IVIG (intravenous immunoglobulin)

Description

IVIG Immune Globulin – Bivigam, Carimune NF, Flebogamma, Gammagard, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Privigen

Background

Immune globulin products from human plasma were first used in 1952 to treat immune deficiency. Intravenous immunoglobulin (IVIG) contains the pooled immunoglobulin G (IgG) immunoglobulins from the plasma of approximately a thousand or more blood donors (1).

IVIG is used to treat various autoimmune, infectious, and idiopathic diseases. IVIG is an approved treatment for graft versus host disease and ITP. It is accepted for use in persons with Kawasaki disease, Guillain-Barré syndrome, and polymyositis/dermatomyositis (1).

Regulatory Status

The immune globulins addressed by this policy are FDA-approved for use in one or more of the following conditions:

- Primary immune deficiency (PID)
- Acute and Chronic Thrombocytopenic Purpura (ITP)
- Prevention of bacterial and viral infections in patients with hypogammaglobulinemia and/or recurrent bacterial and viral infections associated with B-cell Chronic Lymphocytic Leukemia (CLL)
- Prevention of coronary artery aneurysms associated with Kawasaki syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)(2-13)

Off-Label Use: (12-29)

1. Prophylaxis of bacterial and viral infections in pediatric human immunodeficiency virus
There are various types of immune-mediated encephalopathy, including anti-NMDA encephalitis, VGKG-associated limbic encephalopathies, and Hu and Ma2-mediated encephalitis. These have been seen in patients both with cancer and cancer-free of all ages, notably in young adults and children. First-line treatment, showing moderate success, includes the use of IVIGs (14-15).

Immune globulin use is associated with increased risk of thrombosis, particularly in the elderly and patients with risk factors such as cardiovascular disease, hypercoagulopathy, those on estrogen therapy, and patients with central venous catheters. Patients should be monitored carefully for signs and symptoms of thrombosis both at the time of infusion and after infusion. For those patients who will be self-administering the medication, practitioners need to instruct the patients and caregivers on how to monitor for signs and symptoms of thrombosis. Thrombosis may occur regardless of the route of administration (2-13).

IVIG products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, > 65 years of age, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. (2-13)

Other potential complications to monitor include the following (2-13):

**Immunoglobulin A deficiency:** People with this condition have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

**Aseptic meningitis syndrome (AMS):** Rare occurrences of AMS have been reported in association with IVIG treatment. AMS usually begins within several hours to 2 days following
IVIG treatment and is characterized by symptoms including severe headache, drowsiness, fever, photophobia, painful eye movements, muscle rigidity, nausea, and vomiting. AMS may occur more frequently in association with high-dose (2 g/kg) IVIG treatment. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.

**Bleeding complications:** Bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

**Severe reactions:** Severe reactions, such as anaphylaxis or angioneurotic edema, have been reported in association with IV immunoglobulins, even in patients not known to be sensitive to human immunoglobulins or blood products.

**Related policies**
Atgam, GamaSTAN, SCIG

**Policy**
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

IVIG may be considered **medically necessary** for treatment of the following conditions below with the listed requirements.

IVIG may be considered **investigational** for all other indications.

**Prior-Approval Requirements**

**Diagnoses**

Patient must have **ONE** of the following:

1. **Primary Immunodeficiency Disease (PID) with **ONE** of the following:**
   a. Hypogammaglobulinemia, IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency with **ALL** of the following:
      i. Documented history of recurrent bacterial and viral infections
      ii. Impaired antibody response to pneumococcal vaccine
      iii. **ONE** of the following pre-treatment laboratory findings:
         1) Hypogammaglobulinemia: IgG < 500 mg/dL or ≥ 2 SD below the
mean age

2) Selective IgA deficiency: IgA level < 7 mg/dL with normal IgG and IgM levels

3) Selective IgM deficiency: IgM level < 30 mg/dL with normal IgG and IgA levels

4) IgG subclass deficiency: IgG1, IgG2, or IgG3 > 2 SD below the mean age assessed on at least 2 occasions; normal IgG (total) and IgM levels, normal/low IgA levels

