09-J0000-06

Original Effective Date: 12/15/99

Reviewed: 05/13/26

Revised: 10/1/26

Subject: Immune Globulin Therapy

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Position Statement	Dosage/ Administration	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Intravenous immune globulin (IVIG) (Alyglo, Asceniv®, Flebogamma DIF, Gammagard® Liquid, Gammagard Liquid ERC, Gammagard® S/D, Gammagard® S/D Less IgA, Gammaplex®, Gammaked™, Gamunex®-C, Octagam®, Panzyga®, Privigen®, Bivigam®, Yimmugo, and Qivigy) 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 immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune component. The U.S. Food and Drug Administration (FDA) approved and off-label indications are listed below.

Subcutaneous immune globulin (SCIG) (Cutaquig®, Cuvitru™, Gammagard® Liquid, Gammagard Liquid ERC, Gammaked™, Gamunex®-C, Hizentra®,HyQvia®, Xembify®) are FDA approved for the use in primary immunodeficiency. Hizentra is also FDA approved as maintenance therapy for chronic inflammatory demyelinating polyneuropathy (CIDP).

POSITION STATEMENT:

Site of Care: If intravenous immune globulin (IVIG) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46, Site of Care Policy for Select Non-Oncology Medications.

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, or emergency facility is not considered medically necessary. This statement applies to Cutaquig®, Cuvitru™, Hizentra®, HyQvia®, Xembify®, and the following immune globulin products only when administered subcutaneously: Gammagard® Liquid, Gammaked™, Gamunex®-C.

NOTE for Asceniv (J1554): For member contracts that include comparative effectiveness language, the relative cost of Asceniv compared to other immune globulin treatment may be considered in the medical necessity determination as described in the section below entitled Comparative Effectiveness Analysis.

I. **Initiation of intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) meets the definition of medical necessity** when **ALL** of the following are met:

   a. When used for the treatment of an indication in Table 1 and **ALL** of the indication-specific criteria are met

   b. The initial dose will not exceed the FDA label or compendia supported maximum and will be titrated to the minimum effective dose and frequency to sustain clinical response

   c. IVIG will not be used in combination with SCIG

   d. **ONE** of the following:

      i. The request is for Gammagard Liquid, Gammaked, Gamunex-C, Privigen, Flebogamma DIF, or Hizentra

      ii. The request is for Alyglo, Bivigam, Gammagard Liquid ERC, Gammagard S/D, Gammaplex, Octagam, Panzyga, Qivigy, or Yimmugo and the member had an inadequate response, contraindication or intolerance to **TWO** of the following – documentation must be submitted:

         1. Gammagard Liquid
         2. Gammaked
         3. Gamunex-C
         4. Privigen
         5. Flebogamma DIF

      iii. The request is for Cuvitru, Cutaquig, HyQvia, or Xembify, and the member had an inadequate response, contraindication or intolerance to Hizentra – documentation must be submitted

      iv. The request is for Asceniv, and BOTH of the following:

         1. All alternative commercially available IVIG products are **NOT** available for use due to a national drug shortage[a] – documentation must be provided

         2. The member had an inadequate response, contraindication, or intolerance to all alternative commercially available IVIG products – documentation must be submitted

Table 1

Indications and Criteria	
Primary Immunodeficiency	
Agammaglobulinemia	When **ONE** of the following criteria is met - documentation must be submitted: 1. Serum IgG level <200 mg/dL 2. Extremely low (<2%) or absent B cell count (CD19+) **Approval duration**: 6 months

Ataxia telangiectasia	When **BOTH** of the following are met - documentation must be submitted: 1. Lack of protective antibody titers* 2. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months
Common Variable Immune Deficiency (CVID)	When **ALL** of the following criteria are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Lack of protective antibody titers* 3. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
DiGeorge Syndrome	When the following is met: 1. Serum IgG less than 600 mg/dL **OR** documented T cells (CD3) are severely low or absent (<300/microL) - documentation must be submitted **Approval duration**: 6 months
Dedicator of cytokinesis 8 (DOCK-8) deficiency	When **BOTH** of the following are met - documentation must be submitted: 1. Lack of protective antibody titers* 2. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months
Functional Immunodeficiency	When **ALL** of the following criteria are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Lack of protective antibody titers* 3. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
Hyper-IgE syndrome	When **BOTH** of the following are met - documentation must be submitted: 1. Lack of protective antibody titers* 2. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months
Hyper-IgM syndrome or CD40 ligand (CD40L) deficiency	When **ALL** of the following criteria are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Lack of protective antibody titers* 3. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
Hypogammaglobulinemia	When **ALL** of the following criteria are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Lack of protective antibody titers* 3. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
IgG subclass deficiency	When **ALL** of the following are met - documentation must be submitted: 1. Deficiency of one or more IgG subclasses§ below the normal age-specific reference-range(confirmed by 2 measurements at least 1 month apart) 2. Lack of protective antibody titers* 3. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months

Nuclear factor kappa-B essential modulator (NEMO) syndrome	When **ALL** of the following criteria are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Lack of protective antibody titers* 3. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
Severe Combined Immunodeficiency Syndrome (SCID)	When the following is met: 1. Serum IgG less than 600 mg/dL **OR** documented T cells (CD3) are severely low or absent (<300/microL) - documentation must be submitted **Approval duration**: 6 months
Specific antibody deficiency (SAD)	When **BOTH** of the following are met - documentation must be submitted: 1. Lack of protective antibody titers* or response to pneumococcal polysaccharide vaccine diminishes within 6 months 2. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months
Transient hypogammaglobulinemia of infancy	When **BOTH** of the following are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months
Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome	When **BOTH** of the following criteria are met - documentation must be submitted: 1. Serum IgG less than 600 mg/dL 2. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
Wiskott-Aldrich Syndrome	When **ONE** of the following is met - documentation must be submitted: 1. Lack of protective antibody titers* 2. Recurrent, difficult to treat bacterial infections **Approval duration**: 6 months
Secondary Immunodeficiency	
Acquired hypogammaglobulinemia conditions including: • Chronic Lymphocytic Leukemia (CLL)/Small lymphocytic lymphoma (SLL) • Acute Lymphocytic (lymphoblastic) Leukemia (ALL) • Acute Myelogenous Leukemia (AML) • Chronic Myelogenous Leukemia (CML) • Multiple Myeloma (MM) • Non-Hodgkin's Lymphoma	**ONE** of the following - documentation must be submitted: 1. Serum IgG level less than 500 mg/dL 2. For IgG repletion of a pediatric member with hypogammaglobulinemia during therapy or until B-cell recovery 3. To prevent infection in members receiving Bispecific antibody therapy for multiple myeloma (e.g., elranatamab-bcmm (Elrexfio), linvoseltamab-gcpt (Lynozyfic), talquetamab-tgvs (Talvey), teclistamab-cqyv (Tecvayli) 4. Serum IgG level less than 600 mg/dL and **ONE** of the following is met: a. Lack of protective antibody titers* b. Recurrent difficult to treat bacterial infections **Approval duration**: 6 months
Allogeneic hematopoietic stem cell transplant (HSCT) or bone marrow transplantation (BMT)	HSCT or BMT when **ONE** of the following criteria are met: 1. First 100 days post-transplant

