Drug and Biologic Coverage Policy

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Coverage Policy Number 5026

Immune Globulin

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) products:

- Asceniv™ (immune globulin intravenous liquid-sira)
- Bivigam® (immune globulin intravenous)
- Cutaquig® (immune globulin subcutaneous 16.5% solution)
- Cuvitru™ (immune globulin subcutaneous 20% solution)
- Flebogamma® DIF (immune globulin intravenous)
- Gammagard Liquid, Gammagard® S/D < 1 mcg/mL in 5% solution (immune globulin infusion)
- Gammaked™ (immune globulin injection caprylate/chromatography purified)
- Gammaplex® (immune globulin intravenous)
- Gamunex®-C (immune globulin injection caprylate/chromatography purified)
- Hizentra® (immune globulin subcutaneous 20% liquid)
- HyQvia (immune globulin infusion 10% with recombinant human hyaluronidase)

- Octagam® (immune globulin intravenous)
- Panzyga® (immune globulin intravenous-ifas)
- Privigen® Liquid (immune globulin intravenous)
- Xembify® (immune globulin subcutaneous 20% solution)

Additional criteria that support the review for medical necessity exceptions of non-covered products are located in the Non-Covered Product Table by the respective plan type and drug list where applicable.

Intravenous immunoglobulins (IVIG) for COVID-19 uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (COVID-19: Drug and Biologic Therapeutics).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Immune globulin products are considered medically necessary when **BOTH** of the following are met:

1. Individual meets the Specific Medical Necessity Criteria by Condition (follow the below links to the related criteria section)
   - **I. Primary Immunodeficiency Disorder (PID)**
   - **II. Secondary Immunodeficiency**
   - **III. Infectious Disease**
   - **IV. Transplantation**
   - **V. Hematology**
   - **VI. Neurology**
   - **VII. Rheumatology**
   - **VIII. Dermatology**

2. Non-Covered Product Criteria is met, refer to below table

Employer Group and Individual and Family Plan Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Asceniv (immune globulin intravenous ,human - slra, 10% liquid)	Documentation of **EITHER** of the following: 1. Failure, contraindication, or intolerance to **Three** of the following: A. Bivigam B. Flebogamma DIF C. Gammaked D. Gammaplex E. Gamunex-C F. Octagam G. Panzyga H. Privigen 2. Individual requires an immune globulin product with elevated levels of respiratory syncytial virus (RSV) antibodies (for example, if the individual has repeated RSV infections despite adequate IVIG dosing in a compliant individual)
Cuvitru (immune globulin subcutaneous [human] 20% solution)	Documentation of **ONE** of the following: 1. Failure, contraindication, or intolerance to **BOTH** of the following: A. Hizentra B. Xembify

Non-Covered Product	Criteria
	2. Hypersensitivities to polysorbate 80 3. Hyperprolinemia and failure, contraindication, or intolerance to Xembify
Gammagard Liquid (immune globulin intravenous [IVIG])	For Subcutaneous (SC) route. Documentation of failure, contraindication, or intolerance to **THREE** of the following: A. Hizentra B. Cutaquig C. Gammaked D. Gamunex-C E. Xembify For Intravenous (IV) route. Documentation of failure, contraindication, or intolerance to **THREE** of the following: A. Bivigam B. Flebogamma DIF C. Gammaked D. Gammaplex E. Gamunex-C F. Octagam G. Panzyga H. Privigen
Gammagard S/D IgA ≤ 1 mcg/mL (immune globulin intravenous [IVIG])	Documentation of **EITHER** of the following: 1. Failure, contraindication, or intolerance to **THREE** of the following: A. Bivigam B. Flebogamma DIF C. Gammaked D. Gammaplex E. Gamunex-C F. Octagam G. Panzyga H. Privigen 2. Individual requires an IVIG product with the lowest IgA content as defined by **BOTH** of the following: A. IgA levels are less than 7 mg/dL B. Individual has antibodies to IgA, or a history of hypersensitivity to any product containing a higher content of IgA
HyQvia (immune globulin infusion [human] 10% with recombinant human hyaluronidase subcutaneous)	Documentation of failure, contraindication, or intolerance to **THREE** of the following: A. Cutaquig B. Gammaked C. Gamunex-C D. Hizentra E. Xembify

Specific Medical Necessity Criteria by Condition:

I. Primary Immunodeficiency Disorder (PID)

Condition	Criteria for Use

Hypogammaglobulinemia (including Common Variable Immunodeficiency [CVID])	**ALL of the following are met:**
	• **Immunologic evaluation including** documented serum IgG below the lower limits of normal of the laboratory's reported value on at least two occasions
	• **Impaired Antibody Response (EITHER of the following):**
	  ○ Lack of protective antibody titers (tetanus and diphtheria or HiB) measured 3–4 weeks after immunization
	  ○ Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following:
	  ▪ Age < 6 years, < 50% of serotypes are protective (≥ 1.3 mcg/mL per serotype)
	  ▪ Age ≥ 6 years, < 70% of serotypes are protective (≥ 1.3 mcg/mL per serotype)
	• **Recurrent Infection (ALL of the following):**
	  ○ History of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy
	  ○ Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable
	  ○ Supporting diagnostic imaging and/or laboratory results where applicable

IgG Subclass Deficiency	**ALL of the following are met:**
	• **Immunologic evaluation** including documented normal total serum IgG with one or more subclasses, excluding isolated subclass IgG4, below the lower limits of normal of the laboratory's reported value on at least two occasions
	• **Impaired Antibody Response** – Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following:
	  ○ Age < 6 years, < 50% of serotypes are protective (≥ 1.3 mcg/mL per serotype)
	  ○ Age ≥ 6 years, < 70% of serotypes are protective (≥ 1.3 mcg/mL per serotype)
	• **Recurrent Infection (ALL of the following)**
	  ○ History of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy
	  ○ Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable
	  ○ Supporting diagnostic imaging and/or laboratory results where applicable

Selected Specific Primary Immunodeficiency Disorders	**ONE of the following criteria is met:** • Agammaglobulinemia defined as serum IgG < 200 mg/dl • Extremely low (< 2%) or absent B cell count ($CD19^+$) • Documentation of a recognized genetic defect supporting diagnosis (see Appendix 1, Appendix 2, and Appendix 3) • Transient hypogammaglobulinemia of infancy with serum immunoglobulins below the age-specific normal range and **BOTH** of the following:

	○ Evidence of recurrent bacterial sinopulmonary infections requiring antibiotic therapy (IVIG is only used for up to six months before re-evaluating the need for continued treatment) ○ Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination defined as < 50% of serotypes are protective (≥ 1.3 mcg/mL per serotype) • Hyperimmunoglobulinemia E syndrome as evidenced by: ○ Elevated serum IgE level, the presence of staphylococcus-binding IgE, eosinophilia, and recurrent lung and/or skin infections (abscess, chronic eczematous dermatitis) **AND** ○ Impaired Antibody Response (**EITHER** of the following): ▪ Lack of protective antibody titers (tetanus and diphtheria or HiB) measured 3–4 weeks after immunization ▪ Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following: • Age < 6 years, < 50% of serotypes are protective (≥ 1.3 mcg/mL per serotype) • Age ≥ 6 years, < 70% of serotypes are protective (≥ 1.3 mcg/mL per serotype)
Specific Antibody Deficiency (SAD)	**ALL of the following criteria are met:** • **Immunological evaluation** including documented normal serum IgG, IgG subclass, IgA, and IgM • Normal responses to protein antigens (tetanus and diphtheria toxoid) measured 3-4 weeks after immunization • **Inadequate responsiveness** to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following: ○ Age < 6 years, < 50% of serotypes are protective (≥ 1.3 mcg/mL per serotype) ○ Age ≥ 6 years, < 70% of serotypes are protective (≥ 1.3 mcg/mL per serotype) • **Recurrent Infection (ALL of the following):** ○ History of severe and recurrent bacterial sinopulmonary infections despite documentation of both: ▪ Prevnar 7 or Prevnar 13 vaccination ▪ Documented failure/inadequate response, contraindication, or intolerance to the use of prophylactic antibiotic therapy ○ Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable ○ Supporting diagnostic imaging and/or laboratory results where applicable

