Reference number(s)
1985-A

STANDARD MEDICARE PART B MANAGEMENT

Intravenous Immune Globulin (IVIG):

Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga and Privigen

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Primary immunodeficiency
2. Idiopathic thrombocytopenic purpura (ITP)
3. Chronic inflammatory demyelinating polyneuropathy
4. Multifocal motor neuropathy
5. Kawasaki syndrome
6. B-cell chronic lymphocytic leukemia (CLL)
7. Dermatomyositis

B. Compendial Uses

1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
2. Acquired thrombocytopenia
3. Antiphospholipid syndrome
4. Asthma
5. Autoimmune hemolytic anemia
6. Autoimmune neutropenia
7. Bone marrow transplant/hematopoietic stem cell transplant
8. Cerebellar ataxia due to Epstein-Barr virus infection
9. Clostridium difficile colitis
10. Adjunct to Crohn's disease treatment
11. Cytomegalovirus treatment and prophylaxis
12. Desensitization therapy – heart transplant
13. Diabetic amyotrophy
14. Hopkins' syndrome
15. Acute disseminated encephalomyelitis
16. Prophylaxis of enteritis due to rotavirus
17. Epilepsy
18. Gastroenteritis
19. Granulomatosis with polyangiitis
20. Guillain-Barre syndrome
21. Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis

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22. Hemophagocytic syndrome
23. Induction of Factor VIII immune tolerance
24. Measles (Rubeola) prophylaxis
25. Moderate and severe immune checkpoint inhibitor-related toxicities
26. Hypogammaglobulinemia from CAR-T therapy
27. Herpes gestationis
28. Prevention of bacterial infections in HIV infected patients
29. Prevention of bacterial infections in post-surgical or ICU patients
30. Isaacs syndrome
31. Japanese encephalitis virus disease
32. Severe IgA nephropathy
33. Lambert-Eaton myasthenic syndrome
34. Linear IgA dermatosis
35. Lysinuric protein intolerance
36. Prevention of bacterial infections in patients with multiple myeloma
37. Multiple sclerosis
38. Myasthenia gravis
39. Myocarditis
40. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
41. Neonatal jaundice
42. Otitis media
43. Paraneoplastic visual loss
44. Polyarteritis nodosa
45. Polymyositis
46. Post-transplant lymphoproliferative disorder
47. Pure red cell aplasia
48. Pyoderma gangrenosum
49. Renal transplant rejection
50. Respiratory syncytial virus infection
51. Sepsis
52. Stevens-Johnson syndrome
53. Stiff-person syndrome
54. Systemic lupus erythematosus
55. Systemic onset juvenile chronic arthritis
56. Systemic vasculitis
57. Tetanus treatment and prophylaxis
58. Fetal or neonatal thrombocytopenia
59. Toxic epidermal necrolysis
60. Toxic necrotizing fasciitis
61. Toxic shock syndrome
62. Heart transplant rejection
63. Desensitization of highly sensitized patients awaiting renal transplantation
64. Uveitis
65. Varicella prophylaxis
66. Von Willebrand disorder

C. Nationally Covered Indication

Centers for Medicare and Medicaid Services guidelines provide coverage for IG for the following autoimmune mucocutaneous conditions pursuant to the criteria in Section III:

1. Pemphigus vulgaris

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2. Pemphigus foliaceus
3. Bullous pemphigoid
4. Mucous membrane pemphigoid (cicatricial pemphigoid)
5. Epidermolysis bullosa acquisita

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions (where applicable):

A. Primary immunodeficiency
   1. Diagnostic test results
      a. Copy of laboratory report with serum immunoglobulin levels: IgG, IgA, IgM, and IgG subclasses
      b. Vaccine response to pneumococcal polysaccharide vaccine (post-vaccination *Streptococcus pneumoniae* antibody titers)
      c. Pertinent genetic or molecular testing in members with a known genetic disorder
      d. Copy of laboratory report with lymphocyte subset enumeration by flow cytometry
   2. IgG trough level for those continuing with IG therapy

