis in TEN and on the finding that high-dose IVIG were able to antagonize FasL effects. However, it is now widely accepted that granulysin (a cytotoxic protein) is the most important mediator.

Several systematic reviews have focused on IVIG for TEN and/or SJS. Most recently, in 2015, Barron et al identified 13 studies of patients who met diagnostic criteria for TEN or SJS and received IVIG alone or in combination with other medications.⁸⁶ Eight studies included a control group, but none was an RCT. All control patients received corticosteroids and, in 4 studies, patients in the IVIG group received concomitant corticosteroid therapy. A meta-analysis of all included studies did not find a statistically significant benefit of IVIG therapy for mortality (standardized mortality ratio [SMR], -0.32; 95% CI, -0.77 to 0.12). Logistic regression analyses found that there were reductions in SMR as dosage of IVIG increased. A sensitivity analysis of the 2 studies that used the lowest doses of IVIG found a statistically significant reduction in SMR in IVIG-treated groups (SMR=0.70; 95% CI, 0.51 to 0.96). A 2016 meta-analysis also failed to support the clinical benefits of IVIG for TEN.⁸⁷ The largest European cohort study likewise did not demonstrate a significant survival advantage for patients treated with either high- or low-dose IVIG compared with patients treated with supportive care only.⁸⁸ This is a non-covered indication.

**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 a variety of 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**

In 2012, Wang et al published a systematic review on IVIG treatment for adults with refractory dermatomyositis or polymyositis.⁸⁷ Reviewers identified 14 studies including 2 RCTs, 9 prospective case series, and 3 retrospective case series. Eleven of 14 studies included patients
with refractory disease. For example, a 1993 trial by Dalakas et al compared prednisone plus IVIG with prednisone plus placebo in 15 patients with refractory dermatomyositis.\(^{88}\) At 3 months, there were significant increases in muscle strength in the IVIG group, as measured by mean scores on the modified MRC scale and the Neuromuscular Symptom Scale (NSS) (mean modified MRC scale score, 84.6 IVIG vs 78.6 placebo; mean NSS score, 51.4 IVIG vs 45.7 placebo). Repeated transfusions every 6 to 8 weeks can be required to maintain a benefit.

Miyasaka et al (2012) in Japan conducted an RCT of 26 patients with corticosteroid-resistant polymyositis or dermatomyositis who had received high-dose corticosteroid therapy for at least 1 month.\(^{89}\) Patients were randomly assigned to treatment with IVIG (n=12) or placebo (n=14) once daily for 6 consecutive days. The primary end point was change from baseline mean manual muscle test (MMT) scores at 8 weeks. Change in mean MMT was 11.8 points in the IVIG group versus 9.9 points in the placebo group. This difference was not statistically significant (1.9 points; 95% CI, -4.8 to 8.5). Other outcomes also did not differ significantly between groups.

A case series of 35 patients with polymyositis, all of whom had disease that required ongoing glucocorticoid therapy and none could be weaned from glucocorticoids despite trials of 1 or more additional therapies, showed some clinical benefit; 33 patients with initially elevated serum creatine kinase levels showed biochemical improvement; 25 of 35 showed improvement in muscle strength, which returned to near-normal in 10 of the 25 responders; 8 of 11 patients with esophageal dysfunction showed resolution of dysphagia; 12 of the 25 responders had complete clinical responses (absence of myositis activity) while receiving not more than prednisone 6 mg/d.\(^{90}\) Mean follow-up for these patients was 39 months. Five patients discontinued all other medical treatments for myositis. This is a covered indication.

**Inclusion Body Myositis**

Dalakas et al (1997) reported on a double-blind, placebo-controlled crossover study that compared IVIG with placebo in 19 patients with inclusion body myositis.\(^{91}\) There was no statistically significant improvement in overall muscle strength in the IVIG group compared with the control (placebo) group. Two more recent RCTs published in 2000 and 2001 (58 IVIG patients) also found no significant functional improvement when IVIG treatment was compared with placebo.\(^{92,93}\) This is a non-covered indication.
**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.

