Clinical Policy: Immune Globulins

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Line of Business: Medicaid

Coding Implications
Revision Log

Description

The following are immune globulin (IG) products requiring prior authorization: Bivigam™, Carimune® NF, Cuvitru™, Cytogam®, Flebogamma® DIF (5%), Flebogamma® DIF (10%), GamaSTAN® S/D, Gammagard® Liquid, Gammagard® S/D, Gammaked™, Gammaplex®, Gamunex®-C, Hizentra®, Hyqvia®, Octagam® 5%, Octagam® 10%, Privigen®.

FDA Approved Indication(s)

Immunoblobulin (IG) products identified in this policy are approved for the following uses *(see Appendix B below for individual products by route and indication):*

- Immune globulin (intravenous route) (IVIG) formulations:
  - Primary humoral immunodeficiency: for replacement therapy.*
  - Immune thrombocytopenic purpura (ITP) (acute/chronic): Treatment to raise platelet counts, including to prevent bleeding or allow surgery. **
  - Chronic inflammatory demyelinating polyneuropathy (CIDP): Treatment to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.
  - Kawasaki syndrome: Prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients (administered concurrently with aspirin).
  - Multifocal motor neuropathy (MMN): Maintenance therapy to improve muscle strength and disability in adult patients.
  - B-cell chronic lymphocytic leukemia (CLL): Prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell CLL.
  - Cytomegalovirus (CMV): Prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas, heart. In transplants of these organs (other than kidney) from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.
- Immune globulin (subcutaneous route) (SCIG) formulations:
  - Primary humoral immunodeficiency: for replacement therapy.
- Immune globulin (intramuscular route)(IMIG) formulations:
  - Hepatitis A: The prophylactic value of GamaSTAN S/D is greatest when given before or soon after exposure to hepatitis A. GamaSTAN S/D is not indicated in persons with clinical manifestations of hepatitis A or in those exposed >2 weeks previously.
  - Measles (rubeola): To prevent or modify measles give GamaSTAN S/D in a susceptible person exposed <6 days previously. A susceptible person is one who has not been vaccinated and has not had measles previously. GamaSTAN S/D may be especially indicated for susceptible household contacts of measles patients, particularly contacts <1 year of age, for whom the risk of complications is highest. GamaSTAN S/D and measles vaccine should not be given at the same time. If a child is >12 months and has received GamaSTAN S/D, he should be given measles vaccine about 3 months later when the

measles antibody titer will have disappeared. If a susceptible child exposed to measles is immunocompromised, GamaSTAN S/D should be given immediately. Do not administer measles vaccine or any other live viral vaccine to children who are immunocompromised.

- Passive immunization against varicella in immunosuppressed patients is best accomplished by use of Varicella-Zoster Immune Globulin – human (VZIG). If VZIG is unavailable, GamaSTAN S/D, promptly given, may also modify varicella.
- Rubella: The *routine use* of GamaSTAN S/D for prophylaxis of rubella in early pregnancy is of dubious value and cannot be justified. Some studies suggest that the use of GamaSTAN S/D in exposed, susceptible women can lessen the likelihood of infection and fetal damage; therefore, GamaSTAN S/D may benefit those women who will not consider a therapeutic abortion. *[For more information, see CDC Control and Prevention of Rubella: Evaluation and Management of Suspected Outbreaks, Rubella in pregnant women, and surveillance for congenital rubella syndrome. MMWR Recomm Rep. 2001; 50(RR-12):1-23.]*

**Primary humoral immunodeficiency: Labeled indications specifying age differ across products; information common to all products is notated.*
***ITP: Labeled indications specifying acute versus chronic ITP, and age, differ across products; information common to all products is notated.*

Policy/Criteria
Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with Pennsylvania Health and Wellness® that the immune globulin products referenced above are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Intravenous Immune Globulin Formulations (must meet all)**:**

1. Request for IVIG applies to one of the following diagnoses/indications:
   a. Primary humoral immunodeficiency, including but not limited to congenital agammaglobulinemia, common variable immunodeficiency [CVID], X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, severe combined immunodeficiencies, (i and ii):
      i. One of the following IG products is requested: Bivigam, Carimune NF, Flebogamma DIF (5%/10%), Gammagard Liquid or S/D, Gammaked, Gammaplex, Gamunex-C (preferred), Octagam (5%), Privigen;
      ii. If request is not for Gamunex-C, member must have contraindication or clinically significant adverse effects to Gamunex-C;
   b. Immune (idiopathic) thrombocytopenic purpura (ITP) (i and ii):
      i. One of the following IG products is requested: Carimune NF, Flebogamma DIF (10%), Gammagard S/D, Gammaked, Gammaplex, Gamunex-C (preferred), Octagam (10%), Privigen;
      ii. If request is not for Gamunex-C, member must have contraindication or clinically significant adverse effects to Gamunex-C;