B. Myasthenia gravis
   1. Clinical records describing standard treatments tried and failed

C. Secondary hypogammaglobulinemia (e.g., CLL, BMT/HSCT recipients)
   1. Copy of laboratory report with pre-treatment serum IgG level

D. Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN)
   1. Pre-treatment electrodiagnostic studies (electromyography [EMG] or nerve conduction studies [NCS])

E. Dermatomyositis and polymyositis
   1. Clinical records describing standard treatments tried and failed

F. Lambert-Eaton Myasthenic Syndrome (LEMS)
   1. Neurophysiology studies (e.g., electromyography)
   2. A positive anti- P/Q type voltage-gated calcium channel antibody test

G. Idiopathic thrombocytopenic purpura
   1. Laboratory report with pre-treatment/current platelet count
   2. Chronic/persistent ITP: copy of medical records supporting trial and failure with corticosteroid or anti-D therapy (unless contraindicated)

H. Stiff-person syndrome
   1. Anti-glutamic acid decarboxylase (GAD) antibody testing results
   2. Clinical records describing standard treatments tried and failed

I. Toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus
   1. Documented presence of fasciitis (toxic necrotizing fasciitis due to group A streptococcus only)
   2. Microbiological data (culture or Gram stain)

III. CRITERIA FOR INITIAL APPROVAL

A. Primary immunodeficiency

Initial authorization of 6 months may be granted for members with any of the following diagnoses:

1. Severe combined immunodeficiency (SCID) or congenital agammaglobulinemia (e.g., X-linked or autosomal recessive agammaglobulinemia):

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a. Diagnosis confirmed by genetic or molecular testing, or
b. Pretreatment IgG level < 200 mg/dL, or
c. Absence or very low number of T cells (CD3 T cells < 300/microliter) or the presence of maternal T cells in the circulation (SCID only)

2. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non-SCID combined immunodeficiency):
   a. Diagnosis confirmed by genetic or molecular testing (if applicable), and
   b. History of recurrent bacterial infections (e.g., pneumonia, otitis media, sinusitis, sepsis, gastrointestinal), and
   c. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)
3. Common variable immunodeficiency (CVID)
   a. Age 2 years or older, and
   b. Other causes of immune deficiency have been excluded (e.g., drug induced, genetic disorders, infectious diseases such as HIV, malignancy), and
   c. Pretreatment IgG level < 500 mg/dL or ≥ 2 SD below the mean for age, and
   d. History of recurrent bacterial infections, and
   e. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)
4. Hypogammaglobulinemia (unspecified), IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency:
   a. History of recurrent bacterial infections, and
   b. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A), and
   c. Any of the following pre-treatment laboratory findings:
      i. Hypogammaglobulinemia: IgG < 500 mg/dL or ≥ 2 SD below the mean for age
      ii. Selective IgA deficiency: IgA level < 7 mg/dL with normal IgG and IgM levels
      iii. Selective IgM deficiency: IgM level < 30 mg/dL with normal IgG and IgA levels
      iv. IgG subclass deficiency: IgG1, IgG2, or IgG3 ≥ 2 SD below mean for age assessed on at least 2 occasions; normal IgG (total) and IgM levels, normal/low IgA levels
      v. Specific antibody deficiency: normal IgG, IgA and IgM levels
5. Other predominant antibody deficiency disorders must meet a., b., and c.i. in section 4. above.
6. Other combined immunodeficiency must meet criteria in section 2. above.

B. Myasthenia gravis

1. Authorization of 1 month may be granted to members who are prescribed IG for worsening weakness, acute exacerbation, or in preparation for surgery.
   a. Worsening weakness includes an increase in any of the following symptoms: diplopia, ptosis, blurred vision, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Acute exacerbations include more severe swallowing difficulties and/or respiratory failure
   b. Pre-operative management (e.g., prior to thymectomy)
2. Authorization of 6 months may be granted to members with refractory myasthenia gravis who have tried and failed 2 or more standard therapies (e.g., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, rituximab).

C. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Authorization of 3 months may be granted for treatment of chronic inflammatory demyelinating polyneuropathy when the following criteria are met:

1. Disease course is progressive or relapsing/remitting for 2 months or longer
2. Moderate to severe functional disability

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3. The diagnosis was confirmed by electrodiagnostic studies

D. Dermatomyositis or Polymyositis

Authorization of 3 months may be granted when the following criteria are met:

1. Member has at least 4 of the following:
   a. Proximal muscle weakness (upper or lower extremity and trunk)
   b. Elevated serum creatine kinase (CK) or aldolase level
   c. Muscle pain on grasping or spontaneous pain
   d. Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)
   e. Positive for anti-synthetase antibodies (e.g., anti-Jo-1, also called histadyl tRNA synthetase)
   f. Non-destructive arthritis or arthralgias
   g. Systemic inflammatory signs (fever: more than 37°C at axilla, elevated serum CRP level or accelerated ESR of more than 20 mm/h by the Westergren method),
   h. Pathological findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen), and
2. Standard first-line treatments (corticosteroids) and second-line treatments (immunosuppressants) have been tried but were unsuccessful or not tolerated, or
3. Member is unable to receive standard first-line and second-line therapy because of a contraindication or other clinical reason.

E. Idiopathic Thrombocytopenic Purpura (ITP)/Immune Thrombocytopenia

1. Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy: authorization of 1 month may be granted when the following criteria are met:
   a. Children (< 18 years of age)
      i. Significant bleeding symptoms (mucosal bleeding or other moderate/severe bleeding) or
      ii. High risk for bleeding* (see Appendix B), or
      iii. Rapid increase in platelets is required* (e.g., surgery or procedure)
   b. Adults (≥ 18 years of age)
      i. Platelet count < 30,000/mcL, or
      ii. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required*, and
      iii. Corticosteroid therapy is contraindicated and IG will be used alone or IG will be used in combination with corticosteroid therapy
2. Chronic/persistent ITP (≥ 3 months from diagnosis) or ITP unresponsive to first-line therapy: authorization of 6 months may be granted when the following criteria are met:
   a. Platelet count < 30,000/mcL, or
   b. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding* or rapid increase in platelets is required*, and
   c. Relapse after previous response to IG or inadequate response/intolerance/contraindication to corticosteroid or anti-D therapy
3. Adults with refractory ITP after splenectomy: authorization of 6 months may be granted when either of the following criteria is met:
   a. Platelet count < 30,000/mcL, or
   b. Significant bleeding symptoms
4. ITP in pregnant women: authorization through delivery may be granted to pregnant women with ITP.

   * The member's risk factor(s) for bleeding (see Appendix B) or reason requiring a rapid increase in platelets must be provided.

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F. B-cell chronic lymphocytic leukemia (CLL)

Authorization of 6 months may be granted for treatment of B-cell chronic lymphocytic leukemia (CLL) when all of the following criteria are met:

1. IG is prescribed for prophylaxis of bacterial infections.
2. Member has a history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.
3. Member has a pretreatment serum IgG level <500 mg/dL.

G. Bone marrow transplant/hemopoietic stem cell transplant (BMT/HSCT)

Authorization of 6 months may be granted to members who are BMT/HSCT recipients when the following criteria are met:

a. Therapy will be used to prevent the risk of acute graft-versus-host disease, associated interstitial pneumonia (infectious or idiopathic), septicemia, and other infections (e.g., cytomegalovirus infections [CMV], recurrent bacterial infection).
b. Either of the following:
   i. IG is requested within the first 100 days post-transplant.
   ii. Member has a pretreatment serum IgG < 400 mg/dL

H. **Multifocal Motor Neuropathy (MMN)**

Authorization of 3 months may be granted for treatment of multifocal motor neuropathy when the following criteria are met:

1. Member experienced progressive, multifocal, asymmetrical weakness without objective sensory loss in 2 or more nerves for at least 1 month
2. The diagnosis was confirmed by electrodiagnostic studies

I. Guillain-Barre syndrome (GBS)

Authorization of 1 month total may be granted for GBS when the following criteria are met:

1. Member has severe disease with significant weakness (e.g., inability to stand or walk without aid, respiratory weakness)
2. Onset of neurologic symptoms occurred less than 4 weeks from the anticipated start of therapy