II. Secondary Immunodeficiency

Condition	Criteria for Use
Acquired Immunosuppression	Prevention of infection in individuals meeting **ALL** of the following: • Presence of hypogammaglobulinemia (serum IgG < 400 mg/dL) • Immunosuppression is attributed to **ONE** of the following: ○ Major surgery (for example, cardiac transplant) ○ Hematologic malignancy ○ Extensive burns ○ Collagen-vascular disease • Recurrent sinopulmonary infection or history of serious bacterial infection(s)

B-cell Chronic Lymphocytic Leukemia (CLL)	Treatment when **BOTH** of the following are met: • Serum IgG less than 500 mg/dL • Recurrent sinopulmonary infection or history of serious bacterial infection(s)
CMV Viremia	Treatment of refractory CMV viremia (e.g. persistent viral titers despite reduced immunosuppression, antiviral treatment) in cancer or solid organ transplant recipients.
HIV-infected Children	**ONE of the following criteria is met:** • Primary prophylaxis of bacterial infections when hypogammaglobulinemia (serum IgG < 400 mg/dL) is present • Secondary prophylaxis of frequent recurrent serious bacterial infections (e.g., > 2 serious bacterial infections in a 1-year period despite combination ART) when antibiotic prophylaxis is not effective
Multiple Myeloma	Treatment when there is history of serious bacterial infection(s) or there is a recurrent life-threatening infection.

III. Infectious Disease

Condition	Criteria for Use
Measles - Post-Exposure Prophylaxis	Prophylaxis when **ANY** of the following are met: • Pregnant women without evidence of measles immunity • Severe primary immunodeficiency • Individuals who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in individuals who have developed graft-versus-host disease • Individual on treatment for acute lymphoblastic leukemia (ALL) within and until at least 6 months after completion of immunosuppressive chemotherapy • Individuals with a diagnosis of AIDS or HIV-infected persons with severe immunosuppression defined as CD4 percent <15% (all ages) or CD4 count <200 lymphocytes/mm^3 (aged >5 years) and those who have not received MMR vaccine since receiving effective antiretroviral therapy (ART)
Toxic Shock Syndrome (Staphylococcal or Streptococcal)	Acute treatment for **ANY** of the following: • The infection is refractory to aggressive treatment • Presence of an undrainable focus • Persistent oliguria with pulmonary edema
Tetanus	Post-exposure prophylaxis or treatment when Tetanus Immune Globulin is unavailable.
Varicella	Post-exposure prophylaxis when Varicella Immune Globulin is unavailable.

IV. Transplantation

Condition	Criteria for Use
BK Viremia	Treatment of refractory BK viremia (e.g. persistent viral titers despite reduced immunosuppression) in kidney transplant recipients.
Hematopoietic Cell Transplant (HCT)	Prevention of infection in HCT recipients (for example, stem cell or bone marrow transplantation) with hypogammaglobulinemia (serum IgG < 400 mg/dL) and **EITHER** of the following: • Within the first 100 days after transplant • After 100 days and evidence of recurrent infections OR evidence of graft-versus-host-disease (GVHD)
Solid Organ Transplants	Treatment for **EITHER** of the following: • Desensitization therapy prior to and immediately after transplantation

	○ Authorization for a maximum dose of 2 grams/kg monthly for 4 consecutive months. Additional infusions at 12 months and 24 months may be authorized if the individual has not undergone transplantation. • Antibody-mediated rejection (AMR) ○ Initial authorization for a maximum dose of 2 grams/kg monthly for 3 months. Reauthorization for up to 3 months is dependent on documented beneficial clinical response.

V. Hematology

Condition	Criteria for Use
Anemia related to Chronic Parvovirus B19 Infection	Treatment when there is a severe refractory anemia and evidence of viremia.
Evan's Syndrome	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (azathioprine, cyclophosphamide, cyclosporine or prednisone).
Fetal Alloimmune Thrombocytopenia (FAIT)	Treatment when **ALL** of the following: • Documentation of maternal antibodies to paternal platelet antigen • **ONE** of the following: ○ Previous pregnancy complicated by FAIT ○ Fetal blood sampling documents thrombocytopenia
Hepatitis C-associated Thrombocytopenia	Treatment for **ANY** of the following: • Clinically significant bleeding associated with thrombocytopenia • Preoperative treatment prior to a major surgical procedure (for example, splenectomy) • Receiving antiviral treatment for hepatitis C infection or treatment is contraindicated
HIV-associated Thrombocytopenia	Treatment for **ANY** of the following: • Clinically significant bleeding associated with thrombocytopenia • Preoperative treatment prior to a major surgical procedure (for example, splenectomy) • Receiving treatment for HIV infection with antiretroviral therapy **AND** failure, contraindication, or intolerance to corticosteroids
Immune (Idiopathic) Thrombocytopenia (ITP) – Adult	Platelet count < 30,000/mm^3 and **ONE** of the following are met: • Clinical need to rapidly increase the platelet count (examples include, but are not limited to: active bleeding, prior to major surgical procedure, risk of cerebral hemorrhage) • Not a candidate for splenectomy or experienced relapse post-splenectomy **AND** failure, contraindication, or intolerance to **ONE** of the following: ○ Corticosteroids ○ Thrombopoietin receptor agonists (eltrombopag [Promacta®] or romiplostim [Nplate®]) ○ Rituximab (Rituxan®)
Immune (Idiopathic) Thrombocytopenia (ITP) – Pediatric	**ONE of the following are met:** • Clinical need to rapidly increase the platelet count (examples include, but are not limited to: active bleeding, prior to major surgical procedure, risk of cerebral hemorrhage) • Prevention of bleeding during the first 12 months of persistent disease if responsive to previous treatment with IVIG
Immune Thrombocytopenia (ITP) - Pregnancy	Treatment when **ALL** of the following are met: • Diagnosis of thrombocytopenia

	• Failure, contraindication, or intolerance to corticosteroids or clinical need to rapidly increase the platelet count
Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy	Approve for the duration noted if the patient meets **ONE** of the following: Note: Examples of checkpoint inhibitors are: Keytruda (pembrolizumab), Opdivo (nivolumab), Yervoy (ipilimumab), Tecentriq (atezolizumab), Bavencio (avelumab), Imfinzi (durvalumab). • Initial Therapy. Approve for 1 month if the individual meets **ONE** of the following criteria: o The individual has tried a systemic corticosteroid (for example, prednisone, methylprednisolone) and has not adequately responded to therapy o The medication is being started with a systemic corticosteroid o A corticosteroid is contraindicated per the prescriber • Individual is Currently Receiving Immune Globulin. Approve for 6 months if the individual is having a positive response to therapy, as determined by the prescriber, and the prescriber has determined extended therapy is required.
Neonatal Isoimmune Hemolytic Disease in Conjunction with Phototherapy	Acute treatment only.
Post-transfusion purpura	Acute treatment only.
Warm Type Autoimmune Hemolytic Anemia (characterized by predominance of IgG antibodies as opposed to cold type that is predominated by IgM antibodies)	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (azathioprine, cyclophosphamide, cyclosporine, prednisone, plasmapheresis, or splenectomy).