c. Chronic inflammatory demyelinating polyneuropathy (CIDP) (i and ii):
   i. One of the following IG products is requested: Gammaked, Gamunex-C (preferred);
   ii. If request is not for Gamunex-C, member must have contraindication or clinically significant adverse effects to Gamunex-C;
d. Kawasaki syndrome (i and ii):
   i. Gammagard S/D is requested;
   ii. Treatment plan includes aspirin therapy;
e. Multifocal motor neuropathy (MMN):
   i. Gammagard Liquid is requested;
f. B-cell chronic lymphocytic leukemia (CLL) (i and ii):
   i. Gammagard S/D is requested for bacterial infection prophylaxis;
   ii. Pretreatment hypogammaglobulinemia (serum IgG < 500 mg/dl) or history of recurrent bacterial infections;
g. Cytomegalovirus (CMV):
   i. Cytogam is requested for prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas or heart.

Approval duration: 6 months

B. Subcutaneous Immune Globulin Formulations (must meet all)**:**

1. Request for SCIG applies to the following diagnosis/indication:
   a. Primary humoral immunodeficiency, including but not limited to congenital agammaglobulinemia, CVID, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, severe combined immunodeficiencies (i and ii):
      i. One of the following IG products is requested : Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C (preferred), Hizentra, Hyqvia;
      ii. If request is not for Gamunex-C, member must have contraindication or clinically significant adverse effects to Gamunex-C;
2. IG will be administered in a controlled healthcare setting or the treatment plan provides for management of a potential acute hypersensitivity reaction.

Approval duration: 6 months

C. Intramuscular Immune Globulin Formulations (must meet all)**:**

1. Request for intramuscular (IM) GamaSTAN S/D for one of the following indications:
   a. Hepatitis A post-exposure/high-risk prophylaxis (i and ii):
      i. Hepatitis A exposure or at high risk for exposure as follows (a or b):
         a) Exposure to hepatitis A in the past 2 weeks (e.g., household contact, sexual contact, sharing illicit drugs with someone positive for hepatitis A, regular babysitters/caretakers, food handlers at the same establishment as one who is positive for hepatitis A) AND does not have clinical manifestations of hepatitis A;
         b) Traveling to or working in an area endemic for hepatitis A;
      ii. Meets any of the following (a, b or c):
         a) Hepatitis A vaccine is locally unavailable;
         b) History of severe allergic reaction (anaphylaxis) to the hepatitis A vaccine;

c) If either exposed to the virus or traveling in ≤ 2 weeks to an area endemic for hepatitis A, then (1, 2 or 3):
1) Age < 1 year or > 40 years;
2) Chronic liver disease or other chronic medical condition;
3) Immunocompromised;

b. Measles (rubeola) post-exposure prophylaxis (i, ii and iii):
i. Exposure to measles within the past 6 days;
ii. Member has not previously received a measles vaccine AND has not previously had measles;
iii. Meets any of the following (any a - f):
a) Measles vaccine is locally unavailable;
b) History of severe allergic reaction (anaphylaxis) to the measles vaccine;
c) Pregnancy;
d) Immunocompromised;
e) Has been >3 days since exposure;
f) Age <12 months;

c. Chickenpox (varicella) post-exposure prophylaxis (all i - iv):
i. Recent exposure varicella;
ii. Member lacks immunity to varicella;
iii. VZIG is currently unavailable;
iv. Meets any of the following (any a - e):
a) Varicella vaccine is locally unavailable;
b) History of a severe allergic reaction (anaphylaxis) to the varicella vaccine;
c) Pregnancy;
d) Immunocompromised;
e) Newborn of mother who had varicella from 5 days before to 2 days after delivery;

d. Rubella post-exposure prophylaxis (i and ii):
i. Recent exposure to rubella;
ii. Member is pregnant;

Approval duration: one injection total* [*If extended stay (≥ 3 months) in area endemic for hepatitis A, repeat injection every 4-6 months]

D. Other diagnoses/indications

1. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).
2. Compendial uses for IG are approved for the following indications per the CP.PMN.53 Off-label policy:
a. The following fetal/neonatal indications:
i. Thrombocytopenia;
ii. Alloimmune thrombocytopenia;
iii. Infectious disease prophylaxis;
b. Autoimmune hemolytic anemia;
c. Pure red cell aplasia in pediatric population;
d. Prophylaxis of bacterial infection in human immunodeficiency virus infection;
e. Refractory dermatomyositis and polymyositis;

f. Myasthenia gravis;
g. Relapsing-remitting multiple sclerosis;
h. Guillain-Barre syndrome;
i. Pemphigus vulgaris;
j. Stiff-man syndrome;
k. Toxic shock syndrome;
l. Transplant of kidney- pretransplant desensitization of highly sensitized patients

II. Continued Therapy

A. Intravenous Immune Globulin Formulations (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PA.01) applies;
2. Member is responding positively to therapy.

