Subject: Intravenous infusion Immune Globulin (IVIg)	Original Effective Date: 12/6/2007
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DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of **immune globulin products FDA-approved for intravenous infusion (IVIg)** when appropriate criteria are met with consideration for members.

The intent of this coverage policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. **In absence of a product listed below and in addition to applicable criteria outlined within the drug policy, prescribing and dosing information from the package insert is the clinical information used to determine benefit coverage.**

Abbreviations:

- *Immune globulin, intravenous (human)* will be referred to as IVIg since this term is commonly used by clinicians, although the abbreviation used by industry and various regulatory agencies is IGIV.
- *Immune globulin, subcutaneous* will be abbreviated as subcutaneous immune globulin (SCIg).

❖ This policy only addresses non-specified pooled preparations of intravenous immune globulin [i.e. Gammagard, Gamunex, Bivigam, Sandoglobulin, Iveegam, Flebogamma, Octagam, Carimune, and Privigen]. **This policy DOES NOT address other immunoglobulin preparations that at are specifically used for passive immunization to prevent or attenuate infection with specific viral diseases such as respiratory syncytial virus, cytomegalovirus, or hepatitis B.**

❖ Applications of this product for conditions other than those addressed in this policy are considered **OFF-LABEL** and are not addressed in this policy.

❖ Refer to **MCP-268 for Subcutaneous Immune Globulin (SCIg) therapy** requests which address the coverage of immune globulin products FDA-approved for subcutaneous infusion for the treatment of primary immune deficiency.

IMMUNE GLOBULIN

Immune globulins are components of the immune system. There are several types of immune globulin produced by the body (e.g., IgA, IgD, IgE, IgG, IgM). Immune globulins are used as replacement therapy to promote passive immunity in patients with primary humoral immunodeficiency diseases.

This policy addresses therapeutic use immune globulin G (IgG) an antibody produced by the B lymphocytes and administered subcutaneously. References to immune globulin within this guideline refer to immune globulin refer to IgG. IgG products have been referred to in multiple ways, some of which are: immune globulin (IG), immunoglobulin, gamma globulin, and also by its route of administration - intravenous immune globulin (IVIg), immune globulin intravenous (IGIV), subcutaneous immune globulin (SCIg), immune globulin subcutaneous (IgSC).

Human immune globulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Three formulations of human IgG are available depending on the route of delivery:

- **Intravenous infusion (IVIg)** is an antibody-containing solution obtained from the pooled plasma of healthy blood donors, containing 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 basis.

- **Subcutaneous infusion (SCIg): Refer to MCP-268**
  SCIg is used for treating patients with primary immunodeficiencies, a genetic basis for more than 80 different types of primary immunodeficiencies has been discovered, the most common being primary antibody deficiency that is associated with low levels or total lack of normal circulating immunoglobulins. With SCIg, it is possible for patients to self-administer the therapy.

- **Intramuscular (IMIg) depot injections** has been largely abandoned in the United States because volume constraints and pain preclude delivery of sufficient products weekly into each buttock to yield therapeutic serum levels of IgG, leaving recipients susceptible to infections. Thus, this policy focuses on intravenous immune globulin for conditions that typically would be treated in an outpatient setting.

- There is robust evidence to support the use of intravenous immunoglobulin G (IVIg) for primary immunodeficiency. This route of administration allows a large volume per infusion, and is administered relatively infrequently (every three to four weeks), however it must be administered by a trained professional, venous access is required, and it is associated with greater fluctuations in IgG levels, potentially resulting in a greater incidence of adverse effects.

- **Currently, there is no evidence of efficacy differences among the different IVIg products.** However, there are potential differences in adverse effects among the different products. Patients with renal dysfunction, diabetes, sepsis, or age >65 years are at increased risk of developing kidney problems if a sucrose-containing product is used. In general, products with higher IgA content are associated with increased adverse effects. There is a higher chance of adverse effects if the IVIg product is switched after establishing therapy with a particular product

- Immune globulin preparations are available as pre-mixed liquids or lyophilized powders with varying concentrations of IgG. The manufacture of commercial immune globulin products from pooled plasma is a complex multistep process consisting of fractionation, purification, stabilization, virus inactivation, and virus removal and as a result, immune globulin products differ with respect to formulation and composition. Product characteristics such as content (e.g., IgA concentration, stabilizer), volume, and osmolarity may be important considerations for some patients. However, **comparative data are lacking and it is not known whether one specific product is superior for a particular disease or clinical setting. There is a lack of reliable evidence that any one brand of parenteral immunoglobulin is superior to other brands for medically necessary indications.**

- **For applicable conditions that require use of IVIg due to a rapidly progressive disease:** IVIg should be given along with conventional treatment(s) and used only until conventional therapy could take effect when a patient has a rapidly progressive disease where a clinical response cannot be affected quickly enough using conventional agents. The continued administration of immune globulin is not considered medically necessary once conventional therapy takes effect.

- Immune globulin therapy is derived from the pooled plasma of thousands of donors and contains primarily (>98 %) human immunoglobulin G (IgG) with trace amounts of IgA and IgM. The products differ by route of administration [intravenous (IV) or subcutaneous (SC)], specific titers of each IgG subclass, viral inactivation processes, and additives such as sucrose and sodium. While all immune globulins have comparable efficacy in the treatment of immune deficiencies, the products are not interchangeable. **Selection of product should take into consideration various patient factors including diagnosis, condition and severity, individual comorbidities, available alternative treatments, and previous response to intravenous immune globulin therapy.**

FDA INDICATIONS

FDA-APPROVED PRODUCTS AND INDICATIONS

BRAND NAME	ROUTE	PID	ITP	CLL	CIDP	KD	MMN
BIVIGAM	IV	X					
CARIMUNE NF	IV	X	X				
FLEBOGAMMA DIF	IV	X					
GAMMAGARD LIQUID	IV/SC*	X					X
GAMMAGARD S/D	IV	X	X	X		X	
GAMMAKED	IV/SC*	X	X		X		
GAMMAPLEX	IV	X					
GAMUNEX-C	IV/SC*	X	X		X		
HIZENTRA	**SQ**	**X**					
HYQVIA	**SQ**	**X**					
OCTAGAM	IV	X					
PRIVIGEN	IV	X	X				

- Each product varies with FDA-approved indications.
  - Currently there are six (6) indications that are FDA approved for specific Ig products:
    - Primary Immunodeficiency Diseases (PID) [includes, but are not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies]
    - Idiopathic thrombocytopenic purpura (ITP)
    - B-cell chronic lymphocytic leukemia (CLL)
    - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
    - Kawasaki Disease (KD)
    - Multifocal Motor Neuropath (MMN)
  - SCIg products are currently only FDA approved for the **treatment of PID**
  - All conditions are FDA approved for the intravenous (IV) route.
  - IVIg products will not be approved for subcutaneous use, unless FDA approved for that route of administration.
- All available immune globulin replacement products are FDA-approved for use in primary immunodeficiency (PID).[a-e]
- All Ig products (IVIg and SCIg) are FDA approved for the indication of PID. However, only PID[a-e] is FDA-approved for the subcutaneous route (SC).

❖ Immune globulin subcutaneous [human] (SCIg) products are currently labeled for the treatment of primary immunodeficiency syndromes (PID) only.

Black Box Warnings

Thrombosis may occur. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Uses of immune globulin intravenous (IV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (older than 65 years), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs. Privigen does not contain sucrose.

For patients at risk of thrombosis, renal dysfunction or failure, administer at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. ****Refer to Appendix 3 for additional information.***

CLASSIFICATION: Immunoglobulins

RECOMMENDATIONS/COVERAGE CRITERIA

This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Molina Healthcare encourages the Prescriber to reserve prescribing of IVIg for members with severe immune deficiency and who have low antibody levels or for those whom have other well-established indications for therapy with IVIg as described within this policy.

GENERAL CRITERIA: INITIAL AND REAUTHORIZATION [A AND B]

Intravenous infusion Immune Globulin (IVIg) may be authorized for members who meet **General Requirements [A OR B] AND Condition-Specific Requirements (below 'General Criteria' section)** for member's respective condition:

If coverage criteria are met, authorization may be granted for up to a period of **6 months** *unless a specific authorization period is designated in the condition-based criteria*. Continuation of treatment requires submission of a request with required documentation confirming that current coverage criteria are met and continued IVIg therapy is required and demonstrated clinical benefit.

A. INITIAL THERAPY [ALL]

ALL of the following criteria and documentation must be submitted for review: [ALL]

- ❒ Diagnosis: Confirmed by clinical documentation including positive findings on diagnostic testing and/or biopsy results **AND** as specified in the 'Condition-Specific' criteria (as applicable)

- ❒ Prescribed by, or in consultation with, a board-certified specialist, or physician experienced in the treatment of in the management of the condition being treated. Submit consultation notes if applicable. Specific specialist(s) listed may be listed in the 'Condition-Specific Criteria.' Other Prescribers may be considered on a case-by-case basis by Medical Director.

- ❒ Documentation [ALL APPLICABLE]
  - ❍ History and physical examination documenting the severity of the condition, including frequency and severity of infections where applicable
  - ❍ Laboratory results or diagnostic evidence supporting the indication for which immune globulin is requested [e.g. electromyography (EMG), spinal fluid tests, serum tests and biopsy findings]
  - ❍ Previous treatment failures. EXCEPTION: Primary immunodeficiencies diagnosed at birth do not require documentation of previous treatment failures
  - ❍ Clinical/laboratory monitoring AND any metric assessment utilized for **objective** monitoring of progress, such as (list not all inclusive): the Medical Research Council (MRC), INCAT Disability scale, and activities of daily living (ADL) measurements.
    NOTE: Changes in these measures must be clearly documented. Subjective or 'observed' improvement alone is generally insufficient to continue IVIG or to expect coverage.

- ❒ Contraindications/Exclusions to IVIg therapy
  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ IgA deficiency with antibodies to IgA and a history of hypersensitivity
  - ❍ History of anaphylaxis or severe systemic reaction to human immune globulin or product components
  - ❍ Octagam: Contraindicated in patients with acute hypersensitivity reaction to corn.
  - ❍ Privigen: Contraindicated in patients with hyperprolinemia (product contains the stabilizer L-proline)

- ❒ Dosage, Frequency, Administration, Duration of therapy [ALL]
  - ❍ Duration of authorization: Every six (6) month review to assess clinical benefit, unless otherwise stated in 'Condition-Specific Criteria' and may be required on a more frequent basis
  - ❍ Quantity limit: In accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines AND as indicated in 'Condition-Specific' criteria if applicable.
  - ❍ **For dosage/frequency/duration exceeded FDA-labeled indication:** Prescriber must submit supporting documentation in accordance to '**Off-Label Use of Drugs and Biologic Agents MCP-162'**

- ❒ Continuation of treatment [ALL]
  - ❍ Re-authorization for continuation of treatment is required to determine continued need based on documented positive clinical response. Every six (6) month review to assess clinical benefit, unless otherwise stated in 'Condition-Specific Criteria' and may be required on a more frequent basis
  - ❍ Member is closely followed by the prescribing specialist, and treatment response has clearly defined endpoints to measure effectiveness.

- ❒ **EXCEPTION Criteria for NON-PREFERRED IVIg Products**
  If ALL coverage criteria are met, at the discretion of Molina Healthcare, the preferred IVIg product with FDA-labeled indication for member's condition (as applicable) may be authorized. All other IVIg products are not covered unless member meets ANY of the following exception criterion. **Prescriber submit all applicable documentation:** [ALL APPLICABLE]
  - ❍ IgA deficient member who requires products that are low in IgA content [e.g. Flebogamma or Gammagard S/D (refer to **'Appendix 2' for IgA content FDA-approved IVIg products**)]
  - ❍ Objective clinical intolerance to Molina's exclusive IVIg product following 1-2 infusions
  - ❍ Failure on an IVIg product previously and currently stable on an existing product
  - ❍ Risk factors for volume overload (e.g. congestive heart failure, end stage renal disease and renal dysfunction) and physician's order of fluid volume restriction
  - ❍ For emergent administration, e.g. platelets < 30K with bleeding. Authorization for ONE (1) time administration with documentation.