	2. Serum IgG level is less than 400 mg/dL 3. Treatment of viral infection (e.g.,CMV, EBV, RSV) **Approval duration**: 6 months
Chimeric antigen receptor (CAR) T-cell therapy induced reactions and prevention	**ONE** of the following: 1. When used for hypogammaglobulinemia that developed following the use of CAR T-cell therapy (e.g., axicabtagene ciloleucel, brexucabtagene autoleucel, ciltacabtagene autoleucel, ibecabtagene vicleucel, lisocabtagene maraleucel, obecabtagene autoleucel and tisagenlecleucel) 2. When used for the management of grade 4 (G4) cytokine release syndrome that is refractory to high-dose corticosteroids and anti-IL-6 therapy [e.g., tocilizumab (Actemra)] 3. When used for acute inflammatory demyelinating polyneuropathy (AIDP) or bilateral facial palsy 4. To prevent infection prior to B-cell Associated Maturation Antigen-directed CAR T-cell therapy (e.g., ciltacabtagene autoleucel (Carvykti) and idecabtagene vicleucel (Abecma)) for patients with multiple myeloma and IgG levels less than 400 mg/dL **Approval duration**: 6 months
High-risk, preterm, low-birth-weight neonates	Prevention or adjunct treatment for infection **Approval duration**: 3 months
HIV-infected children	When used for prevention of bacterial infection and **ALL** of the following are met: 1. Member is 13 years of age or less 2. CD4+ count is greater than 200/µL 3. IVIG will be used in conjunction with antiretroviral treatment 4. Member's IgG level is less than 400 mg/dL **Approval duration**: 6 months
Immune Checkpoint Inhibitor-related toxicity	When used for **ONE of the** following toxicities that developed after use of a checkpoint inhibitor (e.g., atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab): 1. Moderate to severe pneumonitis if member has an inadequate response to corticosteroids 2. Myasthenia gravis (grade 3 or 4) 3. Guillain-Barré syndrome (grade 2, 3 or 4) 4. Severe peripheral neuropathy (grade 3 or 4) 5. Encephalitis with severe or progressing symptoms or if oligoclonal bands are present 6. Demyelinating disease (e.g., optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis) 7. Severe bullous dermatitis (grade 3 or 4), Stevens-Johnson syndrome, or toxic epidermal necrolysis 8. Severe myositis or dysphagia if member has an inadequate response to corticosteroids

	9. Severe hemolytic anemia or aplastic anemia if member has an inadequate response to corticosteroids 10. Severe thrombocytopenia if member has bleeding 11. Severe myocarditis if member has an inadequate response to corticosteroids 12. HLH-like syndrome **Approval duration**: 6 months
Pediatric Langerhans Cell Histiocytosis	When used in combination with cytarabine for Langerhans Cell Histiocytosis (LCH)-associated abnormal CNS imaging/neurodegeneration (LACI/ND) **Approval duration**: 6 months
Solid organ transplant	When used for **ONE** following: 1. Allosensitized† members awaiting solid organ transplant 2. Treatment of antibody mediated rejection 3. Serum IgG is less than 400 mg/dL 4. Treatment of viral infection (e.g.,CMV, EBV, RSV) **Approval duration**: 6 months
Hematology	
Acute idiopathic thrombocytopenic purpura (ITP)	When **ONE** of the following criteria are met: 1. Member's platelet count is less than 30,000 2. Member's platelet count is is less than 50,000 and the member has symptomatic bleeding or increased risk for bleeding 3. Member's platelet count is less than 100,000 and the member is scheduled to undergo a major surgical procedure (e.g., splenectomy) **Approval duration**: 6 months
Chronic ITP	Treatment when **ALL** of the following criteria are met: 1. Duration greater than 6 months 2. Member has an inadequate response or contraindication to corticosteroid treatment 3. **ONE** of the following: a. Member's platelet count is less than 30,000 b. Member's platelet count is is less than 50,000 and the member has symptomatic bleeding or increased risk for bleeding 4. Other causes of thrombocytopenia (e.g., concurrent illness/disease) have been ruled out **Approval duration**: 1 year
HCV-associated thrombocytopenia	Treatment when **ALL** of the following criteria met: 1. ONE of the following: a. Member's platelet count is less than 30,000 b. Member's platelet count is is less than 50,000 and the member has symptomatic bleeding or increased risk for bleeding

	2. Member has an inadequate response to antiviral therapy or member has contraindication to antivirals **Approval duration**: 6 months
Hemophagocytic lymphohistiocytosis (HLH)	Diagnosis **Approval duration:** 6 months
HIV-associated thrombocytopenia	Treatment when **ALL** of the following criteria are met: 1. **ONE** of the following: a. Member's platelet count is less than 30,000 b. Member's platelet count is is less than 50,000 and the member has symptomatic bleeding or increased risk for bleeding 2. Member has an inadequate response or contraindication to antiretroviral therapy (e.g., high dose zidovudine monotherapy or highly active antiretroviral therapy [HAART]) 3. Member has an inadequate response or contraindication to corticosteroid treatment **Approval duration**: 6 months
Fetal or neonatal Alloimmune Thrombocytopenia (FAIT, NAIT)	Treatment of ante-natal FAIT/NAIT when **both** of the following criteria are met: 1. Prior FAIT birth 2. Detectable maternal antibodies to paternal platelet antigen† are present **Approval duration** 1 year Treatment of post-natal FAIT/NAIT when **ALL** of the following criteria are met: 1. Other causes of thrombocytopenia have been ruled out (e.g., infection, disseminated intravascular coagulation) 2. Member's platelet count is less than 50,000 3. Detectable maternal antibodies to paternal platelet antigen† are present 4. Thrombocytopenia persists after transfusion of anti-negative compatible platelets **Approval duration**: 6 months
ITP in pregnancy	Treatment of ITP when **ONE** of the following criteria are met: 1. To treat symptomatic bleeding 2. To increase platelet count to minimize bleeding risk associated with a procedure (e.g., epidural, C-section) 3. Member's platelet count is less than 50,000 4. History of splenectomy **Approval duration**: 1 year
Post-transfusion purpura**	Acute treatment only (i.e., IVIG is administered within 2-14 days post-transfusion) **Approval duration**: 30 days
Neonatal isoimmune hemolytic disease**	When used for acute treatment in conjunction with phototherapy **Approval duration**: 30 days
Warm antibody autoimmune hemolytic anemia (wAIHA)	Treatment when **ALL** of the following criteria are met:

	1. wAIHA is confirmed by a positive direct Coombs test for immunoglobulin G(IgG), complement (C3d), or both‡ **Approval duration**: 30 days
Evan's Syndrome	Member has an inadequate response, contraindication, intolerance to conventional therapy (e.g., azathioprine, cyclophosphamide, cyclosporine, prednisone) **Approval duration**: 1 year
Neurology	
Autoimmune Encephalitis	Treatment when **ALL** of the following criteria are met: 1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms 2. **ONE** of the following: o New focal CNS findings o Seizures not explained by a previously known seizure disorder o CSF pleocytosis (WBC of more than 5 cells per mm3) o MRI features suggestive of encephalitis 3. Exclusion of alternative causes (Table 4) **Approval duration**: 6 months
Acute Disseminated Encephalomyelitis	Treatment when **ALL** of the following criteria are met: 1. A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause 2. Encephalopathy cannot be explained by fever 3. **ONE** of the following abnormal brain MRI findings: a. Diffuse, poorly demarcated, large (>1-2 cm) lesions predominately involving the cerebral white matter b. T1-hypointense lesions in the white matter c. Deep grey matter abnormalities (e.g. thalamus or basal ganglia) present 4. No new clinical or MRI findings after 3 months of symptom onset 5. Exclusion of alternative causes (Table 4) **Approval duration**: 6 months
Acute treatment of Myasthenia gravis**	Treatment when **ANY** of the following criteria are met: 1. Acute crisis (<5 days treatment) with decompensation (e.g., respiratory failure, inability to perform physical activity) 2. During or prior to initiation of immunosuppressive therapy to prevent disease exacerbation 3. Prior to thymectomy for a member with significant bulbar dysfunction **Approval duration**: 5 days
Refractory Myasthenia gravis	When the member has progressive disease with an inadequate response, contraindication, or intolerance to at least **ONE** of the following: 1. azathioprine