VI. Neurology

Condition	Criteria for Use
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), including Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) (Lewis-Sumner Syndrome)	**For initial authorization**: Treatment when **ALL** of the following **required** elements are met: • Progressive or relapsing motor and/or sensory symptoms of more than one limb **AND** hyporeflexia or areflexia in affected limbs present for at least 2 months as documented by objective measurement • Electrophysiologic findings indicate demyelinating neuropathy (3 of the following 4 criteria are met per the American Academy of Neurology): o Partial conduction block* of ≥ 1 motor nerve o Reduced conduction velocity* of ≥ 2 motor nerves o Prolonged distal latency* of ≥ 2 motor nerves o Prolonged F-wave latencies* of ≥ 2 motor nerves or the absence of F waves • Other causes of demyelinating neuropathy have been excluded (from the European Federation of Neurological Societies and the Peripheral Nerve Society):

	○ Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy ○ Hereditary demyelinating neuropathy ○ Prominent sphincter disturbance ○ Diagnosis of multifocal motor neuropathy ○ IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein ○ Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma and amyloidosis. * Definitions from the American Academy of Neurology • **Partial conduction block** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of < 15% in duration between proximal and distal site stimulation. • **Possible conduction block or temporal dispersion** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of at least 15% in duration between proximal and distal site stimulation. • **Reduced conduction velocity** is a velocity of < 80% of the lower limit of the normal range if the amplitude of the compound muscle action potential (CMAP) is > 80% of the lower limit of the normal range or < 70% of the lower limit if the CMAP amplitude is less than 80% of the lower limit. • **Prolonged distal latency** is more than 125% of the upper limit of the normal range if the CMAP amplitude is more than 80% of the lower limit of the normal range or more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit. • **Absent F wave or F-wave latency** is more than 125% of the upper limit if the CMAP amplitude is more than 80% of the lower limit or latency is more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit. **When available**, results of other pertinent testing to support diagnosis should be provided. This includes, but is not limited to, the following: ○ Cerebrospinal fluid (CSF) examination demonstrating elevated CSF protein with leukocyte count <10/mm^3 ○ MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses ○ Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis **For reauthorizations**, significant improvement in clinical condition has been documented by an objective measurement such as the inflammatory neuropathy cause and treatment group (INCAT) sensory sum score; assessment of grip strength via a hand-held dynamometer (e.g., Jamar, Vigorimeter); or Medical Research Council (MRC) scales or other similar, validated neurological scales **AND**, when applicable, a reduction in the level of sensory loss should be noted (see Appendix 4). **For long-term treatment**, evidence that the dose has been periodically reduced or the treatment withdrawn, and the effects measured.
Guillain-Barré Syndrome (GBS) – including Acute Inflammatory	Acute treatment when **ALL** of the following criteria have been met: • Initial treatment within 4 weeks of the onset of symptoms • No concomitant use of plasmapheresis

Demyelinating Polyneuropathy (AIDP)	• Treatment may be repeated once but should not extend beyond 8 weeks from the onset of symptoms
Lambert-Eaton Myasthenic Syndrome (LEMS)	Treatment when there is failure, contraindication, or intolerance to other symptomatic therapies (for example, acetylcholinesterase inhibitors such as Mestinon and immunosuppressants such as prednisone, azathioprine).
Multifocal Motor Neuropathy (MMN)	Treatment when **BOTH** of the following are present: • Progressive symptoms present for at least 1 month • Diagnosis of *definite* or *probable* MMN as defined by the American Association of Neuromuscular and Electrodiagnostic Medicine (see Appendix 5).
Myasthenia Gravis (MG)	Treatment when **ANY** of the following is present: • Before planned thymectomy or during the post-operative period following thymectomy • During an acute crisis (for example, significant dysphagia, respiratory failure, inability to perform physical activity) – duration of treatment should not exceed 5 days • During initiation of immunosuppressive treatment • For initial treatment of ***refractory*** myasthenia gravis and **ALL** of the following: o Documented failure or inadequate response to pyridostigmine o Documented failure, intolerance or not a candidate (for example,) for corticosteroid maintenance treatment o Documented failure or inadequate response to nonsteroidal immunosuppressive treatment with at least one of the following: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus o Documented failure or contraindication to thymectomy for individuals who are anti-acetylcholine receptor (AChR) antibody positive * Initial therapy for maintenance treatment for refractory MG may be approved up to 12 months.
Opsoclonus-Myoclonus-Ataxia Syndrome	Treatment when there is a documented diagnosis.
Rasmussen Encephalitis	Treatment when there is failure to conventional therapy (corticosteroids, antiepileptic agents).
Relapsing-Remitting Multiple Sclerosis (RRMS)	Treatment as a single agent when there is failure to any **TWO** of the following products indicated for the treatment of relapsing-remitting multiple sclerosis: • Dimethyl fumarate (Tecfidera®)* • Fingolimod (Gilenya™)* • Glatiramer acetate (Copaxone®)* • Interferon beta-1a (Avonex® or Rebif®)* • Interferon beta-1b (Betaseron®, Extavia®)* • Natalizumab (Tysabri®)* • Teriflunomide (Aubagio®)* * Individual plans may require prior authorization or pre-certification.
Stiff Person Syndrome (Moersch-Woltmann Syndrome)	Treatment when **BOTH** of the following are met: • Anti-GAD antibody testing performed • Failure to available standard medical therapy (for example, diazepam, baclofen, phenytoin, clonidine, or tizanidine)

VII. Rheumatology

Condition	Criteria for Use

Dermatomyositis or Polymyositis	Treatment when **BOTH** of the following are present:
	• Documented dermatomyositis or polymyositis established by biopsy
	• **ONE** of the following
	  ○ Failure of standard medical therapy (corticosteroids AND immunosuppressives)
	  ○ Profound, rapidly progressive and/or potentially life threatening muscular weakness

Kawasaki disease	Acute treatment when given in conjunction with aspirin within ten days of onset of symptoms.

VIII. Dermatology

Condition	Criteria for Use
Autoimmune mucocutaneous blistering diseases; such as: • **Bullous Pemphigoid** • **Epidermolysis Bullosa Acquisita** • **Pemphigoid (a.k.a., Cicatricial Pemphigoid)** • **Pemphigus Foliaceus** • **Pemphigus Vulgaris**	Treatment when **EITHER** of the following criteria is met: • Failure, contraindication or intolerance of conventional therapy (corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil) • Rapidly progressive disease in which a clinical response cannot be affected quickly enough using conventional agents. In these situations, IVIG therapy should be given along with conventional treatment(s) and the IVIG used only until conventional therapy takes effect **Note:** IVIG for the treatment of autoimmune mucocutaneous blistering disease is covered only for short-term therapy **(no longer than 6 consecutive months**) and not as a maintenance therapy
Stevens–Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)	Acute treatment only.

See appendices for the following information:
- Appendix 1 – Standard Reference Ranges for Serum Immunoglobulin Levels
- Appendix 2 – Standard Reference Ranges for Serum Immunoglobulin G Subclasses (G1, G2, G3, G4)
- Appendix 3 – Selected Genetic Based Primary Immunodeficiency (PID) Disorders
- Appendix 4 – Examples of Objective Measurements to Assess Clinical Response (CIDP Reauthorization Criteria)
- Appendix 5 – American Association of Neuromuscular and Electrodiagnostic Medicine Consensus Criteria for the Diagnosis of Multifocal Motor Neuropathy

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When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of immune globulin therapy is considered medically necessary for all covered diagnoses when **ALL** of the following are met:

1. The above medical necessity criteria have been met prior to the start of immune globulin therapy
2. The medical condition or disease under treatment has not fully resolved and the treatment has not exceeded any applicable duration listed below.

3. There continues to be a sustained beneficial response to IVIG as evidenced by treatment notes or a clinical narrative detailing progress to date and the expected frequency and duration of any proposed IVIG use going forward.
4. The requested frequency and dosage of IVIG is supported by evidence-based literature.
5. Where clinically appropriate, titration has occurred to the minimum dose and frequency to achieve sustained clinical effect.

Authorization Duration

Initial authorization is up to 6 months unless otherwise stated within the Specific Medical Necessity Criteria by Condition.
Reauthorization is up to 6 months (up to 12 months for PID and for *refractory* MG).

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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

Recommended Dosing

FDA Recommended Dosing

The frequency and amount of immunoglobulin therapy may vary from individual to individual. The proper dosing amount can be determined by monitoring clinical response.

<table>
<tr><th>Product</th><th>FDA Recommended Dosing</th></tr>
<tr><td>Asceniv</td><td>The recommended dose of Asceniv for replacement therapy in primary humoral immunodeficiency (PI) is 300 to 800 mg/kg body weight administered every 3 to 4 weeks. The dose may be adjusted over time to achieve the desired trough levels and clinical response.

Asceniv dose adjustments may be required in patients who fail to maintain trough total IgG concentrations of at least 500 mg/dL with a target of 600 mg/dL. Starting with the second infusion, adjust the dose proportionally, targeting a trough of ≥ 600 mg/dL, based on the previous trough and the associated dose.

For intravenous use only.

