DR.002.D Intravenous Immune Globulin (IVIG)

Original Implementation Date: 07/15/2018
Version [D] Date: 2/23/2023
Last Reviewed Date: December 2022

PRODUCT VARIATIONS

This policy applies to all Health Partners Plans (HPP) product lines unless noted below.

POLICY STATEMENT

Health Partners Plans (HPP) considers Intravenous Immune Globulin (IVIG) medically necessary when used to treat its approved FDA labeled indications AND all the prior authorization criteria listed in the policy are met.

OFF-LABEL USE

Authorization for off-labeled use of medication will be evaluated on an individual basis. Review of an off-labeled request by the Medical Staff will be predicated on the appropriateness of treatment and full consideration of medical necessity. For off label use Medical Directors will review scientific literature and local practice patterns. Medical Directors will review all the provided documentation to assure that:

1. The diagnosis of the disorder is reasonably certain and based on a thorough history and examination and appropriate laboratory testing (such as electromyography (EMG), spinal fluid tests, serum tests, and biopsy findings).
2. Previous treatment failures are documented (when applicable).
3. The requested dose and interval of administration are consistent with recommendations in peer-reviewed literature and professional guidelines for the requested indication.
4. Once treatment is initiated, there is an adequate documentation of improvement for continued treatment to be medically necessary.
    a. An objective quantitative assessment to monitor the progress is required, when applicable.
5. Depending on the diagnosis and clinical circumstances, an attempt is made to decrease/wean the dosage when improvement has occurred. An attempt to stop the IVIG infusion when clinically appropriate for the diagnosis is made if improvement is sustained with dosage reduction. If improvement does not occur with IVIG, continued infusion may not be considered medically necessary (this does not apply to persons with primary immune deficiency diseases).

Off-Labeled use includes the following (not an all-inclusive list):

- Auto immune mucocutaneous blistering diseases.
- Dermatomyositis.
- Fetal/neonatal alloimmune thrombocytopenia (FAIT).
- Guillain-Barre syndrome (GBS).
- Lambert-Eaton myasthenic syndrome.
- Multifocal motor neuropathy.
- Myasthenia gravis.
- Parvovirus B19-induced pure red cell aplasia (PRCA).
- Polymyositis.
- Prophylaxis of bacterial and viral infection in pediatric human immunodeficiency virus (HIV) infection.
- Prophylaxis of bacterial and viral infections in bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) recipients
- Relapsing-Remitting Multiple Sclerosis (not primary or secondary progressive)
- Stiff-person syndrome
- Toxic Shock Syndrome

The use of IVIG or Subcutaneous Immune Globulin (SCIG) is considered experimental, investigational, or unproven for any of the following indications: (this may not be all-inclusive):

- Hashimoto encephalopathy
- Inclusion body myositis (IBM)
- Lyme neuropathy
- Neonatal sepsis
- Pediatric acute-onset neuropsychiatric syndrome (PANS) and Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS), Primary progressive multiple sclerosis (MS) and secondary progressive MS, acute MS exacerbations, or clinically isolated syndrome, recurrent pregnancy loss.

FDA APPROVED INDICATIONS

- Ascenive®
- Atgam®
- Bivigam®
- Carimune NF®
- Flebogamma®
- Gammagard Liquid®
- Gammagard S/D®
- Gammaked®
- Gammaplex®
- Gamunex-C®
- Octagam®
- Panzyga®
- Privigen®
- Thymoglobulin®

(FDA approved indications may vary by product)

PRIOR AUTHORIZATION CRITERIA

Criteria Reference By Medical Condition

- **I.** Primary Immunodeficiency Disorder (PID)
- **II.** Secondary Immunodeficiency
- **III.** Infectious Disease
- **IV.** Transplant
- **V.** Hematology
- **VI.** Neurology
- **VII.** Rheumatology
- **VIII.** Dermatology

I. Primary Immunodeficiency Disorder

A. Therapy is considered medically necessary under the following conditions:

I. Hypogammaglobulinemia (including Common Variable Immunodeficiency [CVID])

1. Labs confirming IgG below the normal reference range on at least two occasions
2. Impaired antibody response to pneumococcal polysaccharide vaccine *or* tetanus and diptheria *or* HiB
3. Recurrent serious bacterial infections that require multiple or extended courses of antibiotics

II. IgG Subclass Deficiency

1. Labs confirming IgG for at least one subclass (excluding subclass IgG4) below the normal reference range on at least two occasions
2. Impaired antibody response to pneumococcal polysaccharide vaccine
3. Recurrent serious bacterial infections that require multiple or extended courses of antibiotics

A. Documentation that underlying conditions (such as asthma, allergic rhinitis) are controlled

III. Primary Immunodeficiency Disorders (other indications)

1. Diagnosis confirmed by genetic or molecular testing (if applicable), *and (the following not applicable for patients < 2 years old)*
2. History of recurrent bacterial infections (such as pneumonia, otitis media, sinusitis, sepsis, gastrointestinal, *and*
3. Impaired antibody response to pneumococcal polysaccharide vaccine (not required for children younger than 2 years of age and members with severe PIDD and very low IGG levels, who generally have poor immunological response to antigens).

