

POLICY Document for Intravenous Immune Globulin (IVIG)

The overall objective of this policy is to support the appropriate and cost effective use of the medication, lower cost site of care and overall clinically appropriate use. This document provides specific information to each section of the overall policy.

Section 1: Site of Care

- Policy information specific to site of care (outpatient, hospital outpatient, home infusion)

Section 2: Clinical Criteria

- Policy information specific to the clinical appropriateness for the medication

Section 1: Site of Care

SITE OF CARE MANAGEMENT PROGRAM GUIDELINES FOR HOSPITAL OUTPATIENT SPECIALTY MEDICATION INFUSION

A. INTRODUCTION

There is a wide variation in the site-of-service utilization patterns for specific medications and therapy classes. This is driven by several factors. Some of these specialty medications are derived from pooled blood plasma, and therefore have the potential for an increased risk of infusion-related complications. This is particularly the case with the IVIG products. There are multiple products in this class that differ in the manufacturing, purification and viral inactivation processes. These differences can affect patient tolerance and a physician's decision to utilize a more acute site of care such as the outpatient hospital. However, many patients that have been established on this treatment with one to several infusions safely administered may be candidates for infusions in a less acute lower-cost site of care.

Outpatient hospital infusion costs may be 2-3 times more compared to other sites of care suggesting an immediate opportunity exists for lowering spend on select specialty medications that require infusion. Services for patients requiring infused specialty medications may be provided through a physician's in office infusion program or free standing ambulatory infusion center. These options provide access to quality care at a lower cost that may be more convenient for the patient. In addition, many patients who receive home or in office infusion therapy have been shown to experience better outcomes, fewer complications and, improved quality of life and preference, including more personalized attention which helps avoid stress.

This document describes the medical necessity criteria required for hospital outpatient infusion of the medications included in this policy.

B. GENERAL REQUIREMENTS: OUTPATIENT MEDICAL NECESSITY

Infusion in a hospital outpatient setting may be considered medically necessary for medications included in this policy when the criteria below OR individual medication policy criteria are met as outlined section C.

1. Clinical documentation that supports one or more of the following:

- a. History of repeated moderate adverse reactions not responding to conventional interventions OR,
 - b. Laboratory confirmation of autoantibody development (autoantibodies to IgA, anti-infliximab, etc)
 - c. The patient is medically unstable which may include respiratory, cardiovascular, or renal conditions that may predispose the member to a severe adverse event that cannot be managed in an alternate setting without appropriate medical personnel and equipment.
 - d. The patient has previously experienced a severe adverse event during or immediately after an infusion including but not limited to: anaphylaxis, anaphylactoid reactions, myocardial infarction, thromboembolism, or seizures.
 - e. Significant venous access issues requiring phlebotomy
2. Patient specific criteria that meets the following:
- a. All alternate non-hospital outpatient settings are not within a reasonable distance from the member's home (10-30miles) AND,
 - b. The patient's home has been determined to be inappropriate for home infusion by a social worker, case manager or previous home nurse assessment or home infusion services are not available due to limited network access

C. MEDICATION SPECIFIC CRITERIA FOR HOSPITAL OUTPATIENT MEDICAL NECESSITY

In addition to the general criteria in Section B, the following guidelines will be applied:

1. IVIG - One or more of the following criteria must be met:

- a. To determine tolerance of the therapy, one infusion or cycle as applicable may be permitted in the hospital outpatient setting
- b. Product (brand) changes – one infusion may be permitted if an ambulatory infusion center is not available within a reasonable distance from the member's home.
- c. Urgent treatment for conditions requiring acute intervention including but not limited to: acute ITP with bleeding, Kawasaki disease, and Myasthenic crisis with respiratory impairment.
- d. Patients with laboratory confirmed IgG or IgE autoantibodies to IgA. Note: routine screening for IgA autoantibodies is not currently recommended.
- e. Patients who have experienced anaphylaxis or an anaphylactoid reaction with intravenous immunoglobulin products.
- f. Pediatric patients who are less than 21 years of age. The use of non-hospital based alternate site infusion services are at the discretion of the prescribing physician.
- g. An inability to tolerate large volume load and the dosing cannot be divided into several smaller infusions.
- h. Patients with a history of renal impairment or thromboembolic complications.

