CLINICAL MEDICATION POLICY	
Policy Name:	Intravenous Immunoglobulin (IVIG) & Subcutaneous Immune Globulin Therapies
Policy Number:	MP-055-MD-PA
Responsible Departments:	Medical Management Medical Policy; Clinical Pharmacy
Provider Notice Date:	07/01/2017
Original Effective Date:	08/01/2017
Annual Approval Date:	05/25/2018
Revision Date:	05/17/2017
Products:	Pennsylvania Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 11

Disclaimer

Gateway Health℠ (Gateway) medical policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Gateway Health™ provides coverage for intravenous immunoglobulin (IVIG) and subcutaneous immune globulin (SCIG) under the medical surgical benefit of the Company's Medicaid products when medically necessary in the treatment of primary immune-deficiency, idiopathic thrombocytopenic purpura, Kawasaki syndrome, chronic inflammatory demyelinating polyneuritis (CIDP), multifocal motor neuropathy, and B-cell chronic lymphocytic leukemia (CLL).

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

DEFINITIONS

Kawasaki Disease – A rare childhood disease of unknown cause that causes inflammation in the walls of medium-sized arteries throughout the body. The disease is also known as mucocutaneous lymph node syndrome.

PROCEDURES

All requests for IVIG or SCIG therapies require a prior authorization and will be screened for medical necessity and appropriateness using the criteria listed below

- Coverage may be provided when the indications and dosing are within the FDA-labeled prescribing information recommendations. *Please refer to the drug-specific FDA-approved prescribing information for updated IVIG and SCIG indications and dosing recommendations.*
- The following IVIG and SCIG are considered medically necessary when the member meets the following criteria below:
    - **IVIG: 5%**
        - Carimune NF
        - Flebogamma DIF
        - Gammagard S/D
        - Gammaplex
        - Octagam
    - **IVIG: 10%**
        - Bivigam NF
        - Flebogamma DIF
        - Gammagard Liquid
        - Gammaked
        - Gamunex-C
        - Octagam
        - Privigen
    - **SCIG:**
        - Cuvitru
        - Gammagard Liquid
        - Gammaked
        - Gamunex-C
        - Hizentra
        - Hyqvia

1. Primary Immunodeficiency (e.g., Congenital agammaglobulinemia, common variable immunodeficiency, hypogammaglobulinemia, Wiskott-Aldrich Syndrome, X-linked agammaglobulinemia, severe combined immunodeficiencies) when the ALL of the following criteria are met:
    - Adults and pediatrics: All IVIG and SCIG therapies except Octagam 10% (IV)
    - Adults only: Hyqvia (SC)
        - Laboratory reports demonstrate IgG level of < 400 mg/dL OR reports demonstrate a lack of ability to produce an antibody response to a protein antigen (e.g., tetanus) or one of the polysaccharide antigens (e.g., pneumococcal polysaccharide or H. Influenza type B)
        - If a member has recurrent bacterial infection and normal IgG levels, a lack of antibody response will be considered adequate to support the diagnosis
        - The member continues to have unexplained recurrent or persistent severe or opportunistic bacterial infections despite adequate treatment
        - Aggressive management of other conditions predisposing to recurrent sinopulmonary infections has been used

- Increased vigilance has been applied and appropriate antibiotic therapy prescribed for infections
- Member has had two or more infections per year due to persistent and significant reduction in total IgG or IgG subclasses
- Benefit approved for three months and is renewable when there is documentation of clinical benefit from immune globulin therapy