B. REAUTHORIZATIONS/CONTINUATION OF THERAPY REQUESTS [ALL]

Ongoing treatment with immunoglobulin is authorized when ALL the following criteria are met: [ALL]

- ❒ Requested IVIg treatment has not exceeded any applicable 'Condition-Specific Criteria' treatment duration
- ❒ Chronic medical condition requires maintenance therapy AND treatment with IVIg has not resolved this chronic condition
- ❒ Positive clinical response or sustained clinical benefit to IVIg therapy, including significant improvement in defined clinical endpoints. If improvement does not occur with IVIg, continued infusion will not be authorized
- ❒ After each 12 months of therapy (on an annual basis): Cessation of IVIg therapy considered **AND** Prescriber/specialist submits the following: [ALL]
  - ❍ an annual review summary with clinical and/or immunological evaluation
  - ❍ documented clinical benefit(s)
  - ❍ a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated or may cause condition to worsen
- ❒ Dosage, frequency, administration, and duration of therapy [ALL]
  - ❍ Prescribed consistent with dose listed in manufacturer package labeling or established clinical literature for the prescribed indication as in the **'Off-Label Use of Drugs and Biologic Agents MCP-162'**
  - ❍ Dose and frequency of immunoglobulin treatment have been titrated to the minimum dose required to achieve/maintain the appropriate clinical outcome
  - ❍ Duration of Approval: Up to 6-months, unless otherwise stated in the 'Condition-Specific Criteria'

CONDITION-SPECIFIC CRITERIA

Intravenous infusion Immune Globulin (IVIg) may be authorized for members who meet the **General Requirements AND the Condition-Specific Requirements** for the member's respective condition: [ALL APPLICABLE]

1. Autoimmune Hemolytic Anemia (AIHA)

AIHA is a relatively uncommon disorder caused by antibodies directed against autologous red blood cells. AIHA is classified as warm, cold (which includes cold hemagglutinin disease (CAD) and paroxysmal cold hemoglobinuria) or mixed, according to the thermal range of the autoantibody. AIHA due to the presence of warm agglutinins is almost always due to the presence of IgG antibodies that react with protein antigens on the RBC surface at body temperature.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ***warm-type*** autoimmune hemolytic anemia confirmed by detection of antibody and/or complement components on the surface of the RBC (usually by the direct antiglobulin (Coombs) test[2])
- ❒ Refractory to, is intolerant of, or contraindicated to available alternative treatments: [ALL APPLICABLE]
  - ❍ failed, has a contraindication to, or intolerance to corticosteroid therapy
  - ❍ immunosuppressive agents
  - ❍ plasmapheresis
  - ❍ had a splenectomy or is the patient at high risk for post-splenectomy sepsis
  - ❍ rituximab

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Use the lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 1,000 mg/kg per day for 5 days
- ❒ Frequency/Quantity Limit: One course per month
- ❒ Duration of Authorization: May authorize up to 6 months (initial and continuation)
- ❒ Reauthorization: Documented initial response and recurrence of clinically significant, symptomatic anemia

2. Autoimmune Mucocutaneous Blistering Diseases (AMBDs)

AMBDs are a group of rare, debilitating and possibly fatal disorders caused by antibodies directed against components of the skin. The diseases are characterized by the formation of extensive blisters evolving to painful erosions on the skin and mucous membranes.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a dermatologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ONE (1) of the following AMBDs: [ONE]
  - ❍ Bullous pemphigoid
  - ❍ Epidermolysis Bullosa Acquisita (EBA)
  - ❍ Mucous membrane pemphigoid (also referred to as Cicatrical Pemphigoid)
  - ❍ Pemphigus Foliaceus
  - ❍ Pemphigus Vulgaris
- ❒ Diagnosis confirmed by biopsy
- ❒ Condition is rapidly progressing, extensive or debilitating
- ❒ Prescribed for use only for short-term therapy (not as long-term, maintenance therapy)
- ❒ Member meets ONE (1) of the following criteria: [ONE]
  - ❍ Failure of conventional therapy [defined as *failure of disease control after an adequate trial of systemic*] **corticosteroids** (i.e. prednisone, prednisolone, methylprednisolone) AND **immunosuppressive agents** (e.g., azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil)
  - ❍ Significant adverse effects of conventional/standard treatment (i.e. diabetes or steroid-induced osteoporosis) are potentially life-threatening, cause significant morbidity or inability to cope with activities of daily living, or require the intervention of a physician or drug therapy
  - ❍ Contraindications to corticosteroid and immunosuppressive agents: [ONE]
    - o Systemic corticosteroids: existing diabetes, clinically significant osteoporosis, fractures, upper GI bleeding, posterior subcapsular cataracts, pseudotumor cerebri, bone marrow suppression, aplastic anemia, clinically significant psychological changes, steroid myopathy, glaucoma
    - o Immunosuppressive agents: significant persistent anemia, clinically significant neutropenia, clinically significant abnormal hepatic function, clinically significant impaired renal function, hemorraghic cystitis, clinically significant bone marrow suppression, history of malignancy
  - ❍ Systemic corticosteroid and immunosuppressive agents are inappropriate due to rapid, debilitating or progressive severity of disease.

    NOTE: IVIg should be given with conventional treatment(s) and used only until conventional therapy could take effect when a patient has a rapidly progressive disease where a clinical response cannot be affected quickly enough using conventional agents. The continued administration of immune globulin is not considered medically necessary once conventional therapy takes effect.

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Use the lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: Up to 2 g/kg in divided doses administered over 2-5 days
- ❒ Frequency/Quantity Limit: One course per month. Dose not to exceed 2 g/kg per course of therapy
- ❒ Duration of Authorization: May authorize up to 3 months
- ❒ Reauthorization: IVIg for the treatment of AMBD may be authorized for **short-term therapy** and not as maintenance therapy *(regular use of repeated courses of IVIg for a continuous cycle of exacerbation and remission constitutes maintenance therapy)*

3. B-Cell Chronic Lymphocytic Leukemia (CLL)

CLL is a blood and marrow disorder characterized by increased numbers of CD5-positive B cells. The underlying cause of CLL is unknown, although it is thought to be genetically linked.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, an oncologist, hematologist, or infectious diseases physician. Submit consultation notes if applicable.
- ❒ Hypogammaglobulinemia defined as an immunoglobulin G (IgG) level of less than 500 mg/dL (5.0 g/L)
- ❒ Recurrent bacterial infections associated with B-cell CLL: One severe bacterial infection within preceding 6 months **OR** TWO (2) or more bacterial infections in a 1-year period

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Use the lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 100 to 600 mg/kg IV monthly
- ❒ Frequency/Quantity Limit: One dose per month. Dose does not exceed 600 mg/kg every 3 to 4 weeks
- ❒ Duration of Authorization: May authorize up to 6 months (initial and reauthorization)
- ❒ Reauthorization: Positive clinical response to therapy as demonstrated by a reduction in the frequency of bacterial infections since the initiation of IVIg therapy
  AND
- ❒ After each 12 months of therapy (on an annual basis): Cessation of IVIg therapy considered and extended as required to enable cessation of therapy **AND** written confirmation from Prescriber/specialist of the following: [ALL]
  - ❍ an annual review with clinical and/or immunological evaluation
  - ❍ demonstrated clinical benefit, including evidence that treatment has been effective in reducing the number or severity of clinical infections
  - ❍ a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated or may cause member's condition to worsen

4. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy

CIDP is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder, which is sometimes called chronic relapsing polyneuropathy, is caused by damage to the myelin sheath (the fatty covering that wraps around and protects nerve fibers) of the peripheral nerves. There is evidence of autoimmune dysfunction in CIDP, although the exact cause of the myelin sheath damage is unknown.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a neurologist. Submit consultation notes if applicable.
- ❒ Diagnosis of CIDP
- ❒ Symmetric or focal neurologic deficits with slowly progressive or relapsing course over 8 weeks (2 months) or longer (with neurophysiological abnormalities)
- ❒ ONE (1) of the following clinical/electro-diagnostic criteria are met: [ONE]
  - ❍ Electrodiagnostic evidence of demyelinating neuropathy in at least two limbs, resulting in muscle weakness or sensory dysfunction confirmed by nerve conduction studies (NCS)
  - ❍ Results of diagnostic testing meet a recognized set of diagnostic criteria as established by the American Academy of Neurology (AAN), Inflammatory Neuropathy Cause and Treatment (INCAT), or EFNS/PNS guideline
- ❒ Baseline strength and weakness (and current strength and weakness for continuation requests) documented using an objective clinical measuring tool (e.g. INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is the lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2,000 mg/kg per month (dose infused over 2 to 5 days; may be given as 1,000 mg/kg/day for 2 days, or 400 mg/kg/day for 5 days)
- ❒ Frequency/Quantity Limit: 1 course per month. Dose not to exceed 2,000 mg/kg per course (initial) and 1,000 mg/kg per course (continuation)
- ❒ Duration of Authorization: May authorize up to 3 months (initial); 6 months (continuation)
- ❒ Reauthorization: [ALL]
  - ❍ Positive clinical response to therapy as measured by an objective scale documented using an objective clinical measuring tool (e.g. INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin) compared to baseline
  - ❍ Titration to the minimum dose and frequency needed to maintain sustained clinical effect (attempts to titrate the dose or the interval of therapy result in worsening of symptoms)

5. Dermatomyositis; Polymyositis

Dermatomyositis is an idiopathic inflammatory myopathy that most commonly affects the skin and muscles and may impact joints. Polymyositis is an idiopathic inflammatory myopathy causing muscle weakness, elevated muscle enzyme levels and is similar to dermatomyositis.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a neurologist or a rheumatologist. Submit consultation notes if applicable.
- ❒ Diagnosis of dermatomyositis or polymyositis confirmed by ***positive*** **biopsy**
- ❒ Documentation of the following: [ALL]
  - ❍ Severe active disease state
  - ❍ Muscle weakness in all upper and/or lower limbs
- ❒ Documented **refractory*** disease that has failed to respond to at least an adequate three (3) month trial of the following first and second-line conventional therapies (unless contraindicated): [BOTH]
  **Refractory disease is evidenced by persistently elevated serum creatine kinase and/or lack of improvement on muscle strength improvement scales*
  - ❍ Corticosteroids (e.g., prednisone)
  - ❍ Immunosuppressants (e.g., azathioprine, methotrexate, cyclophosphamide, and cyclosporine, Rituxan®)
  - ❍ EXCEPTION TO CRITERION: Documentation of profound, rapidly progressive and/or potentially life-threatening muscular weakness refractory to prior therapy
- ❒ A baseline physical examination required. Submit documentation.
  NOTE: Requests for continuation of therapy must demonstrate measurable, objective response within 3 months of initiation (i.e. improvement in CPK levels, increase or stabilization of muscle strength, or EMG abnormalities)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Dosing recommendation: [AS APPLICABLE]
  - ❍ Initial dose: 2,000 mg/kg per month
  - ❍ Maintenance dose: 500 – 1,000 mg/kg per month
- ❒ Quantity limit/Frequency: One course per month for 3 months. Dose does not exceed 2,000 mg/kg per month
- ❒ Duration of authorization: [ONE]
  - ❍ Initial: May authorize up to 3 months
  - ❍ Continuation: May authorize up to 6 months
- ❒ Reauthorization: Continuation of therapy of IVIg is based on objective measures of its sustained effectiveness from baseline as documented by improvements in at least ONE (1) of the following: serum Creatine Kinase (CK) levels, muscle strength, electromyography testing, and/or improvement in rash (for dermatomyositis indication)