Approval duration: 6 months

B. Subcutaneous Immune Globulin Formulations (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PA.01) applies;
2. Member is responding positively to therapy.

Approval duration: 6 months

C. Intramuscular Immune Globulin Formulations (must meet all**):**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PA.01) applies;
2. Member is responding positively to therapy.

Approval duration: one injection total* [*If extended stay (≥ 3 months) in area endemic for hepatitis A, repeat injection every 4-6 months]

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PA.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.PMN.53 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
AMS: aseptic meningitis syndrome
CIDP: chronic inflammatory demyelinating polyneuropathy
CLL: chronic lymphocytic leukemia
CMV: cytomegalovirus
DIF: dual inactivation plus nanofiltration
IG: immune globulin
IgA: immune globulin A
IM: intramuscular
IMIG: immune globulin (IM route)
ITP: immune thrombocytopenic purpura
IV: intravenous
IVIG: immune globulin (IV route)
MMN: multifocal motor neuropathy
NF: nanofiltered
PI: primary [humoral] immunodeficiency
SC: subcutaneous
SCIG: immune globulin (SC route)
S/D: solvent/detergent treated
VZIG: varicella zoster immune globulin
CVID: common variable immunodeficiency

Appendix B: Immune Globulin Products by FDA Labeled Route and Indication

Brand Name	Route			Indication							
	IV	SC	IM	PI	ITP	CIPD	Kawasaki	MMN	CLL	CMV	Hep A*
Bivigam	IV			x†							
Carimune NF	IV			x†	x†						
Cuvitru		SC		x§							
Cytogam	IV									x†	
Flebogamma DIF (5%)	IV			x†							
Flebogamma DIF (10%)	IV			x†	x†						
GamaSTAN S/D			IM								x‡
Gammagard Liquid	IV	SC		x ^				x†			
Gammagard S/D	IV			x†	x†		x†		x†		
Gammaked	IV	SC		x^	x†	x†					
Gammaplex	IV			x†	x†						
Gamunex-C	IV	SC		x^	x†	x†					
Hizentra		SC		x§							
Hyqvia		SC		x§							
Octagam 5%	IV			x†							
Octagam 10%	IV				x†						
Privigen	IV			x†	x†						

*****GamaSTAN also is approved for measles, rubella and varicella post-exposure prophylaxis
Route: †IV only; ^IV or SC; §SC only; ‡IM only

IV. Dosage and Administration

Refer to full prescribing information for specific dosage instructions. Dosage must be individualized and is highly variable depending on the nature and severity of the disease and

on the individual patient response. There is no absolute maximum dosage of immune globulin or hyaluronidase. See Appendix B for FDA labeled route and indication.

V. Product Availability

Drug	Availability
IV administration-Ready to use	
Bivigam (10%):	5, 10 gram single-use vials
Cytogam (5%)* *Contains a standardized amount of antibody to CMV (human)	2.5 gram single-use vial
Flebogamma DIF (5%)	0.5, 2.5, 5, 10, 20 gram single-use vials
Flebogamma DIF (10%)	5, 10, 20 gram single-use vials
Gammaplex (5%)	2.5, 5, 10, 20 gram single-use bottles
Octagam (5%)	1, 2.5, 5, 10, 25 gram single-use bottles
Octagam (10%)	2, 5, 10, 20 gram single-use bottles
Privigen (10%)	5, 10, 20, 40 gram single-use vials
IV administration-lyophilized powder for reconstitution	
Carimune NF	3, 6, 12 gram single-use vials
IV administration- Freeze dried for reconstitution	
Gammagard S/D	5%: 5 gram single-use bottle 10%: 10 gram single-use bottle
IV or SC administration-Ready to use	
Gammagard Liquid (10%)	1, 2.5, 5, 10, 20, 30 gram single-use bottles
Gammaked (10%)	1, 2.5, 5, 10, 20 gram single-use bottles
Gamunex-C (10%)	1, 2.5, 5, 10, 20, 40 gram single-use bottles
SC administration-Ready to use	
Cuvitru (20%)	1, 2, 4, 8 gram single-use vials
Hizentra (20%):	1, 2, 4, 10 gram single-use vials
Hyqvia (10%) IgG and 160 U/mL recombinant human hyaluronidase* *Hyaluronidase increases permeability of the local SC tissue for approximately 24 to 48 hours.	2.5g/200U, 5g/400U, 10g/800U, 20g/1600U, 30g/2400U dual-vial sets
IM administration-Ready to use	
GamaSTAN S/D (15-18%):	2 and 10 mL single-dose vials

VI. References

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Reviews, Revisions, and Approvals	Date	Approval Date