2. Idiopathic thrombocytopenic purpura (ITP) in adults when the ALL of the following criteria are met:
    - Carimune NF 5% (IV): Acute and chronic ITP
    - Gammagard S/D 5% (IV): Chronic ITP
    - Gammaked 10% (IV): Acute and chronic ITP
    - Gammaplex 5% (IV): Chronic ITP
    - Gamunex-C 10% (IV): Acute and chronic ITP
    - Octagam 10% (IV): Chronic ITP
    - Privigen 10% (IV): Chronic ITP
        - Other causes of thrombocytopenia have been ruled out by history and peripheral smear
        - Member is unresponsive to corticosteroid therapy
        - Platelet count is < 30,000/mcL with or without active bleeding OR
        - IVIG is being administered to defer or avoid splenectomy
        - Benefit is approved based on the classification of the condition:
            - Acute ITP: Benefit approved for five days
            - Chronic ITP:
                - Initial: Benefit approved for a maximum of five days
                - Maintenance: Benefit approved for one month and may be reauthorized when platelet counts remain < 30,000/mcL
        - A response to therapy is defined as a platelet count > 30,000/mcL and doubling of the baseline count; a complete response is defined as a platelet count > 100,000/mcL; immune globulin will not be reauthorized in situations where the platelet count is > 100,000/mcL

3. ITP in pediatrics when ALL of the following criteria are met:
    - Carimune NF 5% (IV): Acute and chronic ITP
    - Gammaked 10% (IV): Acute and chronic ITP
    - Gammaplex 5% (IV): Chronic ITP
    - Gamunex-C 10% (IV): Acute and chronic ITP
    - Privigen 10% (IV): Chronic ITP
        - Initial therapy if platelet count < 30,000/mcL when member has emergency bleeding or is at risk for severe life-threatening bleeding OR
        - Members with severe thrombocytopenia (platelet counts < 20,000/mcL) considered to be at risk for intra-cerebral hemorrhage
        - Benefit approved for five days

4. Prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric members when the ALL of the following criteria are met:
    - Gammagard S/D 5% (IV)
        - Member must be receiving concurrent high-dose aspirin therapy

- Benefit approved for two weeks and is renewable with documentation that treatment with the first infusion failed

5. Chronic inflammatory demyelinating polyneuritis (CIDP) when ALL of the following criteria are met:
    - Gammaked 10% (IV)
    - Gamunex-C 10% (IV)
        - Member has progressive, symptomatic MMN (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
        - Benefit approved for three months

6. Maintenance therapy to improve muscle strength and disability in adult members with multifocal motor neuropathy (MMN) when ALL the following criteria are met:
    - Gammagard Liquid 10% (IV)
        - Member has progressive, symptomatic MMN (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
        - Benefit approved for three months

    As manifested in the following conditions: Congenital Agammaglobulinemia, hypogammaglobulinemia, Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, X Linked Immunodeficiency with Hyper-IgM, Severe Combined Immunodeficiencies, Deficient Qualitative or Quantitative Antibody Production.

7. Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL) when ALL of the following criteria are met:
    - *Gammagard S/D 5% (IV)*
        - Member has recurrent bacterial infections
        - Member has pretreatment serum IgG < 600 mg/dL OR
        - Member has evidence of specific antibody deficiency
        - Benefit approved for three months and is renewable upon progression of disease

    Drugs:
    - Adults and pediatrics: All IVIG and SCIG therapies except Octagam 10% (IV)
    - Adults only: HyQvia (SC)

8. Contraindications
    Please refer to the drug-specific FDA-approved prescribing information for updated IVIG and SCIG contraindications:

    - Members who have had a history of anaphylactic or severe systemic reactions to the administration of human immune globulin

- IgA deficient members with antibodies to IgA and a history of hypersensitivity

9. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

Governing Bodies Approval
The FDA has approved numerous formulations of IVIG and SCIG.

On June 7, 1984, the FDA approved Carimune NF® IVIG (human) lyophilized powder product for the treatment of primary immune deficiency diseases (PIDD) and chronic immune thrombocytopenic purpura (ITP).

In 1994, the FDA approved Gammagard S/D® for the treatment of PIDD.

In 2003, the FDA approved both Gamunex-C® and Gammaked® immune globulin intravenous (IVIG) (human) 10 percent liquid products for the treatment of serious infections in individuals with PIDD via intravenous or subcutaneous administration.