Table 1
<table>
<tr><th>Dose</th><th>Initial Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>300-800 mg/kg every 3-4 weeks</td><td>0.5 mg/kg/min (0.005 mL/kg/min) for the first 15 minutes</td><td>Increase gradually every 15 minutes (if tolerated) up to 8 mg/kg/min (0.08 mL/kg/min)</td></tr>
</table></td></tr>
</table>

Bivigam®	The recommended dose of Bivigam for replacement therapy in primary humoral immunodeficiency (PI) is 300 to 800 mg/kg body weight administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical response. Bivigam dose adjustments may be required in patients who fail to maintain trough total IgG concentrations of at least 500 mg/dL with a target of 600 mg/dL. Starting with the second infusion, the dose will be adjusted proportionally, targeting a trough of more than equal to 600 mg/dL, based on the previous trough and the associated dose.
Cutaquig	For subcutaneous use only. Do not inject into a blood vessel. • Before receiving treatment with Cutaquig: Obtain the patient's serum Immunoglobulin G (IgG) trough level to guide subsequent dose adjustments. Dose • Individualize the dose based on the patient's pharmacokinetic and clinical response. Monitor serum IgG trough levels regularly to guide subsequent dose adjustments as needed. • Start Cutaquig treatment one week after the last IGIV/IGSC infusion. *Dose for patients switching to Cutaquig from IGIV:* • Ensure that patients have received Immune Globulin Intravenous (Human) (IGIV) treatment at regular intervals for at least 3 months. • Establish the initial weekly dose of Cutaquig by converting the monthly IGIV dose into an equivalent weekly dose and increasing it using a dose adjustment factor. • To calculate the initial weekly dose of Cutaquig, divide the monthly IGIV dose in grams by the number of weeks between IGIV infusions and then multiply this value with a Dose Adjustment Factor of 1.40. $$\text{Initial weekly dose} = \frac{\text{Previous IGIV dose (in grams)} \times 1.40}{\text{Number of weeks between IGIV doses}}$$ • To convert the dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 6. • Provided the total weekly dose is maintained, any dosing interval from daily up to weekly can be used and will result in systemic IgG exposure that is comparable to the previous IGIV treatment. • On average, serum IgG trough levels were approximately 23% higher during Cutaquig administration compared to those obtained during prior IGIV therapy. • To guide dose adjustments, see prescribing information, Table 1 under Dose Adjustment. *Dose for patients switching to Cutaquig from IGSC:* • Ensure that patients have received IGSC at regular intervals for at least 3 months before switching to Cutaquig. • It is recommended to maintain the same weekly dosing (in grams) of Cutaquig that was used for the previous Immune Globulin Subcutaneous (Human) (IGSC) therapy (in grams). • To convert the dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 6. • Obtain a trough IgG level before switching, monitor clinical response and check the trough IgG level 2 to 3 months after initiating Cutaquig. • To guide dose adjustments, see prescribing information, Table 1 under Dose Adjustment , if the trough IgG level during Cutaquig administration differs from the

	trough IgG level obtained during treatment with the previously administered IGSC product or target trough level.
Cuvitru®	***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.* For subcutaneous infusion only. • Administer at regular intervals from daily up to every two weeks (biweekly). • Individualize dose based on the patient's pharmacokinetic and clinical response. • Monitor serum IgG trough levels regularly to guide subsequent dose adjustments and dosing intervals as needed. • Switching from Immune Globulin Intravenous (Human) treatment (IGIV) or adult patients switching from HyQvia ([Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]: • Begin treatment one week after the patient's last IGIV or HyQvia infusion. • Begin treatment one week after the patient's last IGIV or HyQvia infusion. • Establish initial weekly dose by converting the monthly IGIV or HyQvia dose into equivalent weekly dose and increasing it using a dose adjustment factor. Initial Weekly dose = Previous IGIV or HyQvia dose (in grams)/No. of weeks between IGIV or HYQVIA doses x 1.30. • Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week. • Biweekly dosing: Multiply the calculated weekly dose by 2.
Flebogamma® 5% DIF	Treatment of Primary Immunodeficiency (PI): 300 to 600 mg/kg body weight (6.0 to 12.0 mL per kg) administered every 3 to 4 weeks. As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Adjust the dose according to the clinical response. Adjust the dosage over time to achieve the desired trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.
Flebogamma® 10% DIF	Treatment of Primary Immunodeficiency (PI): 300 to 600 mg/kg body weight (3.0 to 6.0 mL/kg) administered every 3-4 weeks. Treatment of Chronic Primary Immune Thrombocytopenia (ITP): 1 g/kg body weight (10ml per kg) daily for 2 consecutive days As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Dosing should be adjusted according to the clinical response. The dosage may be adjusted over time to achieve the desired serum trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.
Gammagard® Liquid	<u>Primary Immunodeficiency</u> 300 to 600 milligram/kg every 3 to 4 weeks based on clinical response <u>Multifocal Motor Neuropathy</u> Dose range 0.5 to 2.4 grams/kg/month based on clinical response <u>Primary Immunodeficiency</u> Initial dose is 1.37 x previous intravenous dose divided by # of weeks between intravenous doses. Maintenance dose is based on clinical response and target IgG trough level.

<table>
<tr><td>Gammagard® S/D</td><td>Primary Immunodeficiency (PI)
The recommended dose of Gammagard S/D for patients with PI is 300-600 mg/kg infused at 3 to 4 week intervals. Adjust dose according to the clinical response; the frequency and dose of immunoglobulin may vary from patient to patient. No randomized controlled clinical trials are available to determine an optimum target trough serum IgG level.

B-cell Chronic Lymphocytic Leukemia (CLL)
The recommended dose of Gammagard S/D for patients with hypogammaglobulinemia and/or recurrent bacterial infections due to B-cell CLL is 400 mg/kg body weight infused at every 3 to 4 week intervals.

Idiopathic Thrombocytopenic Purpura (ITP)
The recommended dose of Gammagard S/D for patients with chronic ITP is 1 g/kg. The need for additional doses can be determined by clinical response and platelet count. Up to three separate doses may be given on alternate days if required.

Kawasaki Syndrome
The recommended dose of Gammagard S/D for patients with Kawasaki syndrome is either a single 1 g/kg dose or a dose of 400 mg/kg for four consecutive days beginning within seven days of the onset of fever, administered concomitantly with appropriate aspirin therapy (80-100 mg/kg/day in four divided doses).</td></tr>
<tr><td>Gammaked™</td><td>**Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.
• Intravenous Administration Only: ITP and CIDP
<table>
<tr><th>Indication</th><th>Dose</th><th>Initial Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>ITP</td><td>2 g/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min</td></tr>
<tr><td>CIDP</td><td>Loading dose
2 g/kg
Maintenance dose
1 g/kg</td><td>2 mg/kg/min</td><td>8 mg/kg/min
Every 3 weeks</td></tr>
</table>
○ Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Gammaked if renal function deteriorates.
○ For patients at risk of renal dysfunction or thrombosis, administer Gammaked at the minimum infusion rate practicable.

• Intravenous or Subcutaneous Administration: PI
DO NOT ADMINISTER SUBCUTANEOUSLY FOR ITP PATIENTS.
<table>
<tr><th>Route of Administration</th><th>Dose</th><th>Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>Intravenous (IV)</td><td>300-600 mg/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min
Every 3-4 weeks</td></tr>
<tr><td>Subcutaneous (SC)</td><td>1.37 x current IV dose in mg/kg/IV dose interval in weeks</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
15 mL/hr/site (≥ 25 kg)</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
20 mL/hr/site (≥ 25 kg)
Weekly</td></tr>
</table></td></tr>
<tr><td>Gammaplex®</td><td><u>Treatment of Primary Humoral Immunodeficiency</u></td></tr>
</table>

<table>
<tr><td></td><td>The recommended dose of Gammaplex for patients with PI is 300 to 800 mg/kg (6 to 16 mL/kg), administered every 3 to 4 weeks. Adjust the dosage over time to achieve the desired serum trough levels and clinical response. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

Treatment of Chronic Idiopathic Thrombocytopenic Purpura
The recommended dose of Gammaplex for patients with ITP is 1 g/kg (20 mL/kg) on 2 consecutive days, providing a total dose of 2 g/kg. Carefully consider the relative risks and benefits before prescribing the high dose regimen (i.e. 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload. Adequate data on the platelet response to the low dose regimen (e.g. 400 mg/kg per day for 5 consecutive days) are not available for Gammaplex.</td></tr>
<tr><td>Gamunex®-C</td><td>**Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.
• Intravenous Administration Only: Idiopathic Thrombocytopenic Purpura (ITP) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
<table>
<tr><th>Indication</th><th>Dose</th><th>Initial Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>ITP</td><td>2 g/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min</td></tr>
<tr><td>CIDP</td><td>Loading dose
2 g/kg
Maintenance dose
1 g/kg</td><td>2 mg/kg/min</td><td>8 mg/kg/min
Every 3 weeks</td></tr>
</table>
• Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Gamunex-C if renal function deteriorates.
• For patients at risk of renal dysfunction or thrombosis, administer Gamunex-C at the minimum infusion rate practicable.