5) Specific antibody deficiency: normal IgG, IgA and IgM levels

b. SCID (severe combined immunodeficiency disease) or Agammaglobulinemia with ONE of the following:
   i. Confirmed diagnosis by genetic or molecular testing
   ii. Pretreatment IgG level < 200 mg/dL
   iii. Absence or very low number of T cells (CD3 T cells < 300/microliter) or presence of maternal T cells in the circulation (SCID only)

c. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non SCID combined immunodeficiency) with ALL of the following:
   i. Confirmed diagnosis by genetic or molecular testing
   ii. Documented history of recurrent bacterial and viral infections
   iii. Impaired antibody response to pneumococcal vaccine

d. CVID (common variable Immunodeficiency disease) with ALL of the following:
   i. Age 4 years and older
   ii. Documented history of recurrent bacterial and viral infections
   iii. Impaired antibody response to pneumococcal vaccine
   iv. Other causes of immune deficiency have been excluded (eg, drug induced, genetic disorders, infectious diseases such as HIV, malignancy)
   v. Pretreatment IgG level < 500 mg/dL or ≥ 2 SD below the mean for the age

2. Idiopathic thrombocytopenic purpura (ITP)
   a. Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy must ONE of the following:
      i. Children (<18 years of age) with ONE of the following:
         1) Significant bleeding symptoms (mucosal bleeding or
ii. Adults (> 18 years of age) with ONE of the following:
   1) Platelet count < 30,000/mcL
   2) Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required
   AND the following:
   1) Corticosteroid therapy is contraindicated and IVIG will be used alone or IVIG will be used in combination with corticosteroid therapy

b. Chronic/persistent ITP (> 3 months from diagnosis) or ITP unresponsive to first-line therapy with ONE of the following:
   i. Platelet count < 30,000/mcL
   ii. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required
   AND the following:
   i. Relapse after previous response to IVIG or inadequate response, intolerance or contraindication to corticosteroid therapy

c. Adults with refractory ITP after splenectomy must have ONE of the following:
   i. Platelet count < 30,000/mcL
   ii. Significant bleeding symptoms

d. ITP in pregnant women

3. B-cell chronic lymphocytic leukemia with ALL of the following:
   a. IVIG is prescribed for prophylaxis of bacterial and viral infections
   b. Documented history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization
   c. Pretreatment serum IgG level < 500 mg/dL
4. Kawasaki syndrome

5. Prophylaxis of bacterial and viral infections in Bone marrow transplantation (BMT) / Hematopoietic stem cell transplantation (HSCT) Recipients with ALL of the following:
   a. IVIG is prescribed for prophylaxis of bacterial and viral infections
   b. ONE of the following:
      i. IVIG is requested within the first 100 days post-transplant
      ii. Pretreatment serum IgG level < 400 mg/dL

6. Peripheral blood progenitor cell (PBPC) collection

7. Umbilical Cord Stem Cell Transplantation

8. Prophylaxis of bacterial and viral infections in HIV-Infected Pediatric patients with ALL of the following:
   a. Member is ≤ 12 years of age
   b. Primary prophylaxis:
      i. Pretreatment serum IgG level < 400 mg/dL
   c. Secondary prophylaxis:
      i. Documented recurrent bacterial and viral infections (> 2 serious infections in a year)
      ii. NOT able to take combination antiretroviral therapy
      iii. Antibiotic prophylaxis NOT effective

9. Polymyositis or Dermatomyositis with ALL of the following:
   a. Documented clinical features of diagnosis (eg. elevated muscle enzymes, muscle biopsy, supportive diagnostic tests)
   b. Inadequate response, intolerance or contraindication to first-line treatments (corticosteroids or immunosuppressants)

10. Inclusion-body myositis

11. Guillain-Barre Syndrome (GBS) with ALL of the following:
    a. Physical mobility is severely affected such that patient requires an aid to walk
    b. IVIG therapy will be initiated within 2 weeks of symptom onset