On December 15, 2003, the FDA approved Flebogamma® IVIG (human) for the treatment of PIDD.

On May 21, 2004, the FDA approved Octagam® IVIG (human) 5 percent liquid product for the treatment of PIDD.

In 2005, the FDA approved Gammagard Liquid® IVIG (human) 10 percent liquid product for the treatment of PIDD via intravenous or subcutaneous administration.

On July 26, 2007, the FDA approved Privigen®, IVIG (human) 10 percent liquid product for the treatment of PIDD and chronic ITP.

On September 17, 2009 the FDA approved Gammaplex® IVIG (human) 5 percent liquid product for the treatment of PIDD. A subsequent approval for the treatment of chronic ITP was granted on March 8, 2013.

On March 4, 2010, the FDA approved Hizentra® SCIG (human) 20 percent liquid product for the treatment of PIDD.

CODING REQUIREMENTS

Procedure Codes

CPT Codes	Description
90281	Immune globulin (Ig), human, for intramuscular
90283	Immune globulin, (IgIV), human, for intravenous use
90284	Immune globulin, (SCIg), human, for use in subcutaneous infusions, 100 mg each
HCPCS Codes	
J3590	Unclassified biologics

J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1460	Injection, gamma globulin, intramuscular, 1 cc [when specified for disease treatment as described in this document]
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1560	Injection, gamma globulin, intramuscular, over 10 cc
J1561	Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous lyophilized (e.g., powder), not otherwise specified, 500 mg [Carimune]
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard Liquid), non-lyophilized (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (HyQvia), 100 mg immuneglobulin
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg
J7799	NOC drugs, other than inhalation drugs, administered through DME (Subcutaneous Cuvitru)
S9338	Home infusion therapy; immunotherapy, administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment, per diem

Diagnosis Codes

ICD-10 Codes	Description
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D47.2	Monoclonal gammopathy
D68.312	Antiphospholipid antibody with hemorrhagic disorder
D69.51	Post transfusion purpura
D69.59	Other secondary thrombocytopenia
D69.3	Immune thrombocytopenic purpura
D76.3	Other histiocytosis syndromes
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia

D80.7	Transient hypogammaglobulinemia of infancy
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	Di George's syndrome
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
D84.8	Other specified immunodeficiencies
D89.2	Hypergammaglobulinemia, unspecified
D89.9	Disorder involving the immune mechanism, unspecified
G60.3	Idiopathic progressive neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.89	Other inflammatory polyneuropathies
G61.9	Inflammatory polyneuropathy, unspecified
G62.81	Critical illness polyneuropathy
G62.89	Other specified polyneuropathies
M30.3	Mucocutaneous lymph node syndrome (Kawasaki)
P61.0	Transient neonatal thrombocytopenia

Brands of Immune Globulins and FDA-Approved Indications

Brand of Immune Globulin	FDA-Approved Indications
Bivigam	Primary humoral immunodeficiency
Carimune NF	Primary immunodeficiencies, immune thrombocytopenic purpura
Cuvitru	Primary humoral immunodeficiency
Flebogamma	Primary immunodeficiencies
Gammagard	Primary immunodeficiencies
Gammagard S/D	Primary immunodeficiencies, B-Cell chronic lymphocytic leukemia, chronic idiopathic thrombocytopenic purpura, Kawasaki syndrome
Gammaked	Primary immunodeficiencies, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy
Gammaplex	Primary immunodeficiencies
Gammar-P I.V.	Primary immunodeficiencies
Gamunex-C	Primary immunodeficiencies, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy
Hizentra (subcutaneous)	Primary immunodeficiencies
HyQvia	Primary immunodeficiencies
Iveegam EN	Primary immunodeficiencies, Kawasaki syndrome
Octagam	Primary immunodeficiencies
Panglobin	Primary immunodeficiencies, immune thrombocytopenic purpura
Polygam S/D	Primary immunodeficiencies, immune thrombocytopenic purpura, Kawasaki syndrome, B-cell chronic lymphocytic leukemia
Privigen	Primary immunodeficiencies, immune thrombocytopenic purpura