For patients with a history of renal impairment, sucrose containing IVIG products are not recommended. Oliguric renal failure is the most common occurring 1-10 days after infusion. The most important risk factor for thromboembolic complications is advanced age although the presence of several risk factors greatly elevates the risk including: diabetes, hypertension, CAD, smoking, hyperlipidemia, and history of prior cerebrovascular disease.

D. GENERAL CONSIDERATIONS: HOME INFUSION

Home Infusion therapy has the potential to deliver cost-effective, quality care.

Efforts to support patients who can receive infused medications care in a lower-cost setting versus an inpatient or clinic-based setting seems appealing, particular if that lower-cost setting is the patient's home.

Site of Care IVIG

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The home infusion provider will complete an assessment to determine the appropriateness of a patient, caregiver if applicable, and their home prior to initiating care. This assessment may include an evaluation of the following:

1. Accessibility to 911 services and urgent care. Volunteer services may be acceptable if urgent care is readily available.
2. Adequate refrigeration is available if required.
3. Home is not located in a high crime area as determined by local authorities
4. Home environment does not meet general cleanliness standards determined by onsite home nursing assessment

E. BACKGROUND

IVIG

A comprehensive review of the adverse events associated with the administration of IVIG is outside of the scope of this document. Others have prepared excellent reviews of the adverse reactions associated with IVIG, which should be read by those involved with the prescribing and administration of immunoglobulin. Various properties of IVIG preparations can trigger potential adverse events; these properties include sodium content, osmolarity, sugar content, IgA content, and volume load. Recent trends in the manufacture of these products have eliminated some adverse effects observed in early products, but other effects have emerged. Head-to-head comparisons among the available products continues to be lacking in the literature. Given the uncertainty and lack of comparative literature regarding the various available formulations of IVIG, it is reasonable to use higher-acuity sites of service for patients with a history of serious adverse events with multiple products. This is consistent with the site-of-care recommendations from the American Academy of Allergy, Asthma, and Immunology.

Evaluations of the safety and efficacy of IVIG in the home infusion setting are also lacking in the published literature. Many controlled trials studying the efficacy of IVIG for various conditions do include the home as a site of infusion, but a differentiation of adverse events between sites of infusion is not a primary reported outcome. The phase III trial of IVIG for the treatment of Alzheimer's disease allowed for home infusion of IVIG after 3 tolerated infusions in a controlled setting. This suggests that, when approving this protocol, the FDA had convincing evidence to support home administration.

A retrospective analysis of 1,085 home infusions for neuroimmunologic conditions in 70 patients demonstrated a notably low non-serious adverse event rate of 4.7%. However, this study was limited to 1 specific formulation of IVIG and used lower infusion rates than would be considered typical in the studied population; this may have contributed to the low observed reaction rate. Interestingly, 23 patients in this study were naïve to IVIG (32.8%) and only 2 of these patients experienced minor adverse events.

Others evaluating home infusion have demonstrated an adverse event rate of 21.4% in a similar cohort. Comparable to the previous study, a significant proportion of these patients were new to therapy (42.6%). A statistically significant difference between these patients and those treated previously was not observed. In addition, a comparison between neuroimmunologic and immune deficiency patients did not identify a statistically significant difference in adverse reactions.

These studies support the safety of IVIG infusions at home for patients previously treated, as well as those new to the therapy.

