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Policy Number: C21554-A

Immunoglobulin (SCIg, IVIg) MHI

PRODUCTS AFFECTED

ASCENIV 10% Solution for Injection
BIVIGAM 10% Liquid
CUTAQUIG 16.5% Solution for Subcutaneous Infusion
CUVITRU 20% Solution for Subcutaneous Infusion
FLEBOGAMMA DIF 5% Solution for Injection
GAMMAGARD Liquid 10% Solution for Injection
GAMMAGARD S/D 5g, 10g Powder for Injection
GAMMAKED 10%
GAMMAPLEX 5% and 10%
GAMUNEX-C 10% Solution
HIZENTRA 20% Liquid for Subcutaneous
Infusion HYQVIA 10% Solution
OCTAGAM 5%, 10% Liquid Solution
PANZYGA 10% Liquid
PRIVIGEN 10% Liquid
XEMBIFY 20% Solution

COVERAGE POLICY

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

This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:

Primary Immune Deficiency, Acute Idiopathic Thrombocytopenic Purpura (ITP), Chronic Idiopathic Thrombocytopenic Purpura (ITP), ITP In Pregnancy, Autoimmune Hemolytic Anemia, Autoimmune Mucocutaneous Blistering Diseases, B-Cell Chronic Lymphocytic Leukemia (CLL), Chronic Inflammatory Demyelinating Polyneuropathy, Dermatomyositis, Polymyositis, Fetal Alloimmune Thrombocytopenia, Natal Alloimmune Thrombocytopenia, Neonatal Hemochromatosis Prophylaxis, Guillain- Barre Syndrome, Pediatric HIV, Adult HIV Associated Thrombocytopenia, Kawasaki Disease, Lambert-Eaton Myasthenia Syndrome, Multiple Myeloma, Multifocal Motor Neuropathy, Myasthenia Gravis, Post-Transfusion Purpura, Pure Red Blood Cell Aplasia Secondary to Chronic Parvovirus, Opsoclonus Myoclonus Syndrome, Rasmussen Syndrome, Stiff-Person Syndrome, Staphylococcal Or Streptococcal Toxic Shock Syndrome, Transplant (Solid Organ, Allogeneic Bone Marrow Transplant)

REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. ALL INDICATIONS:
   1. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Asceniv, Bivigam, Cutaquig, Cuvitru, Flebogamma, Gammagard, Gammagard S/D, Gammaplex, Gamunex-C, Octagam, Panzyga (immune globulin) include: History of anaphylactic or severe systemic reactions to human immunoglobulin, IgA deficient patients with antibodies against IgA and a history of hypersensitivity; Contraindications to Hizentra (immune globulin): Anaphylactic or severe systemic reaction to human immune globulin or inactive ingredients of Hizentra, such as polysorbate 80; Hyperprolinemia Type I or II (HIZENTRA contains stabilizer L-proline); IgA-deficient patients with antibodies against IgA and a history of hypersensitivity. Contraindications to Hyqvia (immune globulin) include: History of anaphylactic or severe systemic hypersensitivity reactions to Immune Globulin (Human); IgA deficient patients with antibodies against IgA and a history of hypersensitivity; Known systemic hypersensitivity to hyaluronidase including Recombinant Human Hyaluronidase of HYQVIA; Known systemic hypersensitivity to human albumin (in the hyaluronidase solution). Contraindications to Privigen (immune globulin) include: History of anaphylactic or severe systemic reaction to human immune globulin; Hyperprolinemia (PRIVIGEN contains the stabilizer L-proline); IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.
      AND
   2. Documentation of weight used for dosing (ideal body weight, actual body weight, adjusted body weight) or total grams or units prescribed/requested
      NOTE: If basis for dosing weight is not provided (ideal or actual or adjusted), calculate total approved dose/units based on ideal body weight [See Appendix]
      AND
   3. CONDITION SPECIFIC REQUIREMENTS [Listed Below]