Source: Drug Facts & Comparisons, 2009

Normal Immunoglobulin Levels

Reference Ranges mg/dL			
Age Range	**IgA**	**IgG**	**IgM**
0-12 months	0-83	232-1411	0-145
1-3 years	20-100	453-916	19-146
4-6 years	27-195	504-1465	24-210
7-9 years	34-305	572-1474	32-208
10-11 years	53-204	698-1560	31-180
12-13 years	58-359	759-1550	35-239
14-15 years	47-249	716-1711	15-188
16-19 years	61-348	549-1584	23-259
> 19 years	70-400	700-1600	40-230

Source: Pediatric Reference Intervals, AACC Press, Fifth Edition

Reference ranges (g/l) of IgG subclasses and IgG in healthy Caucasian children and adults					
	IgG1	IgG2	IgG3	IgG4	IgG
Age in months					
0-1[1]	2.4-10.6	0.87-4.1	0.14-0.55	0.039-0.56	2.6- 7.8[2]
1-4[1]	1.8-6.7	0.38-2.1	0.14-0.70	0.022-0.36	2.6- 7.8[2]
4-6	1.8-7.0	0.34-2.1	0.15-0.80	0.017-0.23	2.2-11.3
6-12	2.0-7.7	0.34-2.3	0.15-0.97	0.012-0.43	2.6-15.2
Age in years					
1-1.5	2.5-8.2	0.38-2.4	0.15-1.07	0.011-0.62	2.6-13.9
1.5-2	2.9-8.5	0.45-2.6	0.15-1.13	0.011-0.79	2.6-13.9
2-3	3.2-9.0	0.52-2.8	0.14-1.20	0.012-1.06	4.3-13.0
3-4	3.5-9.4	0.63-3.0	0.13-1.26	0.015-1.27	5.2-13.4
4-6	3.7-10.0	0.72-3.4	0.13-1.33	0.017-1.58	5.2-13.4
6-9	4.0-10.8	0.85-4.1	0.13-1.42	0.023-1.89	5.2-14.3
9-12	4.0-11.5	0.98-4.8	0.15-1.49	0.030-2.10	5.2-15.6
12-18	3.7-12.8	1.06-6.1	0.18-1.63	0.035-2.30	5.2-15.6[3]
Adults	4.9-11.4	1.50-6.4	0.20-1.10	0.080-1.40	7.0-16.0

Source: http://ednieuw.home.xs4all.nl/IgGsubclasses/subkl3.htm

1 Depends on the IgG-concentration in the blood of the mother
2 0.5 – 4 months
3 12-16 years

REIMBURSEMENT

Participating facilities will be reimbursed per their Gateway Health℠ contract.

POLICY SOURCE(S)

Prevention and Treatment of Disease. NIH Consensus Statement Online 1990 May 21-23; 8(5):1-23.

Center for Medicare and Medicaid Services (CMS). Decision memo for intravenous immune globulin for autoimmune mucocutaneous blistering diseases (CAG-00109N). Baltimore, MD: CMS; January 22, 2002. Accessed on February 17, 2016 from: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=43&NcaName=Intravenous+Immune+Globulin+for+Autoimmune+Mucocutaneous+Blistering+Diseases&NCDId=46&ncdver=1&CoverageSelection=Both&NCSelection=NCA%7CCAL%7CNCD%7CMEDCAC%7CTA%7CMCD&ArticleType=Ed%7CKey%7CSAD%7CFAQ&PolicyType=Final&KeyWord=HIV&KeyWordLookUp=Doc&KeyWordSearchType=Exact&kq=true&bc=IAAAABAAAgAAAA%3D%3D.

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):1009-101. http://www.neurology.org/content/78/13/1009.long5. Accessed on February 17, 2016.