IV. Specific Antibody Deficiency (SAD)

1. Labs confirming normal IgG, IgG subclass, IgA and IgM levels
2. Normal response to proteins (tetanus and diphtheria toxoid)
3. Impaired antibody response to pneumococcal polysaccharide vaccine
4. Recurrent serious bacterial infections
    A. Documentation that underlying conditions (such as asthma, allergic rhinitis) are controlled

II. Secondary Immunodeficiency

A. Acquired Immunodeficiency due to hematologic malignancy, major surgery (such as heart transplant), extensive burns, collagen-vascular disease
    i. Labs confirming hypogammaglobulinemia (IgG < 400 mg/dL)
    ii. Recurrent sinopulmonary infection or serious bacterial infection(s)

B. B-cell Chronic Lymphocytic Leukemia (CLL)
    i. Labs confirming IgG < 500 mg/dL
    ii. Recurrent sinopulmonary infection or serious bacterial infection(s)

C. HIV-infection in Pediatrics
    i. Primary prophylaxis of bacterial infections
        1. Labs confirming hypogammaglobulinemia (IgG < 400 mg/dL)
    ii. Secondary prophylaxis when the following are met
        1. Recurrent serious bacterial infections
        2. Failure of antibiotic prophylaxis
        3. Documentation that patient is on effective antiretroviral therapy

D. Multiple Myeloma
    i. Recurrent serious bacterial infection(s)

III. Infectious Disease

A. Toxic Shock Syndrome (staphylococcal or streptococcal)
    i. Refractory to aggressive treatment
    ii. Undrainable focus
    iii. Persistent oliguria with pulmonary edema

IV. Transplant

A. BK Viremia
    i. Refrectory BK viremia in kidney transplant

B. CMV Viremia
    i. Refractory CMV viremia in solid organ transplant

C. Hematopoietic Cell Transplant (HCT)
    i. Labs confirming hypogammaglobulinemia (IgG < 400 mg/dL) *AND one of the following:*
        1. Transplant less than 100 days ago *or*
        2. Transplant after 100 days with recurrent infections
        3. Transplant after 100 days with evidence of graft-versus-host-disease

D. Solid Organ Transplant
    i. When being used as desensitization therapy prior to and immediately after transplant *OR*
    ii. When being used for antibody-mediated rejection (AMR)

V. Hematology

A. Parvovirus B19-induced pure red cell aplasia (PRCA)
   i. Severe refractory anemia
   ii. Evidence of parvovirus viremia

B. Fetal Alloimmune Thrombocytopenia (FAIT)
   i. Confirmation of maternal antibodies to paternal platelet antigen *AND one of the following*
      1. Previous FAIT pregnancy *OR*
      2. Fetal blood confirms thrombocytopenia

C. Immune (idiopathic) Thrombocytopenia (ITP) in Adults with Platelet count < 30,000/mm_3 a one of the following:
   i. Clinical need to rapidly replenish platelet count (such as in the setting of acute bleeding, prior to major surgery, risk of cerebral hemorrhage)
   ii. Not a candidate for splenectomy, or is status-post splenectomy *AND*
      1. Failure, contraindication, or intolerance to *all* the following
         a. Corticosteroids
         b. Thrombopoietin receptor agonists (such as eltrombopag or romiplostim)
         c. Rituximab

D. Immune (idiopathic) Thrombocytopenia (ITP) in Pediatrics
   i. Clinical need to rapidly replenish platelet count (such as in the setting of acute bleeding, prior to major surgery, risk of cerebral hemorrhage) *OR*
   ii. Prevention of bleeding during the first 12 months of persistent disease

E. Immune (idiopathic) Thrombocytopenia (ITP) in Pregnancy
   i. Diagnosis of thrombocytopenia *AND*
   ii. Failure, contraindication, or intolerance to corticosteroids *OR*
   iii. Clinical need to rapidly replenish platelet count (such as in the setting of acute bleeding, prior to major surgery, risk of cerebral hemorrhage)