B. PRIMARY IMMUNE DEFICIENCY [IVIG or SCIG]
   1. Documentation of a diagnosis of primary immune deficiency with supporting laboratory evidence of ONE (1) of the following [Documentation required]:
      i. Autosomal recessive agammaglobulinemia
      ii. Autosomal recessive hyperimmunoglobulin M syndrome (HIM)
      iii. Bruton's disease
      iv. Chronic mucocutaneous moniliasis (CMC) or Autoimmune polyendocrinopathy-candidiasis-

ectodermal dystrophy (APCED)
v. Combined immunodeficiency disorder: Ataxia-telangiectasia, DiGeorge syndrome, Nuclear factor κB essential modifier deficiency (NEMO), Nijmegan breakage syndrome, WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome, or Wiskott Aldrich syndrome
vi. Common variable immunodeficiency (CVID)
vii. Congenital hypogammaglobulinemia late onset, ICOS impaired
viii. Congenital / X-linked agammaglobulinemia
ix. Good syndrome (immunodeficiency with thymoma)
x. Hyperimmunoglobulinemia E syndrome
xi. Hypogammaglobulinemia
xii. ICF syndrome
xiii. Polyendocrinopathy and enteropathy (IPEX)
xiv. Selective IgG subclass deficiencies (persistent absence of IgG1, IgG2, and/or IgG3)
xv. Selective IgM deficiency
xvi. Severe combined immunodeficiency
xvii. Specific antibody deficiency
xviii. Transient hypogammaglobulinemia of infancy, short-term treatment of recurrent severe bacterial infections
xix. X-linked immunodeficiency with hyperimmunoglobulin M

AND

2. Laboratory documentation that members initial, pre-treatment, total serum IgG is below the lower limit of the age adjusted laboratory reference range, or more than two standard deviations below the age adjusted mean AND FOR X-linked agammaglobulinemia (Congenital agammaglobulinemia) ONLY: IgA, IgG and IgM levels below the normal range (>2 standard deviations below the age-specific mean) on at least two (2) occasions while the member is clear of infections. [DOCUMENTATION REQUIRED]
AND
3. Documentation that member has clinically significant functional deficiency of humoral immunity as defined by ONE (1) of the following:
    i. Failure to produce antibodies to specific antigens (e.g., lack of or inadequate response to immunizations)
    OR
    ii. History of significant recurrent or persistent bacterial infections (such as recurrent pneumonias, frequent episodes of bacterial infections such as sinusitis, otitis, bronchitis, skin structure infections, or infections of the gastrointestinal tract) or infections that fail to respond adequately to prophylactic antibiotic therapy

AND

4. For Common variable immunodeficiency (CVID), or Unspecified hypogammaglobulinemia ONLY, documentation of the following:
    i. Lack of, or inadequate response to immunization (for example, but not limited to tetanus or pneumococcal antigen)
    AND
    ii. Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been identified and treated aggressively if present

AND

5. Prescriber attestation that there is no evidence of renal (nephrotic syndrome) and gastrointestinal (for example, protein losing enteropathy) causes of hypogammaglobulinemia
AND
6. FOR SUBCUTANEOUS IMMUNOGLOBULIN (SCIG): Documentation that member has been receiving intravenous immune globulin treatment at regular intervals for at least 3 months, OR provider attests member is unable to be established on a dose with IVIG and requires a subcutaneous formulation. [Documentation Required].
AND
7. Quantity Limitation:

IVIG Quantity Limitation: 300-800 mg/kg every 3 to 4 weeks
SCIG Quantity Limitation: weekly dosing in accordance with FDA labeling for product (Note: Initial dosing based on previous IVIG dose)

C. CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) OR POLYRADICULOPATHY [IVIG or Hizentra SCIG ONLY]
1. Documentation of a diagnosis of CIPD with symmetric or focal neurologic deficits with slowly progressive or relapsing course over 8 weeks or longer with neurophysiological abnormalities AND
2. Documentation of member's baseline strength and weakness (and current strength and weakness for continuation requests) documented using an objective clinical measuring tool (e.g. INCAT, MRC, 6- minute timed walking test, Rankin, Modified Rankin), which will be used to monitor member's response to therapy for reauthorization. [DOCUMENTATION REQUIRED] AND
3. Documentation that member has met one of the following clinical/electro-diagnostic criteria [DOCUMENTATION REQUIRED]:
    i. Electrodiagnostic evidence of demyelinating neuropathy in at least two limbs, resulting in muscle weakness or sensory dysfunction confirmed by nerve conduction studies (NCS); OR
    ii. Results of diagnostic testing meet a recognized set of diagnostic criteria as established by the American Academy of Neurology (AAN), Inflammatory Neuropathy Cause and Treatment (INCAT), or EFNS/PNS guideline