6. Fetal or Natal Alloimmune Thrombocytopenia (FAIT/ NAIT)

FAIT/ NAIT is the most common cause of severe thrombocytopenia in the fetus and in otherwise healthy newborn.[1] The mother produces antibodies (IgG) against fetal HPA antigens inherited from the father. These alloantibodies (IgG) can cross the placenta, destroy fetal thrombocytes and may induce severe thrombocytopenia. It is most commonly caused by the HPA-1a antigen (80%).[1-7]

Member meets ALL of the following criteria supported by documentation: [ALL APPLICABLE]

- ❒ Diagnosis of neonatal alloimmune thrombocytopenia (NAIT) or fetal alloimmune thrombocytopenia (FAIT)
- ❒ Prescribed by, or in consultation with, fetal medicine, obstetrics, and hematology/transfusion medicine. Submit consultation notes if applicable.
- ❒ ONE (1) of the following: [A OR B]
  - **A.** For fetal alloimmune thrombocytopenia, member meets ONE (1) of the following criteria: [ONE]
    - ❍ Previous pregnancy affected by FAIT (previously delivered infants with autoimmune thrombocytopenia)
    - ❍ At 20 weeks gestation or later, cordocentesis reveals fetal platelets less than 20,000/ mm^3; or screening reveals platelet alloantibodies
  - **B.** For neonatal alloimmune thrombocytopenia, member must meet **BOTH** of the following criteria: [BOTH]
    - ❍ Member is severely thrombocytopenic (i.e. a platelet count less than 30,000/mm^3) and/or symptomatic
    - ❍ Neonate failed, has a contraindication to, or is intolerant to platelet transfusions

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 1 g/kg/week, increasing to 2 g/kg/week in refractory cases
- ❒ Frequency/Quantity Limit: One course per week until delivery. Dose not to exceed 2 g/kg/week once weekly until delivery
- ❒ Duration of Authorization: Until delivery
- ❒ Reauthorization: No reauthorization. Immune globulin is not authorized for routine use.

7. Guillain-Barré Syndrome (GBS) [also referred to as Acute Inflammatory Demyelinating Polyneuropathy (AIDP)]

GBS is an acquired acute peripheral neuropathy causing limb weakness that progresses over a period of days to weeks.

The syndrome typically presents with rapidly progressive, relatively symmetrical ascending limb weakness consistent with a polyradiculoneuropathy and often with associated cranial nerve involvement. Motor signs and symptoms usually predominate over sensory signs and symptoms. Major complications include respiratory failure and autonomic dysfunction. The disease is monophasic, reaching its nadir usually within two weeks, although arbitrary definition accepts a limit of four weeks. A plateau phase of variable duration follows the nadir before gradual recovery.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a neurologist or a specialist with experience in diagnosing and treating patients with GBS. Submit consultation notes if applicable.
- ❒ Documented functional disability: ***Severe*** GBS [defined as having significant weakness such as inability to walk or stand without aid, respiratory weakness or bulbar weakness] or Miller-Fisher Syndrome (MFS)
- ❒ IVIg therapy is initiated ***within 2 weeks*** and no longer than 4 weeks of onset of neuropathic symptoms
  - ➢ *IVIg should usually be initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms for non-ambulatory adult patients with GBS. (AAN, 2013)*
- ❒ Plasmapheresis is not used concomitantly
  - ➢ *The combination of IVIG and plasmaphoresis used together is not better than either treatment used alone. Combination therapy with plasma exchange and IVIg was not recommended. (AAN, 2013)*

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2,000 mg/kg per month (dose infused over 2 to 5 days- can be given as 1,000 mg/kg/day for 2 days, or 400 mg/kg/day for 5 days)
- ❒ Frequency/Quantity Limit: May be approved up to 2 courses for initial month, then 1 course per month. Dose not to exceed 2,000 mg/kg per course (initial) and 1,000 mg/kg per course (continuation)
- ❒ Duration of Authorization: [ONE]
  - ❍ Initial: May authorize up to 2 months
  - ❍ Continuation: May authorize up to 3 months
- ❒ Reauthorization: [ALL]
  - ❍ Documented functional improvement: Positive clinical response to therapy as measured by an objective scale documented using an objective clinical measuring tool (e.g. INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin) as compared to baseline
  - ❍ Titration to the minimum dose and frequency needed to maintain sustained clinical effect (attempts to titrate the dose or the interval of therapy result in worsening of symptoms)

NOTE:

- ➢ *Corticosteroids (oral and intravenous) have not been found to have a clinical benefit in GBS. Consequently, this class of drugs is not currently employed in treatment of the syndrome. For adult patients with GBS, glucocorticoids are not recommended for treating.*
- ➢ *Immunomodulatory treatment has been used to hasten recovery. IVIg and plasma exchange have proved equally effective. An UpToDate review on "Treatment and prognosis of Guillain-Barré syndrome in adults" (Vriesendorp, 2015) states that "Aside from plasma exchange and IVIg, no other pharmacologic agents have been found to be effective for GBS."*

8. HIV-associated Thrombocytopenia: ADULTS

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, an infectious disease or HIV specialist. Submit consultation notes if applicable.
- ❒ Current use of combination antiretroviral therapy for HIV infection
- ❒ Platelet count *less than* is < 20,000/µL **OR** Presence of clinically significant bleeding complications
- ❒ For Rh-positive patients: Failure of RhIG documented

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Use the lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 400 mg/kg every 2 to 4 weeks
- ❒ Frequency/Quantity Limit: One dose/course per month
- ❒ Duration of Authorization: 3 months
- ❒ Reauthorization: 3 months. The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes.[1]

9. PEDIATRIC HIV: HIV-infected infants and children to prevent recurrent bacterial infections

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, an infectious disease or HIV specialist. Submit consultation notes if applicable.
- ❒ Diagnosis of HIV disease
- ❒ 13 years of age or younger
- ❒ Receiving highly active antiretroviral therapy (HAART)
- ❒ Member meets ONE (1) of the following conditions: [ONE]
  - ❍ Hypogammaglobulinemia (pretreatment serum IgG less than 400 mg/dL) **AND** Recurrent serious bacterial infections defined as two (2) or more infections such as bacteremia, meningitis, or pneumonia in a 1-year period
    - ➢ *Current guidelines recommend IVIg use among HIV-infected children who have hypogammaglobulinemia (IgG <400 mg/dL) to prevent serious bacterial infections.[1] IVIG is no longer recommended for primary prevention of SBIs in children, unless hypogammaglobulinemia is present.*
  - ❍ Failure to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine
  - ❍ Reside in areas where measles is highly prevalent and who have not developed an antibody response after TWO doses of measles, mumps, and rubella virus vaccine
  - ❍ Has chronic bronchiectasis that is sub-optimally responsive to antimicrobial and pulmonary therapy

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: Recommended dose for pediatrics: 400 mg/kg every 4 weeks
- ❒ Frequency/Quantity Limit: One dose per month
- ❒ Duration of Authorization: May authorize up to 6 months (initial and continuation)
- ❒ Reauthorization: Documentation of current IgG levels at time of reauthorization request that are in the low to normal range and evidence of clinical improvement (i.e. decreased occurrence of infections)

Immune or Idiopathic Thrombocytopenic Purpura (ITP)-- Retire: MCP-127 IVIg for ITP

ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. ITP is divided into chronic and acute forms. The goal of medical care for ITP is to increase the platelet count to a safe level, permitting patients to live normal lives while awaiting spontaneous or treatment-induced remission.

10. ADULT: ACUTE ITP

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ITP with duration of illness *less than* 6 months
- ❒ Prescribed for when a rapid increase in platelet count is necessary (such as in an acute bleeding episode or prior to surgery) or when the platelet count is significantly low is required for ANY of the following conditions: [ONE]
  - ❍ Platelet counts remain persistently at, or below, 30,000/mm^3 despite prior treatment with corticosteroids or splenectomy
  - ❍ To defer or avoid splenectomy
  - ❍ To correct thrombocytopenia prior to major, invasive surgical procedures (i.e. splenectomy) when a rapid increase in platelet count is necessary. NOTE: Generally, if platelet count is < 50,000 per mm^3 OR if the patient is undergoing major surgery (e.g., central nervous system or cardiac surgery) the platelet count is < 75,000 per mm^3
  - ❍ To correct thrombocytopenia, platelet count is significantly low: Less than 30,000/mm^3
  - ❍ Persistent or potentially life-threatening hemorrhage in members with severe thrombocytopenia (platelet counts less than 20,000/mm^3) considered to be at risk for intracerebral hemorrhage
- ❒ Diseases known to be associated with "secondary" thrombocytopenia have been ruled out by history, physical examination, complete blood cell count and examination of the peripheral blood smear

- ❒ Failure or clinically significant adverse effects to systemic corticosteroid (e.g., prednisone) or patient is unresponsive to Rho(D) Immune Globulin (RhIG)
  EXCEPTION: Pediatric members meeting above criteria
  NOTE: Rho(D) immune globulin is not necessarily recommended or preferred in place of IVIg; however may be utilized instead in Rho(D) *positive, non-splenectomized* patients, with a *negative* direct antiglobulin test (DAT)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 1,000 mg/kg body weight given on 1 or 2 consecutive days OR 400 mg/kg body weight given on each of 2 to 5 consecutive days
- ❒ Frequency/Quantity Limit: One dose
- ❒ Duration of Authorization: 5 days
- ❒ Reauthorization: No reauthorization

11. ADULT: CHRONIC idiopathic thrombocytopenic purpura (ITP)

Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. The goal is to maintain platelet count at a level that prevents spontaneous bleeding or bruising.

Member meets ALL of the following criteria as supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ITP with duration of illness ***greater than 6 months***
- ❒ No concurrent illness/disease explaining thrombocytopenia
- ❒ Platelet counts persistently at, or below, 30,000/mm^3
- ❒ Member is symptomatic, at high risk for bleeding or post-splenectomy sepsis
- ❒ Splenectomy and/or prior treatment with systemic corticosteroid (e.g., prednisone), unless failure,* contraindication, or intolerance to corticosteroids. Documentation required.
  **A response may be defined as a platelet count ≥ 30,000/mm^3 and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions > 7 days apart and the absence of bleeding.*
  **A failure would be defined as a platelet count < 30,000/mm^3 or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.*

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose [Dosing may vary with the product]
  - ❍ Initial: 1 or 2 g/kg total over 2 to 5 days
  - ❍ Maintenance: 800-1,000 mg/kg
- ❒ Frequency/Quantity Limit: every 2 to 6 weeks based on platelet count and dose does not exceed 2 g/kg total (initial) or up to 1,000 mg/kg (maintenance)
- ❒ Duration of Authorization: May authorize up to 6 months
- ❒ Reauthorization: [ALL]
  - ❍ Documented initial response to IVIg therapy
    AND
  - ❍ Continued thrombocytopenia, defined as a platelet count of < 20,000 OR less than 30,000 cells/m3 and clinically significant bleeding
    OR
    Member is scheduled for an invasive procedure with high risk of bleeding

12. PEDIATRIC: Idiopathic thrombocytopenic purpura (ITP)

Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. The goal is to maintain platelet count at a level that prevents spontaneous bleeding or bruising.