IVIG therapy is proposed for SLE because of its immunomodulatory properties and also because it prevents infection in patients taking immunosuppressive drugs. A 2014 systematic review by Sakthiswary et al identified 13 studies on IVIG for treatment of SLE. Three studies had control groups, and only 1 was an RCT. Most studies had small sample sizes; only 3 had more than 50 patients, and the single RCT included only 14 patients. In a meta-analysis of 6 studies (n=216 patients), there was a statistically significant difference in SLE disease activity in IVIG-treated groups (SMD=0.58; 95% CI, 0.22 to 0.95). This analysis was limited because there were few data in non-IVIG treated patients. A meta-analysis of data from 8 studies on the effect of IVIG on complement levels found a pooled response rate of 30.9% (95% CI, 22.1% to 41.3%). Findings on other outcomes were not pooled. However, there has been limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE. This is a **non-covered** indication.

**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. This is a **non-covered** indication.

Two RCTs have studied the potential benefit of IVIG in this disease. Noseworthy et al (2001) planned to randomize 60 patients with persistent acuity loss after optic neuritis to IVIG or placebo. The trial was terminated early after 55 patients were enrolled because investigators did not find a difference in the logMAR visual scores at 6 months (p=0.766). Roed et al (2005) randomized 68 in the acute phase of optic neuritis to IVIG (n=34) or placebo (n=34). They found no differences in the visual outcome measure and disease activity as measured by magnetic resonance imaging after 6 months.

**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. A 2012 systematic review of IVIG therapy for Crohn disease did not identify any randomized or nonrandomized controlled trials.\textsuperscript{99} Reviewers found 5 case reports of IVIG used for single patients with Crohn disease, and the remaining literature identified included conference papers, abstracts only, or a nonsystematic review. This is a \textbf{non-covered} indication.

**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. Published literature on the use of IVIG in hemophagocytic syndrome is limited to small case series.\textsuperscript{100-102}

A 2012 systematic review on diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics identified 156 cases; a portion of these patients were treated with IVIG.\textsuperscript{103} Steroids were the most common treatment. IVIG was used in 30% of children and in 4% of adults. Hemophagocytic syndrome-related mortality occurred in 32% of children and in 28% of adults. This is a \textbf{non-covered} indication.

**Warm Antibody Autoimmune Hemolytic Anemia**

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

Published literature on the use of IVIG in warm antibody autoimmune hemolytic anemia is limited to observational data for 37 patients pooled from 3 institutions\textsuperscript{104} and a case report.\textsuperscript{105} Overall, 29 (39.7%) of 73 patients responded to IVIG therapy. Because of limited therapeutic value, it is used in patients refractory to conventional therapy with prednisone and splenectomy or as a conjunctive therapy in patients with very severe disease. Further, the effect is usually transient, unless repeated courses are given every 3 weeks. This is a \textbf{covered} indication.

**Antiphospholipid Syndrome**

Antiphospholipid syndrome is an autoimmune disease that results from the development of antibody against phospholipids protein, which causes venous or arterial thromboses and/or pregnancy morbidity.
Published literature on the use of IVIG in antiphospholipid syndrome includes a pooled analysis of 250 single case reports from a registry.\textsuperscript{106} Results showed that a higher proportion of patients survived after the episode of antiphospholipid syndrome if they received triple therapy of anticoagulants, corticosteroids, plasma exchange, and/or IVIGs compared to combinations that did not use plasma exchange, IVIG, or both. This is a \textit{covered} indication.

\section*{Alloimmune Processes}

\subsection*{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. This is a \textit{covered} indication.

There are no RCTs evaluating the efficacy of IVIG or steroids alone versus placebo in alloimmune thrombocytopenia. Trials of this nature would be unethical because of the known risk of ICH with this condition. Rayment et al (2011), in a Cochrane systematic review, summarized the results of 4 RCTs on the maternal administration of corticosteroids and IVIG in pregnancies with neonatal alloimmune thrombocytopenia in 206 patients.\textsuperscript{107} Reviewers concluded that the optimal management of fetomaternal alloimmune thrombocytopenia remains unclear. Lack of complete data sets for 2 trials and differences in interventions precluded the pooling of data from these trials. Bussel et al did not find any differences in the fetal platelet counts between IVIG and IVIG with steroids.\textsuperscript{108} Although there was no placebo-controlled arm, results can be compared with the course in a prior affected sibling, because the natural history of the disease suggests that subsequent births should be similarly, if not more severely, affected with thrombocytopenia. The study reported a mean increase in platelet count of 69,000/mL. There were no instances of ICHs, although hemorrhage had occurred previously in 10 untreated siblings. Berkowitz et al did not demonstrate a difference in standard risk pregnancies but did demonstrate that IVIG and prednisone was more effective in raising the fetal platelet count in high-risk pregnancies.\textsuperscript{109} The Berkowitz et al trial in 2007 showed good outcomes and comparable results between the IVIG group and the IVIG plus prednisone group in standard-risk pregnancies.\textsuperscript{110} Paridaans et al (2015) evaluated the effectiveness of a lower dose of IVIG (0.5 g/kg/wk vs 1 g/kg/wk) in a RCT of 23 women.\textsuperscript{111} The primary outcome was fetal or neonatal ICH.
The median newborn platelet count was 81×109/L in the 0.5-g/kg group versus 110×109/L in the 1-g/kg group (p=0.644).