Section 2: Clinical Criteria

Intravenous Immune Globulin (IVIG):

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

POLICY

I. INDICATIONS

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

A. FDA-Approved Indications

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

B. Compendial Uses

1. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections or pediatric acute onset neuropsychiatric syndrome (PANDAS)
2. Prophylaxis of bacterial infections in pediatric human immunodeficiency virus (HIV) infection
3. Prophylaxis of bacterial infections in bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) recipients
4. Dermatomyositis
5. Polymyositis
6. Myasthenia gravis
7. Guillain-Barré syndrome
8. Lambert-Eaton myasthenic syndrome
9. Fetal/neonatal alloimmune thrombocytopenia
10. Parvovirus B19-induced pure red cell aplasia
11. Stiff-person syndrome
12. Management of immune checkpoint inhibitor-related nervous system adverse events

All other indications are considered experimental/investigational and are not a covered benefit.

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review:

A. Primary immunodeficiency

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

2. IgG trough level for those continuing with IVIG therapy
- B. Secondary hypogammaglobulinemia (CLL, HIV, BMT/HSCT recipients)
 1. Copy of laboratory report with pre-treatment serum IgG level (when applicable)
- C. Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN)
 1. Pre-treatment electrodiagnostic studies (electromyography [EMG] or nerve conduction studies [NCS])
 2. For CIDP, pre-treatment cerebrospinal fluid (CSF) analysis (when available)
- D. Dermatomyositis and polymyositis
 1. Pre-treatment electrodiagnostic studies (EMG/NCS)
 2. Pre-treatment muscle biopsy report (when available)
- E. Lambert-Eaton Myasthenic Syndrome (LEMS)
 1. Neurophysiology studies (e.g., electromyography) (when applicable)
 2. A positive anti- P/Q type voltage-gated calcium channel antibody test (when applicable)

III. CRITERIA FOR INITIAL APPROVAL

1. Primary Immunodeficiency

Initial authorization of 12 months may be granted for members with any of the following diagnoses:

- a. Severe combined immunodeficiency (SCID) or congenital agammaglobulinemia (eg, X-linked or autosomal recessive agammaglobulinemia):
 - i. Diagnosis confirmed by genetic or molecular testing, or
 - ii. Pretreatment IgG level < 200 mg/dL, or
 - iii. Absence or very low number of T cells (CD3 T cells < 300/microliter) or the presence of maternal T cells in the circulation (SCID only)
- b. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non-SCID combined immunodeficiency):
 - i. Diagnosis confirmed by genetic or molecular testing (if applicable), and
 - ii. History of recurrent bacterial infections (eg, pneumonia, otitis media, sinusitis, sepsis, gastrointestinal), and
 - iii. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)
- c. Common variable immunodeficiency (CVID):
 - i. Age 4 years or older
 - ii. Other causes of immune deficiency have been excluded (eg, drug induced, genetic disorders, infectious diseases such as HIV, malignancy)
 - iii. Pretreatment IgG level < 500 mg/dL or ≥ 2 SD below the mean for age
 - iv. History of recurrent bacterial infections
 - v. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)
- d. Hypogammaglobulinemia (unspecified), IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency:
 - i. History of recurrent bacterial infections
 - ii. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)
 - iii. Any of the following pre-treatment laboratory findings:
 - i. Hypogammaglobulinemia: IgG < 500 mg/dL or ≥ 2 SD below the mean for age
 - ii. Selective IgA deficiency: IgA level < 7 mg/dL with normal IgG and IgM levels
 - iii. Selective IgM deficiency: IgM level < 30 mg/dL with normal IgG and IgA levels
 - iv. IgG subclass deficiency: IgG1, IgG2, or IgG3 ≥ 2 SD below mean for age assessed on at least 2 occasions; normal IgG (total) and IgM levels, normal/low IgA levels
 - v. Specific antibody deficiency: normal IgG, IgA and IgM levels
- e. Other predominant antibody deficiency disorders must meet a., b., and c.i. in section 4. above.
- f. Other combined immunodeficiency must meet criteria in section 2. above.