Member meets ALL of the following criteria as supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ITP and no concurrent illness/disease explaining thrombocytopenia
- ❒ Prescribed for ACUTE OR CHRONIC ITP [ONE]
  - ❍ For ACUTE ITP: [ONE]
    - ❍ Prescribed as initial therapy if platelet count < 20,000/ul
    - ❍ Severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage
      NOTE: IVIg not indicated if only mild manifestations of bleeding.
  - ❍ Chronic ITP: [ALL]
    - ❍ In high risk persons when platelet count low (platelet counts less than 20,000/ul) OR persons symptomatic (*e.g. head trauma or anticipated procedure*)
    - ❍ Failure of other therapies
      OR
    - ❍ Member is a high risk for post-splenectomy sepsis

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.* [ONE: ACUTE OR CHRONIC]

- ❒ **ACUTE ITP: [ALL]**
  - ❍ Recommended Dose: 1,000 mg/kg body weight given on 1 or 2 consecutive days OR 400 mg/kg body weight given on each of 2 to 5 consecutive days
  - ❍ Frequency/Quantity Limit: One dose
  - ❍ Duration of Authorization: 5 days
  - ❍ Reauthorization: No reauthorization

- ❒ **CHRONIC ITP: [ALL]**
  - ❍ Recommended Dose [Dosing may vary with the product]
    - o Initial: 1 or 2 g/kg total over 2 to 5 days
    - o Maintenance: 800-1,000 mg/kg
  - ❍ Frequency/Quantity Limit: every 2 to 6 weeks based on platelet count and dose does not exceed 2 g/kg total (initial) or up to 1,000 mg/kg (maintenance)
  - ❍ Duration of Authorization: May authorize up to 6 months
  - ❍ Reauthorization: [ALL]
    - o Documented initial response to IVIg therapy
      AND
    - o Continued thrombocytopenia, defined as a platelet count of < 20,000 OR less than 30,000 cells/m^3 and clinically significant bleeding
      OR
      Member is scheduled for an invasive procedure with high risk of bleeding.

13. ITP in Pregnancy

The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist. Submit consultation notes if applicable.
- ❒ Member is **pregnant** and meets ONE (1) of the following criteria supported by documentation: [ALL]
  - ❍ Platelet counts less than 10,000/mm^3 in the third trimester, despite an adequate course of corticosteroids, unless use of steroids are contraindicated, or not tolerated
  - ❍ Platelet counts < 30,000/mm^3 associated with bleeding before vaginal delivery or C-section
  - ❍ Previously delivered infants with autoimmune thrombocytopenia
  - ❍ Platelet counts < 55,000/mm^3 during the current pregnancy
  - ❍ Past history of splenectomy

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 1,000 mg/kg/day for 1 to 2 days
- ❒ Frequency/Quantity Limit: One dose per month until the estimated date of delivery
- ❒ Duration of Authorization: Authorization through delivery as determined necessary by Prescriber
- ❒ Reauthorization: No reauthorization after term of pregnancy

14. Neonatal hemochromatosis, prophylaxis

Neonatal hemochromatosis is a rare gestational condition in which iron accumulates in the fetal tissues in a distribution like that seen in hereditary hemochromatosis. Extensive liver damage is the dominant clinical feature, with late fetal loss or early neonatal death.[1]

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, gastroenterologist, hematologist, and a hepatologist. Submit consultation notes if applicable.
- ❒ Member is pregnant
- ❒ History of pregnancy ending with neonatal hemochromatosis

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Use the lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 1,000 mg/kg weekly to pregnant woman (usually from the 18th week until end of gestation)
- ❒ Frequency/Quantity Limit: One dose per week until delivery
- ❒ Duration of Authorization: Until delivery
- ❒ Reauthorization: No reauthorization. Immune globulin is not authorized for routine use.

15. Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Refer to MCP-094 Intravenous Immunoglobulin (IVIg) for Kawasaki Disease

Kawasaki disease is an acute, febrile, multi-system disease of children and young infants often involving the coronary arteries. Coronary artery aneurysms may occur from the second week of illness during the convalescent stage. The cause of the condition is unknown but there is evidence that the characteristic vasculitis results from an immune reaction characterized by T-cell and macrophage activation to an unknown antigen, secretion of cytokines, polyclonal B-cell hyperactivity, and the formation of autoantibodies to endothelial cells and smooth muscle cells. It is likely that in genetically susceptible individuals, one or more uncharacterized common infectious agents, possibly with super-antigen activity, may trigger the disease.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a pediatric cardiologist or a pediatric infectious diseases physician. Submit consultation notes if applicable.
- ❒ Diagnosis of Kawasaki Disease or Incomplete (Atypical) Kawasaki Disease
  **Diagnosis must be established; there is no specific lab test; diagnosis is established by meeting the following criteria.*
- ❒ ONE (1) of the following: **[ONE: A OR B]**
  - **A.** Diagnosis is confirmed by a Cardiologist, Allergist or Rheumatologist
    - ➢ *Diagnosis is best confirmed by a clinician experienced in the diagnosis and management of KD so as to avoid misdiagnosis and unnecessary treatment.*[1]
  - **B.** Four of the following five symptoms are present:
    - ❍ Mucous membrane changes such as strawberry tongue and dry fissured lips without discrete lesions
    - ❍ Changes in the extremities such as edema of the hands and feet
    - ❍ Enlarged lymph nodes in the neck
    - ❍ Diffuse red rash covering most of the body
    - ❍ Redness of the eyes
- ❒ Fever persisting at least 5 days
- ❒ Treatment is being initiated within ten (10) days of onset of fever

  OR

  Diagnosis *after* ten (10) days of disease onset and member continues to exhibit manifestations of inflammation or evolving coronary artery disease
    - ➢ *The effectiveness of IVIg therapy is best established for patients treated within the first 7 to 10 days of illness.*[A] *The AHA and AAP guidelines recommend that IVIg be administered to children with KD within the first 10 days of illness, and if possible, within the first seven days of illness.*[A,1]
- ❒ Concomitant aspirin treatment given with immune globulin
    - ➢ *Evidence supports IVIg therapy with aspirin. Combination with high-dose aspirin is more effective than aspirin alone in decreasing the risk of CA aneurysms, and there is a dose-response effect of IVIg.*[1]
    - ➢ *The AAP, American Heart Association (AHA), and American College of Chest Physicians (ACCP) state that combined therapy with IGIV and aspirin should be administered as soon as possible after Kawasaki disease is diagnosed or strongly suspected (optimally within 7-10 days of disease onset).*[3,4,5]
    - ➢ *The AAP and AHA recommend high-dose aspirin (80 to 100 mg/kg/day), but it is not clear that this dose is more effective than the lower doses used in some clinical trials (30 to 50 mg/kg per day).*[1] *The total daily aspirin dose of 30 to 50 mg/kg per day is administered in four divided doses (maximum dose 4 g per day).*
- ❒ Exclusion of other diseases with similar findings, including but not limited to ANY of the following: [ANY]
  - ❍ Viral infections (i.e., measles, adenovirus, enterovirus, Epstein-Barr virus)
  - ❍ Scarlet fever
  - ❍ Staphylococcal scalded skin syndrome
  - ❍ Toxic shock syndrome
  - ❍ Bacterial cervical lymphadenitis
  - ❍ Drug hypersensitivity reactions
  - ❍ Stevens-Johnson syndrome
  - ❍ Juvenile rheumatoid arthritis
  - ❍ Rocky Mountain spotted fever
  - ❍ Leptospirosis
  - ❍ Mercury hypersensitivity reaction (acrodynia)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: A single dose of intravenous immune globulin (IVIg; 2 g/kg) administered over 8 to 12 hours[1,2] OR a dose of 400 mg/kg for 4 consecutive days
- ❒ Frequency/Quantity Limit: Single authorization of two (2) doses given *within 10 days* of symptom onset
  NOTE: It is preferable that IVIg be administered within the first 10 days of illness, before aneurysms typically develop, however IVIg may also be administered even beyond this 10-day window in patients with evidence of persistent vasculitis or systemic inflammation (e.g., persistent fever); however there are no studies indicating the benefit of prolonged use after the tenth day.
- ❒ Duration of Authorization: One-time authorization only
- ❒ Reauthorization: No reauthorization

16. Lambert-Eaton Myasthenia Syndrome (LEMS)

LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes. The primary goal of treatment for LEMS is to identify and treat any tumors or other underlying disorders.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a neurologist. Submit consultation notes if applicable.
- ❒ Diagnosis of LEMS confirmed by electro-physiologic studies
- ❒ Unresponsive, contraindication, or intolerance to other symptomatic therapies: [ALL APPLICALBLE]
  - ❍ Acetylcholinesterase inhibitors (e.g., Mestinon®)
  - ❍ Immunosuppressants (e.g., corticosteriods, azathioprine)
  - ❍ dalfampridine (Ampyra®)
- ❒ Immune globulin is used as an alternative to plasma exchange if weakness is severe or when there is difficulty with venous access for plasmapheresis.
  - ➢ *Plasmapheresis may be a useful adjunct for patients with severe or rapidly developing neurological deficit (Szczepiorkowski, et al., 2010; National Institutes of Health [NIH], Jul 2012; Smith, et al., 2003).*
- ❒ Impaired function (e.g., unable to stand or walk without aid), measured by a standard clinical scale and/or objective findings on a physical exam at the time of initial therapy. Documentation required.

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2,000 mg/kg administered over 2 to 5 days
- ❒ Frequency/Quantity Limit: One dose per month for 6 months. Dose does not exceed 2,000 mg/kg per month
- ❒ Duration of Authorization: May authorize up to 6 months
- ❒ Reauthorization: [ALL]
  - ❍ Consult/assessment by a neurologist required (if prescriber is not a neurologist)
  - ❍ Documented improvement in muscle function/strength as demonstrated by objective findings of either:
    - o Improvement in functional scores activities of daily living (ADL) or quantitative muscle scores or Medical Research Council (MRC) muscle assessment; OR
    - o Stabilization of disease as defined by stable functional scores (ADLs) or quantitative muscle scores or MRC muscle assessment after previous evidence of deterioration in one of these scores

17. Multiple Myeloma (MM)

MM is a malignant tumor of plasma cells associated with impaired function of immunoglobulins, which are an essential component of the immune system. Patients with MM are at increased risk of infection, due to a combination of several factors, including immunoparesis and physical factors.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist, oncologist, or infectious diseases specialist. Submit consultation notes if applicable.
- ❒ Member in stable, **plateau phase** disease AND (greater than 3 months since diagnosis)
  NOTE: Plateau phase is defined as the time when other causative organisms that may be present due to dysfunction in other immunologic cells besides the B-cell lines of defense are *less likely* to be present. IVIg in any other phase does not meet criteria
- ❒ Member not undergoing induction chemotherapy or patient is not in relapse phase
- ❒ Member is at high risk of recurrent infections as evidenced by: [ONE: 1 OR 2]
  - A. IgG level < 600 mg/dL (normal range IgG=723-1,685 mg/dL)
    AND
    Documentation of life threatening, laboratory-proven bacterial infection within the preceding 6 months
    OR
    Two (2) or more bacterial infections in the preceding year requiring IV antibiotic infusion therapy in the home or in the hospital
  - B. Presence of a specific antibody deficiency as evidenced by: [ONE]
    - ❍ Low normal IgG levels during acute sepsis episodes, OR
    - ❍ Failure to mount an appropriate IgG humoral immune response on challenge with pneumococcal vaccine

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 200-400 mg/kg every 4 to 6 weeks
- ❒ Frequency/Quantity Limit: One dose per month. Dose does not exceed 600 mg/kg per month
- ❒ Duration of Authorization: May authorize up to 6 months (initial and continuation)
- ❒ Reauthorization: Six-month review to assess clinical benefit. Prescriber submit current evidence of clinical improvement, such as decreased occurrence of infections
- ❒ After each 12 months of therapy (on an annual basis): Cessation of IVIg therapy considered and extended as required to enable cessation of therapy **AND** written confirmation from Prescriber/specialist of the following: [ALL]
  - ❍ an annual review with clinical and/or immunological evaluation
  - ❍ demonstrated clinical benefit, including evidence that treatment has been effective in reducing the number or severity of clinical infections
  - ❍ a trial period of cessation of IVIg for the purpose of immunological evaluation is medically contraindicated or may cause member's condition to worsen

18. Myasthenia Gravis: ACUTE myasthenic crisis, **Myasthenic Exacerbation**

Myasthenia gravis is an autoimmune disease characterized by autoantibodies directed against the acetylcholine receptors of the muscle end plate that induce muscle weakness and pronounced fatigability. Initial treatment focuses on the use of cholinesterase inhibitors to overcome the post-synaptic blockade.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a neurologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ***severe*** myasthenia gravis or myasthenic crisis*

  **Myasthenic crisis is a life-threatening condition defined as weakness from acquired myasthenia gravis that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles*.