**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. Patients with RSA frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss. This is a non-covered indication.

A 2006 Cochrane review of various immunotherapies for treating recurrent miscarriage concluded that IVIG therapy provides no significant beneficial effect over placebo in preventing further miscarriages. Recently published meta-analyses that included 11 RCTs also found no significant difference in the frequency of the number of live birth with IVIG versus placebo or treatment as usual. A 1999 blinded RCT of 41 women treated with IVIG or saline placebo also found no differences in live birth rates. Likewise, a 2000 multicenter RCT comparing heparin plus low-dose aspirin with or without IVIG in women with lupus anticoagulant, anticardiolipin antibody, or both, found no significant differences. In addition, a 2002 RCT of 58 women with at least 4 unexplained miscarriages compared IVIG to placebo and analyzed results by intention to treat. The live birth rate was similar for both groups; also, there were no differences in neonatal data (eg, birth weight, gestational age at delivery). Other nonrandomized but controlled trials have also reported no benefit for IVIG treatment.

**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 infection. This syndrome is not well-understood and diagnosis of PANDAS requires expert consultation. This is a non-covered indication.

Two RCTs were identified. In 2016, Williams et al randomized 35 children who met diagnostic criteria for PANDAS and had moderate-to-severe obsessive-compulsive disorder symptoms to treatment with 2 treatment sessions of IVIG or placebo. After a 6-week double-blind
treatment phase, there was the option of continuing treatment on an open-label basis for nonresponders. The primary outcome at 6 weeks, the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score, did not differ significantly between groups. There was a mean decrease in the CY-BOCS of 23.9% in the IVIG group and 11.7% in the placebo group (effect size, 0.28; 95% CI, -0.39 to 0.95). Improvement in other outcomes (eg, mean Clinical Global Impressions improvement scores) also did not differ significantly between groups. A total of 24 participants met criteria for nonresponse at 6 weeks and received open-label IVIG. At week 12, scores on the CY-BOCS improved significantly compared with 6 weeks; however, the 12-week analysis did not include a placebo comparison.

A 1999 RCT by Perlmutter et al included 30 children who had new or severe exacerbations of obsessive-compulsive disorder or tic disorder after streptococcal infections. Patients were randomized to IVIG, plasma exchange, or placebo (10 per group). At the 1-month follow-up, IVIG and plasma exchange showed statistically significant improvements in obsessive-compulsive symptoms, anxiety, and overall functioning. The study included only 10 children who were treated with IVIG.

**Autism Spectrum Disorder**

Autism spectrum disorder is neurodevelopmental disorder characterized by deficits in social communication and social interaction and restricted repetitive patterns of behavior, interests, and activities. This is a **non-covered** indication.

The evidence base supporting the use of IVIG in autism includes 3 case series. The first included 10 patients with abnormal immune parameters who received IVIG therapy monthly. After 6 months, 5 of 10 patients showed marked improvement in several autistic characteristics. Remaining 2 case series failed to replicate these findings. In the second, 1 of 10 patients showed improvements in autistic symptoms after receiving IVIG. No improvements were observed in the third series. There are no randomized comparative trials evaluating IVIG therapy in autism.

**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. This is a **non-covered** indication.

The evidence base supporting the use of IVIG treatment for CRPS consists of 1 crossover double-blinded RCT published by Goebel et al in 2010; it was conducted at an academic pain
management center in the U.K. The trial randomized 13 patients refractory to standard treatment to IVIG or normal saline. Median daily pain intensity score for each 14-day period was 6.21 after IVIG infusion versus 7.35 after saline infusion, a difference of 1.14 points. Authors reported that the mean pain intensity was 1.55 points lower after IVIG than after saline (95% CI, 1.29 to 1.82; p<0.001). This is a short-term RCT with a small number of patients, and findings need to be confirmed in larger trials with longer follow-up. The optimal dose and treatment regimen are unknown.

