JOHNS HOPKINS MEDICINE / JOHNS HOPKINS HEALTHCARE	Johns Hopkins HealthCare LLC **Pharmacy Public** **Medical Management Drug Policies**	*Policy Number*	MMDP015
		Effective Date	01/01/2019
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	Subject **Immune Globulin (IV and Subcutaneous products)**	*Revision Date*	11/10/2021
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This document applies to the following Participating Organizations:

US Family Health Plan

Keywords: Asceniv, Bivigam, BivigamCarimune, Cuvitru, Flebogamma, Gammagard, Gammagard Liquid, Gammaked, Gammaplex, Gammunex C, Gamunex, Hizentra, HyQvia, Immune Globulin, IV Products, Octagam, Panglogulin, Panzyga, Privigen, Subcutaneous, Xembify

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Intravenous Immune Globulin (IVIG) [Bivigam, Carimune NF, Gammagard S/D, Panglobulin, Flebogamma, Gammaplex, Gamimune N, Gamunex, Gammaked, Octagam, Privigen, Panzyga, Asceniv] and Subcutaneous Immune Globulin (SCIG) [Hizentra, HyQvia, Gamunex C, Gammagard liquid, Cuvitru, Xembify] products will require prior authorization for medical benefit coverage to ensure appropriate use. The process for initiating a prior authorization request can be found in policy PHARM 20.

II. POLICY CRITERIA

A. **IVIG products** may be approved for patients who have one of the diagnoses listed below and meet the following criteria:

1. **Primary Humoral Immunodeficiencies** : *Immunodeficiencies such as Hyper IgM Syndrome (Immunodeficiency with near/normal IgM and absence of IgG, IgA), Common variable immunodeficiency, Selective IgG subclassdeficiency, Severe combined immunodeficiency, Specific Antibody Deficiency, Wiskot-Aldrich Syndrome, and X-Linked immunodeficiency*
   a. **Evidence of Agammaglobulinemia**:
      I. Documentation of ONE of the following:
         i. Total IgG level less than 200mg/dl
         ii. Patient is an infant with BTK gene or absence of B lymphocytes
   b. **Evidence of Persistent Hypogammaglobulinemia**:
      1. Documentation has been provided showing the following:
         i. Total IgG level less than 400mg/dl
         ii. Lack of ability to produce an antibody response to a protein (e.g tetanus) or polysaccharide antigen (e.g. Pneumococcal polysaccharide or H. Influenza type B.)

A. Serum antibody titers to pneumococcus should be measured prior to immunization and three to six weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (e.g., Pneumovax); at least 14 polysaccharide antigens should be tested.
B. Polysaccharide nonresponsiveness is defined as less than 4-fold rise in antibody titer and lack of protective antibody titer (specific IgG antibody titer less than 1.3 mcg/ml) in greater than 30 percent of antigens tested (more than 50 percent in children ages 2 to 5 years).

iii. Documentation of an infection history meeting ONE of the following criteria*:
A. Two or more bacterial infections per year due to persistent and significant reduction in total IgG (except for reduction of total IgG due to IgG subclass deficiency)
B. Recurrent or persistent severe bacterial infections with normal total IgG or IgG subclass deficiency despite prophylactic antibiotics, treatment antibiotics, and immunization with conjugate vaccine if not responsive to polysaccharide vaccine, and appropriately aggressive management of underlying conditions that may predispose to recurrent infection, such as asthma or allergic rhinitis

c. Initial IVIG dose is 300-600 mg/kg every 3-4 weeks. Depending on the product, prescribing information can range from 200-800 mg/kg every 3-4 weeks. Dosing should be titrated to the minimum amount needed for adequate patient response.