	2. cyclosporine 3. mycophenolate mofetil 4. tacrolimus 5. methotrexate **Approval duration**: 6 months
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Treatment when **ALL** of the following criteria are met: 1. Member's clinical course is relapsing and remitting or progressive for more than 2 months 2. Member's disease has been confirmed by electrophysiologic findings that demonstrate any 3 of the following – documentation must be submitted: a. Partial conduction block of 1 or more motor nerves b. Reduced conduction velocity of 2 or more motor nerves c. Prolonged distal latency of 2 or more motor nerves d. Prolonged F-wave latencies of 2 or more nerves or the absence of F-waves 3. Member's disease has been confirmed by **BOTH** of the following physiologic findings a. Hypo- or areflexia b. Motor or sensory impairment of more than one limb **Approval duration**: 1 year
Multifocal Motor Neuropathy (MMN)	Treatment when the following criteria are met: 1. Member's disease has been confirmed by electrophysiologic findings including **BOTH** of the following – documentation must be submitted: a. Presence of either – Probable conduction block in at least two motor nerve segments – Definite conduction block in at least one motor nerve segment and probable conduction block in a different motor nerve segment b. Normal results for sensory nerve conduction on all tested nerves 2. Progressive symptoms are present for one or more months **Approval duration**: 1 year
Guillain-Barré Syndrome (GBS)- Acute inflammatory demyelinating neuropathy (AIDP)	**Acute treatment** when **ALL** of the following criteria are met: 1. Member has severe disease (e.g., is unable to walk) 2. Onset of symptoms occurred within the last 4 weeks 3. No concomitant plasma exchange therapy **Approval duration**: 1 year
Lambert-Eaton Myasthenic Syndrome (LEMS)	Member has an inadequate response, contraindication, or intolerance to available standard therapy (e.g., acetyl cholinesterase inhibitors, prednisone, and azathioprine).

	Approval duration: 1 year
Rasmussen's encephalitis	Member has an inadequate response, contraindication, or intolerance to conventional therapy (e.g., immunosuppressants, surgery) **Approval duration**: 6 months
Stiff Person Syndrome (Moersch-Woltmann Syndrome)	Member has an inadequate response, contraindication, or intolerance to available standard medication therapy (e.g., diazepam, baclofen, phenytoin, clonidine, or tizanidine). **Approval duration**: 1 year
Rheumatic Disorders	
Dermatomyositis or Polymyositis	Treatment when **BOTH** of the following criteria are met – documentation must be submitted: 1. Member has an inadequate response or contraindication to corticosteroids (e.g., prednisone) 2. Member has an inadequate response or contraindication to immunosuppressants (e.g., azathioprine, methotrexate, cyclophosphamide) **Approval duration**: 1 year
Hemophagocytic lymphohistiocytosis/ Macrophage Activation Syndrome (HLH/MAS) in known or suspected Still's disease/systemic Juvenile Idiopathic Arthritis (sJIA)	Diagnosis **Approval duration**: 6 months
Kawasaki Disease**	Diagnosis **Approval duration**: 3 months
Multisystem Inflammatory Syndrome in Children (MIS-C) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection**	Diagnosis **Approval duration**: 30 days
Infectious Disease	
Staphylococcal or streptococcal Toxic Shock Syndrome**	Acute treatment when **one** of the following is met: 1. Infection refractory to aggressive treatment 2. Presence of an undrainable focus 3. Persistent oliguria with pulmonary edema **Approval duration**: 30 days
Measles post-exposure prophylaxis**	When one of the following is met: 1. Member is immunocompromised (HIV, transplant, etc). 2. Member is pregnant without evidence of measles immunity **Approval duration**: 3 months
Maternal-fetal transmission of HIV in women who are in their third trimester of pregnancy**	When used in conjunction with antiretroviral treatment **Approval duration**: 4 months
CMV pneumonia**	When all of the following are met: 1. Member is immunocompromised 2. Member has an inadequate response to standard treatment 3. Therapy is in combination with ganciclovir or foscarnet Appproval duration: 10 days
RSV**	When all of the following are met: 1. Member is immunocompromised

	2. Member has an inadequate response to standard treatment Appproval duration: 10 days
Parvovirus B19**	When **ALL** of the of following are met: 1. Member is immunocompromised 2. Severe anemia associated with bone marrow suppression Appproval duration: 5 days
Varicella-zoster post-exposure prophylaxis**	When Varicella-zoster immune globulin is unavailable or contraindicated and **ONE** of the following is met: 1. Member is immunocompromised 2. Member is pregnant without evidence of varicella immunity 3. Member is a neonate exposed at time of delivery 4. Member was exposed during hospitalization and is born premature (>28 weeks gestation) and mother does not have evidence of immunity 5. Member was exposed during hospitalization and is born premature at a low birth weight (<28 weeks gestation and weighs < 1 kg at birth) Appproval duration: 1 dose
Dermatology	
Autoimmune mucocutaneous blistering diseases such as: • Pemphigus vulgaris • Pemphigus folacious • Bullous pemphigoid • Mucous membrane pemphigoid • Epidermolysis Bullosa Acquisita	Treatment when **EITHER** of the following criteria are met: 1. Member has an inadequate response or contraindication to conventional therapy (corticosteroids, azathioprine, cyclophosphamide, or mycophenolate) 2. Member has rapidly progressive disease in which conventional therapy would not achieve a response quickly enough **AND** IVIG will be initiated along with concurrent conventional therapy. **Approval duration**: 6 consecutive months
Other conditions	
Other FDA-approved, or NCCN supported diagnosis (not previously listed above)	When **ONE** of the following is met: 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation **Approval duration**: 6 months
***** Lack of protective antibody titers requires laboratory confirmation of failure to produce antibodies 3 to 4 weeks following tetanus (<0.1 IU/mL) OR failure to produce antibodies 4 to 8 weeks after administration of pneumococcal polysaccharide vaccine based on the following measures:	

- Age < 6 years, Concentration greater than 1.3 mcg/mL for <50% of serotypes
- Age ≥ 6 years, Concentration greater than 1.3 mcg/mL for <70% of serotypes

** Diagnosis excluded from continuation criteria (i.e., initiation criteria must be met)
† Quest diagnostics can perform the enzyme immunoassay that detects serum or plasma antibodies directed towards HLA class I antigens and platelet specific antigens (HPA-1 through HPA-8).
‡ Quest diagnostics can perform the Direct Coombs test.
§ IgG4 levels excluded

II. Continuation of intravenous (IV), or subcutaneous (SC)immune globulin (including transitioning between products) **meets the definition of medical necessity** for the indications in Table 1 (exceptions noted) when **ALL** of the following criteria are met:

1. The member has been previously approved by Florida Blue or another health plan in the past 2 years for an indication in Table 1, **OR** the member has previously met all indication-specific criteria
2. The member has a beneficial response to therapy – documentation must be provided (e.g., medical record, chart note, lab report)
3. In clinically appropriate indications, dose is titrated to the minimum effective dose and frequency to sustain clinical response
4. IVIG will not be used in combination with SCIG
5. **ONE** of the following:
    i. The request is for Gammagard Liquid, Gammaked, Gamunex-C, Privigen, Flebogamma DIF, or Hizentra
    ii. The request is for Alyglo, Bivigam, Gammagard Liquid ERC, Gammagard S/D, Gammaplex, Qivigy, Octagam, Panzyga or Yimmugo, and **ONE** of the following:
        1. The member had an inadequate response, contraindication or intolerance to **TWO** of the following – documentation must be submitted:
            a. Gammagard Liquid
            b. Gammaked
            c. Gamunex-C
            d. Privigen
            e. Flebogamma DIF
        2. The provider must submit a clinical reason as to why the member is unable to switch to Gammagard Liquid, Gammaked, Gamunex-C, Privigen, or Flebogamma DIF – documentation must be submitted
    iii. The request is for Cuvitru, Cutaquig, HyQvia, or Xembify, and the member has inadequate response, contraindication or intolerance to Hizentra – documentation must be submitted
    iv. The request is for Asceniv, and BOTH of the following:
        1. All commercially available IVIG products are **NOT** available for use due to a national drug shortage[a] – documentation must be provided
        2. The member had an inadequate response, contraindication, or intolerance to all alternative commercially available IVIG products – documentation must be submitted

Approval duration: 1 year (6-month duration for encephalitis, encephalomyelitis and checkpoint inhibitor encephalitis indications in Table 1)

[a] To verify non-availability, the status of all products must be listed as “Currently in Shortage” on the ASHP Current Shortages webpage (Drug Shortages List (ashp.org)) AND all listed manufactures must have all strengths unavailable

II. **Intravenous immune globulin (IVIG) or subcutaneous (SC)immune globulin (J1459, J1554, J1555, J1556, J1557, J1559, J1561, J1566, J1568, J1569, J1572, J1575, J1599, 90283, 90284): is considered experimental or investigational for the following conditions (not all-inclusi**ve) due to the lack of clinical data to support the effects of better health outcomes:

- Aplastic anemia
- Adult AIDS
- Asthma
- Autism
- Chronic fatigue syndrome
- Chronic progressive multiple sclerosis
- Chronic sinusitis
- Cystic fibrosis
- Diabetes mellitus
- Diamond blackfan anemia
- Epilepsy (adult or pediatric)
- Hemolytic uremic syndrome
- Inclusion body myositis
- Nonimmune thrombocytopenia
- Other vasculitides, besides Kawasaki disease
- Paraneoplastic syndrome
- Red cell aplasia
- Refractory rheumatoid arthritis and other connective tissue diseases
- Recurrent spontaneous abortion
- Thrombotic thrombocytopenic purpura
- Upper respiratory infection, recurrent
- Prophylaxis of preterm or low birth weight infants without signs or symptoms of infection.

III. **Intravenous immune globulin (IVIG) or subcutaneous (SC) immune globulin does not meet the definition of medical necessity** for the following conditions:

- Relapsing remitting multiple sclerosis
- Steven-Johnson syndrome
- Toxic epidermal necrolysis

COMPARATIVE EFFECTIVENESS ANALYSIS: This section only applies to member contracts that contain a comparative effectiveness analysis within the definition of Medical Necessity. If a service meets

the medical necessity criteria set forth above in the Position Statement, then an analysis under this comparative effectiveness section should be applied, solely for coverage and payment purposes.

ASCENIV (J1554): A comparative effectiveness analysis of Asceniv has determined alternative forms of immune globulin therapy produce the same or similar outcome and are less costly. Asceniv is considered not medically necessary as a result of the limited published clinical evidence demonstrating any clinical benefit over other forms of immune globulin therapy. There are no robust clinical studies demonstrating benefits associated with Asceniv treatment as compared to other forms of immune globulin therapy. There is a need for more well-designed clinical studies with sizable comparator cohorts for analysis of benefits on health outcomes.

Table 2: Immune globulin product comparison

Product	Administration	Cost Estimate	FDA label Indications
Alyglo	IV	$$$	PI
Asceniv	IV	$$$$$$$	PI
Bivigam	IV	$	PI
Flebogamma DIF - Preferred	IV	$	PI
Gammagard Liquid ERC	IV/SC	$$	PI
Gammagard Liquid - Preferred	IV/SC	$$	CIDP MMN PI
Gammagard S/D	IV	$$	Chronic ITP CLL Kawasaki disease PI
Gammaked - Preferred	IV/SC	$$	CIDP ITP PI
Gammaplex	IV	$$	Chronic ITP PI
Gamunex-C - Preferred	IV/SC	$	CIDP ITP PI
Octagam 10%	IV	$$	Chronic ITP Dermatomyositis
Octagam 5%	IV	$	PI
Panzyga	IV	$$	Chronic ITP CIDP PI
Privigen- Preferred	IV	$$	Chronic ITP CIDP PI
Qivigy	IV	$$$	PI
Yimmugo	IV	$$$	PI
Cutaquig	SC	$$$	PI

Cuvitru	SC	$$$	PI
Hizentra-Preferred	SC	$$$	CIDP PI
HyQvia	SC	$$$	CIDP PI
Xembify	SC	$$$	PI

CIDP=chronic inflammatory demyelating myelinating polyneuropathy;CLL= B-cell chronic lymphocytic leukemia; ITP= idiopathic thrombocytopenic purpura; KS=Kawasaki syndrome; IV= intravenous; MNM = multifocal motor neuropathy, PI= primary (humoral) immunodeficiency and other primary immunodeficiencies, SC= subcutaneous

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Dosage is highly variable depending on individual response, indication or product selected. Refer to prescribing literature (e.g., package insert, etc.).

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 30kg/m^2 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): Dosing formulas:
BMI = 703 x (weight in pounds/height in inches^2)
IBW(kg) for males = 50 + [2.3 x (height in inches – 60)]
IBW(kg) for females = 45.5 + [2.3 x (height in inches – 60)]
Adjusted body weight = IBW + 0.5 (actual body weight – 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.

CONTRAINDICATIONS/PRECAUTIONS

Immune Globulin (IV, SC)

Black Box Warning

- IVIG products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Use caution in patients predisposed to acute renal failure (age> 65 yrs, use of nephrotoxic drugs, preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, paraproteinemia) and administer at the minimum concentration available and the minimum rate of infusion practicable. Renal effects are more common with high sucrose content and high osmolality. Members should be appropriately hydrated prior to administration.
- Thrombosis may occur regardless of the route of administration and in the absence of known risk factors. Risk is increased with advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, estrogen use, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Administer in patients at risk of

thrombosis at the minimum dose and infusion rate practical and ensure adequate hydration prior to therapy. Monitor for signs and symptoms of thrombosis and assess blood viscosity in persons at risk for hyperviscosity.

Contraindications

- Hereditary intolerance to fructose, including infants and neonates in whom tolerance to sucrose or fructose has not been established.
- Hyperprolinemia (Type I or II): L-proline contained in Hizentra and Privigen.
- Hypersensitivity to immune globulin or any component of the formulation (including polysorbate 80, hyaluronidase). Anaphylaxis, inflammatory reactions, characterized by a rise in temperature, chills, nausea, and vomiting, and hypersensitivity reactions may occur.
- Persons with selective IgA deficiency with antibodies against IgA, and a history of hypersensitivity.