**Alzheimer Disease**

Three placebo-controlled double-blind, randomized trials in patients with Alzheimer disease were identified. Two RCTs included patients with mild-to-moderate Alzheimer disease. In a 2013 trial by Dodel et al with 56 patients, the primary outcome (area under the curve of plasma amyloid β (Aβ1–40) did not differ between the IVIG and the placebo groups. Secondary outcomes, including cognitive and functional scales, also did not differ between groups. In 2017, Relkin et al reported on 390 patients treated with 1 of 2 doses of IVIG (0.2 or 0.4 g/kg every 2 weeks for 18 months) or placebo. The primary outcomes were change from baseline to 18 months on the cognitive subscale of the Alzheimer Disease Assessment scale and on the Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory. Neither outcome was significantly improved in either IVIG groups compared with the placebo group.

The third RCT, published by Kile et al in 2017, included 50 patients with mild cognitive impairment (MCI) related to Alzheimer disease. Patients were stratified into early and late MCI stages based on scores on the Clinical Dementia Rating, Sum of Boxes test (1 or less for the early MCI group and more than 1 for the late MCI group). Patients received a total IVIG dose of 2g/kg over 5 sessions, or placebo. The primary outcome was brain atrophy, defined as annualized percent change in the ventricular volume (APCV) measured by magnetic resonance imaging. In unadjusted analyses, APCV did not differ significantly between groups at 12 months or 24 months. In a subgroup analysis, the APCV was significantly lower in the IVIG compared with placebo group in patients with early MCI but not late MCI at 12 months, and there was not a significant difference at 12 months in either the early or late MCI groups. Secondary outcomes, cognition scores, and conversion to Alzheimer disease dementia did not differ between the IVIG and placebo groups at 12 or 24 months. As with the primary outcome, for several secondary outcomes, IVIG showed a significant benefit in the early MCI group at 12 months but not 24 months.

Three double-blind placebo-controlled randomized trials have been published evaluating IVIG in patients with Alzheimer disease. With the exception of a few subgroup analyses by MCI status,
IVIG did not show significantly better outcomes than placebo for brain atrophy, level of plasma amyloid β (Aβ)1–40, and cognition and function. Studies differed in factors such as treatment protocols, outcomes assessed, and 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI. This is a non-covered indication.

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. This is a non-covered indication.

Results of a double-blind, placebo-controlled, randomized crossover trial of IVIG versus placebo in 11 patients with paraproteinemeric IgM demyelinating polynueopathy showed only a mild and transitory effect in 3 patients. A subsequent 2012 RCT of 22 patients focused on short-term outcomes at 2 weeks. No significant differences were found between the treatment and placebo groups.

Chronic Fatigue Syndrome

Chronic fatigue syndrome, also called as systemic exertion intolerance disease, it is a complex and controversial disease with multiple definitions. This is a non-covered indication.

Numerous non-comparative studies have shown subjective benefits of IVIG therapy on chronic fatigue syndrome but a double-blind, randomized, placebo-controlled trial in 99 patients with chronic fatigue syndrome reported no therapeutic benefit of IVIG.

Acute Myocarditis

Acute myocarditis is a sudden inflammation of myocardium that can occurs 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 postinfectious inflammatory reaction or a combination of the two. This is a non-covered indication.
Multiple case reports have suggested that patients with acute myocarditis may benefit from high-dose IVIG.\textsuperscript{98} Spontaneous rapid or gradual improvement is common with acute myocarditis, and improvement noted in these case series may have been part of the natural history of the disease. The literature has been summarized in a Cochrane systematic review\textsuperscript{131} that included 1 placebo-controlled randomized trial of 62 adult patients with recent-onset dilated cardiomyopathy\textsuperscript{132} and a quasi-randomized study of 83 children with suspected viral encephalitis and associated myocarditis with a left ventricular ejection fraction less than 0.40.\textsuperscript{133} Both trials were rated as very low quality and had high risk of bias. In the RCT of adults, event-free survival did not differ significantly but favored the control group (OR=0.52; 95% CI, 0.12 to 2.30). The major limitation was that some patients did not have viral myocarditis because only 10 of 62 patients showed inflammation on cardiac biopsy. In the quasi-randomized trial in children, the incidence of event-free survival was 25 (96%) of 26 in the treated group and 44 (77%) of 57 in the control group (OR=7.39; 95% CI, 0.91 to 59.86).

