

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.

IVIG Criteria 2017

CVS Caremark is an independent company that provides pharmacy benefit management services to CareFirst BlueCross BlueShield and CareFirst BlueChoice, Inc. members.

CareFirst BlueCross BlueShield is the shared business name of CareFirst of Maryland, Inc. and Group Hospitalization and Medical Services, Inc. CareFirst BlueCross BlueShield and CareFirst BlueChoice, Inc. are both independent licensees of the Blue Cross and Blue Shield Association. The Blue Cross and Blue Shield Names and Symbols are registered trademarks of the Blue Cross and Blue Shield Association. © Registered trademark of CareFirst of Maryland, Inc.

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.

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):

Bivigam[®], Carimune[®] NF, Flebogamma[®] DIF, Gammagard[®] Liquid, Gammagard[®] S/D, Gammaked[™], Gammaplex[®], Gamunex[®]-C, Octagam[®], 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. Prophylaxis of bacterial infections in pediatric human immunodeficiency virus (HIV) infection
2. Prophylaxis of bacterial infections in bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) recipients
3. Dermatomyositis
4. Polymyositis
5. Myasthenia gravis
6. Guillain-Barre syndrome
7. Lambert-Eaton myasthenic syndrome
8. Fetal/neonatal alloimmune thrombocytopenia
9. Parvovirus B19-induced pure red cell aplasia
10. Stiff-person syndrome

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. Idiopathic thrombocytopenic purpura (immune thrombocytopenia)
 - 1. Laboratory report with pre-treatment platelet count

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 12 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. 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 mg/dL.
2. Re-authorization of 6 months may be granted when the following criterion is met:
 - a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

C. 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 \leq 12 years of age.
 - b. IVIG is prescribed for primary prophylaxis of bacterial infections and pretreatment serum IgG < 400 mg/dL, or
 - c. IVIG is prescribed for secondary prophylaxis of bacterial infections
 - i. History of recurrent bacterial infections (> 2 serious bacterial infections in a 1-year period)
 - ii. Member is not able to take combination antiretroviral therapy.
 - iii. Antibiotic prophylaxis was tried but was not effective (eg, trimethoprim-sulfamethoxazole).
2. Re-authorization of 6 months may be granted when the following criterion is met:
 - a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

D. 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 mg/dL.
2. Re-authorization of 6 months may be granted when the following criterion is met:
 - a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

E. 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. Electrodiagnostic studies are consistent with multifocal demyelinating abnormalities
 - c. Elevated CSF protein (when available)
2. Re-authorization of 12 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. In those who are clinically stable and receiving long-term treatment (ie, more than 1 year), the dose has been tapered and/or treatment withdrawn to determine whether continued treatment is necessary
 - c. IVIG is being used at the lowest effective dose and frequency

F. 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. Electrodiagnostic studies are consistent with motor conduction block
 - c. Normal sensory nerve conduction studies

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

G. 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

H. Guillain-Barre Syndrome (GBS)

Authorization of 2 months total may be granted when the following criteria are met:

1. Physical mobility is severely affected such that member requires an aid to walk.
2. IVIG therapy will be initiated within 2 weeks of symptom onset.

I. Myasthenia Gravis

Authorization of 1 month may be granted to members who are prescribed IVIG for worsening weakness, acute exacerbation, or in preparation for surgery.

1. 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.
2. Pre-operative management (eg, prior to thymectomy)

J. Lambert-Eaton Myasthenic Syndrome (LEMS)

Authorization of 12 months may be granted for LEMS.

K. Kawasaki Syndrome

Authorization of 1 month may be granted for pediatric members who are prescribed IVIG for Kawasaki syndrome.

L. 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.

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

Authorization of 6 months may be granted for pregnant women who are prescribed IVIG for 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 in members who have experienced an inadequate response or intolerance, or have a contraindication to first-line therapy such as a benzodiazepine (eg, diazepam) and/or baclofen.

IV. CONTINUATION OF THERAPY

Reauthorization criteria apply to members who are currently receiving IVIG therapy through a paid pharmacy or medical benefit. All other members (including new members) must meet initial authorization criteria.