- ❒ Prescribed for the treatment of ***acute*** myasthenic crisis in member experiencing disease exacerbation and/or decompensation (e.g. difficulty swallowing, acute respiratory failure, major functional disability responsible for the discontinuation of physical activity; of physical activity, disabling weakness requiring hospital admission)
- ❒ Coventional/Alternate treatments have been unsuccessful or are contraindicated, include, but are not limited to: [ALL]
  - ❍ Plasma exchange
  - ❍ Immunosuppressive therapy (e.g. azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, cyclophasphamide)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: One course of treatment of 400-600 mg/kg per day for 3 to 5 consecutive days
- ❒ Frequency/Quantity Limit: One (1) course
- ❒ Duration of Authorization: 1 month only
- ❒ Reauthorization: No reauthorization. Current evidence does not support the use of immune globulin maintenance therapy for generalized myasthenia gravis.[2,3,4]

19. Multifocal Motor Neuropathy (MMN)

MMN is a rare neurological disorder characterized by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a neurologist. Submit consultation notes if applicable.
- ❒ Diagnosis of ***progressive, symptomatic*** multifocal motor neuropathy (as characterized by limb weakness or motor involvement having a motor nerve distribution in at least two nerves)
- ❒ Electrophysiological findings rule out other possible conditions that may not respond to IVIg
- ❒ Baseline strength and function documented using an objective clinical measuring tool (e.g. INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2,000 mg/kg/month administered over 2 to 5 days
- ❒ Frequency/Quantity Limit: One dose per month for 6 months. Dose does not exceed 2,000 mg/kg per month
- ❒ Duration of Authorization: May authorize up to 6 months (initial and reauthorization)
- ❒ Reauthorization: [ALL]
  - ❍ For stable patients on maintenance treatment, review by a neurologist is required at least annually.
  - ❍ Clinical results document an improvement in strength and function within three weeks of the start of the infusion period. Prescriber submit current strength and function report using an objective clinical measuring tool (e.g. INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin)
  - ❍ Continued need is demonstrated by documentation that attempts on an annual basis to titrate the dose or the interval of therapy result in worsening of symptoms

20. Post-Transfusion Purpura (PTP) [Hemolytic Transfusion Reaction]

PTP is a rare bleeding disorder caused by alloantibodies specific to platelet antigens. PTP is characterized by the development of severe, sudden and self-limiting thrombocytopenia occurring 5-10 days after a blood transfusion.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, a hematologist. Submit consultation notes if applicable.
- ❒ Diagnosis of post-transfusion purpura
- ❒ Decreased platelet count (*generally* less than 10,000/mm^3)
- ❒ 2 to 14 days post-transfusion with bleeding **OR** experienced bleeding complications due to thrombocytopenia

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended dose: 400–500 mg/kg per day for 5 days **OR** 1,000 mg/kg per day for 2 days
- ❒ Frequency/Quantity limit: Dose does not exceed 1,000 mg/kg for 2 days
- ❒ Duration of Authorization: One time only for 5 days
- ❒ Continuation of Treatment: No reauthorization

21. Pure Red Blood Cell Aplasia (PRCA): Secondary to Chronic (Persistent) Parvovirus B19 Infection

Parvovirus B19 infects and lyses red cell precursors, which can cause pure red cell aplasia. IVIg therapy is usually reserved for patients with chronic parvovirus infection and chronic anemia.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, an infectious diseases specialist, immunologist, hematologist, or transplant specialist. Submit consultation notes if applicable.
- ❒ Diagnosis of PRCA secondary to parvovirus B19 infection
- ❒ ***Chronic*** Parvovirus B19 infection with severe anemia associated with bone marrow suppression (i.e., Hgb <10 or Hct < 30)
- ❒ ***Chronic*** immunodeficient condition (e.g., HIV infection, solid organ transplants [e.g., renal, liver], chemotherapy for hematologic malignancy)
    - ➢ *Chronic parvovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parvovirus and anemia may spontaneously resolve.*

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2-4 g/kg, divided as 400 mg/kg/day for 5–10 days, 1,000 mg/kg/day for 3 days or 0.5 g/kg weekly for 4 weeks
- ❒ Frequency/Quantity Limit: One dose per month for 6 months
- ❒ Duration of Authorization: May authorize up to 6 months
- ❒ Reauthorization: Documentation of initial response, parvovirus, and recurrence of significant anemia

22. PRIMARY HUMORAL IMMUNODEFICIENCIES (PID)

PID comprise a group of more than 120 separate conditions. Many of these are manifest by failure of protective antibody production. Some PID does not involve antibody failure, such as chronic granulomatous disease and deficiencies of complement components. In these cases, antibody replacement therapy is not justified.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed by, or in consultation with, an allergist, clinical immunologist, otolaryngologist or an infectious disease physician. Submit consultation notes if applicable.
- ❒ Diagnosis of primary immunodeficiency
- ❒ Clinically significant functional deficiency of humoral immunity as evidenced by one of the following:
  - ❍ Documented failure to produce antibodies to specific antigens
  - ❍ History of significant recurrent infections
- ❒ No evidence of renal (nephrotic syndrome) and gastrointestinal (for example, protein losing enteropathy) as causes of hypogammaglobulinemia
- ❒ Initial, pre-treatment total serum IgG is below the lower limit of the age adjusted laboratory reference range, or more than two standard deviations below the age adjusted mean
- ❒ Documented diagnosis primary immunodeficiency with laboratory evidence: [ONE]
  - ❍ Autosomal recessive agammaglobulinemia
  - ❍ Autosomal recessive hyperimmunoglobulin M syndrome (HIM)
  - ❍ Bruton's disease
  - ❍ Chronic mucocutaneous moniliasis (CMC or APCED)
  - ❍ Combined immunodeficiency disorders
    - o Ataxia-telangiectasia
    - o DiGeorge syndrome
    - o Nijmegan breakage syndrome
    - o WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome
    - o Wiskott Aldrich syndrome
  - ❍ Common variable immunodeficiency (CVID)
  - ❍ Congenital hypogammaglobulinemia late onset, ICOS impaired
  - ❍ Congenital / X-linked agammaglobulinemia
  - ❍ Good syndrome (immunodeficiency with thymoma)
  - ❍ Hyperimmunoglobulinemia E syndrome
  - ❍ Hypogammaglobulinemia
  - ❍ ICF syndrome
  - ❍ Polyendocrinopathy and enteropathy (IPEX)
  - ❍ Selective IgG subclass deficiencies (persistent absence of IgG1, IgG2, and/or IgG3)
  - ❍ Selective IgM deficiency
  - ❍ Severe combined immunodeficiency
  - ❍ Specific antibody deficiency
  - ❍ Transient hypogammaglobulinemia of infancy, short-term treatment of recurrent severe bacterial infections
  - ❍ X-linked immunodeficiency with hyperimmunoglobulin M

- ❒ For X-linked agammaglobulinemia (Congenital agammaglobulinemia) ONLY: [ALL]
  - ❍ IgA, IgG and IgM levels must be below the normal range (>2 standard deviations below the age-specific mean) on at least two (2) occasions while the member is clear of infections
  - ❍ Documented recurrent bacterial infections resulting from low IgG or serious bacterial infections

- ❒ For Common variable immunodeficiency (CVID), or Unspecified hypogammaglobulinemia ONLY: [ALL]
  - ❍ History of significant recurrent or persistent, severe bacterial infections (such as recurrent pneumonias, frequent episodes of bacterial infections such as sinusitis, otitis, bronchitis, skin structure infections, or infections of the gastrointestinal tract); AND
  - ❍ Inadequate response or hypersensitivities to prophylaxis/treatment with antibiotics; AND

- ❍ Lack of, or inadequate response to immunization (for example, but not limited to tetanus or pneumococcal antigen); AND
- ❍ Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been identified and treated aggressively if present

❒ For combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect (e.g., ataxia-telangiectasis, DiGeorge syndrome, nuclear factor κB essential modifier deficiency [NEMO]) ONLY: [ONE]
- ❍ Two (2) or more bacterial infections per year due to persistent and significant reduction in total IgG or IgG subclasses
- ❍ Unexplained recurrent or persistent severe bacterial infections
- ❍ Infections that fail to respond adequately to prophylactic antibiotic therapy

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*
❒ Recommended Dose: 300-600 mg/kg every 4 weeks, titrated based on individual.s response
❒ Frequency/Quantity Limit: One dose per month and dose does not exceed 600 mg/kg
❒ Duration of Authorization: May authorize up to 6 months (initial and continuation of treatment)
❒ Reauthorization: Documented current IgG levels that are in the low to normal range and evidence of clinical improvement, such as reduction of the number and severity of clinical infections

23. Opsoclonus Myoclonus Syndrome (OMS)
Opsoclonus myoclonus is a rare neurological disorder that may occur in association with tumors (paraneoplastic) or viral infections and is characterized by an unsteady, trembling gait, myoclonus and opsoclonus (irregular, rapid eye movements). It is more common in children.

Member meets ALL of the following criteria supported by documentation: [ALL]
❒ Prescribed by, and treatment monitored by, a neurologist
❒ Member meets ONE (1) of the following sets [A OR B]
A. Younger than 18 years of age:
- ❍ Clinical assessment indicates significant disability, as measured by an objective clinical score (i.e. the Cerebellar Functional System Score with a value of at least 2 points)
  NOTE: As there is no validated measure for OMS, the Cerebellar Functional System Score has been selected from the Expanded Disability Status Scale (Kurtzke 1983). Refer to 'Definition' section of MCP for additional information on Cerebellar Functional System Score

B. Age 18 and older (adults)
- ❍ Trial and failure or contraindication to a standard course of corticosteroid therapy
- ❍ Clinical assessment demonstrates disability (i.e. as measured by the cerebellar functional system score with a value of at least two points)

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*
❒ Recommended Dose: 400 – 1,000 mg/kg given monthly
❒ Frequency/Quantity Limit: 2,000 mg/kg per month given over 2 to 5 days
❒ Duration of Authorization: 6 months (initial and continuation)
❒ Reauthorization: Clinical documentation of effectiveness is necessary for continuation of IVIg therapy. Efficacy of Ig treatment is demonstrated by improvement in symptoms of OMS and improvement in, or no deterioration of disability. Documentation of the following required [ALL]
- ❍ Clinical improvement or stability in opsoclonus symptoms

- ❍ No further deterioration or some improvement in the degree of disability (i.e. as measured by the Cerebellar Functional System Score)

NOTE: If there has been no improvement or clinical benefits after six months of treatment, IVIg therapy will not be authorized.