Precautions

- Antibodies to PH20 (recombinant human hyaluronidase) can develop and cross react with endogenouse PH20 which is known to be expressed in adult male testes, epididymis and sperm. It is unknown if these antibodies interfere with fertilization in humans.
- Cardiovascular: elevations of systolic and diastolic blood pressure have been observed and blood pressure should be monitored during and following infusion.
- Endocrine: Falsely elevated glucose measurements may occur.
- Hematologic: Hemolysis and delayed hemolytic anemia may occur. Severe hemolysis-related renal dysfunction, renal failure and disseminated intravascular coagulation have been reported.
- Infection: infusion into or around an infected area can spread a localized infection.
- Infusion reactions: Severe hypersensitivity reactions have been reported and fever, chills, nausea vomiting may occur. Monitoring is recommended and discontinue for severe reactions.
- Immunologic: IVIG products are of human plasma origin and may contain infectious agents (including the Cruetzfeldt-Jakob disease agent).
- Metabolic: Hyperproteinemia, increased serum viscosity and hyponatremia or hypernatremia may occur.
- Neurologic: Aseptic meningitis syndrome may occur with high doses (≥1 gram/kg or rapid infusion).
- Pregnancy: IVIG is classified as Pregnancy risk category C. No complications to the fetus have been reported, but it has not been well studied in pregnant women.
- Renal: Acute renal dysfunction can rarely occur, usually within seven days of use. Avoid use in members with CrCl < 10 ml/min. Use caution in elderly and those with renal disease, diabetes, sepsis, volume depletion, concomitant nephrotoxic agents, etc., due to the risk of renal dysfunction. Consider infusion at a rate less than maximum. Baseline renal function should be assessed prior to starting IVIG and periodically during administrations. Ensure that members are well-hydrated prior to therapy. If renal function worsens, consider discontinuing therapy or using products that do not contain sucrose (e.g. Gamunex).
- Respiratory: Transfusion-related acute lung injury may occur.
- Subcutaneous administration: Not recommended for ITP due to increased risk of hematoma. Do not inadvertently infuse subcutaneous form due to increased risk of thrombosis.

- Thrombosis: Use caution in members with a history of thrombotic events or cardiovascular disease. There is clinical evidence of a possible association between thrombotic events (i.e., deep vein thrombosis, myocardial infarction, cerebral vascular accident, etc.) and the administration of IVIG.
- Volume: Expanded fluid volume may cause overload with high-dose regimens for chronic ITP.

BILLING/CODING INFORMATION:

Note: This list of codes may not be all-inclusive.

HCPCS Coding:

J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1552	Injection, immune globulin (Alyglo), 500 mg
J1553	Injection, immune globulin (Yimmugo), 100 mg
J1554	Injection, immune globulin (Asceniv), 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (BIVIGAM), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1558	Injection, immune globulin (Xembify), 100 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex-C, Gammaked), intravenous, non-lyophilized (e.g., liquid), 500mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g. powder) not otherwise specified, 500 mg (use for Carimune NF, Panglobulin NF, and Gammagard S/D)
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500mg
J1569	Injection, immune globulin, (Gammagard liquid, Gammagard liquid ERC), 500mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500mg
J1575	Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immune globulin
J1576	Injection, immune globulin (Panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1577	Injection, immune globulin (Qivigy), 100 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg
J3590	Unclassified biologics

CPT Coding:

90283	Immune Globulin (IgIV), human, for intravenous use
90284	Immune Globulin (SCIg), human, for use in subcutaneous infusions

ICD-10 Diagnoses Codes That Support Medical Necessity (IVIG, SCIG – J1459, J1551, J1552, J1553, J1554, J1555, J1556, J1557, J1558, J1559, J1561, J1566, J1568, J1569, J1572, J1575, J1576, J1577, J1599, 90283, 90284):

A48.3	Toxic shock syndrome
B01.0 – B01.89	Varicella
B05.0 – B05.89	Measles
B06.0 – B06.89	Rubella
B18.2	Chronic viral hepatitis C

B20	Human immunodeficiency virus [HIV] disease
B25.0 – B25.9	Cytomegalovirus disease
B27.00 – B27.99	Infectious mononeucleosis (Epstein Barr virus)
B34.3	Parvovirus infection
B97.4	Respiratory syncytial virus
C82 – C85.9	Lymphomas (nonhodgkins)
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C91.0 – C91.02	Acute lymphoblastic leukemia
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C92.00 – C92.02 C92.40 – C92.42 C92.50 – C92.52 C92.60 – C92.62 C92.A0 – C92.A2	Acute myeloblastic leukemia
C92.1 – C92.12	Chronic myeloblastic leukemia
D59.0	Drug-induced autoimmune hemolytic anemia
D59.10	Autoimmune hemolytic anemia, unspecified
D59.11	Warm autoimmune hemolytic anemia
D69.3	Immune thrombocytopenic purpura
D69.41	Evans syndrome
D69.42	Congenital and hereditary thrombocytopenia purpura
D69.49	Other primary thrombocytopenia
D69.51	Posttransfusion purpura
D69.59	Other secondary thrombocytopenia
D69.6	Thrombocytopenia, unspecified
D76.1	Hemophagocytic lymphohistiocytosis
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia (Specific antibody deficiency)
D80.7	Transient hypogammaglobulinemia of infancy
D80.8	Other immunodeficiencies with predominant antibody defects
D80.9	Immunodeficiency with predominantly antibody defects, unspecified
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.30	Adenosine deaminase deficiency
D81.31	Severe combined immunodeficiency due to adenosine deaminase deficiency
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	DiGeorge Syndrome
D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus
D82.4	Hyperimmunoglobulin E (IgE) syndrome
D82.8	Immunodeficiency associated with other specified major defects

D82.9	Immunodeficiency associated with major defect, unspecified
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with prominent immunoregulatory T-cell disorder
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
D84.81	Immunodeficiency due to conditions classified elsewhere
D84.821	Immunodeficiency due to drugs
D84.89	Other immunodeficiencies
D84.9	Immunodeficiency unspecified
D89.810	Acute graft-versus-host disease
D89.834 – D89.839	Cytokine release syndrome
G04.00 – G04.02	Acute disseminated encephalitis and encephalomyelitis
G04.81	Other encephalitis and encephalomyelitis
G25.82	Stiff-man syndrome
G60.3	Idiopathic progressive neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathies, unspecified
G61.0	Guillian-Barre syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.82	Multifocal motor neuropathy
G61.9	Inflammatory polyneuropathy, unspecified
G62.89	Other specified polyneuropathies
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
J20.5	Acute bronchitis due to RSV
L10.0	Pemphigus vulgaris
L10.2	Pemphigus foliaceous
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.30	Acquired epidermolysis bullosa, unspecified
L12.31	Epidermolysis bullosa due to drug
L12.35	Other acquired epidermolysis bullosa
L13.8 – L13.9	Other specified bullous disorders
M06.1	Adult-onset Still’s disease
M08.09	Unspecified juvenile rheumatoid arthritis, multiple sites
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site
M30.3	Mucocutaneous lymph node syndrome (Kawasaki)
M33.00 – M33.09	Juvenile dermatopolymyositis, organ involvement
M33.20 – M33.29	Polymyositis, organ involvement
M33.90 – M33.99	Dermatopolymyositis, organ involvement unspecified
O98.511 – O98.519	Other viral diseases complicating pregnancy
O98.713	HIV disease complicating pregnancy
P07.00 – P07.30	Disorders relating to short gestation and low birthweight code
P35.0	Congenital rubella syndrome
P35.8	Other congenital viral diseases
P35.9	Congenital viral disease, unspecified
P55.0 – P55.1 P55.8 – P55.9	Hemolytic disease or fetus or newborn due to isoimmunization
P61.0	Transient neonatal thrombocytopenia

