IMMUNE GLOBULIN THERAPY

▪ Injection (IGIM)
▪ Intravenous (IGIV)
▪ Subcutaneous (SCIG)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Immune globulin (IG), also known as immune serum globulin (ISG) or gamma globulin (GG), is an antibody-containing solution taken from donated human blood. Immune globulin contains antibodies to over 10 million antigens.

Injectable immune globulin (IGIM) is used to prevent infectious diseases following exposure and in the treatment of immunoglobulin deficiencies. Intravenous immune globulin, also known as IVIG or IGIV, is used to correct immune deficiencies in individuals with inherited or acquired immunodeficiencies. IVIG has also been investigated in diseases thought to have an autoimmune origin. Subcutaneous immune globulin (SCIG) is used for the treatment of primary immune deficiency.
IMMUNE GLOBULIN THERAPY (cont.)

Definitions:

Multiple sclerosis, relapsing/remitting:
Mix of acute attacks and stable periods

Criteria:

Injectable Immune Globulin (IGIM):

- IGIM is considered *medically necessary* for ANY of the following indications:
  1. Hypogammaglobulinemia
  2. Immunoglobulin deficiency (gamma globulin deficiency)
  3. Non-sensitized Rh negative pregnant women or following delivery (Rhogam®)
  4. To prevent infectious disease following exposure to ANY of the following:
     - Botulism
     - Hepatitis
     - Measles
     - Rabies
     - Rubella
     - Tetanus
     - Vaccinia (a derivative of small pox)
     - Varicella (VZIG)

- VariZIG® IGIM is considered *medically necessary* for ANY of the following indications:
  1. Following varicella zoster virus exposure in high-risk individuals with documentation of ANY of the following:
     - Immunocompromised individuals
     - Newborns of mothers with varicella shortly before or after delivery
     - Premature infants
     - Infants less than one year of age
     - Adults without evidence of immunity
     - Pregnant women

- IGIM for all other indications not previously listed or if above criteria not met is considered *experimental or investigational* based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome.
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

Subcutaneous Immune Globulin (SCIG):

- Subcutaneous Immune Globulin (SCIG) (Hizentra®, Gamunex®-C, Gammaked™ and Gammagard Liquid) replacement therapy is considered medically necessary for primary humoral immunodeficiency (PI) to include, but not limited to:

  1. Congenital agammaglobulinemia
  2. Common variable immunodeficiency (CVID)
  3. Severe combined immunodeficiencies (SCID)
  4. X-linked agammaglobulinemia (XLA)
  5. Wiskott-Aldrich syndrome
  6. Hypogammaglobulinemia

Hizentra and Gammagard Liquid are indicated for individuals 2 years of age and older (see package insert).

- SCIG for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

Intravenous Immune Globulin (IGIV, IVIG):

- IGIV is considered *medically necessary* for ANY of the following indications:

1. Primary immune deficiency syndromes, including combined immunodeficiencies, to include, *but not limited to*:
   - X-linked agammaglobulinemia (Bruton’s) immunodeficiency
   - X-linked hyper-IgM syndrome
   - Agammaglobulinemia, congenital
   - Severe combined immunodeficiency (SCID)
   - Wiskott-Aldrich syndrome
   - Ataxia telangiectasia
   - Hypogammaglobulinemia
   - Common variable immunodeficiency (CVID)

2. Acute humoral rejection
3. Autoimmune mucocutaneous blistering disease
   - Pemphigus
   - Pemphigoid
   - Pemphigus vulgaris
   - Pemphigus foliaceus
   - Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)

4. Autoimmune and inflammatory disorders
   - Dermatomyositis refractory to treatment with corticosteroids; in combination with other immunosuppressive agents
   - Kawasaki syndrome

5. Neuroimmunological
   - Myasthenia gravis in individuals with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of steroids and/or azathioprine
   - Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in individuals with contraindications to plasma exchange
   - Guillain-Barre syndrome
   - Chronic inflammatory demyelinating polyneuropathy (CIDP) in individuals with progressive symptoms for at least two months
   - Multifocal motor neuropathy
   - Eaton-Lambert myasthenic syndrome not responsive to anticholinesterase medications and/or corticosteroids
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

Intravenous Immune Globulin (IGIV, IVIG): (cont.)