24. Rasmussen Syndrome (RS) [also known as Rasmussen Encephalitis (RE) or Chronic Focal Encephalitis]

RS/RE is a rare neurological, progressive, focal encephalitis that is commonly accompanied by focal seizures, hemiparesis and cognitive decline. It is generally considered to be a disease of childhood, with most cases occurring in children younger than 10 years, although adult onset cases do occur. The precise etiology of RE remains unknown, but immune-mediated injury is considered central in the pathogenesis.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescriber is a neurologist or neurosurgeon
- ❒ Prescribed for **short-term** amelioration of encephalitis prior to definitive surgical therapy
  NOTE: IVIg is not recommended for long-term therapy for Rasmussen's encephalitis as surgical treatment is the current standard of care.
- ❒ Intractable focal motor seizures and progressive neurologic deterioration (dementia, hemiparesis)
- ❒ History of failure, contraindication, or intolerance to antiepileptic drugs and corticosteroids

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2,000 mg/kg (dose infused over 2 to 5 days- can be given as 1,000 mg/kg/day for 2 days, or 400 mg/kg/day for 5 days)
- ❒ Frequency/Quantity Limit: 2,000 mg/kg per month
- ❒ Duration of Authorization: Up to 3 months (or 3 courses of therapy) only
- ❒ Reauthorization: IVIg is not recommended for long-term therapy for Rasmussen's encephalitis as surgical treatment is the current standard of care. Exception for continuation of treatment requires review and determination by a Medical Director. Additional information may be requested and discussion with Prescriber may be necessary.

25. Stiff-Person Syndrome (Moersch-Woltmann Syndrome)

Stiff-person syndrome is a chronic disorder with features of an autoimmune disease involving painful muscle spasms and rigidity. SPS treatments are aimed at symptom relief and/or modulation of the underlying aberrant immune process.

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescriber is a neurologist
- ❒ Diagnosis of Stiff-Person Syndrome (Moersch-Woltmann Syndrome) by supportive testing including EMG findings, anti-glutamic acid decarboxylase antibodies, and/or anti-amphiphysin antibodies
- ❒ Significant disability as measured by objective scale (i.e. Modified Rankin Functional ADL Score or the Distribution of Stiffness Index)
- ❒ Baseline physical exam
- ❒ History of failure, contraindication or intolerance to conventional therapy to at least two (2) of the following treatments: benzodiazepines, baclofen, phenytoin, clonidine and/or tizanidine

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2g/kg divided over 5 days
- ❒ Frequency/Quantity Limit: 2,000 mg/kg per month

- ❒ Duration of Authorization: May authorize up to 3 months initially and 6 months for continuation of treatment
- ❒ Reauthorization: Clinical documentation of effectiveness demonstrated by objective findings of improvement in symptoms of stiffness. Functional improvement compared to baseline as measured using an objective clinical measuring tool. Prescriber submit documentation of relief of symptoms of stiffness and disability as demonstrated objective findings of improvement in symptoms of stiffness [i.e. Functional Assessment ADL, Modified Rankin Score and a Distribution of Stiffness Index Score (greater than the qualifying baseline scores)]
  NOTE: If there has been no improvement or clinical benefits after six months of treatment, IVIg therapy will not be authorized.

26. Stapylococcal or Streptococcal Toxic Shock Syndrome (TSS) [ALL]

TSS is an acute, multi-system, toxin-mediated illness which may typically result in shock and multi-organ failure early in its clinical course. Causes include toxin-producing strains of Staphylococcus aureus and Invasive Group A Streptococcus (e.g. Streptococcus pyogenes). IVIg is recommended as an adjunctive therapy in children with severe toxin-related infection showing failure to improve despite best standard care.[2]

Member meets ALL of the following criteria supported by documentation: [ALL]

- ❒ Prescribed for severe, life-threatening case of streptococcal or staphylococcal TSS
- ❒ Failure to achieve rapid improvement with antibiotic therapy and other supportive measures (fluids, inotropes, vasopressors)
- ❒ Individual is severely ill with ANY ONE of the following: [ANY]
  - ❍ Infection refractory to several hours of aggressive therapy
    - ➢ *Intravenous immunoglobulin should be considered in patients in whom there has been no clinical response within the first six hours of aggressive therapy.*[3]
  - ❍ Presence of an undrainable focus
  - ❍ Persistent oliguria with pulmonary edema

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*

- ❒ Recommended Dose: 2g/kg divided over 5 days x 1 cycle
- ❒ Frequency/Quantity Limit: 2,000 mg/kg dose
- ❒ Duration of Authorization: 1 course (1 month) only. May consider repeat administration after 48 hours if there remains a poor response to treatment.
- ❒ Reauthorization: No reauthorization

26. Allogenic Bone Marrow Transplant (BMT)/Hematopoietic Stem Cell Transplantation (HSCT)
BMT, also referred to as HSCT or hematopoietic cell transplant, is a type of treatment for cancer (and a few other conditions as well). HSCT involves the IV intravenous infusion of autologous or allogeneic stem cells to reestablish hematopoietic function in patients whose bone marrow or immune system is damaged or defective.

Member meets ALL of the following criteria supported by documentation: [ALL]
- ❒ Prescribed by, or in consultation with, a hematologist, oncologist or infectious diseases physician. Submit consultation notes if applicable.
- ❒ Prescribed for ONE (1) of the following:
  - ❍ Prophylaxis of acute graft vs. host disease (GVHD)
  - ❍ Prophylaxis treatment against infection (i.e. cytomegalovirus)
- ❒ Confirmed **allogeneic** (not autologous) BMT/ HSCT
  - ➢ *Routine use of IVIg among autologous recipients is not recommended, according to the Centers for Disease Control and Prevention.*
- ❒ ONE (1) of the following: [ONE]
  - ❍ *Within* the first 100 days post-transplant, OR
  - ❍ *After* 100 days or greater post-transplant: Documented IgG less than 400mg/dL or CMV, EBV or RSV infection **AND** ONE (1) of the following conditions: [ONE]
    - o Severe hypogammaglobulinemia: Documented IgG level less than 400 mg/dL required
    - o Primary immunodeficiency disease
    - o CMV, EBV, or RSV infection

Authorization Limit *Dose and quantity authorized in accordance to FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. Goal is lowest dose possible that achieves the appropriate clinical outcome.*
- ❒ Recommended Dose: 500mg/kg/week x 90 days, then 500 mg/kg/month up to 360 days post-transplant
- ❒ Frequency/Quantity Limit: Does not exceed 600 mg/kg once weekly for the first 90 days of therapy, then monthly up to 360 days after transplantation. Therapy does not exceed 360 days past patient's allogeneic bone marrow transplantation
- ❒ Duration of Authorization: May only be reauthorized for up to 360 days post-allogeneic bone marrow transplantation. Routine administration of IVIg > 90 days after HSCT is not recommended in absence of hypogammaglobulinemia.
- ❒ Reauthorization: As stated in the 'GENERAL CRITERIA: REAUTHORIZATIONS/CONTINUATION OF THERAPY REQUESTS' criteria

27. Solid Organ Transplantation: Refer to MCP-237 Intravenous Immune Globulin (IVIg) Therapy for Solid Organ Transplant

COVERAGE EXCLUSIONS

All other uses of **Intravenous infusion Immune Globulin (IVIg)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy or supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage will not be authorized by this policy. *This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.*

- ❒ Experimental/Investigational Use: Indications not supported by CMS recognized compendia or acceptable peer reviewed literature

- ❒ Applications of **IVIg** for conditions other than primary immunodeficiencies are considered off-label in the United States and are not addressed in this policy. Refer to the off-label coverage for prescription drugs and biologics policy for complete criteria: **Off-Label Use of Drugs and Biologic Agents MCP-162.**

- ❒ Any Ig product for prophylaxis against disease

- ❒ **Multiple Sclerosis**
  - ❖ The American Academy of Neurology (AAN) guideline (Goodin, 2008) *Disease modifying therapies in multiple sclerosis*, addresses IVIg for the treatment of multiple sclerosis and states:
    - ➢ The studies of intravenous immunoglobulin (IVIg), to date, have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in RRMS (Type C recommendation*). The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (Type C recommendation: *Possibly effective, ineffective or harmful for the given condition in the specified population.)*
      Reference: Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002; 58(2):169-178. Reaffirmed July 19, 2008.
  - ❖ The current evidence is inadequate to assess the value of IVIG in the treatment of multiple sclerosis. IVIg may be useful in individuals as a second-line therapy in acute relapses of RRMS, but is generally not considered effective for maintenance therapy of MS or in slowing disease progression.

- A position statement from the American Academy of Asthma, Allergy and Immunology (Orange, et al., 2005)[A] states that "the decision to administer IVIg to patients with primary deficiencies in antibody production should be based on: 1) abnormalities of serum immunoglobulin concentrations; 2) clinical history of infections; and, when appropriate, 3) the demonstrated inability to produce antibody normally following antigenic stimulation."

  Guidelines from the American Academy of Asthma, Allergy & Immunology (Orange, et al., 2006) state; "Reduced levels of serum immunoglobulin in patients with recurrent bacterial infections coupled with a lack of response to protein or polysaccharide vaccine challenges (i.e., patients who cannot make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both) is a clear indication for IgG replacement.[B]

EVIDENCE-BASED PRACTICE GUIDELINES

American Academy of Neurology
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 (AAN 2012)

AAN's evidence-based guideline on "Intravenous immunoglobulin in the treatment of neuromuscular disorders" (Patwa et al, 2012) states the following:

- IVIg is as efficacious as plasmapheresis and should be offered for treating Guillain-Barré syndrome (GBS) in adults (Level A).
- IVIg is effective and should be offered in the long-term treatment of chronic inflammatory demyelinating polyneuropathy (Level A).
- IVIg is probably effective and should be considered for treating moderate-to-severe myasthenia gravis and multifocal motor neuropathy (Level B).
- IVIg is possibly effective and may be considered for treating non- responsive dermatomyositis in adults and Lambert-Eaton myasthenic syndrome (Level C).
- Evidence is insufficient to support or refute use of IVIG in the treatment of immunoglobulin M paraprotein-associated neuropathy, inclusion body myositis, polymyositis, diabetic radiculoplexoneuropathy, or Miller Fisher syndrome, or in the routine treatment of post-polio syndrome or in children with GBS (Level U).
- IVIg combined with plasmapheresis should not be considered for treating GBS (Level B). More data are needed regarding IVIG efficacy as compared with other treatments/treatment combinations.

The Immune Deficiency Foundation (IDF) Guidelines
In 2011, the Immune Deficiency Foundation (IDF) published guidelines on diagnosis and clinical care for primary immunodeficiency diseases. The guidelines support clinicians determine the possible type of PI and the screening diagnostic tests that should be ordered based on the site of infection. Although there are several different types of PI, the types that result in antibody production defects are those that are eligible for IgG therapy.[E]

- The IDF recommends regular IgG therapy for patients with identified antibody deficiency disorders.
- The guidelines state the IVIG product should be dosed every 2-4 weeks and SCIG should be given every 1-14 days.
- **It is recommended that an immunologist should participate in the determination of the proper dose and interval for IgG therapy in each patient.**
- **Should IgG treatment be required IV or SC administration are both recommended, and one product is not preferentially recommended over any other product.**[E]

Canadian Blood Services and Canada's National Advisory Committee Guidelines[D]
The Canadian Blood Services and Canada's National Advisory Committee on Blood and Blood Products led a joint initiative to create guidelines for treatment of PI with immunoglobulin therapy. While the guidelines are primarily

intended for health care professionals in Canada, many of their recommendations may be applied in other parts of the world, including the United States.
The National Advisory Committee on Blood and Blood Products and Canadian Blood Services issued practice guidelines on the use of IVIg in primary immune deficiency in 2010.[D] The recommendations were based on interpretation of available evidence and where evidence was lacking, consensus of expert clinical opinion. The guidelines were constructed from an expert panel consisting of physicians from large pediatric and adult tertiary care centers who frequently cared for patients with primary immune deficiency, methodology experts, and members from the National Advisory Committee on Blood and Blood Products. The levels of evidence and grades used for each recommendation were adapted from the Canadian Task Force on Preventative Health Care. The levels of evidence describe the methodological rigor of the study, and the grades of recommendation comprise the level of evidence and clinical expertise. Relevant recommendations include the following:

- Give immunoglobulin to patients with primary antibody deficiency to reduce infections. (Level of evidence: I, Grade of recommendation: A)
- Give immunoglobulin to reduce hospitalization and organ damage. (I, A)
- Give immunoglobulin to improve survival and quality of life. (III, A)
- **With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one manufacturer of IG over another for currently available products. (I to II-2, I)**
- **With respect to clinical efficacy for reducing infections, IVIG and SCIG preparations should be considered equivalent. (I and II, B)**
- Do not give IMIG for replacement therapy for primary immune deficiency. (I, D)
- Start IVIG at a dose of 400 to 600 mg/kg per 4 weeks or SCIG at a dose of 100 to 150 mg/kg per week in most patients. (III, B)
- Patient and practitioners should be aware that patients with primary immune deficiency may require immunoglobulin replacement therapy indefinitely. (II-3, A)

Other recommendations in the 2010 guideline in regards to IVIg treatment of primary immune deficiencies include:

- If there is end-organ damage, the dose and/or frequency of immune globulin can be increased.
- Patients with primary immune deficiency may require immune globulin therapy indefinitely.
- Although higher trough levels of IVIg may be associated with clinical response; the goal of IVIg dose increases should be to improve clinical effectiveness and not merely to increase trough levels.