    AND
4. FOR HIZENTRA SUBCUTANEOUS IMMUNOGLOBULIN (SCIG): Documentation that member has been receiving intravenous immune globulin treatment at regular intervals for at least 3 months [DOCUMENTATION REQUIRED] AND
5. Quantity limitation:
    IVIG: Loading dose: 2,000 mg/kg in divided doses over 2 to 5 consecutive days (e.g., 400 mg/kg once daily for 5 days); maintenance 1g/kg administered in 1 or 2 infusions on consecutive days every 3 weeks
    SCIG (HIZENTRA): 0.2 g/kg – 0.4 g/kg weekly
    Note: Per package labeling, if CIDP symptoms worsen while on 0.4 g/kg Hizentra weekly, consider re-initiating IVIG and discontinuing Hizentra.

D. ACUTE IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) [IVIG ONLY]
1. Documentation of a diagnosis of ITP with a duration of illness of *less* than 6 months AND
2. Prescriber attestation that member does not have a concurrent illness or disease which explains the thrombocytopenia, including diseases known to be associated with "secondary" thrombocytopenia. AND
3. Documentation that member meets one of the following [DOCUMENTATION REQUIRED]:
    i. Member has severe thrombocytopenia (platelet counts less than 20,000/mm^3) and is considered to be at risk for intracerebral hemorrhage
    OR
    ii. A rapid increase in platelet count is necessary to correct thrombocytopenia prior to major, invasive surgical procedures and platelet count is less than 100,000/mm^3
    OR
    iii. ADULTS ONLY: Platelet counts remain persistently at, or below, 30,000/mm^3 despite prior treatment with corticosteroids or splenectomy

    AND
4. Quantity Limitations: 2000 mg/kg divided over 2-5 days; No reauthorization

Reviewer Note: NOTE: Rho(D) immune globulin is not necessarily recommended or preferred in place of IVIg; however, may be utilized instead in Rho(D) positive, non-splenectomized patients, with a negative direct antiglobulin test (DAT)

E. CHRONIC IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) [IVIG ONLY]

1. Documentation of a diagnosis of ITP with a duration of illness of *greater* than or equal to 6 months
   AND
2. Prescriber attestation that member does not have a concurrent illness or disease which explains the thrombocytopenia, including diseases known to be associated with "secondary" thrombocytopenia.
   AND
3. Documentation that member meets one of the following [DOCUMENTATION REQUIRED]:
   i. Member has platelet counts persistently at or below 20,000/mm^3
      OR
   ii. Member has a platelet count less than 30,000/mm^3 whose degree of thrombocytopenia and clinical condition(s) increase the risk of bleeding (e.g. hypertension, renal insufficiency, concomitant antiplatelet agents or anticoagulant medications, alcoholism, infections, undergoing a medical or dental procedure with blood loss anticipation, recent surgery, head trauma)

   AND
4. Documentation that member has had a documented failure, intolerance, or contraindication to one of the following: (i) corticosteroids [e.g. prednisone, dexamethasone] OR (ii) splenectomy
   AND
5. Quantity Limitations: 2000 mg/kg divided over 2-5 days, every 2 to 6 weeks depending on platelet count.

F. ITP IN PREGNANCY [IVIG ONLY]

1. Documentation that member is currently pregnant and meets one of the following [DOCUMENTATION REQUIRED]:
   i. Member has a platelet count less than 30,000/mm^3 or clinically relevant bleeding is present
      OR
   ii. Platelet count less than 50,000/mm^3 prior to labor and delivery (36 weeks gestation or sooner if delivery is imminent)
      OR
   iii. Previously delivered infants with autoimmune thrombocytopenia
      OR
   iv. Past history of a splenectomy

   AND
2. Quantity Limitations: 2000 mg/kg divided over 2-5 days, every 2 to 6 weeks until delivery

G. AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) [IVIG ONLY]

1. Documentation of a diagnosis of warm-type autoimmune hemolytic anemia confirmed by detection of antibody and/or complement components on the surface of the red blood cell, such as the **direct** antiglobulin (Coombs) test [DOCUMENTATION REQUIRED]
   AND
2. Documentation of an inadequate response, intolerance, or contraindication both corticosteroids and rituximab.
   AND
3. Quantity Limitation: 500 mg/kg once daily for 4 days or 1 g/kg once daily for 2 days