- IGIV is considered *medically necessary* for ANY of the following indications: (cont.)

  6. Hematologic

  - Idiopathic Thrombocytopenic Purpura (ITP), acute, severe
    - Acute ITP with major bleeding, e.g., life-threatening bleeding and/or clinically important mucocutaneous bleeding
    - Acute ITP with severe thrombocytopenia and at high risk for bleeding complications
    - Acute ITP with severe thrombocytopenia and a slow or inadequate response to corticosteroids
    - Acute ITP with severe thrombocytopenia and a predictable risk of bleeding in the future, e.g., procedure or surgery with high bleeding risk

  - ITP, chronic of at least 6 months duration with persistent thrombocytopenia despite treatment with corticosteroids and splenectomy
  - Neonatal alloimmune thrombocytopenia
  - Bone marrow transplant
    - Prevention of graft-vs-host disease in bone marrow transplant
    - Prevention of infection in bone marrow transplant

  - B-cell chronic lymphocytic leukemia in individuals with hypogammaglobulinemia and/or recurrent bacterial infection
  - Warm antibody autoimmune hemolytic anemia refractory to corticosteroids and immunosuppressive agents
  - Anti-phospholipid syndrome
  - Severe anemia due to parvovirus B19
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

Intravenous Immune Globulin (IGIV, IVIG): (cont.)

- IGIV is considered *medically necessary* for ANY of the following indications: (cont.)

  7. Infectious diseases

- Prevention of infection in association with ANY of the following diagnoses:
  - Human Immunodeficiency Virus (HIV)
  - Toxic shock syndrome
  - Kawasaki disease
  - Primary defective antibody synthesis

  8. Transplantation

- Before solid organ transplant for treatment of an individual at high risk of antibody mediated rejection (AMR) including highly sensitized individuals and those receiving an ABO incompatible organ
- After solid organ transplant for treatment of antibody mediated rejection (AMR)

  9. Prevention

- Prevention of infection in preterm (<37 weeks’ gestational age) and/or low birth weight (<2500 g) neonates

  10. Multiple sclerosis, relapsing/remitting after failure of Avonex®, Copaxone® or similar drugs, or other drugs are contraindicated.
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

**Intravenous Immune Globulin (IGIV, IVIG):** (cont.)

Orphan drugs listed in the Facts & Comparisons drug resource are found in the Keeping Up section of that resource. Those that have been approved for marketing are denoted by the footnote a.

- IGIV for the following orphan drug uses may be reviewed and approved at the RN level of review with documentation that the drug is being used for treatment of **ONE** of the following:
  1. Polymyositis that is refractory to treatment (this does not include inclusion body myositis)
  2. Stiff person syndrome

- IGIV for all other indications not previously listed or if above criteria not met is considered **experimental or investigational** based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome.

These indications include, **but are not limited to:**

- Abortion, recurrent spontaneous
- Acquired factor VIII inhibitors
- Acute lymphoblastic leukemia
- Adrenoleukodystrophy
- Alzheimer's disease
- Aplastic anemia
- Asthma
- Autism
- Behcet syndrome
- Birdshot retinopathy
- Chronic fatigue syndrome
- Chronic sinusitis
- Complex regional pain syndrome (CRPS)
- Crohn disease
- Cystic fibrosis
- Demyelinating optic neuritis
- Demyelinating polyneuropathy associated with IgM paraproteinemia
- Diabetes mellitus
- Diamond-Blackfan anemia
- Epidermolysis bullosa acquisita
- Epilepsy
- Fisher syndrome
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

**Intravenous Immune Globulin (IGIV, IVIG):** (cont.)

- IGIV for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome.

These indications include, but are not limited to: (cont.)