DEFINITIONS

Antibody: Specialized gamma globulin proteins found in the blood or lymph that act as an immune defense against foreign agents (antigens).

Antigen: A substance, that when introduced into the body stimulates the production of an antibody. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs.

Cerebellar Functional System Score
The cerebellar functional system score was chosen to demonstrate initial disability and response.
Values of the cerebellar functional system score are:

0. Normal: no evidence of cerebellar dysfunction
1. Abnormal signs without disability
2. Mild ataxia
3. Moderate ataxia
4. Severe ataxia (all limbs or gait)
5. Unable to perform coordinated movements due to ataxia

Changes in opsoclonus symptoms will be rated as:

i. Deterioration in symptoms
ii. Symptoms stable
iii. Mild improvement
iv. Moderate improvement

v. Significant improvement

Immune globulin: Replacement therapy for primary immunodeficiency; IgG antibodies against bacterial and viral agents; spectrum of antibodies that interact with and alter the activity immune system cells; antibodies capable of reacting with cells such as erythrocytes.

Intravenous infusion immune globulin (IVIg) 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 basis. Several IVIg products are available for clinical use in the United States.

The Inflammatory Neuropathy Cause and Treatment (INCAT) scale is used to access functional disability of both upper and lower extremity components in chronic inflammatory demyelinating polyneuropathy (CIDP). The INCAT scale has upper and lower extremity components, with a maximum of 5 points for the upper extremity (arm disability) and a maximum of 5 points for the lower extremity (leg disability), which add up to a maximum of 10 points (where 0 is normal and 10 is severely incapacitated). The INCAT scores may be used to evaluate the effectiveness and need for IVIG. IVIG may be discontinued when there is a lack of clear clinical improvement (i.e., a decline in INCAT disability score or failure to improve by 1 point at 6 weeks following the initial infusion or return to baseline at any time following initial improvement of 1 point).

The Medical Research Council (MRC) scale is used to grade muscle strength. Scale: 0 = no muscle movement; 1 = flicker of muscle movement; 2 = trace movement but not able to fully overcome gravity; 3 = just able to overcome gravity, but not against resistance; 4 = moves against resistance, but weak; 5 = full strength against resistance.

APPENDIX

Appendix 1: Immuneglobulin available in the U.S. for INTRAVENOUS use[1]

Intravenous Immunoglobulin
Bivigam: 10% (1 g/10 mL) in 50 mL, 100 mL vials
Carimune NF powder for injection: 3 g, 6 g, 12 g bottles
Flebogamma DIF: 5% (50 mg/mL) in 10 mL, 50 mL, 100 mL, 200 mL, 400 mL vials; 10% (5 g/50 mL) in 50 mL, 100 mL, 200 mL vials
Gammagard: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL vials
Gammagard S/D powder for injection: 2.5 g, 5 g, 10 g bottles
Gammaked: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL vials
Gammaplex: 5% (50 mg/mL) in 50 mL, 100 mL, 200 mL, 400 mL vials
Gamunex-C: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 400 mL vials
Octagam: 5% (50 mg/mL) in 20 mL, 50 mL, 100 mL, 200 mL, 500 mL
Octagam: 10% (50 mg/mL) in 20 mL, 50 mL, 100 mL, 200 mL
Privigen: 10% (100 mg/mL) in 50 mL, 100 mL, 200 mL, 400 mL vials

Subcutaneous Immunoglobulin
Gammagard: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL vials
Gammaked: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL vials
Gamunex-C: 10% (1 g/10 mL) in 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 400 mL vials
Hizentra protein solution for subcutaneous injection: 20% (0.2 g/mL) in 5 mL, 10 mL, 20 mL, 50 mL vials
HyQvia: 10% (1 g/10 mL) in 25 mL, 50 mL, 100 mL, 200 mL, 300 mL vials and 160 U/mL recombinant human hyaluronidase in 1.25 mL, 2.5 mL, 5 mL, 10 mL, 15 mL vials

IgA content FDA-approved IVIg products

Per AHFS[a]: All commercially available preparations of IVIg contain trace amounts of IgA, but the amount varies among the different preparations. In a limited number of patients who reacted to IVIg preparations containing higher IgA concentrations, IVIg preparations depleted of IgA (0.4-2.9 MCP/mL of IgA) were better tolerated. However, the concentration of IgA that will not provoke a reaction to IgA is not known. Therefore, all IVIg preparations carry the risk of inducing an anaphylactic reaction to IgA and a risk of anaphylaxis may exist despite the use of preparations containing only trace amounts of IgA.

- Carimune® NF contains trace amounts of IgA.
- Flebogamma® 5% DIF contain less than 50 MCP/mL of IgA.
- Gammagard® Liquid 10% contains an average of 37 MCP/mL of IgA.
- Gammagard® S/D is available in a formulation containing less than 2.2 MCP/mL and a formulation containing less than 1 MCP/mL of IgA. Clinical studies were conducted using the formulation containing less than 2.2 MCP/mL of IgA; no clinical studies were specifically conducted using the formulation containing less than 1 MCP/mL of IgA.
- Gammaplex® 5% Liquid contains trace amounts of IgA (less than 10 MCP/mL).
- The IgA content in Gamunex®-C 10% averages 46 MCP/mL.
- Hizentra® 20% contains 50 MCP/mL or less of IgA.
- Octagam® 5% contains 200 MCP/mL or less of IgA.
- Privigen® 10% Liquid contains 25 MCP/mL or less of IgA.

Appendix 2: Product properties of the IG agents

Agent	Stabilizing Agent	IgG Content	IgA Content	Sodium Content
Bivigam	Glycine	>96%	<0.2 mg/mL	0.1-0.140M
Carimune NF	Sucrose	>96%	Trace amounts	20 mg/g of protein
Flebogamma DIF	Sorbitol	>97%	<100 MCP/mL	Trace amounts
Gamastan S/D	Glycine	NR	NR	Present
Gammagard	Glycine	>98%	~37 MCP/mL	None
Gammagard S/D	Glycine, Glucose	>90%	<2.2 MCP/mL	8.5 mg/mL
Gammaked	Glycine	>98%	~0.046 mg/mL	NR
Gammaplex	Glycine	>95%	<10 MCP/mL	0.3g
Gamunex-C	Glycine	>98%	46 MCP/mL	NR
Hizentra	Proline	>98%	<50 MCP/mL	Trace amounts
Hyqvia	Glycine		37 MCP/mL	None
Octagam	Maltose	>96%	<0.2 mg	<30ml/L
Privigen	Proline	>98%	<25 MCP/mL	Trace amounts

Key: NR = not reported

References:
Lexi-Comp I, ed Drug Information Handbook. 21st ed. Hudson, OH: Lexi-Comp; 2015.
McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. AHFS 2015 Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2015.

Appendix 3: Black Box Warnings and Precautions

Black Box Warnings from the product information labels (2013-2015) for the intravenous Ig formulations include the following:

- Thrombosis may occur with immune globulin products. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
- For individuals at risk of thrombosis, administer immune globulin product at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in individuals at risk for hyperviscosity.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of human immune globulin intravenous (IVIg) products in predisposed individuals. Individuals predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or individuals receiving known nephrotoxic drugs.
- Renal dysfunction and acute renal failure occur more commonly in individuals receiving IVIG products that contain sucrose.
- For individuals at risk of renal dysfunction or renal failure, administer IVIG at the minimum infusion rate practicable.

Additional warnings and precautions from the production information labels (2013) include the following:

- IgA deficient individuals with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine and urine output in individuals at risk of developing acute renal failure.
- Hyperproteinemia, increased serum viscosity and hyponatremia may occur in individuals receiving IVIG therapy.
- Thrombosis may occur. Monitor individuals with known risk factors for thrombosis and consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome (AMS) may occur in individuals receiving IVIg therapy, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IVIg treatment. Monitor individuals for signs and symptoms of hemolysis and hemolytic anemia.
- Monitor individuals for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI).
- Individuals receiving IVIG for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for development of fever, chills, nausea, and vomiting.
- IVIG is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- Passive transfer of antibodies may confound serologic testing.

The subcutaneous Ig product information labels (2013) note reactions similar to other immune globulin products may occur. The most common adverse reactions with subcutaneous injections include local reactions (that is, swelling, redness, heat, pain and itching at the injection site).

Refer to specific product information labels for additional warnings and precautions.

Appendix 3: Black Box Warnings and Precautions

The Myasthenia Gravis Foundation of America Clinical Classification divides MG into 5 main classes and several subclasses[3]:

Myasthenia Gravis Foundation of America Clinical Classification [25]

Class	Description
I	Any eye muscle weakness, possible ptosis, no other evidence of muscle weakness elsewhere
II	Eye muscle weakness of any severity, mild weakness of other muscles
IIa	Predominantly limb or axial muscles
IIb	Predominantly bulbar and/or respiratory muscles
III	Eye muscle weakness of any severity, moderate weakness of other muscles
IIIa	Predominantly limb or axial muscles
IIIb	Predominantly bulbar and/or respiratory muscles
IV	Eye muscle weakness of any severity, severe weakness of other muscles
IVa	Predominantly limb or axial muscles
IVb	Predominantly bulbar and/or respiratory muscles
V	Intubation needed to maintain airway

Reference: Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 2000 Jul 12. 55(1):16-23.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
90283	Immune Globulin (IgIV), human, for intravenous use
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liguid), 500 mg
J1561	Injection, immune globulin, (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Only Carimune NF, Panglobulin NF and Gammagard S/D should be billed using this code)
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg

J1569	Injection, immune globulin, (Gammagard), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg

REFERENCES

PACKAGE INSERT, FDA, DRUG COMPENDIA

- Bivigam [Prescribing Information] Boca Raton, FL; Biotest Pharmaceuticals: April 2014.
- Carimune Nonfiltered [Prescribing Information] Bern, Switzerland: CSL Behring AG; October 2013.
- Flebogamma 5% DIF [Prescribing Information] Barcelona, Spain: Instituto Grifols, S.A.; August 2014.
- Flebogamma 10% DIF [Prescribing Information] Barcelona, Spain: Instituto Grifols, S.A.; July 2014.
- Gammagard Liquid [Prescribing Information] Westlake Village, CA; Baxter Healthcare Corporation; September 2013.
- Gammagard S/D [Prescribing Information] Westlake Village, CA: Baxter Healthcare Corporation; September 2013.
- Gammaked [Prescribing Information] Research Triangle Park, NC: Grifols Therapeutic Inc.; September 2013.
- Gammaplex [Prescribing Information] Hertfordshire, United Kingdom: Bio Products Laboratory Limited; June 2014.
- Gamunex-C [Prescribing Information] Research Triangle Park, NC: Grifols Therapeutics Inc.; July 2014.
- Octagam 5% [Prescribing Information] Hoboken, NJ: Octapharma USA Inc.; November 2013.
- Octagam 10% [Prescribing Information] Vienna, Austria: Octapharma Pharmazeutika Produktionsges m.b.H; December 2014.
- Privigen [Prescribing Information] Bern, Switzerland: CSL Behring AG; December 2013.

a. American Hospital Formulary Service (AHFS). Drug Information 2016. Immune Globulin. [STAT!Ref Web site]. Available at http //online.statref.com [via subscription only]. Accessed January 2016.
b. Micromedex Healthcare Series [Internet database]. DrugDex®. Greenwood Village, Colo Thomson Micromedex. ImmuneGlobulin. Available at http //www.thomsonhc.com/micromedex2/librarian [via subscription only]. Accessed January 2016.
c. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2016. Available from Wolters Kluwer Health, Inc.
d. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2016. URL: http://www.clinicalpharmacology.com.
e. Lexi-Comp Online. (2016). AHFS DI. Immune Globulin. Retrieved January 2016 from Lexi-Comp Online with UpToDate Online.