**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.

Imazio et al (2016) conducted a systematic review and summarized data of 30 patients (4 case series, 13 case reports).\textsuperscript{133} Approximately 47\% of patients had idiopathic recurrent pericarditis, 10\% had an infective cause, and the remainder had systemic inflammatory disease. IVIG was generally administered at a dose of 400 to 500 mg/kg/d for 5 consecutive days, with repeated cycles according to the clinical response. Overall, recurrences occurred in 26.6\% of cases after the first IVIG cycle, and 22 (73.3\%) of the 30 patients were recurrence-free after a mean follow-up of approximately 33 months. This is a **non-covered** indication.

**Stiff Person Syndrome**

Stiff person syndrome is 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. This is a **covered** indication.
Multiple case reports have suggested that patients with stiff person syndrome may benefit from IVIG. The benefit was confirmed in a small crossover randomized comparing IVIG with placebo in 16 patients with stiff person syndrome and anti-GAD65 autoantibodies. After a 1-month washout period, patients were crossed over to 3 months of the alternative treatment. Stiffness scores decreased significantly on IVIG, but not on placebo, regardless of order. Eleven (69%) patients were able to walk more easily or without assistance; the frequency of falls decreased, and patients were able to perform work-related or household tasks. The duration of benefit lasted 6 weeks to 1 year without additional treatment.

**Noninfectious Uveitis**

Noninfectious uveitis is the inflammation of eye that results from noninfectious causes such as eye trauma, anomalous immune processes, or unknown etiology. Two small case series of 18 and 10 patients, respectively, reported measurable improvements in visual acuity after IVIG therapy. Collectively, these 2 studies represent insufficient evidence to draw conclusions about efficacy. This is a non-covered indication.

**Postpolio 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. This is a non-covered indication.

In 2015, Huang et al published a systematic review and meta-analysis of RCTs and nonrandomized prospective studies on IVIG treatment of postpolio syndrome. Reviewers identified 3 RCTs (n=241 patients) and 5 prospective studies (n=267 patients). The primary outcomes of interest were severity of pain, fatigue, and change in muscle strength 2 to 3 months after IVIG administration. Meta-analyses of RCT data found no statistically significant differences between IVIG- and placebo-treated groups for any of these outcomes. For example, the pooled mean difference in pain scores (0-to-10 visual analog scale) from the 3 RCTs was -1.02 (95% CI, -2.51 to 0.47). Meta-analysis of the 2 RCTs that reported change in fatigue scores found a WMD of 0.28 (95% CI, -1.56 to 1.12). The small number of RCTs and the negative findings of this systematic review represent insufficient evidence of the efficacy of IVIG for postpolio syndrome.
Necrotizing Fasciitis

In 2017, Madsen et al published a placebo-controlled randomized trial evaluating IVIG for patients with necrotizing soft issue infection (eg, necrotizing fasciitis). The trial included 100 patients with confirmed necrotizing soft tissue infection who were admitted or had planned admissions to the intensive care unit. The primary outcome was patient-reported physical function at 6 months, assessed using the Physical Component Summary score of the 36-Item Short-Form Health Survey. The mean Physical Component Summary score adjusted for site of infection was 36 in the IVIG group and 21 in the placebo group. The difference between groups was not statistically significant (p=0.81). Other outcomes (ie, mortality, use of life support in the intensive care unit, bleeding, amputation) did not differ significantly between groups.

Clinical Input Received through 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 following approval of the December 2012 update of the policy. 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 is 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 (SCIG) infusion.

**American Academy of Allergy, Asthma, and Immunology**

In 2015, the American Academy of Allergy, Asthma, and Immunology (AAAAI) published practice parameters for the diagnosis and management of primary immunodeficiency. AAAAI 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, the 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 PP compared either to plasmapheresis or IVIG alone; and the optimum dosage of IVIG.