J. Lambert-Eaton myasthenic syndrome (LEMS)

Authorization of 6 months may be granted for LEMS when the following criteria are met:

1. Diagnosis has been confirmed by either of the following:
   a. Neurophysiology studies (e.g., electromyography)
   b. A positive anti- P/Q type voltage-gated calcium channel antibody test
2. Anticholinesterases (e.g., pyridostigmine) and amifampridine (e.g., 3,4-diaminopyridine phosphate, Firdapse) have been tried but were unsuccessful or not tolerated
3. Weakness is severe or there is difficulty with venous access for plasmapheresis

K. **Kawasaki syndrome**

Authorization of 1 month may be granted for treatment of Kawasaki syndrome in pediatric patients.

L. Stiff-person syndrome

Authorization of 6 months may be granted for stiff-person syndrome when the following criteria are met:

1. Diagnosis has been confirmed by anti-glutamic acid decarboxylase (GAD) antibody testing
2. Member had an inadequate response to first-line treatment (benzodiazepines and/or baclofen)

M. Moderate and severe immune checkpoint inhibitor-related toxicities

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Authorization of 1 month may be granted for management of immune checkpoint-inhibitor toxicities when all of the following criteria are met:

1. Member has experienced a moderate or severe adverse event to a PD-1 or PD-L1 inhibitor (e,g., pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab)
2. The offending medication has been held or discontinued
3. Member experienced one or more of the following adverse events: myocarditis, bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, myasthenia gravis, peripheral neuropathy, encephalitis, transverse myelitis, severe inflammatory arthritis, Guillain-Barre syndrome, or steroid-refractory myalgias or myositis

N. Acute disseminated encephalomyelitis

Authorization of 1 month may be granted for acute disseminated encephalomyelitis in members who have had an insufficient response or a contraindication to intravenous corticosteroid treatment.

O. Autoimmune mucocutaneous blistering disease

Authorization of 6 months may be granted for treatment of biopsy proven autoimmune mucocutaneous blistering diseases when all of the following criteria are met:

1. Member has one of the following diagnoses: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid), or epidermolysis bullosa acquisita.
2. At least one of the following criteria is met regarding prior treatment with conventional therapy:
    a. Member has failed conventional therapy
    b. Member has a contraindication to conventional therapy
    c. Member has rapidly progressive disease and a clinical response could not be affected quickly enough using conventional agents, and IG will be given in combination with conventional treatment.
3. IG will be used for short-term control of the member's condition and will not be used as maintenance therapy.

P. Autoimmune hemolytic anemia

Authorization of 6 months may be granted for treatment of autoimmune hemolytic anemia in members who do not respond or have a contraindication to corticosteroids or splenectomy.

Q. Autoimmune neutropenia

Authorization of 6 months may be granted for treatment of autoimmune neutropenia where treatment with G-CSF (granulocyte colony stimulating factor) is not appropriate.

R. Acquired Thrombocytopenia

Authorization of 1 month may be granted for acquired thrombocytopenia.

S. Prevention of bacterial infections in patients with multiple myeloma

Authorization of 6 months may be granted for multiple myeloma in members who have recurrent, serious infections despite the use of prophylactic antibiotics.

T. Japanese encephalitis virus disease

Authorization of 1 month may be granted for Japanese encephalitis virus disease

U. Measles (Rubeola) prophylaxis

Authorization of 1 month may be granted for postexposure prophylaxis to prevent or modify symptoms of measles (rubeola) in susceptible members exposed to the disease less than 6 days previously.

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V. Multiple sclerosis
Authorization of 6 months may be granted for treatment of relapsing-remitting multiple sclerosis (RRMS).

W. Stevens-Johnson syndrome
Authorization of 1 month may be granted for severe cases of Stevens-Johnson syndrome

X. Tetanus treatment and prophylaxis
Authorization of 1 month may be granted for treatment or postexposure prophylaxis of tetanus as an alternative when tetanus immune globulin (TIG) is unavailable.

Y. Toxic epidermal necrolysis
Authorization of 1 month may be granted for severe cases of toxic epidermal necrolysis

Z. Toxic shock syndrome
Authorization of 1 month may be granted for staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the member has persistent oliguria with pulmonary edema.