VI. Neurology

A. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
   i. Progressive or relapsing and remitting symptoms for two months or longer *AND*
   ii. Present in more than one limb
   iii. Hyporeflexia or areflexia in affected limbs
   iv. Electrophysiologic findings indicate demyelinating neuropathy (*at least 3 of the following*)
      1. Partial conduction block of ≥ 1 motor nerve
      2. Reduced conduction velocity of ≥ 2 motor nerves
      3. Prolonged distal latency of ≥ 2 motor nerves
      4. Prolonged F-wave latencies of ≥ 2 motor nerves or the absence of F waves
   v. The following causes of demyelinating neuropathy have been excluded *(from the European Federation of Neurological Societies and the Peripheral Nerve Society):*
      1. Borrelia burgdorferi infection (Lyme disease)
      2. Diphtheria, drug or toxin exposure probably to have caused the neuropathy
      3. Hereditary demyelinating neuropathy
      4. Prominent sphincter disturbance

5. Diagnosis of multifocal motor neuropathy
6. IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein
7. Other causes for demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma and amyloidosis

B. Guillain-Barre Syndrome (GBS)
   i. Symptoms began less than 6 weeks ago
   ii. Severe disease requiring assistance to ambulate

C. Lambert-Eaton Myasthenic Syndrome
   i. Failure, contraindication, or intolerance to symptomatic therapies (acetylcholinesterase inhibitors such as mestinon and immunosuppresants such as prednisone, azathioprine)

D. Multifocal Motor Neuropathy (MMN)
   i. Diagnosis of definite or probable MMN supported by nerve conduction studies showing focal demyelination and conduction block in motor nerves and normal sensory nerves
   ii. Findings rule out other conditions that may not respond to IVIG treatment

E. Myasthenia Gravis (acute)
   i. In the setting of acute crisis (approve up to 5 days)
   ii. In the setting of thymectomy (prior to and acutely for post-operative period)
   iii. When initiating immunosuppressive treatment

F. Myasthenia Gravis (refractory, *up to 12 month approval*)
   i. Failure, contraindication, or intolerance to pyridostigmine, *AND*
   ii. Failure, contraindication, or intolerance to corticosteroid maintenance treatment, *AND*
   iii. Failure, contraindication, or intolerance to (at least one of the following)
      1. azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus
   iv. Confirmation of failure or contraindication to thymectomy

G. Relapsing-Remitting Multiple Sclerosis (RRMS)
   i. Failure of *TWO* formulary products indicated for the treatment RRMS

H. Stiff-Person Syndrome
   i. Confirmation of anti-glutamic acid decarboxylase (GAD) antibodies
   ii. Failure of at least two of the following from different classes:
      1. benzodiazepines, baclofen, gabapentin, valproate, levetiracetam, clonidine, tizanidine

VII. Rheumatology

A. Dermatomyositis or Polymyositis
   i. Diagnosis confirmed by muscle biopsy
   ii. Failure of corticosteroids
   iii. Failure of least two other immunosuppressants (such as azathioprine, cyclosporine, mycophenolate, methotrexate, tacrolimus, cyclophosphamide, etc.)
   iv. Acute and profound muscular weakness

B. Kawasaki Disease
   i. For the prevention of coronary artery aneurysms at the time of diagnosis

VIII. Dermatology

A. Auto-immune Mucocutaneous Blistering disease (such as bullous pemphigoid, epidermolysis bullosa aquisita, mucus membrane pemphigoid (or cicatricial pemphigoid)) [not to be approved as maintenance therapy, *approvable up to 6 consecutive months*)]
   i. In the setting of severe disease that is extensive and debilitating
   ii. Failure, contraindication, or intolerance to standard therapy (such as azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus)

B. Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)
   i. Approvable for acute treatment

Initial Authorization is up to 6 months unless otherwise noted within specific criteria by indication.

Authorization for renewal is up to 6 months (up to 12 months for Pid and refractory mg)**.**

DOSAGE AND ADMINISTRATION

Dosing Recommendations:

- Patient's dose should be reduced to the lowest necessary to maintain benefit for their condition
- Patients who have tolerated dose reduction and continue to show sustained improvement should have had a trial of treatment discontinuation, with the following exceptions:
  - PID would be excluded from a trial of discontinuation
  - HIV-infected children should show satisfactory control of the underlying disease (e.g., undetectable viral load, CD4 counts elevated above 200 or >15% [ages 9 months-5years] on antiretroviral therapy, etc.]
  - Solid organ transplant, CLL, and MM patients should not be at an increased risk of infection
- Dosing should be calculated using adjusted body weight if one or more of the following criteria are met:
  - Patient's body mass index (BMI) is 30 kg/m2 or more; OR
  - Patient's actual body weight is 20% higher than his or her ideal body weight (IBW)
- Use the following dosing formulas to calculate the adjusted body weight (round dose to nearest 5-gram increment in adult patients):
  - BMI = 703 x (weight in pounds/height in inches2)
  - IBW (kg) for males = 50 kg + [2.3 kg (height in inches- 60)]
  - IBW (kg) for females = 45.5 kg + [2.3 kg (height in inches – 60)]
  - AdjBW = IBW + [0.4 + (TBW-IBW)]
- This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.
- Dose by indication (not all inclusive):

- Auto-immune blistering diseases: Up to 2 g/kg divided over 5 days in a 28-day cycle
- Bone Marrow or Stem Cell Transplant: 500 mg/kg once weekly x 90 days, then 500 mg/kg every 3 to 4 weeks for up to 360 days post-transplant
- CIDP: 2 g/kg divided over 2-5 days initially, then 1 g/kg administered in 1-2 infusions every 21 days
- CLL/MM: 400 mg/kg every 3 to 4 weeks
- Dermatomyositis/Polymyositis: 2 g/kg divided over 2 to 5 days in a 28-day cycle
- FAIT: up to 2 g/kg/week until delivery
- Guillain-Barre: 2 g/kg divided over 5 days x 1 course
- ITP: 2 g/kg divided over 5 days or 1 g/kg once daily for 2 consecutive days in a 28-day cycle
- Kawasaki's Disease (pediatric patients) 1 g/kg to 2 g/kg x 1 course
- Multifocal Motor Neuropathy: Up to 2.4 g/kg in a 28-day cycle
- Myasthenia Gravis: 1-2 g/kg divided as either 0.5 g/kg daily x 2 days or 0.4 g/kg daily x 5 days x 1 course
- Neonatal Alloimmune Thrombocytopenia: 1 g/kg x 1 dose may be repeated once if needed.
- Pediatric HIV: 400 mg/kg every 2 to 4 weeks
- PID: 200 to 800 mg/kg every 21 to 28 days
- Stiff Person: 2 g/kg divided over 5 days in a 28-day cycle
- Toxic shock syndrome: 2 g/kg divided over 3 days x 1 course

RISK FACTORS/SIDE EFFECTS

IgA deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur. Aseptic meningitis syndrome (AMS) may occur, especially with high doses or rapid infusion. Hemolysis that is either intravascular or due to enhanced red blood cell sequestration may occur.

Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia. Elevations of systolic and diastolic blood pressure (including cases of hypertensive urgency) have been observed during/shortly following Privigen infusion. These blood pressure elevations were resolved or significantly improved within hours with either observation alone or changes in oral anti-hypertensive therapy.

Check patients for a history of hypertension and monitor blood pressure during and following Privigen infusion. Products are made from human blood and may contain infectious agents, e.g., viruses, the variant Creutzfeldt Jakob disease [vCJD] agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Antithymocyte globulins can cause anaphylaxis when injected intravenously.

MONITORING

Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure. Monitor patients for pulmonary adverse reactions (transfusion-r

BLACK BOX WARNING

Thrombosis, renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with intravenous immune globulin

CLINICAL EVIDENCE

N/A

BACKGROUND

N/A

CODING

Note*:* The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that *may* be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT® is a registered trademark of the American Medical Association.

CPT Code	Description
N/A	N/A

HCPCS Code	Description
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1554	Injection, immune globulin (Asceniv), 500 mg
J1556	Injection, immune globulin (Bivigam), 500 mg

J1557	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 Codes	Description
N/a	N/a

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making.

Policy Bulletins are developed by Health Partners Plans (HPP) to assist in administering plan benefits and constitute neither offers of coverage nor medical advice.

This Policy Bulletin may be updated and therefore is subject to change.

For HealthChoices (Medicaid) and Children's Health Insurance Program (CHIP) products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2022 Annual review. Added: Asceniv® and PANZYGA® J1599 was added to the coding table.	D	2/23/2023

Policy formatting revised.		
2021 Annual review. Primary inherited immunodeficiency (PID) broken out into multiple sections. Additional specialists added. J1554 added to coding table.	C	7/1/2021
2020 Annual policy review. Updated policy language to include additional prior authorization criteria.	B	8/1/2020
2019 Annual policy review. Coding table added. No changes to policy language.	A	7/15/2018
New Policy	A	7/15/2019

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