**Chronic Lymphocytic Leukemia**

The National Comprehensive Cancer Network (NCCN) guidelines on chronic lymphocytic leukemia (CLL) recommend IVIG as supportive care for patients with CLL: 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.¹⁴¹

**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.²⁶ The guidelines, endorsed by the American Academy of Pediatrics (AAP), the Infectious Diseases Society of America, and other agencies/societies, included the following statement: “Intravenous (IV) immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia.”
Neonatal Sepsis

AAP 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.
- The American Society for Hematology (ASH) recommends the following as treatment for ITP in the pediatric population:
  - First-line treatment to consist of a single dose of IVIG or a short course of corticosteroids.
  - IVIG is recommended if a rapid increase in platelets is needed.
  - Splenectomy should be deferred for at least 12 months, unless there is severe disease that does not respond to IVIG, corticosteroids, rituximab
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 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


Chronic Inflammatory Demyelinating Polyneuropathy

The 2012 AAN guidelines on the treatment of neuromuscular disorders have 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 on the use of IVIG for the treatment of neurologic disorders. The guidelines indicated that the efficacy of IVIG for the treatment of CIDP is proven (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 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 is proven (level A).
Eaton-Lambert Myasthenic Syndrome

The 2012 AAN guidelines on the treatment of neuromuscular disorders have stated that IVIG is possibly effective and may be considered for treating Lambert-Eaton myasthenic syndrome (level C).\(^5^9\)

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 contraindication to one of the other treatments or, particularly, in children.\(^1^4^6\)

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).\(^5^9\) There was insufficient evidence to compare IVIG and plasmapheresis in treatment of these patients.

EFNS issued guidelines on the use of IVIG to treat neurologic disorders.\(^1^4^3\) 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 is proven (level A).

Relapsing-Remitting Multiple Sclerosis

In 2002, AAN published a technology assessment on therapies for multiple sclerosis.\(^8^3\) The assessment was reviewed and reaffirmed in 2008. AAN’s rating system was A (established as effective), B (probably effective, ineffective, or harmful), C (possibly effective, ineffective, or harmful), or U (data inadequate). 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 RRMS (type C recommendation).
• Current evidence suggests that IVIG is of little benefit with regard to slowing disease progression (type C recommendation).

EFNS issued guidelines on the use of IVIG for the treatment of neurologic disorders. 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 (TEN) and Stevens-Johnson syndrome. These guidelines are accredited by the National Institute for Health and Care Excellence (NICE). The guidelines indicated that evidence for the use of IVIG for the treatment of TEN 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 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 is often 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.\(^{40}\)

- 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.\(^{148}\) The guidelines, accredited by NICE, 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.\(^{149}\) 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**

NAC and CBS guideline on neurologic conditions did not recommend IVIG for autism.\(^{149}\)

In 2014, the American Academy of Child and Adolescent Psychiatry (AACAP) published practice parameters for the assessment and treatment of autism spectrum disorder.\(^{150}\) AACAP parameters do not address the use of IVIG for the treatment of autism spectrum disorder.
**Chronic Fatigue Syndrome**

In 2007, NICE issued guidance on the diagnosis and management of chronic fatigue syndrome. The guidance was reviewed in 2014 and no changes to the recommendations were made at that time. The guidance has 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 is 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. The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

**Stiff Person Syndrome**

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

**Postpolio Syndrome**

EFNS updated its guidelines on the definition and management of postpolio syndrome. The guidelines indicated that IVIG could have a modest therapeutic effect on postpolio syndrome, though there were limitations to the study evidence (small sample size, inadequate comparators, appropriate dosage). Due to these limitations, the EFNS concluded that IVIG cannot be recommended as a standard.

**Medicare National Coverage**

In 2002, the Centers for Medicare and Medicaid Services published a national coverage determination on IVIG for treatment of autoimmune mucocutaneous blistering diseases. 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 ongoing 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00892112a</td>
<td>Intravenous Immunoglobulin (IVIg) for Parvovirus B19(PVB19) Mediated Cardiomyopathy</td>
<td>50</td>
<td>Mar 2018</td>
</tr>
<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>Sep 2020</td>
</tr>
<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>NCT02899702</td>
<td>Effectiveness of Intravenous Immunoglobulins (IVIG) in Toxic Shock Syndromes in Children (IGHN2)</td>
<td>156</td>
<td>Jan 2021</td>
</tr>
<tr>
<td>NCT03194815</td>
<td>IVIG and Rituximab in Antibody-associated Psychosis - SINAPP52 (SINAPP52)</td>
<td>80</td>
<td>Dec 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