• Intravenous or Subcutaneous Administration: Primary Humoral Immunodeficiency (PI)
• DO NOT ADMINISTER SUBCUTANEOUSLY FOR ITP PATIENTS.
<table>
<tr><th>Route of Administration</th><th>Dose</th><th>Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>Intravenous (IV)</td><td>300-600 mg/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min
Every 3-4 weeks</td></tr>
<tr><td>Subcutaneous (SC)</td><td>1.37 x current IV dose in mg/kg/IV dose interval in weeks</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
15 mL/hr/site (≥ 25 kg)</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
20 mL/hr/site (≥ 25 kg)
Weekly</td></tr>
</table>
</td></tr>
<tr><td>Hizentra®</td><td>**Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.
For subcutaneous infusion only.

<u>PI</u>
Before switching to Hizentra, obtain the patient's serum IgG trough level to guide subsequent dose adjustments.</td></tr>
</table>

	• Weekly: Start Hizentra 1 week after last Immune Globulin Intravenous (Human) (IGIV) infusion. Initial weekly dose = Previous IGIV dose (in grams) × 1.37 No. of weeks between IGIV doses • Biweekly (every 2 weeks): Start Hizentra 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly IGSC infusion. Administer twice the calculated weekly dose. • Frequent dosing (2 to 7 times per week): Start Hizentra 1 week after the last IGIV or IGSC infusion. Divide the calculated weekly dose by the desired number of times per week. • Adjust the dose based on clinical response and serum IgG trough levels. CIDP • Initiate therapy with Hizentra 1 week after the last IGIV infusion. • Recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) body weight per week o In the clinical study after transitioning from IGIV to HIZENTRA, a dose of 0.4 g/kg (2 mL/kg) body weight per week was also safe and effective to prevent CIDP relapse • If CIDP symptoms worsen, on 0.2 g/kg (1 mL/kg) body weight per week, consider increasing the Hizentra dose from 0.2 g/kg to 0.4 g/kg body weight per week. o If CIDP symptoms worsen on 0.4 g/kg body weight per week, consider re-initiating therapy with IGIV, while discontinuing Hizentra • Monitor patient's clinical response and adjust duration of therapy based on patient need
HyQvia®	***Refer to the prescribing information (product label) for complete dosing information.* For subcutaneous use only. Initiation of Treatment with HyQvia • For patients previously on another IgG treatment, administer the first dose approximately one week after the last infusion of their previous treatment. • Increase the dose and frequency from a 1-week dose to a 3- or 4-week dose • Initiating treatment at a full monthly dose was not evaluated in the clinical trial. For patients switching from Immune Globulin Intravenous (Human) [IGIV] treatment: Administer HyQvia at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up. For patients naïve to IgG treatment or switching from Immune Globulin Subcutaneous (Human) [IGSC]: Administer HyQvia at 300 to 600 mg/kg at 3 to 4 week intervals, after initial ramp-up. Individualization of Dose: If HyQvia is administered at the same dose and frequency, the serum IgG levels from HyQvia should be comparable to serum IgG levels from intravenous treatment.
Octagam® 5%	The dose of Octagam 5% liquid for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight (6-12 ml/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses. If a patient is at risk of measles exposure (i.e., outbreak in US or travel to endemic areas outside of the US) and receives a dose of less than 400 mg/kg every 3 to 4 weeks, the dose should be increased to at least 400 mg/kg. If a patient has been exposed to measles, this dose should be administered as soon as possible after exposure.

<table>
<tr><td>Octagam®
10%</td><td>Administer Octagam 10% at a total dose of 2 g/kg, divided into two doses of 1 g/kg (10mL/kg) given on two consecutive days.</td></tr>
<tr><td>Panzyga®
10%</td><td>Dose
<table>
<tr><th>Indication</th><th>Dose</th><th>Initial Infusion Rate (first 30 min)</th><th>Maximum Infusion Rate in New Patients** (as tolerated)</th><th>Maximum Infusion Rate in Experienced Patients*** (as tolerated)</th></tr>
<tr><td>Treatment of Primary Humoral Immunodeficiency (PI)*</td><td>300 to 600 mg/kg body weight (3-6 mL/kg) administered every 3 to 4 weeks</td><td>1 mg/kg/min (0.01 mL/kg/min)</td><td>8 mg/kg/min (0.08 mL/kg/min)</td><td>12 or 14 mg/kg/min (0.12 or 0.14 mL/kg/min)</td></tr>
<tr><td>Treatment of Chronic Immune Thrombocytopenia (ITP)</td><td>2 g/kg, divided into two daily doses of 1 g/kg (10 mL/kg) given on two consecutive days</td><td>1 mg/kg/min (0.01 mL/kg/min)</td><td>8 mg/kg/min (0.08 mL/kg/min)</td><td></td></tr>
</table>
*Significant differences in the half-life of IgG among patients with PI may necessitate the dose and frequency of immunoglobulin therapy to vary from patient to patient. Determine the proper dose and frequency by monitoring the clinical response. Adjust dose over time to achieve the desired trough levels of IgG and clinical responses.
**Patients receiving Panzyga (or another IGIV) for the first time or more than 8 weeks since a prior treatment.
*** Experienced patients received greater than 3 (12 mg/kg/min) to 6 (14 mg/kg/min) infusions every 3-4 weeks.

Following the initial infusion, the infusion rate may be gradually increased every 15-30 minutes to a maximum of 14 mg/kg/min (0.14 mL/kg/min) in PI and to 8 mg/kg/min (0.08 mL/kg/min) in chronic ITP in adults, as tolerated. The recommended ramp-up for an infusion is 1, 2, 4, and 8 mg/kg/min (0.01, 0.02, 0.04, and 0.08 mL/kg/min) in new PI and ITP patients (i.e., patients who have not previously received any IGIV product), and 1, 4, 8, and 12 or 14 mg/kg/min (0.01, 0.04, 0.08, and 0.12 or 0.14 mL/kg/min) in experienced PI patients (i.e., patients who have previously received any IGIV product).</td></tr>
<tr><td>Privigen®</td><td><u>Dosage for Primary Humoral Immunodeficiency (PI)</u>
The recommended dose of Privigen for patients with PI is 200 to 800 mg/kg (2 to 8 mL/kg), administered every 3 to 4 weeks. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable. Adjust the dosage over time to achieve the desired serum IgG trough levels and clinical responses. No randomized, controlled trial data are available to determine an optimal trough level in patients receiving immune globulin therapy.