12. Fetal alloimmune thrombocytopenia (F/NAIT)

13. Myasthenia gravis with ALL of the following:
    a. Worsening weakness includes an increase in any of the following symptoms:
i. Diplopia  
ii. Ptosis  
iii. Blurred vision  
iv. Dysarthria  
v. Dysphagia  
vi. Difficulty chewing  
vii. Impaired respiratory status  
viii. Fatigue  
ix. Limb weakness

b. Pre-operative management

14. Multiple sclerosis

15. Multifocal motor neuropathy (MMN) with **ALL** of the following:  
   a. Weakness without objective sensory loss in 2 or more nerves  
   b. Electrodagnostic studies are consistent with motor conduction block  
   c. Normal sensory nerve conduction studies

16. Neoplastic disease

17. Chronic inflammatory demyelinating polyneuropathy (CIDP) with **ALL** of the following:  
   a. Moderate to severe functional disability  
   b. Electrodagnostic studies are consistent with multifocal demyelinating abnormalities

18. Autoimmune encephalitis

19. Lambert-Eaton Myasthenic syndrome (LEMS)

20. Parvovirus B 19-induced pure red cell aplasia (PRCA)

21. Stiff-person Syndrome with **ALL** of the following:  
   a. Inadequate response, intolerance or contraindication to first-line treatments (benzodiazepine or baclofen)

**AND ONE** of the following:
a. Monitor patients carefully for signs and symptoms of thrombosis both at the time of infusion and after infusion
b. Patients or caregivers have been instructed on how to monitor for signs and symptoms of thrombosis when self-administering the medication

Prior – Approval *Renewal* Requirements

**Diagnoses**

Patient must have **ONE** of the following:

1. Primary Immunodeficiency Disease (PID) with **ONE** of the following:
   a. Hypogammaglobulinemia, IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency
   b. SCID (severe combined immunodeficiency disease) or Agammaglobulinemia
   c. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non SCID combined immunodeficiency)
   d. CVID (common variable Immunodeficiency disease)
      i. Age 4 years and older

   **AND ALL** of the following:
      a. Reduction in frequency of bacterial and viral infections has been documented since initiation
      b. IgG trough levels are monitored at least yearly and maintained at or above the lower range of normal for age (when applicable for indication)
      c. The prescriber will re-evaluate the dose of the IVIG and reconsider a dose adjustment

2. Idiopathic thrombocytopenic purpura (ITP)

3. B-cell chronic lymphocytic leukemia
   a. Reduction in frequency of bacterial and viral infections has been documented since initiation

4. Kawasaki syndrome

5. Prophylaxis of bacterial and viral infections in Bone marrow transplantation (BMT) / Hematopoietic stem cell transplantation (HSCT) Recipients
a. Reduction in frequency of bacterial and viral infections has been documented since initiation

6. Peripheral blood progenitor cell (PBPC) collection

7. Umbilical Cord Stem Cell Transplantation

8. Prophylaxis of bacterial and viral infections in HIV-Infected Pediatric
   a. Reduction in frequency of bacterial and viral infections has been documented since initiation

9. Polymyositis or Dermatomyositis
   a. Significant improvement in disability and maintenance of improvement since initiation

10. Inclusion-body myositis

11. Guillain-Barre Syndrome (GBS)

12. Fetal alloimmune thrombocytopenia (F/NAIT)

13. Myasthenia gravis

14. Multiple sclerosis

15. Multifocal motor neuropathy (MMN) with ALL of the following:
   a. Significant improvement in disability and maintenance of improvement since initiation

16. Neoplastic disease

17. Chronic inflammatory demyelinating polyneuropathy (CIDP) with ALL of the following:
   a. Significant improvement in disability and maintenance of improvement since initiation
   b. IVIG is being used at the lowest effective dose and frequency
   c. Chronic stable patients have been tapered and/or treatment withdrawn to determine whether continued treatment is necessary
18. Autoimmune encephalitis