Re-authorization of 24 months may be granted when the following criteria are met:

1. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy, AND
2. IgG trough levels are monitored at least yearly and maintained at or above the lower range of normal for age (when applicable for indication), OR
3. The prescriber will re-evaluate the dose of IVIG and consider a dose adjustment (when appropriate).

Gammagard Liquid, Gamunex-C, and Gammaked may be administered intravenously or subcutaneously for primary immunodeficiency.

B. Myasthenia Gravis

1. Authorization of 1 month may be granted to members who are prescribed IVIG for worsening weakness, acute exacerbation, or in preparation for surgery.
 - a. Worsening weakness includes an increase in any of the following symptoms: diplopia, ptosis, blurred vision, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Acute exacerbations include more severe swallowing difficulties and/or respiratory failure
 - b. Pre-operative management (eg, prior to thymectomy)
2. Authorization of 12 months may be granted to members with refractory myasthenia gravis who have tried and failed 2 or more of standard therapies (eg, corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, rituximab).

C. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

1. Initial authorization of 3 months may be granted when the following criteria are met:
 - a. Moderate to severe functional disability
 - b. The diagnosis was confirmed by electrodiagnostic studies and the evaluation of cerebrospinal fluid (CSF)
2. Re-authorization of 24 months may be granted when the following criteria are met:
 - a. Significant improvement in disability and maintenance of improvement since initiation of IVIG therapy
 - b. IVIG is being used at the lowest effective dose and frequency

D. Dermatomyositis or Polymyositis

1. Initial authorization of 3 months may be granted when the following criteria are met:
 - a. Diagnosis established by clinical features (eg, proximal weakness, rash), elevated muscle enzyme levels, electrodiagnostic studies, and muscle biopsy (when available); supportive diagnostic tests include autoantibody testing and muscle imaging (eg, MRI), and
 - b. Standard first-line treatments (corticosteroids or immunosuppressants) have been tried but were unsuccessful or not tolerated, or
 - c. Member is unable to receive standard first-line therapy because of a contraindication or other clinical reason.
2. Re-authorization of 12 months may be granted when the following criterion is met:
 - a. Significant improvement in disability and maintenance of improvement since initiation of IVIG therapy

E. Idiopathic Thrombocytopenic Purpura (Immune Thrombocytopenia)

1. Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy: authorization of 1 month may be granted when the following criteria are met:
 - a. Children (< 18 years of age)
 - i. Significant bleeding symptoms (mucosal bleeding or other moderate/severe bleeding) or
 - ii. High risk for bleeding* (see Appendix B), or

- iii. Rapid increase in platelets is required* (eg, surgery or procedure)
 - b. Adults (≥ 18 years of age)
 - i. Platelet count $< 30,000/\text{mCL}$, or
 - ii. Platelet count $< 50,000/\text{mCL}$ and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required*, and
 - iii. Corticosteroid therapy is contraindicated and IVIG will be used alone or IVIG will be used in combination with corticosteroid therapy
2. Chronic/persistent ITP (≥ 3 months from diagnosis) or ITP unresponsive to first-line therapy: authorization of 6 months may be granted when the following criteria are met:
 - a. Platelet count $< 30,000/\text{mCL}$, or
 - b. Platelet count $< 50,000/\text{mCL}$ and significant bleeding symptoms, high risk for bleeding* or rapid increase in platelets is required*, and
 - c. Relapse after previous response to IVIG or inadequate response/intolerance/contraindication to corticosteroid or anti-D therapy
3. Adults with refractory ITP after splenectomy: authorization of 6 months may be granted when either of the following criteria is met:
 - a. Platelet count $< 30,000/\text{mCL}$, or
 - b. Significant bleeding symptoms
4. ITP in pregnant women: authorization through delivery may be granted to pregnant women with ITP.