<u>Dosage for Chronic Immune Thrombocytopenic Purpura (ITP)</u>
The recommended dose of Privigen for patients with chronic ITP is 1 g/kg (10 mL/kg) administered daily for 2 consecutive days, resulting in a total dosage of 2 g/kg. Carefully consider the relative risks and benefits before prescribing the high dose regimen (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

<u>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)</u>
Privigen may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to five consecutive days. Privigen may be administered as a</td></tr>
</table>

	maintenance infusion of 1 g/kg (10 mL/kg) administered in a single infusion given in one day or divided into two doses given on two consecutive days, every 3 weeks. Maintenance therapy beyond 6 months has not been studied.
Xembify	For subcutaneous infusion only. Before switching to Xembify, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. Dose Individualize the dose based on the patient's pharmacokinetic and clinical response. Measure the patient's serum IgG trough level as early as 5 weeks after initiating Xembify treatment to determine if a dose adjustment is needed. Monitor the patient's IgG trough level every 2 to 3 months to determine subsequent dose adjustments and dosing intervals as needed. Doses divided over the course of a week or once weekly achieve similar exposure when administered regularly at steady-state. For frequent dosing (2-7 times per week), divide the calculated weekly dose by the desired number of times per week. For dose adjustments, calculate the difference (in mg/dL) of the patient's serum IgG trough level from the target IgG trough level, then find this difference in Table 1 (below). Locate the corresponding amount (in mL) by which to increase or decrease the weekly dose based on the patient's body weight. For example, if a patient with a body weight of 70 kg has an actual IgG trough level of 900 mg/dL and the target level is 1,000 mg/dL, this results in a difference of 100 mg/dL. Therefore, increase the weekly dose of subcutaneous dose by 5 mL. The patient's clinical response should be the primary consideration in dose adjustment. If a patient on Xembify does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of a previous treatment, adjust the dose accordingly.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each

HCPCS Codes	Description
E0779	Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater
E0781	Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 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), non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 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
J1575	Injection, immune globulin/hyaluronidase, (HyQvia), 100 mg immunoglobulin
J1576	Injection, immune globulin (panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg (Code effective 07/01/2023)
J1599†	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg (Code effective until 06/30/2023)

†Note: When used to represent Panzyga

ICD-10-CM Diagnosis Codes	Description
A35	Other tetanus
A48.3	Toxic shock syndrome
B20	Human immunodeficiency virus [HIV] disease
B34.3	Parvovirus infection, unspecified
C90.00-C90.02	Multiple myeloma
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D59.0	Drug-induced autoimmune hemolytic anemia
D59.10-D59.19	Other autoimmune hemolytic anemias
D69.3	Immune thrombocytopenic purpura
D69.41	Evans syndrome
D69.51	Post-transfusion purpura
D69.59	Other secondary thrombocytopenia
D71	Functional disorders of polymorphonuclear neutrophils
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
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
D81.6	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	Di George's syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function

D83.2-D83.9	Common variable immunodeficiency
D89.89†	Other specified disorders involving the immune mechanism, not elsewhere classified
G04.81	Other encephalitis and encephalomyelitis
G11.3	Cerebellar ataxia with defective DNA repair
G25.82	Stiff-man syndrome
G35††	Multiple sclerosis
G61.0	Guillain-Barre syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.82	Multifocal motor neuropathy
G61.89	Other inflammatory polyneuropathies
G62.89	Other specified polyneuropathies
G70.01	Myasthenia gravis with (acute) exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
G71.3	Mitochondrial myopathy, not elsewhere classified
G71.8	Other primary disorders of muscles
G72.89	Other specified myopathies
G73.3	Myasthenic syndromes in other diseases classified elsewhere
H55.89	Other irregular eye movements
L10.0	Pemphigus vulgaris
L10.1	Pemphigus vegetans
L10.2	Pemphigus foliaceous
L10.3	Brazilian pemphigus [fogo selvagem]
L10.4	Pemphigus erythematosus
L10.5	Drug-induced pemphigus
L10.89	Other pemphigus
L10.9	Pemphigus, unspecified
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
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified
L13.8	Other specified bullous disorders
L14	Bullous disorders in diseases classified elsewhere
L51.1	Stevens-Johnson syndrome
L51.2	Toxic epidermal necrolysis [Lyell]
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.00-M33.19	Dermatopolymyositis
M33.20-M33.29	Polymyositis
M33.90-M33.99	Dermatopolymyositis, unspecified
M35.9†	Systemic involvement of connective tissue, unspecified
M36.0	Dermato(poly)myositis in neoplastic disease
P55.0-P55.9	Hemolytic diseases of newborn
P61.0	Transient neonatal thrombocytopenia

T86.11	Kidney transplant rejection
T86.19	Other complication of kidney transplant
T86.21	Heart transplant rejection
T86.298	Other complications of heart transplant
T86.31	Heart-lung transplant rejection
T86.39	Other complications of heart-lung transplant
T86.41	Liver transplant rejection
T86.49	Other complications of liver transplant
T86.810	Lung transplant rejection
T86.818	Other complications of lung transplant
T86.91	Unspecified transplanted organ and tissue rejection
T86.99	Other complications of unspecified transplanted organ and tissue
Z20.4	Contact with and (suspected) exposure to rubella
Z20.820	Contact with and (suspected) exposure to varicella

†Note: Experimental/Investigational/Unproven/Not Covered when used to report Pediatric Autoimmune Neuropsychiatric Disorder Associated with Group A Streptococci (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

††Note: Experimental/Investigational/Unproven/Not Covered when used to report primary progressive multiple sclerosis (PPMS), secondary progressive MS, acute MS exacerbations, or clinically isolated syndrome

Experimental/Investigational/Unproven/Not Covered:

ICD-10-CM Diagnosis Codes	Description
A69.22	Other neurologic disorders in Lyme disease
F28	Other psychotic disorder not due to a substance or known physiological condition
G63	Polyneuropathy in diseases classified elsewhere
G72.41	Inclusion body myositis [IBM]
G93.49	Other encephalopathy
N96	Recurrent pregnancy loss
P36.0-P36.9	Bacterial sepsis of newborn

Background

OVERVIEW
Immune globulin intravenous (IVIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of these products (except Octagam 10%) are FDA-approved for replacement therapy in patients with primary immune deficiencies due to defects in humoral immunity. The following indications are FDA-approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy,** to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[7,9,12,67]
- **Dermatomyositis (or polymyositis).** Octagam 10% is indicated for the treatment of dermatomyositis in adults.[11] Patients with dermatomyositis treated with Octagam were under treatment with corticosteroids

and/or maximally two immune-suppressants OR patients had previous failure or intolerance with a corticosteroid and at least one additional immunosuppressive drug.[33] IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32]

- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,4,6-9,11,12,15,23-25]
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.[6,26]
- **Multifocal motor neuropathy** in adults as maintenance therapy to improve muscle strength and disability.[5]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies.[1-10,12,15,16,25] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous infusion for primary immunodeficiency.[5,7,9] IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[3,4,7-10,12,13,17,25,45]

IVIG is prepared from pooled plasma collected from a large number of human donors.[1-12,15,16,25] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans. Asceniv contains not only antibodies which satisfy the requirement to treat patients with PID, it also has elevated levels of respiratory syncytial virus (RSV) antibodies.[19]

IVIG also is used for many off-label indications. Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

- **Antibody-mediated rejection (AMBR) in transplantation:** Current strategies for treatment of antibody-mediated rejection include plasmapheresis, IVIG, and T-cell or B-cell-depleting agents.[75] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,76] Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes) recommends a combination of corticosteroids, plasmapheresis, IVIG, and anti-CD-20 antibody and lymphocyte-depleting antibody for antibody-mediated rejection.[76,77] As in desensitization therapy, much of the information for IVIG use is in patients with kidney transplants, but the same principles apply to transplantation of other organs and tissues. Immune globulin has been used in lung transplant patients to treat ABMR[20,44,80], and a scientific statement from the American Heart Association states that primary therapy for ABMR in patients with heart transplants may include IVIG, plasmapheresis, high-dose corticosteroids, and anti-lymphocyte antibodies.[36]
- **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita:** Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy.[28-30] International expert recommendations for the management of pemphigus note that first-line treatment includes corticosteroids and anti-CD20 monoclonal antibodies. First-line corticosteroid-sparing agents include azathioprine and mycophenolate mofetil and other corticosteroid-sparing agents include IVIG.[2]
- **Cytomegalovirus (CMV) pneumonia in patients with cancer or transplant-related infection:** For CMV pneumonia, therapy consists of ganciclovir IV injection (or foscarnet IV injection if CMV is ganciclovir-resistant). The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 2.2022 – August 19, 2022) note IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.[31]
- **Desensitization therapy prior to and immediately after transplantation:** Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many of the same principles

apply to transplantation of other organs and tissues.[34,35] Current protocols include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletions with rituximab for IV infusion.[18]