Hizentra®, Immune Globulin Subcutaneous (Human) [package insert]. Kankakee, IL: CSL Behring LLC; 03/2010, Revised 09/2013. http://www.hizentra.com/professional/prescribing-information.aspx.

Gürcan HM, Jeph S, Ahmed AR. Intravenous immunoglobulin therapy in autoimmune mucocutaneous blistering diseases: a review of the evidence for its efficacy and safety. Am J Clin Dermatol. 2010; 11(5):315-26. http://www.ncbi.nlm.nih.gov/pubmed/20642294. Accessed on February 18, 2016.

Muley SA, Parry GJ. Multifocal motor neuropathy. J Clin Neurosci. 2012 Jun 26. http://www.ncbi.nlm.nih.gov/pubmed/22743043. Accessed on February 18, 2016.

Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurol. 2012; 11(6):493-502. http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(12)70093-5/abstract. Accessed on February 18, 2016.

Gamunex®-C [package insert]. Research Triangle Park, NC: Grifols Therapeutics Inc.; 2003, Revised 09/2013. http://druginserts.com/lib/other/meds/gamunex-c-1/.

Octagam [package insert]. Hoboken, NJ: Octapharma USA INC; 2004, Revised 09/2014. http://druginserts.com/lib/rx/meds/octagam-immune-globulin-human.

GAMMAGUARD LIQUID [package insert]. Westlake Village, CA: Baxter International Inc.; 2005, Revised 09/2013. http://gammagard.com/primary-immunodeficiency/patient/. Accessed on February 18, 2016.

Vivaglobin® [package insert]. Kankakee, IL: CSL Behring LLC; 2006, Revised 04/2010. http://druginserts.com/lib/rx/meds/vivaglobin/. Accessed on February 18, 2016.

Cytogam® [package insert]. Kankakee, IL: CSL Behring LLC; 2007, Revised 08/2012. http://labeling.cslbehring.com/PI/US/Cytogam/EN/Cytogam-Prescribing-Information.pdf. Accessed on February 18, 2016.

Privigen® [package insert]. Kankakee, IL: CSL Behring LLC; 2007, Revised 11/2016. Accessed on February 18, 2016. http://labeling.cslbehring.com/PI/US/Privigen/EN/Privigen-Prescribing-Information.pdf.

Gammaplex® [package insert]. Raleigh, NC: BPL Inc.; 2009, Revised 09/2014. Accessed on February 18, 2016. http://www.gammaplex.com/download/Gammaplex-5pct-US-PI-VSUS7PI_page_layout.pdf.

HyQvia Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase [FDA package insert]. 2014. http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM414440.pdf. Accessed on February 18, 2016.

Ayer G, Souayah N. Efficacy and safety of home infusion of intravenous immunoglobulin in multifocal motor neuropathy: A longitudinal study. J Amer Academy Neurol. 2014; 10(82). Sup P7.111. http://www.neurology.org/content/82/10_Supplement/P7.111.short. Accessed on February 18, 2016.

Abolhassani H, Sadaghiani MS, Aghamohammadi A, Ochs HD, Rezaei N. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta-analysis. J Clin Immunol. 2012 Dec; 32(6):1180-92. http://www.ncbi.nlm.nih.gov/pubmed/22730009. Accessed on February 18, 2016.

American Academy of Allergy Asthma & Immunology (AAAAI). Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/IVIG-guiding-principles.pdf. Accessed on February 18, 2016.

Policy History

Date	Activity
02/17/2015	Initial policy developed
07/05/2015	Provider effective date
05/01/2017	Revised-Format changes; Removal of all non-FDA approved indications; Under Procedure section, formatting changes and added appropriate drugs under each medical condition; Added CPT/HCPCS & ICD-10 Coding section; Added Table of brand drugs and FDA approved indications; Added reference table of normal immunoglobulin levels; Updated reference section
05/17/2017	Medical Director approval
08/01/2017	Provider effective date