H. AUTOIMMUNE MUCOCUTANEOUS BLISTERING DISEASES (AMBDs) [IVIG ONLY]
1. Documentation of a diagnosis of one of the following AMBDs confirmed by biopsy [DOCUMENTATION REQUIRED]: i. Bullous pemphigoid; ii. Epidermolysis Bullosa Acquisita (EBA); iii. Mucous membrane pemphigoid (also referred to as Cicatrical Pemphigoid); iv. Pemphigus Foliaceus; or v. Pemphigus Vulgaris
AND
2. Prescriber attestation that immunoglobulin has been prescribed for short term therapy only (not as long-term maintenance therapy).
NOTE: Regular use of repeated courses of IVIg for a continuous cycle of exacerbation and remission constitutes maintenance therapy. IVIg should be given with conventional treatment(s)and used only until conventional therapy can take effect.
AND
3. A. Documentation of an inadequate response, intolerance, or contraindication both corticosteroids (i.e. prednisone, prednisolone, methylprednisolone) AND immunosuppressive agents (e.g., azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil) [DOCUMENTATION REQUIRED]
OR
B. Documentation that use of systemic corticosteroids and immunosuppressive agents are inappropriate due to rapid, debilitating or progressive disease severity [DOCUMENTATION REQUIRED]
NOTE: Contraindications to systemic corticosteroids: existing diabetes, clinically significant osteoporosis, fractures, upper GI bleeding, posterior subcapsular cataracts, pseudotumor cerebri, bone marrow suppression, aplastic anemia, clinically significant psychological changes, steroid myopathy, glaucoma
NOTE: Contraindications to immunosuppressive agents: significant persistent anemia, clinically significant neutropenia, clinically significant abnormal hepatic function, clinically significant impaired renal function, hemorrhagic cystitis, clinically significant bone marrow suppression, history of malignancy
AND
4. Quantity Limitation: 2,000 mg/kg in divided doses (2- 5 days) every 30 days

I. B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) [IVIG ONLY]
1. Documentation that member has a diagnosis of B-cell Chronic Lymphocytic Leukemia (CLL)
AND
2. Documentation that member has hypogammaglobulinemia, with IgG level less than 500 mg/dL [DOCUMENTATION REQUIRED]
AND
3. Documentation that member has had recurrent (two) bacterial infections in the previous 12 months OR one severe bacterial infection in the previous 6 months which were associated with B-cell CLL AND
4. Quantity Limitation: 600 mg/kg every 3 to 4 weeks

J. DERMATOMYOSITIS OR POLYMYOSITIS [IVIG ONLY]
1. Documentation of a diagnosis of dermatomyositis or polymyositis confirmed by positive biopsy
AND
2. Prescriber attestation that member has severe active disease with muscle weakness in all upper and/or lower limbs
AND
3. Documentation of member's baseline physical examination, including an objective measure, such as CPK or EMG, which can be used to assess objective response to therapy. [DOCUMENTATION REQUIRED].
AND
4. A. Documentation of an inadequate response, intolerance, or contraindication both corticosteroids (i.e., prednisone, prednisolone, methylprednisolone) AND immunosuppressive agents (e.g., azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil)

[DOCUMENTATION REQUIRED] OR
B. Documentation that use of systemic corticosteroids and immunosuppressive agents are inappropriate due to rapid progressive or potentially life-threatening muscular weakness refractory to prior therapy. [DOCUMENTATION REQUIRED]
AND

5. Quantity Limitation: Loading dose: 2000 mg/kg; maintenance dose 500-1000 mg/kg every 30 days

K. FETAL OR NATAL ALLOIMMUNE THROMBOCYTOPENIA (FAIT/NAIT) [IVIG ONLY]
1. Documentation of a diagnosis of Neonatal alloimmune thrombocytopenia (NAIT) or fetal alloimmune thrombocytopenia (FAIT)
AND
2. For fetal autoimmune thrombocytopenia: Documentation the member meets ONE of the following [DOCUMENTATION REQUIRED]:
    i. Member has a history of previous pregnancy affected by FAIT (previously delivered infants with autoimmune thrombocytopenia)
    OR
    ii. Member is 20 weeks gestation or later and cordocentesis reveals fetal platelets less than20,000/ mm3; or screening reveals platelet alloantibodies