- **Guillain Barre syndrome (GBS):** The American Academy of Neurology recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms.[37] The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.[38] IVIG is not indicated or proven to be effective in patients mildly affected with GBS.[32,38]
- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency):** Clinical guidelines for immunoglobulin use by the National Health Service- England note secondary antibody deficiency can be hypogammaglobinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.[27] NCCN guidelines regarding management of immunotherapy-related toxicities (version 1.2022 – February 28, 2022) recommends that after anti-CD19 chimeric antigen receptor (CAR)-T cell therapy, IVIG replacement should be considered for patients with serum IgG levels < 400 to 600 mg/dL and serious or recurrent infections.[73]
- **Hematopoietic cell transplantation (HCT) to prevent infections:** HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend IVIG for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is used to prevent infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL). NCCN guidelines on prevention and treatment of cancer-related infections discussed similar recommendations.[31]
- **Human Immunodeficiency virus (HIV)- or Hepatitis C-associated thrombocytopenia:** Secondary ITP can occur in patients with HIV infection.[23,24] It can also occur in patients with Hepatitis C. The American Society of Hematology (ASH) guidelines for ITP recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV. ASH also recommends IVIG for secondary ITP associated with Hepatitis C.[23,24]
- **HIV-infected infants and children to prevent recurrent infections:** IVIG is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (immunoglobulin G < 400 mg/dL).[40] Clinicians providing care for adolescents are advised to use the US Department of Health and Human Services Adult and Adolescent HIV-guideline for the care of post-pubertal adolescents (sexual maturity rating [SMR] 4 and 5) and to use the pediatric guideline for guidance on the care of adolescents at SMR 3 or lower.[40]
- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy:** NCCN guidelines for the management of immunotherapy-related toxicities (version 1.2022 – February 28, 2022) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy; as treatment for severe myasthenia gravis; encephalitis; cardiovascular adverse events; musculoskeletal adverse events; moderate or severe GBS; transverse myelitis; bullous dermatitis; and Stevens-Johnson syndrome/toxic epidermal necrolysis.[73] The American Society of Clinical Oncology also has practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.[74] These practice guidelines address the above mentioned indications along with other conditions (e.g., severe cutaneous skin adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome:** Limited but moderate- to high-quality evidence from randomized controlled trials have shown that 3,4-diaminopyridine or IVIG was associated with improved muscle strength score and compounded muscle action potential amplitudes. IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies.[18]

- **Multiple myeloma:** Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.[31] The NCCN guidelines on multiple myeloma (version 1.2023 – September 14, 2022) notes that IVIG should be considered in the setting of recurrent, serious infections and/or hypogammaglobulinemia (immunoglobulin G ≤ 400 mg/dL).[42]
- **Multiple sclerosis, acute severe exacerbation or relapses:** Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotrophic hormone, plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.[43] During pregnancy, relapses severe enough to require treatment can be safely managed with a short-term course of corticosteroids after the first trimester. Methylprednisolone is the preferable agent because it is metabolized before crossing the placenta.[43]
- **Myasthenia gravis:** Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.[65] Symptomatic and immunosuppressive treatment of myasthenia gravis includes pyridostigmine as initial therapy in most patients. Corticosteroids or immunosuppressive therapies are used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal immunosuppressive agent (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. In patients with refractory myasthenia gravis, chronic IVIG and chronic plasma exchange (PLEX), cyclophosphamide, or rituximab may be used. PLEX and IVIG are recommended as short-term treatments in patients with myasthenia gravis with life-threatening effects such as respiratory insufficiency or dysphagia; to prepare for surgery in patients with significant bulbar dysfunction; when rapid response is needed; when other treatments are not adequate; and before starting corticosteroids if necessary to prevent or minimize exacerbations. IVIG can be considered as maintenance therapy in patients with refractory myasthenia gravis or in patients with relative contraindications to immunosuppressive agents. Refractory myasthenia gravis is defined as the post intervention status is unchanged or worse after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning as defined by the patient or physician.
- **Passive immunization for measles (post-exposure prophylaxis):** When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at ≥ 12 months, unless the patient is severely immunocompromised. The Advisory Committee on Immunization Practices recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complication from measles: infants < 12 months of age; pregnant women without evidence of measles immunity; and severely immunocompromised persons.[13] For infants < 12 months of age, intramuscular IG is used; infants 6 through 11 months of age can receive measles, mumps, and rubella vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients.
- **Post-exposure prophylaxis for varicella OR treatment or post-exposure prophylaxis for tetanus:** Children infected with HIV without a history of previous chickenpox OR children who have not received two doses of varicella vaccine should receive VariZIG or, if not available, IVIG within 10 days after close contact with a person who has chickenpox or shingles.[41,46] VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferably within 4 days, and as late as 10 days after exposure.[47] Per the CDC, if tetanus immune globulin is not available, clinicians can use immune globulin at a dose of 200 to 400 mg/kg.[48]
- **Parvovirus B19 infection and pure red blood cell aplasia, immunologic subtype:** In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[49] The guidelines from the American Society of Transplantation Infectious Diseases Community of Practice state that IVIG is frequently used for the treatment of solid organ transplant recipients with symptomatic parvovirus B19 infection.[66] IA Canadian expert panel of

hematologists recommend prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type pure red blood cell aplasia.[22] The panel considers IVIG a reasonable second-line option for this serious condition.

- **Stiff-Person Syndrome (Moersch-Woltman Syndrome):** Per the European Federation of Neurological Societies, IVIG should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have severe disability in carrying out daily activities.[32]
- **Thrombocytopenia, feto-neonatal alloimmune:** Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.[50,51] First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive therapy.

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy,** for maintenance therapy in adults.
- **Primary humoral immune deficiency (PID**), for replacement therapy, including but not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-5,7-9] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only. Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous (IV) infusion for PID. HyQvia is indicated for SC infusion only, with sequential infusion of the recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion. The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the IG. HyQvia has a Limitation of Use that the safety and efficacy of chronic use of recombinant human hyaluronidase in HyQvia have not been established in conditions other than PID.

Experimental, Investigational, or Unproven Uses

There is insufficient evidence in the peer-reviewed, published scientific literature to support safety and efficacy of intravenous immune globulin (human) (IVIG) in Lyme neuropathy, Hashimoto encephalopathy (HE), inclusion body myositis (IBM), neonatal sepsis, pediatric acute-onset neuropsychiatric syndrome (PANS) or pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS), primary progressive multiple sclerosis (MS), secondary progressive MS, acute MS exacerbations, clinically isolated syndrome (MS), and recurrent pregnancy loss.

Hashimoto encephalopathy (HE) is an uncommon autoimmune syndrome associated with neuropsychiatric manifestations responsive to steroid treatment. Until randomized, controlled clinical trials evaluating the use of IVIG in HE are completed and IVIG becomes a standard of care, its' use is considered experimental, investigational and unproven.

The clinical practice guidelines state the treatment of IBM with IVIG is unlikely to be effective and is not recommended as routine therapy. (Orange, 2006)

The American Academy of Pediatrics provides guidelines for the management of neonatal sepsis. There are no recommendations made or discussion of IVIG for the use in suspected or proven early-onset neonatal sepsis. (Polin, 2012) In addition, a Cochrane review concluded that the use of IVIG in suspected or proven neonatal infection is not recommended. (Ohlsson, 2015)

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a clinical diagnosis given to children who have a sudden onset of neuropsychiatric symptoms including obsessions, compulsions, or food restriction. Streptococcal infections cause exacerbation of symptoms in some children with obsessive-compulsive and tic disorders, possibly as an autoimmune response. This syndrome is referred to as Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS). According to the PANS Research

Consortium (PRC) immunomodulatory task force, treatment protocols must include immunological interventions for PANS cases in which the symptoms appear as neuroinflammation or postinfectious autoimmunity, as seen in the PANDAS subgroup. (Frankovich, 2017) However, most of the information about PANS/PANDAS has been obtained by studying individuals with long-standing obsessive-compulsive disorder (OCD) or tic disorder in research centers. The treatment guidelines in the review article cited are based on the expertise of healthcare professionals and scientists treating individuals with PANS. Randomized, controlled clinical trial studies are needed before immunological interventions become a standard of therapy.