Regulatory Status

Several intravenous immunoglobulin (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 conditions:\(^1\):

- 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>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>09/01/04</td>
<td>Replace Policy - Policy renumbered from PR.8.01.103. No changes to dates.</td>
</tr>
<tr>
<td>05/10/05</td>
<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>
</tr>
<tr>
<td>04/11/06</td>
<td>Replace Policy - Scheduled review; minor clarification changes to the policy statement; policy reviewed and approved by P&amp;T 3/28/06.</td>
</tr>
<tr>
<td>06/02/06</td>
<td>Disclaimer and Scope update - No other changes.</td>
</tr>
<tr>
<td>12/21/06</td>
<td>Codes Updated - No other changes.</td>
</tr>
<tr>
<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 IVIg. Reviewed by P&amp;T on March 27, 2007.</td>
</tr>
<tr>
<td>08/23/07</td>
<td>Codes Updated - No other changes.</td>
</tr>
<tr>
<td>03/11/08</td>
<td>Cross Reference Updated - No other changes.</td>
</tr>
<tr>
<td>05/13/08</td>
<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>
</tr>
<tr>
<td>01/13/09</td>
<td>Code Updates - Code added, J1459; effective 1/1/09.</td>
</tr>
<tr>
<td>06/09/09</td>
<td>Replace Policy - Policy updated with literature search. Policy updated to include b cell diagnosis under the medically necessary statement. Reviewed by P&amp;T committee March 2009.</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>01/27/12</td>
<td>Codes updated; HCPCS codes J1557 and J7183 added.</td>
</tr>
<tr>
<td>02/21/12</td>
<td>Code update; HCPCS code J1559 added to the policy.</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>11/26/12</td>
<td>Update Related Policies. Add 5.01.526.</td>
</tr>
<tr>
<td>12/09/13</td>
<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>
</tr>
<tr>
<td>03/10/14</td>
<td>Annual Review. Organ transplant rejection deleted from investigational list because it has been considered medically necessary since 2010.</td>
</tr>
<tr>
<td>08/11/15</td>
<td>Interim Review. Policy tabled at August MPC meeting for further revisions and formatting changes.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>01/20/16</td>
<td>Coding update. New HCPCS code J1575, effective 1/1/16, added to policy.</td>
</tr>
<tr>
<td>01/27/16</td>
<td>Minor edit. Reordered codes in coding table for numeric order.</td>
</tr>
<tr>
<td>02/01/16</td>
<td>Coding update. HCPCS code J1556 added to policy.</td>
</tr>
<tr>
<td>05/01/16</td>
<td>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.</td>
</tr>
<tr>
<td>05/17/16</td>
<td>Minor edit. Corrected typo related to INCAT sensory sum score.</td>
</tr>
<tr>
<td>07/01/16</td>
<td>Interim Review, approved June 14, 2016. Correction made to site of service administration criteria.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Interim update, approved September 13, 2016. Coding updated. Policy moved into new policy format.</td>
</tr>
<tr>
<td>11/01/16</td>
<td>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.</td>
</tr>
<tr>
<td>02/01/17</td>
<td>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.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>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.</td>
</tr>
<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</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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</tr>
<tr>
<td>01/01/18</td>
<td>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>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>09/01/18</td>
<td>Minor update. Re-added Consideration of Age information, which was inadvertently removed during a previous update.</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). ©2018 Premera All Rights Reserved.

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Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can 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 S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Français (French):

Deutsche (German):

中文 (Chinese):
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คุณมีสิทธิ์ที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย (TTY: 800-842-5357)

Román (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется прийти к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

ไทย (Thai):
ประกาศนี้มีข้อความสำคัญเกี่ยวกับการป้องกันสุขภาพและการช่วยเหลือของคุณผ่าน Premera Blue Cross และมีการกำหนดระยะเวลาหรือเงื่อนไขที่คุณจะต้องปฏิบัติเพื่อรักษาการประกันสุขภาพของคุณได้อย่างถูกต้องที่มีไว้ก่อน คุณมีสิทธิ์ที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่เสียค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357).

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Przywóczek, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utraty pożyczki ubezpieczeniowej lub pomocy związanej z kosztami. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwoń pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):