AA. Systemic lupus erythematosus (SLE)
Authorization of 6 months may be granted for severe, active SLE in members who have experienced inadequate response, intolerance or have a contraindication to first and second line therapies.

BB. Toxic Necrotizing Fasciitis Due To Group A Streptococcus
Authorization of 1 month may be granted for members with fasciitis due to invasive streptococcal infection

CC. Varicella prophylaxis
Authorization of 1 month may be granted for postexposure prophylaxis of varicella in susceptible individuals when varicella-zoster immune globulin (VZIG) is unavailable.

DD. Other indications
Authorization of 6 months may be granted for the following indications:

1. Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy or CAR-T therapy
2. Antiphospholipid syndrome
3. Asthma
4. Cerebellar ataxia due to Epstein-Barr virus infection
5. Clostridium difficile colitis
6. Adjunct to Crohn's disease treatment
7. Cytomegalovirus treatment and prophylaxis when the member is undergoing a transplant
8. Desensitization therapy – heart transplant
9. Diabetic amyotrophy
10. Hopkins' syndrome
11. Prophylaxis of enteritis due to rotavirus
12. Epilepsy
13. Fetal or neonatal thrombocytopenia
14. Gastroenteritis
15. Granulomatosis with polyangiitis

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16. Hemolytic disease of fetus or newborn due to RhD isoimmunization
17. Hemophagocytic syndrome
18. Induction of Factor VIII immune tolerance
19. Herpes gestationis
20. Prevention of bacterial infections in HIV infected patients
21. Prevention of bacterial infections in post-surgical or ICU patients
22. Isaacs syndrome
23. Severe IgA nephropathy
24. Linear IgA dermatosis
25. Lysinuric protein intolerance
26. Myocarditis
27. Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
28. Neonatal jaundice
29. Otitis media
30. Paraneoplastic visual loss
31. Polyarteritis nodosa
32. Post-transplant lymphoproliferative disorder
33. Pure red cell aplasia
34. Pyoderma gangrenosum
35. Renal transplant rejection
36. Respiratory syncytial virus infection
37. Sepsis
38. Systemic onset juvenile chronic arthritis
39. Systemic vasculitis
40. Heart transplant rejection
41. Desensitization of highly sensitized patients awaiting renal transplantation
42. Uveitis
43. Von Willebrand disorder

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

A. **Primary Immunodeficiency**
Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with IG
2. The member is receiving benefit from therapy. Benefit is defined as:
   a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IG therapy, AND
   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), OR
   c. The prescriber will re-evaluate the dose of IG and consider a dose adjustment (when appropriate).

B. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**
Authorization for 6 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with IG
2. The member is receiving benefit from therapy. Benefit is defined as:

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a. Significant improvement in disability and maintenance of improvement since initiation of IG therapy, AND
b. IG is being used at the lowest effective dose and frequency

C. Acquired Thrombocytopenia, Acute disseminated encephalomyelitis, Guillain-Barre syndrome, Japanese encephalitis virus disease, Kawasaki syndrome, Measles prophylaxis, Moderate and severe immune checkpoint inhibitor-related toxicities, Steven's Johnson syndrome, Tetanus treatment and prophylaxis, Toxic epidermal necrolysis, Toxic shock syndrome, Toxic Necrotizing Fasciitis Due To Group A Streptococcus, Varicella prophylaxis
Authorization for members who are requesting authorization for continuation of therapy of IG must meet all initial authorization criteria.

D. All other indications
Authorization of 6 months may be granted when ALL of the following criteria are met:
1. The member is currently receiving therapy with IG
2. IG is being used to treat an indication enumerated in Section III
3. The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

V. APPENDICES

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine
- Age 2 years and older: impaired antibody response demonstrated to vaccination with a pneumococcal polysaccharide vaccine
- Not established for children less than 2 years of age
- Excludes the therapy initiated in the hospital setting

Appendix B: Examples of Risk Factors for Bleeding (not all inclusive)
- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (e.g., peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession or lifestyle predisposes patient to **trauma** (e.g., construction worker, fireman, professional athlete)

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