CLINICAL TRIALS, DEFINITIONS, PEER-REVIEWED PUBLICATIONS

Autoimmune Mucocutaneous Blistering Diseases

1. Ahmed AR and Dahl MV. Consensus Statement on the Use of Intravenous Immunoglobulin Therapy in the Treatment of Autoimmune Mucocutaneous Blistering Diseases. Arch Dermatol. 2003;139:1051-1059.
2. Schrier, SL. Warm autoimmune hemolytic anemia: Treatment. UpToDate. Sep 11, 2015. Available at: http://www.uptodate.com/contents/warm-autoimmune-hemolytic-anemia-treatment?source=see_link#H20 Accessed on: Feb 2016

Allogenic Bone Marrow Transplant (BMT)/ Allogenic Hematopoietic Stem Cell Transplantation (HSCT)

1. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000;49(No. RR-10):1-128.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy
1. Sander HW, Latov N. Research criteria for defining patients with CIDP. Neurology. 2003; 608 (Suppl 3):S8-S15.

Dermatomyositis/Polymyositis
1. Wang DX, Shu XM, Tian XL, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. Clin Rheumatol. 2012;31(5):801-6. Epub 2012 Jan 26.

Autoimmune Hemolytic Anemia (AIHA)
1. 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):S9-56.

Neonatal hemochromatosis (FAIT/ NAIT)
1. Knisely AS, Mieli-Vergani G, Whitington PF. Neonatal hemochromatosis. Gastroenterol Clin North Am. 2003 Sep;32(3):877-89, vi-vii.

Fetal or Natal Alloimmune Thrombocytopenia (FAIT/ NAIT)
1. Bertrand G, Drame M, Martageix C, Kaplan C (2011) Prediction of the fetal status in noninvasive management of alloimmune thrombocytopenia. Blood 117: 3209-3213.
2. Risson DC, Davies MW, Williams BA (2012) Review of neonatal alloimmune thrombocytopenia. J Paediatr Child Health 48: 816-822.
3. American College of Obstetricians and Gynecologists (ACOG). Management of early pregnancy loss. ACOG Bulletin #24. 2001, Feb 12.
4. American College of Obstetricians and Gynecologists: Thrombocytopenia in pregnancy. ACOG practice bulletin, Number 6, September 1999. Clinical management guidelines for obstetrician- gynecologists. Int J Gynaecol Obstet 1999 Nov; 67(2): 117-28.
5. Fernandes CJ. Neonatal Thrombocytopenia. UpToDate.Accessed July 7, 2014. Available at: http://www.uptodate.com/contents/neonatal-thrombocytopenia?source=search_result&search=IVIG+for+neonaltal+alloimmune+thrombocytopenia&selectedTitle=1%7E150
6. Giers G, Wenzel F, Fischer J, et al. Retrospective comparison of maternal vs. HPA-matched donor platelets for treatment of fetal alloimmune thrombocytopenia. Vox Sang. 2010 Apr;98(3 Pt 2):423-30. Epub 2009 Oct 27.
7. Paidas MJ. Neonatal alloimmune thrombocytopenia: Parental evaluation and pregnancy management. UpToDate. January 2016.

Guillain-Barre Syndrome (GBS)
1. Hughes RA, et al. Intravenous immunoglobulin for Guillain-Barre syndrome. The Cochrane Library. 2004;(1):CD002063.
2. Hughes RA, Wijdicks EF, Barohn R, et al. Practice parameter: immunotherapy for Guillain-Barré syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2003; 61:736.
3. Vriesendorp FJ. Treatment and prognosis of Guillain-Barré syndrome in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2015.
4. 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. 2008 Sep;15(9):893-908.

HIV-associated Thrombocytopenia: ADULTS
1. Kiehl MG et al. "A controlled trial of intravenous immune globulin for the prevention of serious infections in adults with advanced human immunodeficiency virus infection." Arch Intern Med 1996;156:2545-50.

Pediatric HIV: Bacterial infection in HIV-infected children
1. Mofenson, LM, Brady, MT, Danner, SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious

Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009 Sep 4;58(RR-11):1-166. PMID: 19730409
2. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Department of Health and Human Services. Updated November 2013.
Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed on February 2016.

Immune Thrombocytopenia (ITP)

1. George J, Arnold D. Immune Thrombocytopenia (ITP) in adults: Initial Treatment and Prognosis. UpToDate. March 04, 2015. Available at: http://www.uptodate.com/contents/immune-thrombocytopenia-itp-in-adults-initial-treatment-and-prognosis?source=search_result&search=ITP&selectedTitle=2%7E150
2. Bussel J. Immune Thrombocytopenia (ITP) in Children: Initial Management. UpToDate. April 8, 2015. Available at: http://www.uptodate.com/contents/immune-thrombocytopenia-itp-in-children-initial-management?source=search_result&search=ITP&selectedTitle=4%7E150
3. Bussel J. Immune Thrombocytopenia (ITP) in Children: Management of Chronic Disease. UpToDate. December 12, 2014. Available at: http://www.uptodate.com/contents/immune-thrombocytopenia-itp-in-children-management-of-chronic-disease?source=search_result&search=ITP&selectedTitle=3%7E150.
4. Martí-Carvajal AJ, Peña-Martí GE, Comunián-Carrasco G. Medical treatments for idiopathic thrombocytopenic purpura during pregnancy. Cochrane Database Syst Rev. 2009 Oct 7. CD007722.

Kawaski Disease (KD)

1. Sundel, R. Incomplete (atypical) Kawasaki disease. In: UpToDate, Klein-Gitelman, M., UpToDate, Waltham, MA, 2015. Accessed January 2016.
2. Sundel, R. Kawasaki disease: Initial treatment and prognosis. In: UpToDate, Klein-Gitelman, M., UpToDate, Waltham, MA, 2015. Accessed January 2016.
3. American Academy of Pediatrics. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.
4. Newburger JW, Takahashi M, Gerber MA et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004; 110:2747-71.
5. Monagle P, Chalmers E, Chan A et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(6 Suppl):887S-968S. [PubMed 18574281]
6. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, **American Heart Association.** Circulation 2004; 110:2747.

Lambert-Eaton Myasthenic Syndrome (LEMS)

1. Elovaara, I, Apostolski, S, van Doorn, P, et al. European Federation of Neurological Societies (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. 2008 Sep;15(9):893-908. PMID: 18796075
2. Patwa, HS, Chaudhry, V, Katzberg, H, Rae-Grant, AD, So, YT. 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 (AAN). Neurology. 2012 Mar 27;78(13):1009-15. PMID: 22454268
3. Keogh, M, Sedehizadeh, S, Maddison, P. Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database Syst Rev. 2011(2):CD003279. PMID: 21328260

4. Stickler DE, Huff JS, Kleinschmidt P. Lambert-Eaton Myasthenic Syndrome (LEMS) Treatment & Management. Updated 05/03/13. Available at: http://emedicine.medscape.com/article/1170810-treatment#showall. http://emedicine.medscape.com/article/1170810-medication Accessed: Feb 2016

Multifocal Motor Neuropathy (MMN)

1. Aminoff MJ, Greenberg DA, Simon RP. Sensory Disorders. In: Aminoff MJ, Greenberg DA, Simon RP, eds. *Clinical Neurology*. 9th ed. New York, NY: MCGraw-Hill; 2015.
2. GBS-CIDP foundation guidelines https://www.gbs-cidp.org/wp-content/uploads/2012/01/PTOTGuidelines.pdf.
3. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. 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*. Mar 27 2012;78(13):1009-1015.
4. van Schaik IN, van den Berg LH, de Haan R, Vermeulen M. Intravenous immunoglobulin for multifocal motor neuropathy. Cochrane Database Syst Rev. 2005(2):CD004429.

Myasthenic Exacerbation

1. 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.
2. Elovaara I, 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. European Journal of Neurology 2008;15(9):893-908.
3. Hayes Medical Technology Directory. Intravenous Immunoglobulin for Myasthenia Gravis. Lansdale, PA: Hayes, Inc.; October 5, 2012.
4. 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 Mar 27;78(13):1009-15.

Multiple Myeloma

1. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2014). © 2013 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org Accessed Feb 2016

Primary Immunodeficiency

1. Orange J, Hossny E, Weiler C, 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. J Allergy Clin Immunol 2006;117(4 Suppl): S525-53.
2. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005 May;94(5 Suppl 1):S1-63.
3. American Academy of Allergy, Asthma, & Immunology. Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency. December 2011. Available at http://www.aaaai.org/practice-resources?Practice-Tools/ivig-toolkit.aspx.
4. Yong PL, Boyle J, Ballow M, et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. Clin Immunol. 2010 May;135(2):255-63. doi: 10.1016/j.clim.2009.10.003. Epub 2009 Nov 14

Post-Transfusion Purpura (hemolytic transfusion reaction)

1. Clare Taylor, et. al. Immunological Complications of Blood Transfusion. Transfusion Alter Transfusion Med. 2008;10(3):112-126. Available at: http://www.medscape.com/viewarticle/583195_7. Accessed on February 2016.

Rasmussen syndrome

1. Feasby T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfusion Medicine Reviews 2007;21(2 Suppl 1):S57-107.

2. Orange J, Hossny E, Weiler C, 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. J Allergy Clin Immunol 2006;117(4 Suppl): S525-53.

Stiff-Person Syndrome

1. Elovaara I, 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. European Journal of Neurology 2008;15(9):893-908.
2. Feasby T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfusion Medicine Reviews 2007;21(2 Suppl 1):S57-107.
3. Orange J, Hossny E, Weiler C, 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. J Allergy Clin Immunol 2006;117(4 Suppl): S525-53.
4. McKeon A, Robinson MT, McEvoy KM, et al. Stiff-man syndrome and variants: clinical course, treatments, and outcomes. Arch Neurol. 2012 Feb;69(2):230-8. doi: 10.1001/archneurol.2011.991.
5. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. Ann Intern Med. 1999 Oct 5;131(7):522-30.

Toxic Shock Syndrome (TSS)

1. Stevens, DL. Treatment of streptococcal toxic shock syndrome: Treatment. UpToDate. Dec 16, 2015. Available at: http://www.uptodate.com/contents/warm-autoimmune-hemolytic-anemia-treatment?source=see_link#H20 Accessed on: Feb 2016
2. Department of Health Clinical Guidelines for Intravenous Immunoglobulin Use. 2011 Available at: www.ivig.nhs.uk
3. Lappin E and Ferguson A. Gram-Positive Toxic Shock Syndromes. Lancet Infect Dis 2009; 9: 281-290