OR

3. For neonatal alloimmune thrombocytopenia (NAIT): Documentation that member meets ALL of the following [DOCUMENTATION REQUIRED]:
    i. Member is severely thrombocytopenic (i.e. platelet count less than 30,000/mm3) and/or symptomatic
    AND
    ii. Neonate failed, has a contraindication to, or is intolerant to platelet transfusions

AND

4. Quantity Limitation: FAIT: 1000 mg/kg (starting) -2000 mg/kg (max dose for refractory cases) weekly until delivery; NAIT: 1000 mg/kg per dose, for up to 2 doses

L. GUILLAIN-BARRE SYNDROME (GBS) [IVIG ONLY]
1. Documentation of a diagnosis of Guillain-Barré Syndrome (GBS) [also referred to as Acute Inflammatory Demyelinating Polyneuropathy (AIDP)] [DOCUMENTATION REQUIRED]
AND
2. Documentation that member has functional disability due to Severe GBS [defined as having significant weakness such as inability to walk or stand without aid, respiratory weakness or bulbar weakness] or Miller-Fisher Syndrome (MFS)
AND
3. Prescriber attestation that IVIg will not be used concomitantly with plasmapheresis
AND
4. Documentation that IVIg therapy is being initiated within 2 weeks, and no longer than 4 weeks, of onset of neuropathic symptoms
AND
5. Quantity Limitation: 2000 mg/kg divided over 2 to 5 days

M. PEDIATRIC HIV [IVIG ONLY]
1. Documentation that member has a diagnosis of HIV
AND
2. Member is currently age 13 or younger
AND
3. Prescriber attestation (or pharmacy claims supporting) that member is currently using highly active antiretroviral therapy (HAART) for HIV
AND

4. Member meets ONE of the following [DOCUMENTATION REQUIRED]:
    i. Hypogammaglobulinemia (pretreatment serum IgG less than 400 mg/dL) AND Recurrent serious bacterial infections defined as two (2) or more infections such as bacteremia, meningitis, or pneumonia in a 1-year period
    OR
    ii. Member failed to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine
    OR
    iii. Member resides in areas where measles is highly prevalent and has not developed an antibody response after TWO doses of measles, mumps, and rubella virus vaccine
    OR
    iv. Member has chronic bronchiectasis that is sub-optimally responsive to antimicrobial and pulmonary therapy

    AND
5. Quantity Limitation: 400 mg/kg every 2 to 4 weeks

N. ADULT HIV ASSOCIATED THROMBOCYTOPENIA [IVIG ONLY]
1. Documentation of a diagnosis of HIV associated thrombocytopenia
    AND
2. Documentation that member has a platelet count less than 20,000/µL OR has clinically significant bleeding [DOCUMENTATION REQUIRED]
    AND
3. Prescriber attestation (or pharmacy claims supporting) that member is currently using combination antiretroviral therapy for HIV
    AND
4. For Rh-positive members, documentation of a failure of RhIg
    AND
5. Quantity Limitation: 1000 mg/kg daily for 2 days

O. KAWASAKI DISEASE (MUCOCUTANEOUS LYMPH NODE SYNDROME) [IVIG ONLY]
1. Documentation of a diagnosis of Kawasaki Disease or Incomplete (Atypical) Kawasaki Disease defined as having FOUR of the following 5 symptoms [DOCUMENTATION REQUIRED]:
    i. Mucous membrane changes such as strawberry tongue and dry fissured lips without discrete lesions
    ii. Changes in the extremities such as edema 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

    AND
2. Documentation that member has had a fever which has persisted for at least 5 days
    AND
3. Prescriber attestation that treatment is being initiated within ten days of fever onset OR that member has been diagnosed after ten days of onset and the member continues to exhibit manifestations of inflammation or evolving coronary artery disease.
    NOTE: The effectiveness of IVIg therapy is best established for patients treated within the first 7to 10 days of illness. The AHA and AAP guidelines recommend that IVIg be administered to children with KD within the first 10 days of illness, and if possible, within the first seven days
    of illness.
    AND
4. Prescriber attestation that concomitant aspirin will be given with immune globulin
    AND