- Hemolytic uremic syndrome
- Hemophagocytic syndrome i.e., hemophagocytic lymphohistiocytosis
- IGG subclass deficiency
- Immune-mediated neutropenia
- Inclusion-body myositis
- Morphea
- Multiple myeloma
- Myasthenia gravis in individuals responsive to immunosuppressive treatment
- Necrotizing fasciitis
- Nonimmune thrombocytopenia
- Opsoclonus-myoclonus
- Other vasculitides besides Kawasaki disease, including vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA; e.g., Wegener granulomatosis, polyarteritis nodosa), Goodpasture syndrome, and vasculitis associated with other connective tissue diseases
- Paraneoplastic syndromes, other than Eaton-Lambert myasthenic syndrome
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- Polyradiculoneuropathy other than chronic inflammatory demyelinating polyneuropathy (CIDP)
- Recent onset dilated cardiomyopathy
- Recurrent otitis media
- Red cell aplasia
- Refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus
- Scleroderma
- Sepsis including neonatal sepsis
- Thrombotic thrombocytopenic purpura
- Uveitis
IMMUNE GLOBULIN THERAPY (cont.)

Criteria: (cont.)

Botulism Immune Globulin Intravenous (BIG-IV), BabyBIG®:

- BabyBIG is considered medically necessary for treatment of individuals less than 1 year of age with infant botulism caused by toxin type A or B.

- BabyBIG for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

1 The safety and efficacy of BabyBIG has not been tested in other pediatric, adult, or geriatric populations.

Resources:


IMMUNE GLOBULIN THERAPY (cont.)

Resources: (cont.)


13. Drug Facts & Comparisons®. Hepatitis B Immune Globulin (HBIG); Immune Globulin (IGIM); Rho (D) Immune Globulin (Rho[D] IGIM); Tetanus Immune Globulin (TIG); Varicella-Zoster Immune Globulin (VZIG), 05/2001.


IMMUNE GLOBULIN THERAPY (cont.)

Resources: (cont.)

IMMUNE GLOBULIN THERAPY (cont.)

Resources: (cont.)


FDA Product Approval Information for BabyBIG:

- FDA-approved indication: For the treatment of patients below one year of age with infant botulism caused by toxin type A or B.

- FDA-approved dosage: The recommended total dosage of BabyBIG is 1 mL/kg (50 mg/kg), given as a single intravenous infusion as soon as the clinical diagnosis of infant botulism is made.

FDA Product Approval Information for Hizentra:

- FDA-approved indication: As replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
IMMUNE GLOBULIN THERAPY (cont.)

Resources: (cont.)

FDA Product Approval Information for Gammagard Liquid:

- FDA-approved indication: As replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age or older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies. Gammagard Liquid is indicated as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN).

FDA Product Approval Information for Gammaked, Gamunex-C:

- FDA-approved indication: As replacement therapy of primary humoral immunodeficiency. This includes, but is not limited to congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

For the treatment of patients with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.

For the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.
IMMUNE GLOBULIN THERAPY (cont.)

Resources: (cont.)

FDA Product Approval Information for VariZIG:

- FDA-approved indication: Post-exposure prophylaxis in high risk individuals. High risk groups include: immunocompromised children and adults, newborns of mothers with varicella shortly before or after delivery, premature infants, infants less than one year of age, adults without evidence of immunity, pregnant women. VariZIG is intended to reduce the severity of varicella.

VariZIG IGIM is contraindicated for ANY of the following indications:

1. History of anaphylactic or severe systemic reactions to human globulins
2. IgA-deficiency with antibodies against IgA and history of hypersensitivity

Administer VariZIG as soon as possible following varicella zoster virus (VZV) exposure, ideally within 96 hours for greatest effectiveness.

There is no convincing evidence that VariZIG reduces the incidence of chickenpox infection after exposure to VZV.

There is no convincing evidence that established infections with VZV can be modified by VariZIG administration.

There is no indication for the prophylactic use of VariZIG in immunodeficient children or adults when there is a past history of varicella, unless the individual is undergoing bone marrow transplantation.

Consider a second full dose of VariZIG for high risk individuals who have additional exposures to varicella greater than three weeks after initial VariZIG administration.

The passive transfer of antibodies with immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. Defer vaccination with live virus vaccines until approximately three months after VariZIG administration.