T45.1X5A T45.1X5D T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs
T45.AX5A T45.AX5D T45.AX5S	Adverse effect of immune checkpoint inhibitors and immunostimulant drugs
T86.00 – T86.99	Complications of transplanted organs
Z20.4	Contact with or exposure to rubella
Z20.820	Contact or exposure to varicella
Z20.828	Contact or exposure to other viral diseases
Z29.9	Encounter for other prophylactic measures
Z41.8	Prophylactic immunotherapy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

PPO Blue Script: Prior authorization is required. Authorization forms may be obtained from the Medication Review Unit of the Healthcare Program Management division.

Medicare Advantage Products: The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Intravenous Immune Globulin for the Treatment of Autoimmune Mucotaneous Blistering Disease, (250.3) located at cms.gov. The following Local Coverage Determinations (LCDs) were reviewed on the last guideline revised date: Intravenous Immune Globulin (L33610, L34007, L34771) located at fcso.com. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Agammaglobulinemia: lack of antibodies.

Antibody: a protein substance developed in response to and interacting specifically with an antigen. This antigen-antibody reaction forms the basis of immunity.

Antigen: a substance that induces the formation of antibodies that interact specifically with it.

Dysgammaglobulinemia: deficiencies in one or more classes of immunoglobulins in the blood.

Hypogammaglobulinemia: not enough antibodies relapsing/remitting: coming and going, worsening then improving.

Immunodeficiency: a deficiency of immune response or a disorder characterized by deficient immune response.

Immunoglobulin: one of a family of closely related proteins capable of acting as antibodies; five classes are IgG, IgA, IgM, IgD, and IgE.

Immunomodulator: an agent that specifically or nonspecifically augments or diminishes immune response, i.e., an adjuvant, immunostimulant or immunosuppressant.

Isohemagglutinin: a hemagglutinin that agglutinates the erythrocytes of other individuals of the same species.

Isoimmunization: the development of specific antibodies as a result of antigenic stimulation using material derived from the red blood cells of another individual.

Kawasaki Disease: a syndrome of unknown etiology, usually affecting infants and young children, associated with vasculitis of the large common vessels and numerous other systemic signs.

NEMO Syndrome: Nuclear factor kappa-B essential modulator (NEMO) deficiency results from mutations in the inhibitor of kappa-B kinase gamma chain gene. Disease characteristics may include immunodeficiency, ectodermal dysplasia and abnormal thermal regulation.

Specific Antibody Disorder: an immune disease in which children and adults fail to develop the immune response to the polysaccharide coating on bacteria but who otherwise have normal antibody levels.

WHIM Syndrome: Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome is a rare congenital immunodeficiency characterized by susceptibility to papilloma viruses, lymphocytopenia with decreased memory B-cell counts, hypogammaglobulinemia, and peripheral neutropenia with retention of mature neutrophils in the bone marrow.

RELATED GUIDELINES:

None applicable.

OTHER:

Documentation of medical necessity should include the following:

1. Care Provider Notes
2. All Laboratories Studies.

Table 3: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

Table 4: Excluded differential diagnosis in autoimmune encephalitis

Disorder
CNS infection
Septic encephalopathy
Metabolic encephalopathy
Drug toxicity (including use of illicit drugs, neurotoxic effect of prescribed medications, posterior reversable encephalopathy, idiosyncratic reaction (neuroleptic malignant syndrome), drug interaction (serotonergic syndrome), or drug withdrawal)
Cerebrovascular disease
Neoplastic disorders
Creutzfeldt-Jakob disease
Epileptic disorders
Rheumatologic disorders (e.g., lupus, sarcoidosis, other)

Kleine-Levin
Reye syndrome (children)
Mitochondrial diseases
Inborn errors of metabolism (children)

REFERENCES:

1. Academy of Neurology Guideline Summary for Clinicians. Immunotherapy for Guillian Barré Syndrome. Available at http://www.aan.com/professionals/practice/pdfs/gbs_guide_aan_mem.pdf (Accessed 2012 July 18)
2. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database Syst Rev. 2002;(3):CD003313.
3. Al-Hertz W, Bousfiha A, Casanova JL et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Front Immunol. 2014;5: 162.
4. Alyglo (immune globulin intravenous, human-stwk), 10% liquid [package insert]. GC Biopharma USA, Inc. Teaneck (NJ): December 2023.
5. American Academy of Neurology. Accessed 07/17/2012.
6. American Academy of Pediatrics, AAP Grand Rounds 17:3-4 (2007). Predicting Treatment Failures in Kawasaki Disease. Accessed 03/18/08.
7. American Academy of Pediatrics. Pediatrics Vol. 99 No. 2 February 1997, pp. e2. Jenson HA and Pollock BH, Meta-analyses of the Effectiveness of Intravenous Immune Globulin for Prevention and Treatment of Neonatal Sepsis.
8. American College of Obstetrician-Gynecologists. ACOG practice bulletin. Thrombocytopenia in pregnancy. 2019; 133 (3): e181 – e193.
9. AHFS Drug Information. Bethesda (MD): American Society of Health-System Pharmacists, Inc; 2023 [cited 2023 Apr 6].
10. American Medical Association CPT Coding, 2009 professional edition.
11. Anderson D, Ali K, blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev 2007;21(2): Suppl 1:S9-S56.
12. Asceniv 10% Liquid (human immune globulin- slra) [package insert]. ADMA Biologics. Boca Raton (FL): April 2019.
13. Bivigam (human immune globulin) [package insert]. Biotest Pharmaceuticals. Boca Raton (FL): January 2018.
14. Bonilla FA, Khan DA, Ballas ZK et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136 (5): 1186-1205.
15. Cantiniaux S, Azulay JP, Boucraut J, Pouget J, Attarian S. Stiff man syndrome: clinical forms, treatment and clinical course. Ref Neurol (Paris). 2006 Sep; 162(8-9): 832-9.
16. Carimune NF (human immune globulin g) [package insert]. CSL Behring, LLC, Kankakee (IL): May 2018.
17. Chong H, Membe S, Cimon K, Roifman C, Kanani A, Morrison A. Subcutaneous Versus Intravenous Immunoglobulin for Primary Immunodeficiencies: Systematic Review and Economic Evaluation. Health Technology Assessment (HTA), Issue 98, January 2008.
18. Center for Disease Control and Prevention. www.cdc.gov. Accessed June 24, 2015.
19. Clinical Pharmacology [Internet]. Elsevier/ Gold Standard; 2024 [cited 2024 Dec 2] Available from: www.clinicalpharmacology.com