V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

VI. OTHER

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

VII. APPENDICES

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine

- Age 6 years and older: antibody levels are not ≥ 1.3 mcg/mL for at least 70% of serotypes in the vaccine
- Age 2 to 5 years: antibody levels are not ≥ 1.3 mcg/mL for at least 50% of serotypes in the vaccine
- Not established for children less than 2 years of age

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)

REFERENCES:

SECTION 1

1. Siegel J. Immune globulins: therapeutic, pharmaceutical, cost, and administration considerations. *Pharmacy Practice News*. 2013;January:1-8. Available at: www.clinicaloncology.com/download/Immune_globulins_ppn0113_WM.pdf. Accessed February 2014.
2. Caress JB, Kennedy BL, Eickman KD. Safety of intravenous immunoglobulin treatment. *Expert Opin Drug Saf*. 2010;9(6):971-979.
3. Pierce R, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfusion Medicine Reviews*. 2003;17(4):241-251.
4. Gelfand EW. Differences between IGIV products: impact on clinical outcome. *International Immunopharmacology*. 2006;6:592-599
5. Bonilla FA. Intravenous immunoglobulins: adverse reactions and management. *J Allergy Clin Immunol*. 2008;122(6):1238-1239.
6. Siegel J. The product: all intravenous immunoglobulins are not equivalent. *Pharmacotherapy*. 2005;25(11 Pt 2):78S-84S.
7. American Academy of Allergy, Asthma & Immunology. IVIg Toolkit. Guidelines for the Site of Care for Administration of IGIV Therapy. <https://www.aaaai.org/practice-resources/management-tools-and-technology/ivig-toolkit.aspx>. Published December 2011. Accessed July 24, 2012.

8. Baxter Healthcare Corporation. Alzheimer's disease cooperative study (ADCS). Bethesda (MD): National Library of Medicine (US). 2000- [cited 2012 July 10]. NLM Identifier: NCT00818662. <http://clinicaltrials.gov/ct2/results?term=NCT00818662>
9. Rigas M, Tandan R, Sterling RJ. Safety of liquid intravenous immunoglobulin for neuroimmunologic disorders in the home setting: a retrospective analysis of 1085 infusions. *J Clin Neuromuscul Dis.* 2008;10(2):52-55.
10. Souayah N, Hasan A, Khan HM, Yacoub HA, Jafri M. The safety profile of home infusion of intravenous immunoglobulin in patients with neuroimmunologic disorders. *J Clin Neuromuscul Dis.* 2011;12(Suppl 4):S1-10.

SECTION 2

1. Bivigam [package insert]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; October 2013.
2. Carimune NF [package insert]. Kankakee, IL: CSL Behring LLC; September 2013.
3. Flebogamma 10% DIF [package insert]. Los Angeles, CA: Grifols Biologicals, Inc.; January 2016.
4. Flebogamma 5% DIF [package insert]. Los Angeles, CA: Grifols Biologicals, Inc.; April 2015.
5. Gammagard Liquid [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; April 2014.
6. Gammagard S/D [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; April 2014.
7. Gammagard S/D IgA less than 1 mcg/mL [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; September 2013.
8. Gammaked [package insert]. Fort Lee, NJ: Kedrion Biopharma, Inc.; September 2013.
9. Gammplex [package insert]. Hertfordshire, United Kingdom: Bio Products Laboratory; July 2015.
10. Gamunex-C [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; July 2014.
11. Octagam 10% [package insert]. Hoboken, NJ: Octapharma USA, Inc.; April 2015.
12. Octagam 5% [package insert]. Hoboken, NJ: Octapharma USA, Inc.; October 2014.
13. Privigen [package insert]. Kankakee, IL: CSL Behring LLC; November 2013.
14. DRUGDEX® System (electronic version). Truven Health Analytics, Ann Arbor, MI. Available at <http://www.micromedexsolutions.com> [available with subscription]. Accessed May 25, 2016.
15. AHFS Drug Information. <http://online.lexi.com/lco>. Accessed May 25, 2016.
16. Orange JS, Hossny EM, Weiler CR, 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;417(4 Suppl):S525-553.
17. 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. Available at

http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed June 7, 2016.

18. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.
19. Feasby T, Banwell B, Bernstead T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev*. 2007;21(2):S57-S107.
20. Donofrio PD, Berger A, Brannagan TH 3rd, 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(5):890-900.
21. 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;15(9):893-908.
22. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2012;78(13):1009-1015.
23. Anderson D, Kaiser A, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. *Transfus Med Rev*. 2007;21(2):S9-S56.
24. Picard C, Al-Herz W, Bousfiha A, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. *J Clin Immunol*. 2015; 35(8):696-726.
25. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015;136(5):1186-205.e1-78.
26. Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest section of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2012;130:S1-S24.
27. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. *Clin Exp Immunol*. 2013;174(2):203-11.
28. Immune Deficiency Foundation. About primary immunodeficiencies. Specific disease types. <http://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/>. Accessed Jun 13, 2016.