2. **Acquired/Secondary Humoral Immunodeficiencies:**
a. **Chronic Lymphocytic Leukemia (CLL) with hypogammaglobulinemia**:
I. Documentation has been provided showing an intended use for prevention of recurrent bacterial infections, with the following evidence:
i. Patient has an IgG level less than 600mg/dL or specific antibody deficiency
ii. Documentation of ONE of the following:
A. Documented severe bacterial infection within the preceding 6 months, or 2 more bacterial infections in one year
B. Evidence of specific antibody deficiency
iii. Initial IVIG dose is 400 mg/kg every 4 weeks (applicable for CLL, AML, CML)

b. **Multiple Myeloma**:
I. Documentation has been provided showing the patient is in the “Plateau Phase” of disease (> 3 months since diagnosis)
II. Patient has an IgG less than 600mg/dL
III. Documented 2 or more significant infections in last year or a single life threatening infection, OR patient has poor IgG response to the pneumococcal vaccine
IV. Initial IVIG dose is 200-400 mg/kg every 4 to 6 weeks

3. **Adult Idiopathic Thrombocytopenic Purpura:**
a. Documentation of one of the following:
I. Patient had trial and failure with corticosteroids and platelet count is less than 30,000/mm3
II. The requested product is being used to increase platelet counts prior to invasive major surgical procedures (e.g., splenectomy)
III. The requested product is being used to defer or avoid splenectomy
IV. The requested product is being used in a patient with severe thrombocytopenia (platelet counts less than 20,000/mm3) considered to be at risk for intracerebral hemorrhage
V. IVIG dose is 1,000-2,000 mg/kg (can be given as 1,000 mg/kg/day for 2 days, or 400 mg/kg/day for 5 days)

4. **Pediatric Idiopathic Thrombocytopenic Purpura**:
   a. Acute ITP:
      I. Documentation of ONE of the following:
         i. Platelet count less than 20,000/mm3, and patient has emergency bleeding, or is at risk for severe life-threatening bleeding
         ii. Severe thrombocytopenia (platelet count less than 20,000/mm3), and patient is considered to be at risk for intracerebral hemorrhage
      II. IVIG dose is 800-1,000mg/kg (infused as a single dose)
   b. Chronic ITP:
      I. Documentation that the patient is at high risk, supported by low platelet count, or symptomatic status, and ONE of the following:
         i. Failure of other therapies
         ii. High risk for post-splenectomy sepsis
      II. IVIG dose is 1 to 2gm/kg divided in equal doses given over 2 to 5 days
5. **Chronic Refractory Idiopathic Thrombocytopenic Purpura:**
   a. Patient is 10 years of age or older
   b. Documented thrombocytopenia for greater than 6 months without a concurrent disease explanation
   c. Prior treatment with corticosteroids and splenectomy has failed or member is at high risk for post-splenectomy sepsis
   d. IVIG dose is 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)
6. **Idiopathic Thrombocytopenic Purpura in Pregnancy:**
   a. Documentation has been provided showing the patient meets ONE of the following:
      I. Previously delivered infants with autoimmune thrombocytopenia
      II. Platelet counts less than 50,000/mm^3 during current pregnancy
      III. Past history of splenectomy
      IV. Refractory to steroids with platelet counts less than 10,000/mm^3 in the third trimester
      V. Platelet counts less than 30,000/mm^3 associated with bleeding before vaginal delivery or C-section
   b. IVIG dose is 1,000 mg/kg/day for 1 to 2 days.
7. **Bacterial Infection Prevention in Bone Marrow Transplant (BMT) or Hematopoietic Stem Cell Transplant (HSCT)** :
   a. Documentation showing an intended use for prophylaxis in BMT or HSCT transplant recipient
   b. Documentation showing ONE of the following:
      I. Therapy is initiated within 100 days after transplant
      II. Therapy is being initiated after 100 days post-transplant and ONE of the following:
         i. IgG less than 400mg/dL
         ii. Documentation shows primary immunodeficiency disease
         iii. Documentation shows CMV, EBV or RSV infection
   c. IVIG dose is 500mg/kg administered on day 7 and day 2 before transplant, and then once weekly.
8. **Myasthenia Gravis**:
   a. Acute Exacerbation, or Surgery Preparation:
      I. Documentation showing short-term use as prior to surgery or child-birthing, or as a temporary treatment while the patient is reaching therapeutic levels of another medication therapy
      II. Documented severe decompensation (e.g. respiratory failure or disabling weakness)