20. Cutaquig 16.5% solution (human immune globulin subcutaneous – hipp). Octapharma USA Inc. Hoboken (NJ): December 2018.
21. Cuvitru (human immune globulin subcutaneous) [package insert]. Baxalta US, Inc. Westlake Village (CA): September 2016.
22. Donofrio PD, Berger A, Brannagan TH et al. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM Ad Hoc committee. Muscle Nerve 2009;40:890-900.
23. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2024 Dec 2].
24. Elovaara I, Apostolski S, van Doorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol. 2009; 16: 547.
25. Fazekas F, Lublin FD, Li D et al. Intravenous immunoglobulin in relapsing-remitting multiple sclerosis: a dose-finding trial. Neurology. 2008; 71: 265-71.
26. Feasby T, Banwell B, Benstead T, Bril V, Brouwers M, Freedman M, Hahn A, Hume H, Freedman J, Pi D, Wadsworth L. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev. 2007. Apr; 21(2 Suppl 1): S57-107.
27. Flebogamma DIF (human immune globulin g) [package insert]. Grifols Biologicals, Inc. Los Angeles (CA): December 2017.
28. Gaidos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. 2012.
29. Gammagard S/D Less IgA (human immune globulin g) [package insert]. Takeda Pharmaceuticals U.S.A., Cambridge, MA: November 2025.
30. Gammagard Liquid (human immune globulin g) [package insert]. Takeda Pharmaceuticals U.S.A., Cambridge, MA: September 2024.
31. Gammagard Liquid ERC (human immune globulin g) [package insert]. Takeda Pharmaceuticals U.S.A., Cambridge, MA: October 2025.
32. Gammaked (human immune globulin g) [package insert]. Grifols Therapeutics, Inc. Research Triangle Park (NC): September 2016
33. Gammaplex (human immune globulin g) [package insert]. BPL, Inc. Durham (NC): December 2016.
34. Gamunex-C (human immune globulin g) [package insert]. Grifols Therapeutics, Inc. Research Triangle Park (NC): March 2017.
35. Geng J, Dong J, Li Y et al. Intravenous immunoglobulins for epilepsy. Cohrane Database Syst Rev. 2011; 1: CD008557.
36. Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood 2013;121(1):38-47.
37. Geva-Dayan K, Shorer Z, Menascu S et al. Immunoglobulin treatment for severe childhood epilepsy. Pediatr Neurol. 2012: 46: 375-81.
38. Goodin D.S., Frohman E.M., Garmany G.P. et al. Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. 2002: 58: 169-178.
39. Gold R, Stangel M, Dalakas MC. Drug Insight: the use of intravenous immunoglobulin in neurology-therapeutic considerations and practical issues. Nat Clin Pract Neurol. 2007 Jan; 3(1): 36-44.
40. Graus F, Titulaer MJ, Balu R et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016 Apr; 15(4); 391-404.

41. Gurcan HM, Ahmed AR. Efficacy of various intravenous immunoglobulin therapy protocols in autoimmune and chronic inflammatory disorders. Ann Pharmacother. 2007 May; 41(5): 812-23.
42. Henderson LA, Canna SW, Friedman KG et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. Arthritis & Rheumatology. 2021 Apr; 73 (4): e13 – e29.
43. Hizentra (human immune globulin g) [package insert]. CSL Behring, LLC, Kankakee (IL): March 2018.
44. Hyqvia (human immune globulin with recombinant human hyaluronidase for subcutaneous administration) [package insert]. Baxalta US, Inc. Westlake Village (CA): September 2016.
45. Ingenix, HCPCS Level II Coding, 8 Expert.
46. Keskin DB, Stern JN, Fridkis-Hareli M, Razzaque Ahmed A. Cytokine profiles in pemphigus vulgaris patients treated with intravenous immunoglobulins as compared to conventional immunosuppressive therapy. Cytokine. 2008 Mar; 41(3): 315-21.
47. Kymriah (tisagenlecleucel) [package insert]. Novartis. East Hanover, (NJ): August 2017.
48. Lechner K, Jager Ulrich. How I treat autoimmune hemolytic anemias in adults. Blood 2010;116(11):1831-38.
49. Lockman J, Burns TM. Stiff-person syndrome. Curr Treat Options Neurol. 2007 May; 9(3): 234-40.
50. Mydlarski PR, Ho V, Shear NH. Canadian consensus statement on the use of intravenous immunoglobulin therapy in dermatology. J Cutan Med Surg. 2006 Sep-Oct; 10(5): 205-21.
51. McCrindle BW, Rowley AH, Newburger JW et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017; 135 (17): e927-e999.
52. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed March 6, 2026.
53. Neunert C, Lim W, Crowther M, et al. Clinical guideline update on immune thrombocytopenia: an evidence based practice guideline developed by the American Society of Hematology. Blood 2011; Epub ahead of print.
54. Neunert C, Terrell DR, Arnold DM, et al. The American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829- 3866.
55. Norton A, Roberts I. Management of Evans syndrome. Br J Haematol 2005;132:125-37.
56. Octagam (human immunoglobulin g solution) [package insert]. Octapharma USA Inc, Hoboken (NJ): November 2015.
57. Orange JS, et. al. Use of Intravenous Immunoglobulin in Human Disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. The Journal of Allergy and Clinical Immunology. April 2006, Vol. 117 No. 4, S525 – S533.
58. 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 & Immunology. J Allergy Clin Immunol 2012; 130:S1-24.
59. Panzyga (immune globulin intravenous, human - ifas) [package insert]. Octapharma USA, Inc, Hoboken (NJ): August 2018.
60. Patwa HS, Chaudhry V, Katzberg H et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the therapeutics and technology assessment subcommittee of the American academy of neurology. Neurology 2012;78:1009-15.

61. Perez EE, Orange JS, Bonilla F et al. Update on the use of immunoglobulin in human disease: A review of evidence - Work group report of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2017: 139: S1 – 46.
62. Peterson JA, McFarland JG, Curtis BR, et al. Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis, and management. Br J Haematol 2013;161(1):3-14.
63. Pohlau D, Przuntek H, Sailer M, Bethke F, Koehler J, Konig N, Heesen C, Spath P, Andresen I. Intravenous immunoglobulin in primary and secondary chronic progressive multiple sclerosis: a randomized placebo controlled multicentrre study. Mult Scler. 2007 Nov; 13(9): 1107-17.
64. Privigen (human immune globulin g) [package insert]. CSL Behring, LLC, Kankakee (IL): September 2017.
65. Sanders DB, Wolfe GI, Benatar M et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016; 87: 1-7.
66. Segura S, Iranzo P, Martinez-de Pablo I, Mascaro JM Jr, Alsina M, Herrero J, Herrero C. High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases. J Am Acad Dernatol. 2007 Jun; 56(6): 960-7.
67. Shearer WT, Dunn E, Notarangelo LD et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. J Allergy Clin Immunol. 2014; 133(4): 1092.
68. Shehata N, Palda V, Bowen T. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev. 2010 Jan; 24 Suppl 1: S28-50.
69. Shimanovich I, Nitschke M, Rose C, Grabbe J, Zillikens D. Treatment of severe pemphigus with protein A immunoadsorption, rituximab and intravenous immunoglobulins. Br J Dernatol. 2008 Feb; 158(2): 382-8.
70. Soelberg Sorensen P. Intravenous polyclonal human immunoglobulins in multiple sclerosis. Neurodegener Dis. 2008; 5(1): 8-15.
71. Sorensen R, Paris K. Selective antibody deficiency with normal immunoglobulins. UpToDate Last updated 6/17/10.
72. Vafaie J, Schwartz RA, Lin RY. Immunoglobulin G Deficiency. E Medicine. Last updated 03/22/05.
73. Van Schaik I. Leger J.M., Nobile-Orazio E. et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy. Report of a Joint Task Force on the European Federation of Neruological Societies and the Peripheral Nerve Society – first revision. Joint Task Force of the EFNS and the PNS. J Periph Nervous System 15: 295-301.
74. Walker L, Pirmohamed M, Marson AG. Immunomodulatory interventions for focal epilepsy syndromes. Cochrane Database Syst Rev. 2013; 6: CD0009945.
75. Xembify 20% solution (human immune globulin subcutaneous – klhw). Grifols Therapeutics LLC. Research Triangle Park (NC). July 2019.
76. Yescarta (axicabtagene ciloleucel) [package insert]. Kite Pharma, Inc. Santa Monica, (CA): October 2017.
77. Yimmugo (immune globulin intravenous - dira) [package insert]. Biotest AG. Dreieich, Germany: June 2024.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/13/26.