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

F. B-cell Chronic Lymphocytic Leukemia (CLL)

1. Initial authorization of 6 months may be granted when the following criteria are met:
 - a. IVIG is prescribed for prophylaxis of bacterial infections.
 - b. Member has a history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.
 - c. Member has a pretreatment serum IgG level $< 500 \text{ mg/dL}$.
2. Re-authorization of 6 months may be granted when a reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

G. Prophylaxis of Bacterial Infections in HIV-Infected Pediatric Patients

1. Initial authorization of 6 months may be granted to pediatric members with HIV infection when the following criteria are met:
 - a. Member is ≤ 12 years of age.
 - b. IVIG is prescribed for primary prophylaxis of bacterial infections and pretreatment serum IgG $< 400 \text{ mg/dL}$, or
 - c. IVIG is prescribed for secondary prophylaxis of bacterial infections for members with a history of recurrent bacterial infections (> 2 serious bacterial infections in a 1-year period)
2. Re-authorization of 6 months may be granted when a reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

H. Prophylaxis of Bacterial Infections in BMT/HSCT Recipients

1. Initial authorization of 6 months may be granted to members who are BMT/HSCT recipients when the following criteria are met:
 - a. IVIG is prescribed for prophylaxis of bacterial infections.
 - b. Either of the following:
 - i. IVIG is requested within the first 100 days post-transplant.
 - ii. Member has a pretreatment serum IgG $< 400 \text{ mg/dL}$.
2. Re-authorization of 6 months may be granted when a reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

I. Multifocal Motor Neuropathy (MMN)

1. Initial authorization of 3 months may be granted when the following criteria are met:
 - a. Weakness without objective sensory loss in 2 or more nerves
 - b. The diagnosis was confirmed by electrodiagnostic studies
2. Re-authorization of 24 months may be granted when significant improvement in disability and maintenance of improvement have occurred since initiation of IVIG therapy

J. Guillain-Barre Syndrome (GBS)

Authorization of 2 months total may be granted for the treatment of GBS.

K. Lambert-Eaton Myasthenic Syndrome (LEMS)

Authorization of 6 months may be granted for LEMS when the diagnosis has been confirmed by either of the following:

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

L. Kawasaki Syndrome

Authorization of 1 month may be granted for pediatric members with Kawasaki syndrome.

M. Fetal/Neonatal Alloimmune Thrombocytopenia (F/NAIT)

Authorization of 6 months may be granted for treatment of F/NAIT.

N. Parvovirus B19-induced Pure Red Cell Aplasia (PRCA)

Authorization of 6 months may be granted for parvovirus B19-induced PRCA.

O. Stiff-person Syndrome

Authorization of 6 months may be granted for treatment of stiff-person syndrome.

P. Management of immune checkpoint inhibitor-related nervous system adverse events

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

1. Member has experienced a moderate or severe adverse event to a PD-1 or PD-L1 inhibitor (eg, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab)
2. The offending medication has been held or discontinued
3. Member experienced one or more of the following nervous system adverse events: pneumonitis, myasthenia gravis, peripheral neuropathy, encephalitis or transverse myelitis

Q. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections or pediatric acute onset neuropsychiatric syndrome (PANDAS)

Authorization of 6 months may be granted for management of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections or pediatric acute onset neuropsychiatric syndrome

IV. CONTINUATION OF THERAPY

Authorization may be granted for continuation of therapy when either the following criteria is met:

- a. For conditions with reauthorization criteria listed under section III: Members who are currently receiving IVIG therapy must meet the applicable reauthorization criteria for the member's condition.
- b. For all other conditions, all members (including new members) must meet initial authorization criteria.

V. OTHER

When Gammagard Liquid, Gamunex-C and Gammaked will be administered subcutaneously, they may be approved for primary immunodeficiency only.

VI. APPENDICES

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine

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

Appendix B: Examples of Risk Factors for Bleeding (not all inclusive)

- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (eg, peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession or lifestyle predisposes patient to trauma (eg, construction worker, fireman, professional athlete)

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