III. Documented failure or intolerance to alternative treatments such as plasma exchange, immunosuppressants, or corticosteroids
IV. IVIG dose is administered over 2 to 5 days

b. Refractory Myasthenia Gravis:
1. Documentation showing chronic decompensation
2. Documented failure or intolerance to other treatments including plasmapheresis, pyridostigmine, and immunosuppressive therapy, such as azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide
3. IVIG dose is 2,000mg/kg per month (dose infused over 2 to 5 days [can be given as 1,000mg/kg/day for 2 days, or 400mg/kg/day for 5 days])

9. **Kawasaki Disease**:
a. Documentation showing a diagnosis of Kawasaki Disease, as well as:
I. Fever present for at least 5 days
II. AND at least 4 of the following 5 conditions are present:
i. Mucous membrane changes such as a red tongue and dry fissured lips
ii. Swelling of the hands and feet
iii. Enlarged lymph nodes in the neck
iv. Diffuse red rash covering most of the body
v. Redness of the eyes
III. IVIG dose is 2,000 mg/kg, as a single infusion over 8-12 hours given within 10 days of onset of symptoms. The dose may be administered after 10 days of symptoms if there is continued evidence of inflammation or evolving coronary artery disease. A second dose of 2000 mg/kg may be administered 36 hours after the first dose for refractory disease.

10. **Bacterial infection prevention in HIV infected children:**
a. Documentation showing at least ONE of the following in an HIV positive member less than 13 years of age who has received vaccines if appropriate for his/her immune status (or has documentation of refusal of vaccines) and is taking combination antiretroviral therapy (cART) or has received appropriate guidance and support to take cART:
I. Serum IgG concentration less than 400mg/dL
II. Recurrent serious bacterial infections defined as 2 or more infections such as bacteremia, meningitis or pneumonia in a one year period
III. Failure to form antibodies to common antigens such as measles, pneumococcal, and/or Haemophilus influzenzae type B vaccine
IV. Living in areas where measles is highly prevalent and who have not developed an antibody response after two doses of measles, mumps, and rubella live virus vaccine.
V. Exposure to measles (one dose only)
VI. Chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy.
b. IVIG dose is 400 mg/kg every 4 weeks

11. **Multifocal Motor Neuropathy**:
a. Documentation showing the patient has progressive multifocal motor neuropathy
b. Documentation of electrophysiologic study which excludes other conditions that would not respond to IVIG
c. IVIG dose is 500 - 2,400 mg/kg per month (typically, dose infused over 2 to 5 days-ie, can be given as 1,000 mg/kg/day for 2 days, or 400 mg/kg/day for 5 days)

12. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**:

a. Documentation showing the following:
   I. Patient has symmetric or focal neurologic deficits with slowly progressive or relapsing course over 2 months or longer with neurophysiological abnormalities
   II. Electrodiagnostic study consistent with the diagnosis
b. Initial IVIG dose is 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)