GUIDELINE UPDATE INFORMATION:

12/15/99	Medical Coverage Guideline Reformatted.
01/01/01	Annual HCPCS coding update.
07/15/01	3rd quarter HCPCS coding update.
12/15/02	Revision; consisting of updating coding.
01/01/06	HCPCS update, deleted expired codes J1563 and J1564, added new codes J1566 and J1567.
05/15/06	Review; added subcutaneous immune globulin.
01/01/07	HCPCS update, added J1562. MCG revised to include Medicare Part D as a program exception.
04/15/07	Review and revision; consisting of changing lab values for CVID for what is considered deficient, added note for CVID regarding normal IVIg but failure to produce antibodies with 2 consecutive pneumococcal or tetanus vaccines, added tables of IVIg laboratory values under OTHER, reformatted and updated references.
06/15/07	Revision; consisting of reformatting guideline; added HCPCS codes, modified criteria for agammaglobulinemia and updated references.
01/01/08	Annual coding update. Added CPT-4 code 90284, HCPCS codes J1561, J1568, J1569, J1571, J1572, J1573 and J2791. Deleted HCPCS codes J1567, Q4087, Q4088, Q4090, Q4091 and Q4092.
04/01/08	2nd Quarter HCPCS coding update (added Q4097).
04/15/08	Review and revision; consisting of renaming MCG, added 2 new indications, reformatted and updated references and links.
01/01/09	Annual HCPCS coding update: revised descriptor for code J1572; deleted codes Q4097, 90765 and 90766; added 96365, 96366, and J1459.
07/15/09	Review and revision; consisting of updating references.
06/15/10	Revision; consisting of adding new agent.
09/15/10	Review and revision; consisting of updating references and review of current literature.
10/01/10	Revision; consisting of removing criteria for MMN and updating references.
01/01/11	Revision; consisting of updating coding.
05/15/11	Revision; consisting of further defining indications and reformatting the position statement.
09/15/11	Review and revision to guideline; consisting of no changes to the position statement.
11/15/11	Revision to guideline; consisting of refining coverage criteria for functional immunodeficiency and updating coding.
01/01/12	Revision to guideline; consisting of updating coding.
09/15/12	Review and revision to guideline; consisting of updating position statement, precautions, coding and references.
12/15/12	Revision to guideline; consisting of updating coding.
03/15/13	Revision to guideline; consisting of updating position statement to include continuation criteria and adding new intravenous product.
05/15/13	Revision; Program Exceptions section updated.
08/15/13	Review and revision to guideline; consisting of revising position statement and updating references.
8/15/14	Review and revision to guideline; consisting of revising position statement and updating references.
01/01/15	Revision to guideline; consisting of update to Position Statement, Billing/Coding Information,
03/15/15	Revision to guideline; consisting of updating description and position statement.
08/15/15	Review and revision to guideline; consisting of revising position statement, warnings/precautions, coding and references.
09/15/15	Revision to guideline; consisting of updating coding.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/16	Annual HCPCS coding update: added code J1575.

08/15/16	Review and revision to guideline; consisting of revising description, position statement, dosing, warnings/precautions, coding and references.
09/15/16	Revision to site of service statement.
10/01/16	Update to ICD-10 codes.
10/15/16	Revision to site of service statement.
11/15/16	Revision to guideline; consisting of updating description and site of service statement with a new formulation.
08/15/17	Review and revision to guideline; consisting of revising position statement, coding and references.
10/15/17	Review and revision to guideline; consisting of updating position statement, coding and references.
01/01/18	Annual HCPCS coding update: added HCPCS code J1555.
03/15/18	Revision to guideline; consisting of updating position statement, coding and references.
04/15/18	Revision to guideline; consisting of updating position statement, coding and references.
07/15/18	Review and revision to guideline; consisting of revising position statement and updating references.
12/15/18	Revision to guideline; consisting of revising description and references.
09/15/19	Review and revision to guideline; consisting of revising position statement, description, coding and references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
05/15/20	Revision to guideline consisting of updating the position statement.
07/01/20	Revision: Added HCPCS code J1558.
10/01/20	Revision to ICD-10 coding.
12/15/20	Review and revision to guideline; consisting of updating the position statement, coding and references.
01/01/21	Revision: Added HCPCS code C9072 and deleted code C9399.
03/15/20	Revision to guideline; consisting of updating the position statement and coding.
04/01/21	Revision: Added HCPCS code J1554 and deleted code C9072.
11/15/21	Review and revision to guideline; consisting of updating the position statement, program exceptions, and references.
07/01/22	Revision: Added HCPCS code J1551.
10/01/22	Review and revision to guideline; consisting of updating the position statement to include step through preferred IVIG agents and inclusion of CAR T-cell associated cytokine release syndrome. Update to coding and references.
05/15/23	Review and revision to guideline; consisting of updating the position statement to include autoimmune encephalitis, acute disseminated encephalitis, and Rasmussen's encephalitis.
07/01/23	Revision: Added HCPCS code J1576.
02/15/24	Review and revision to guideline; consisting of updating the position statement to include Alyglo and updating references.
10/01/24	ICD-10 coding update.
01/01/25	Revision: Added HCPCS code J1552.
01/15/25	Review and revision to guideline; consisting of updating the position statement to include Yimmugo, updating acquired secondary hypogammaglobulinemia, and updating the use for chronic ITP, immune checkpoint inhibitor toxicity, CAR-T cell induced reactions, and refractory myasthenia gravis.
10/01/25	Review and revision to guideline; consisting of updating the position statement to include HyQvia as a non-preferred agent, updating acquired secondary hypogammaglobulinemia, and inclusion of HLH or HLH/MAS with known or suspected Still’s disease/sJIA.
04/01/26	Revision: Added HCPCS code J1553.

04/15/26	Revision to guideline; including addition of Qivigy as a non-preferred agent and updated criteria for Asceniv. Included NCCN supported oncology indications for acquired hypogammaglobulinemia, CAR-T therapy, pediatric Langerhans Cell Histiocytosis, and immune checkpoint inhibitor toxicity.
05/15/26	Revision to guideline; including addition of Gammagard Liquid ERC as a non-preferred agent.
06/15/26	Revision to guideline; including addition of comparative effectiveness statement for Asceniv. Updated the position statement for IgG subclass deficiency and acquired hypogammaglobulinemia conditions.
07/01/26	Revision: Added HCPCS code J1577. Updated description for code J1569.
10/01/26	Revision to ICD-10 codes.