IVIG (intravenous immunoglobulin)

**Description**

IVIG Immune Globulin – Bivigam, Flebogamma, Gammagard, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, 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)(2-11)

**Off-Label Use:** (12-27)
1. Prophylaxis of bacterial and viral infections in pediatric human immunodeficiency virus (HIV) infection
2. Prophylaxis of bacterial and viral infections in bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) recipients
3. Dermatomyositis
4. Polymyositis
5. Myasthenia gravis
6. Guillain-Barre syndrome
7. Lambert-Eaton myasthenic syndrome
8. Fetal/neonatal alloimmune thrombocytopenia
9. Parvovirus B19-induced pure red cell aplasia
10. Stiff-person syndrome

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 (13-14)

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 (2-11).

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.(2-11)

Other potential complications to monitor include the following (2-11): **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, Cablivi, 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 indicated 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 documented indications:

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 with in the past 3 months) must have ONE
of the following:

i. Children (<18 years of age) with **ONE** of the following:
   1) Significant bleeding symptoms (mucosal bleeding or moderate/severe bleeding)
   2) High risk for bleeding
   3) Rapid increase in platelets is required (eg. Surgery or procedure)

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)

**AND 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. ITP unresponsive to first-line therapy

**AND 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:
ii. Relapse after previous response to IVIG or inadequate response, intolerance or contraindication to corticosteroid therapy

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

e. 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 **ONE** 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. Electrodiagnostic studies are consistent with multifocal demyelinating abnormalities

18. Autoimmune encephalitis
   a. Confirmation of diagnosis with TWO of the following tests:
      i. Neuroimaging
      ii. Electroencephalography (EEG)
      iii. Lumbar puncture
      iv. Serologic testing

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 for ALL indications:
   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

   AND the following for ALL indications:
   a. NO concurrent therapy with another IVIG / SCIG product

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
   a. Improvement in disability and maintenance of improvement since initiation confirmed by neurological exam

19. Lambert-Eaton Myasthenic syndrome (LEMS)

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

21. Stiff-person Syndrome

**AND ONE** of the following for ALL indications:
   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
AND the following for **ALL** indications:
  a. **NO** concurrent therapy with another IVIG / SCIG product

**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**
September 2013.


20. Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology...
Interest section of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2012;130:S1-524.


### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</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>
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<tr>
<td>March 2009</td>
<td>Added PrIVIGen to Immune Globulins and updated format.</td>
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<tr>
<td>November 2009</td>
<td>Off-label uses clarified; removed Gamimune, Gammar PIV, Venoglobulin-1 and Venoglobulin-S; all of which are no longer on the market.</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>
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<td>Date</td>
<td>Event Description</td>
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<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>
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<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 BIIVGam</td>
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<tr>
<td>June 2013</td>
<td>Annual editorial review and reference update</td>
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<tr>
<td>June 2013</td>
<td>FDA: New Boxed Warning for Clot Risk with Immune Globulin, reference update</td>
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<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>
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<tr>
<td>November 2014</td>
<td>Addition of a line-extension of Gamunex-C 40/400ml</td>
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<tr>
<td>December 2014</td>
<td>Annual editorial review and reference update</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>August 2016</td>
<td>Addition of Autoimmune encephalitis</td>
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<tr>
<td>October 2016</td>
<td>Transfer of Hizentra and Hyqvia from criteria to 5.20.08</td>
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<tr>
<td>November 2016</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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<tr>
<td>December 2016</td>
<td>Annual review</td>
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<tr>
<td>March 2017</td>
<td>Annual review</td>
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<tr>
<td>October 2017</td>
<td>Addition of initiation requirement for Autoimmune encephalitis with confirmation of diagnosis with TWO of the following tests: neuroimaging, electroencephalography (EEG), lumbar puncture, or serologic testing and renewal requirement of improvement in disability and maintenance of improvement since initiation confirmed by neurological exam</td>
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<tr>
<td>December 2017</td>
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<tr>
<td>January 2018</td>
<td>Change of Myasthenia gravis requirements from ALL to ONE of the following</td>
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<tr>
<td>March 2018</td>
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<tr>
<td>October 2018</td>
<td>Addition of Panzyga</td>
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<tr>
<td>November 2018</td>
<td>Annual review and reference update. Carimune NF removed from market</td>
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<tr>
<td>June 2019</td>
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**Keywords**
This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 20, 2019 and is effective on July 1, 2019.