13. **Guillain Barre Syndrome:**
    a. Documentation showing the following:
       I. The patient was diagnosed with Guillain Barre Syndrome with the first two weeks of illness
       II. The patient has a functional disability such as respiratory weakness, or inability to walk without aid
       III. Immune Globulin is being initiated no later than 4 weeks after symptom onset
       IV. Plasmapheresis will not be used concomitantly with immune globulin
    b. IVIG dose is 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)
14. **Lambert-Eaton Myasthenic Syndrome (LEMS)**
    a. Documentation showing the following:
       I. Diagnosis of LEM with confirmation from electrodiagnostic studies
       II. Failure, contraindication, or intolerance to all other categories of therapies which include acetylcholinesterase inhibitors, aminopyridines, and immunosuppressants
       III. IVIG is being used as an alternative to plasma exchange for severe weakness, or if there is difficulty with venous access
    b. Initial IVIG dose is 2,000 mg/kg (dose infused over 2 to 5 days). Maintenance dose is repeat dose no more frequently than every 4 weeks.
15. **Stiff Person Syndrome (Moersch-Woltmann Syndrome)**
    a. Documentation showing the following:
       I. Diagnosis of Stiff Person Syndrome with severe impairment of daily activities such as difficulty walking or frequent falls
       II. Failure, contraindication, or intolerance to first line therapy (e.g. benzodiazepines, baclofen)
    b. IVIG dose is 2,000 mg/kg, infused over 2 to 5 days.
16. **Dermatomyositis /Polymyositis:**
    a. Documentation showing the following:
       I. Diagnosis of Dermatomyositis or Polymyositis
       II. Patient has severe, rapidly progressive and/or potentially life threatening muscular weakness
       III. Failure, contraindication, or intolerance to corticosteroids and immunosuppressants, such as azathioprine, cyclosporine, or methotrexate
    b. Initial IVIG dose is 2,000 mg/kg, infused over 2 to 5 days, with maintenance dose being 500-1000 mg/kg/ month
17. **Hashimoto's Encephalopathy:**
    a. Documentation showing the following:
       I. Diagnosis of severe Hashimoto's Encephalopathy
       II. Patient has had progressive neurologic decline
       III. Failure, contraindication, or intolerance to corticosteroid therapy
    b. IVIG dose is administered up to 5 days
18. **CAR-T therapy associated Hypogammaglobulinemia:**

1. Documentation showing the following:
    1. Patient is being treated with a CAR-T therapy agent (i.e. Kymriah [tisagenlecleucel] or Yescarta [axicabtagene ciloleucel])
    2. Patient has an IgG less than 400mg/dL
2. Initial IVIG dose is 400 mg/kg every 4 weeks

B. **SCIG products** may be approved for patients who have one of the diagnoses listed below and meet the following criteria:

1. **Primary Humoral Immunodeficiencies** : *Immunodeficiencies such as Hyper IgM Syndrome (Immunodeficiency with near/normal IgM and absence of IgG, IgA), Common variable immunodeficiency, Selective IgG subclassdeficiency, Severe combined immunodeficiency, Specific Antibody Deficiency, Wiskot-Aldrich Syndrome, and X-Linked immunodeficiency*
    a. **Evidence of Agammaglobulinemia**:
        I. Documentation of ONE of the following:
            i. Total IgG level less than 200mg/dL
            ii. Patient is an infant with BTK gene or absence of B lymphocytes
    b. **Evidence of Persistent Hypogammaglobulinemia**:
        1. Documentation has been provided showing the following:
            i. Total IgG level less than 400mg/dl
            ii. Lack of ability to produce an antibody response to a protein (e.g tetanus) or polysaccharide antigen (e.g. Pneumococcal polysaccharide or H. Influenza type B.)
                A. Serum antibody titers to pneumococcus should be measured prior to immunization and three to six weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (e.g., Pneumovax); at least 14 polysaccharide antigens should be tested.
                B. Polysaccharide nonresponsiveness is defined as less than 4-fold rise in antibody titer and lack of protective antibody titer (specific IgG antibody titer less than 1.3 mcg/ml) in greater than 30 percent of antigens tested (more than 50 percent in children ages 2 to 5 years).
            iii. Documentation of an infection history meeting ONE of the following criteria*:
                A. Two or more bacterial infections per year due to persistent and significant reduction in total IgG (except for reduction of total IgG due to IgG subclass deficiency)
                B. Recurrent or persistent severe bacterial infections with normal total IgG or IgG subclass deficiency despite prophylactic antibiotics, treatment antibiotics, and immunization with conjugate vaccine if not responsive to polysaccharide vaccine, and appropriately aggressive management of underlying conditions that may predispose to recurrent infection, such as asthma or allergic rhinitis