19. Lambert-Eaton Myasthenic syndrome (LEMS)

20. Parvovirus B 19-induced pure red cell aplasia (PRCA)

21. Stiff-person Syndrome

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits
Duration 12 months

Prior – Approval Renewal Limits
Duration 12 months

Rationale

Summary
IVIG is used to provide immediate passive immunity after suspected exposure to an organism for which no active immunization exists or if there is inadequate time to develop active immunization, and as replacement therapy for patients with antibody deficiencies. The passive immunity imparted by IVIG is capable of attenuating or preventing infectious diseases or deleterious reactions from toxins, mycoplasma, parasites, bacteria, and viruses. The IVIG products differ in the preparation method, viral inactivation steps, stabilizing agent, osmolality, and IgA content (1).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of IVIG while maintaining optimal therapeutic outcomes.

References
<table>
<thead>
<tr>
<th>Section:</th>
<th>Prescription Drugs</th>
<th>Effective Date:</th>
<th>January 1, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsection:</td>
<td>Biologicals</td>
<td>Original Policy Date:</td>
<td>March 8, 2002</td>
</tr>
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<td>Subject:</td>
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### Policy History

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>September 2008</td>
<td>FDA approved Gamunex for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) on 9/12/08. CIDP is approvable as off-label use for all Immune Globulins</td>
</tr>
<tr>
<td>March 2009</td>
<td>Added PriIVIgen to Immune Globulins and updated format.</td>
</tr>
<tr>
<td>November 2009</td>
<td>Off-label uses clarified; removed Gamimmune, Gammar PIV, Venoglobulin-1 and Venoglobulin-S; all of which are no longer on the market.</td>
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<tr>
<td>April 2010</td>
<td>Line extension of Hizentra, FDA approved 3/4/2010, for the treatment of...</td>
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<tr>
<td>Date</td>
<td>Events</td>
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<tr>
<td>September 2011</td>
<td>Line extension of Gamunex-C, FDA approved 10/14/2011, for primary immunodeficiency.</td>
</tr>
<tr>
<td>September 2011</td>
<td>Line extension of Gammaked, FDA approved 8/3/2011, for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP).</td>
</tr>
<tr>
<td>December 2012</td>
<td>Annual editorial review and update</td>
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<tr>
<td>February 2013</td>
<td>Line addition of BIVIGam</td>
</tr>
<tr>
<td>June 2013</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>June 2013</td>
<td>FDA: New Boxed Warning for Clot Risk with Immune Globulin, reference update</td>
</tr>
<tr>
<td>December 2013</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>February 2014</td>
<td>Revision to criteria requirements that self-administering patients are instructed to how to monitor for signs and symptoms of thrombosis.</td>
</tr>
<tr>
<td>September 2014</td>
<td>Line-addition of Octagam 10%. Reference update</td>
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<tr>
<td>November 2014</td>
<td>Addition of HyQvia for all indications</td>
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<tr>
<td>December 2014</td>
<td>Addition of a line-extension of Gamunex-C 40/400ml</td>
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<tr>
<td>March 2015</td>
<td>Annual editorial review and reference update</td>
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<tr>
<td>June 2016</td>
<td>Annual editorial review and reference update</td>
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<tr>
<td></td>
<td>Addition of CVID (common variable Immunodeficiency disease)</td>
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<tr>
<td>August 2016</td>
<td>Policy code changed from 5.05.03 to 5.20.03</td>
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<tr>
<td>October 2016</td>
<td>Addition of Autoimmune encephalitis</td>
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<tr>
<td></td>
<td>Transfer of Hizentra and Hyqvia from criteria to 5.20.08</td>
</tr>
<tr>
<td></td>
<td>Addition of all indication pre-requisites and new indications: Lambert-Eaton Myasthenic syndrome (LEMS), Parvovirus B 19-induced pure red cell aplasia (PRCA), Stiff-person Syndrome, Guillain-Barre Syndrome (GBS)</td>
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<td>December 2016</td>
<td>Annual review</td>
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**Keywords**

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2016 and is effective on January 1, 2017.

Deborah M. Smith, MD, MPH