IVIG is not recommended for treatment of secondary progressive MS, as add-on therapy for acute exacerbations, or for chronic symptoms in MS. Additionally, there is insufficient evidence to make recommendations regarding use in clinically isolated syndrome or primary progressive MS. (Elovaara, 2008)

Data evaluating IVIG for prevention of recurrent pregnancy loss is limited, and significant differences between treatment and placebo groups have not been consistently demonstrated in the published scientific literature. A Cochrane review of 20 randomized trials indicated there was no improvement in live births with various immunotherapies, including intravenous immune globulin. (Wong, 2014) A randomized, controlled trial evaluating use of IVIG compared to placebo for recurrent secondary miscarriage found no benefit of IVIG over placebo. (Christiansen, 2015)

Note: The standard threshold for lower limit of normal is two standard deviations below the mean. This number may vary among different laboratories.

Appendix 1

Standard Reference Ranges for Serum Immunoglobulin Levels

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

Normal Serum Immunoglobulin Levels (mg/dL)			
Age	**IgA**	**IgG**	**IgM**
0 – 30 days	1 – 7	**611 – 1542**	0 – 24
1 mo	1 – 53	**241 – 870**	19 – 83
2 mo	3 – 47	**198 – 577**	16 – 100
3 mo	5 – 46	**169 – 558**	23 – 85
4 mo	4 – 72	**188 – 536**	26 – 96
5 mo	8 – 83	**165 – 781**	31 – 103
6 mo	8 – 67	**206 – 676**	33 – 97
7 – 8 mo	11 – 89	**208 – 868**	32 – 120
9 – 11 mo	16 – 83	**282 – 1026**	39 – 142
1 yr	14 – 105	**331 – 1164**	41 – 164
2 yr	14 – 122	**407 – 1009**	46 – 160
3 yr	22 – 157	**423 – 1090**	45 – 190
4 yr	25 – 152	**444 – 1187**	41 – 186
5 – 7 yr	33 – 200	**608 – 1229**	46 – 197
8 – 9 yr	45 – 234	**584 – 1509**	49 – 230

Immunoglobulins, Serum Quantitative. Effective February 16, 2016. Accessed 3/14/2017. Available at: http://www.aruplab.com/guides/ug/tests/0050630.jsp

Appendix 2

Standard Reference Ranges for Serum Immunoglobulin G Subclasses (1, 2, 3, and 4)

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

Normal Serum Immunoglobulin G Subclass Levels (mg/dL)				
Age	**IgG1**	**IgG2**	**IgG3**	**IgG4**
Cord Blood	435-1084	143-453	27-146	1-47
0-2 months	218-498	40-167	4-23	1-33

3-5 months	143-394	23-147	4-70	1-14
6-8 months	190-388	37-60	12-62	1-16
9-23 months	288-880	30-327	13-82	1-65
2 years	170-950	22-440	4-69	0-120
3-4 years	290-1065	28-315	4-71	0-90
5-6 years	330-1065	57-345	8-126	2-116
7-8 years	225-1100	42-375	9-107	0-138
9-10 years	390-1235	61-430	10-98	1-95
11-12 years	380-1420	73-455	16-194	1-153
13-14 years	165-1440	71-460	12-178	2-143
15 years & older	240-1118	124-549	21-134	7-89

Immunoglobulin G Subclass Levels (1, 2, 3, 4). Effective February 16, 2016. Accessed 3/14/2017 Available at: http://www.aruplab.com/guides/ug/tests/0050577.jsp

Appendix 3

Selected Genetic Based Primary Immunodeficiency Syndrome (PID)

Condition	Features
Autosomal recessive agammaglobulinemia (ARA)	• Recurrent sinopulmonary bacterial infections • Extremely low or absent IgG, IgM and IgA • IGHM, CD79a, CD199b, BLNK, or LRRC8 gene impaired
Autosomal recessive hyperimmuno-globulin M syndrome (HIM)	• Group of disease characterized by normal or elevated levels of serum IgM with low or absent IgG and IgA levels. • AICDA or UNG gene impaired
Combined immunodeficiency disorders (not all-inclusive)	• Ataxia-telangiectasia (A-T) • Wiskott Aldrich syndrome (WAS), • DiGeorge syndrome (DGS) • Nijmegen breakage syndrome (NBS) • Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM)
Congenital Hypogammaglobulinemia	• Late onset • Inducible Co-Stimulator (ICOS) impaired
Congenital/X-linked agammaglobulinemia (XLA)	• Bruton's Disease • BTK gene impaired
Hyperimmuno-globulinemia E syndrome (HIES)	• Includes recurrent lung and skin infections (e.g., chronic eczema) • Facies with coarse and/or asymmetric features • Type 1 is characterized by STAT3 mutation (also known as Job syndrome) • Type 2 is characterized by DOCK8 mutation
Hypogammaglobulinemia, unspecified	• Primary hypogammaglobulinemia • Normal cellular immunity • Does not meet diagnostic criteria for a specific disorder
ICF Syndrome	• Abnormal Facies • Respiratory Tract Infections • Hypogammaglobulinemia Characteristic Chromosomal Abnormalities
Specific Antibody Deficiency (SAD)	• Generally does not require IVIG replacement for control of recurrent bacterial infections Rare individuals will have infection susceptibility with normal vaccine responses

Selective IgG subclass deficiencies (IGGSD)	• Persistent absence of IgG1, IgG2, and/or IgG3 • Generally does not require IVIG replacement for control of recurrent bacterial infections Rare individuals will have infection susceptibility with normal vaccine responses
Severe combined immunodeficiency disorder (SCID)	• Complete absence of specific immunity • Most susceptible to entire range of possible pathogens May be life threatening
Transient hypogammaglobulinemia of infancy	• Recurrent bacterial sinopulmonary infections and frequent viral illnesses Only requires short-term IVIG replacement for recurrent severe bacterial infections

Appendix 4
Examples of Objective Measurements to Assess Clinical Response (CIDP Reauthorization Criteria)

Measurement Tool	Description
Medical Research Council (MRC) Scale for Muscle Strength - MRC Sum Score	• Ranges from 0 (“total paralysis”) to 60 (“normal strength”) • Summation of the MRC grades (range, 0–5) given in full numbers of the following muscle pairs - upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, foot dorsal flexors • Individual effort is graded on a scale of 0-5 as follows: o Grade 5 - Muscle contracts normally against full resistance. o Grade 4 - Muscle strength is reduced but muscle contraction can still move joint against resistance. o Grade 3 - Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side. o Grade 2 - Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane. o Grade 1 - Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle. o Grade 0 - No movement is observed
Hand-held dynamometer (e.g., Jamar, Vigorimeter)	Hand held device for measuring grip strength
Inflammatory Neuropathy Cause and Treatment group (INCAT) sensory sum score	• Ranges from 0 (“normal sensation”) to 20 (“most severe sensory deficit”) • Sensory scale comprises pin prick and vibration sense plus a two point discrimination value in the arms and legs

*Studies demonstrate that the MRC sum score, hand grip strength measured by the Vigorimeter, and the INCAT sensory summary score demonstrate good clinimetric properties in individuals with immune mediated polyneuropathies (CIDP, GBS, etc.) The Rankin and modified Rankin are primarily used in stroke individuals.

Appendix 5

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Consensus Criteria for the Diagnosis of Multifocal Motor Neuropathy

Criteria for **definite** multifocal motor neuropathy

1) Weakness without objective sensory loss in the distribution of two or more named nerves. During the early stages of symptomatic weakness, the historical or physical finding of diffuse, symmetric weakness excludes multifocal motor neuropathy.
2) Definite conduction block (see Table 1 of the complete reference) is present in two or more nerves outside of common entrapment sites.*
3) Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block.
4) Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.

Criteria for **probable** multifocal motor neuropathy

1) Weakness without objective sensory loss in the distribution of two or more named nerves. During the initial weeks of symptomatic weakness, the presence of diffuse, symmetric weakness excludes multifocal motor neuropathy.
2) The presence of either:
   a. Probable conduction block in two or more motor nerve segments that are not common entrapment sites, or
   b. Definite conduction block in one motor nerve segment and probable conduction block in a different motor nerve segment, neither of which segments are common entrapment sites.
3) Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block, when this segment is technically feasible for study (that is, this is not required for segments proximal to axilla or popliteal fossa).
4) Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested.
5) The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.

** Median nerve at wrist; ulnar nerve at elbow or wrist; peroneal nerve at fibular head.* (Olney, 2003)

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