2. **Additional indication for Hizentra**:
    a. Hizentra may also be approved for **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP**):
        I. Documentation showing the following:
            i. Patient has symmetric or focal neurologic deficits with slowly progressive or relapsing course over 2 months or longer with neurophysiological abnormalities
            ii. Electrodiagnostic study consistent with the diagnosis

III. AUTHORIZATION PERIOD/LIMITATIONS

A. Initial approval may be given for 3 months of therapy for an FDA-approved, or guideline-supported, dosing regimen.
1. IVIG and SCIG products will only be approved for their FDA-approved route of administration, and treatment age group

B. Continuation of therapy may be approved in 6-month intervals with documentation showing the patient has stable disease and is having a beneficial response to treatment. Supporting objective measures such as improved Inflammatory Neuropathy Cause and Treatment (INCAT), Activities of Daily Living (ADL) or Medical Research Council (MRC) scores are required as applicable to the treated diagnosis.
   1. Below are additional requirements for specific indications:
      1. For autoimmune disorders, including Primary Humoral Immunodeficiency and Acquired/Secondary Humoral Immunodeficiency with recurrent infections and Hypogammaglobulinemia:
         1. Reduction of persistent bacterial infections
         2. Reduction of hospitalization related to infectious illness
         3. Stable disease
         4. Lab values showing normalized trough IgG (ideally greater than 600 mg/dL) are not required, but can be considered when documenting treatment to desired outcome.
      2. For IgG subclass deficiency: patient must meet the continuation of therapy criteria for Primary Humoral Immunodeficiency. Additionally, immune globulin should be discontinued approximately one year after the initiation of therapy and every 2 years thereafter.
         1. Immune response to protein and/or polysaccharide antigens should be re-evaluated at least 3 months after discontinuation of immune globulin.
      3. For Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy:
         1. Positive clinical response to therapy as measured by an objective scale (INCAT, Rankin, Modified Rankin, or MRC scale)
         2. Requested dosing should remain within recommended guidelines stated in policy above.
         3. Documentation of titration to the minimum dose and frequency needed to maintain sustained clinical effect.
   2. Long term treatment requires documentation of titration to the minimum dose and frequency needed to maintain sustained clinical effect. If improvement is sustained with the dosage reduction, there should be an attempt to stop immune globulin therapy, when clinically appropriate.

IV. EXCLUSIONS

IVIG and SCIG products will **not** be covered for the following:

- Acute Lymphoblastic Anemia
- Acute Renal Failure
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic Lateral Sclerosis (ALS)
- Aplastic Anemia
- Asthma
- Atopic Dermatitis
- Autism
- Autoimmune autonomic neuropathy
- Autoimmune liver disease
- Behcet's Syndrome
- Cardiomyopathy
- Chronic Fatigue Syndrome
- Chronic Sinusitis

- Cystic Fibrosis
- Demyelinating Optic Neuritis
- Diabetes
- Diamond-Blackfan Anemia
- Eczema
- Fahr's Disease
- Endotoxemia
- Erythroblastosis Fetalis
- Goodpasture's Syndrome
- Hemolytic Uremic Syndrome
- Immune-related Neutropenia
- Inclusion body myositis
- Lumbosacral plexopathy
- Motor neuron syndromes
- Multiple Sclerosis
- Narcolepsy/cataplexy
- Neonatal hemolytic disease
- Nephropathy, membranous
- Nephrotic Syndrome
- Nonimmune thrombocytopenia
- Ophthalmopathy, euthyroid
- Otitis Media
- Paraproteinemic neuropathy
- Polyarteritis Nodosa
- Polyneuritis
- Post Infection Sequelae
- Post-polio syndrome
- Recent onset dilated cardiomyopathy
- Recurrent spontaneous abortion
- Reiter's syndrome
- Scleroderma
- Septic Shock
- Rheumatoid Arthritis
- Still's disease
- Thrombotic Thrombocytopenic purpura
- Tic Disorder
- Urticaria
- Uveitis
- Vasculitic syndromes
- Wegener's Granulomatosis Rheumatoid Arthritis
- Any indications or uses that are not FDA-approved, or guideline-supported

V. RECOMMENDED DOSAGE

1. Please refer to the FDA-approved prescribing information for the specific IVIG or SCIG product regarding appropriate dosing.

2. For the clinically supported off-label diagnoses discussed in this policy, the dosage, frequency, and duration of IVIG therapy should be supported by evidence based literature and adjusted based upon severity, alternative available treatments, and previous response to immune globulin therapy.

VI. CODES

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Note: The following CPT/HCPCS codes are included below for informational purposes. Inclusion or exclusion of a CPT/HCPCS code(s) below does not signify or imply member coverage or provider reimbursement. The member's specific benefit plan determines coverage.

Medication	HCPCS/CPT Code
Bivigam 5 GM/50ML SOLN Injection, immune globulin (Bivigam), 500 mg	J1556
Carimune NF 6 GM SOLR J1566 Injection, immune globulin, intravenous, lyophilized (e.g powder), not otherwise specified, 500 mg	J1566
Gammagard S/D SOLR Injection, immune globulin, intravenous, lyophilized (e.g. powder), not otherwise specified, 500 mg	J1566
Panglogulin SOLR Injection, immune globulin, intravenous, lyophilized (e.g. powder), not otherwise specified, 500 mg	J1566
Flebogamma/Flebogamma DIF Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), 500 mg	J1572
Gammaplex Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), 500 mg	J1557
Gamunex-C/Gammaked Injection, immune globulin, non-lyophilized (e.g. liquid), 500 mg	J1561
Octagam Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), 500 mg	J1568
Privigen Injection, immune globulin intravenous, non-lyophilized (e.g liquid), 500 mg	J1459
Hizentra 1 GM/5ML SOLN Injection, immune globulin, 100 mg	J1559
Hyqvia 2.5 GM/25ML KIT Injection, immune globulin/hyaluronidase, 100 mg immune globulin Hyqvia 20 GM/200ML KIT Injection, immune globulin/hyaluronidase, 100 mg immune globulin Hyqvia 30 GM/300ML KIT Injection, immune globulin/hyaluronidase, 100 mg immune globulin Hyqvia 10 GM/100ML KIT Injection, immune globulin/hyaluronidase, 100 mg immune globulin Hyqvia 5 GM/50ML KIT Injection, immune globulin/hyaluronidase, 100 mg immune globulin	J1575
Gammagard liquid Injection, immune globulin, non-lyophilized, (e.g. liquid), 500 mg	J1569
Cuvitru Injection, immune globulin, 100 mg , (SCIG)	J1555

Panzyga Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), 500 mg Asceniv 5GM/50ML Solution Injection, immune globulin, intravenous, non-lyophilized	J1599
Xembify Injection, immune globulin, 100 mg	J1558

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VIII. APPROVALS

Signature on file at JHHC

DATE OF REVISION	SUMMARY OF CHANGE
12/19/2018	Policy Creation
04/17/2019	Addition of Cuvitru and Panzyga as applicable drugs reviewed under this policy

11/15/2019	Updated layout and clarified coverage criteria for both IVIG and SCIG products
01/15/2020	Added criteria for Hashimoto's Encephalopathy and presented policy for USFHP adoption effective 3/1/2020
07/15/2020	Addition of Xembify as an applicable drug reviewed under this policy
01/20/2021	Reinstated clinical criteria for refractory myasthenia gravis; Added clinical criteria for Hypogammaglobulinemia from CAR-T therapy
02/17/2021	Clarification regarding the inclusion of Asceniv as an applicable drug reviewed under this policy
11/10/2021	Removed Priority Partners as an applicable LOB

Review Date: 12/19/2018, 04/17/2019, 01/15/2020, 07/15/2020, 01/20/2021, 04/21/2021

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