5. Prescriber attestation that other diseases with similar findings have been excluded including:
    i. Viral infections (i.e., measles, adenovirus, enterovirus, Epstein-Barr virus)
    ii. Scarlet fever
    iii. Staphylococcal scalded skin syndrome
    iv. Toxic shock syndrome
    v. Bacterial cervical lymphadenitis
    vi. Drug hypersensitivity reactions
    vii. Stevens-Johnson syndrome
    viii. Juvenile rheumatoid arthritis
    ix. Rocky Mountain spotted fever
    x. Leptospirosis
    xi. Mercury hypersensitivity reaction (acrodynia)

AND

6. Quantity Limitation: 2000 mg/kg, which may be administered as a single dose or divided over 5 days

P. LAMBERT-EATON MYASTHENIA SYNDROME (LEMS) [IVIG ONLY]

1. Documentation of a diagnosis of Lambert-Easton Myasthenia Syndrome (LEMS) which has been confirmed by electro-physiologic studies
AND
2. Documentation that member has impaired function (e.g., inability to stand or walk without an aid) which has been measured by a standard clinical scale (e.g. Activities of Daily Living Score, quantitative muscle scores, or Medical Research Council Muscle Assessment) or objective findings based on initial therapy. NOTE: Improvement in objective muscle function/strength is required for reauthorization. [DOCUMENTATION REQUIRED]
AND
3. Documentation that member has had a trial with lack of response or has a contraindication or intolerance to ALL of the following:
    i. Acetylcholinesterase inhibitors (e.g., Mestinon)
    ii. Immunosuppressants (e.g., corticosteroids, azathioprine)
    iii. Dalfampridine or amifampridine (Firdapse/Ruzurgi)

AND

4. Provider attestation that immune globulin is needed as an alternative to plasma exchange due to severe weakness or difficulty with venous access for plasmapheresis
AND
5. Quantity Limitation: 2000 mg/kg, which may be administered over 2 to 5 days every 4 to 8 weeks

Q. MULTIPLE MYELOMA [IVIG ONLY]

1. Documentation that member has a diagnosis of multiple myeloma and is at high risk for recurrent infections as defined by ONE of the following [DOCUMENTATION REQUIRED]:
    i. IgG level less than 600 mg/dL and two (2) or more bacterial infections in the preceding year requiring IV antibiotic infusion therapy in the home or in the hospital
    OR
    ii. IgG level less than 600 mg/dL and member has had a life-threatening, laboratory proven bacterial infection in the previous 6 months
    OR
    iii. IgG less than 400 mg/dL with recurrent infections OR
    iv. Member failed to mount an appropriate IgG humoral immune response on challenge with pneumococcal vaccine

AND

2. Documentation that member is in a stable, plateau phase of the disease AND the member is not undergoing induction chemotherapy or experiencing a relapse

AND

3. Quantity Limitation: 200-400 mg/kg, administered every 4 to 6 weeks

R. MYASTHENIA GRAVIS [IVIG ONLY], ACUTE myasthenic crisis, Myasthenic Exacerbation:
1. Documentation of a diagnosis myasthenia gravis confirmed by positive serologic test for anti- acetylcholine receptor (AchR) antibodies [DOCUMENTATION REQUIRED]
NOTE: Due to its specificity, testing for autoantibodies against the acetylcholine receptor (AChR-Ab) should be performed on all patients. Demonstration of binding antibodies, possible in approximately 85 percent of patients with generalized disease, provides the laboratory confirmation of myasthenia gravis. In select patients, assays for blocking and modulating antibodies may also be helpful. If the AChR-Abs are negative, an assay for antibodies to muscle-specific tyrosine kinase (MuSK) should be performed.
AND
2. Documentation that IVIg has been prescribed for the treatment of an ACUTE myasthenic crisis in member experiencing disease exacerbation and/or decompensation (e.g., difficulty swallowing, acute respiratory failure, major functional disability responsible for the discontinuation of physical activity; of physical activity, disabling weakness requiring hospital admission) [DOCUMENTATION REQUIRED]
AND
3. Documentation that member meets ONE of the following:
    i. Member is currently receiving immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine) for long-term management of myasthenia gravis
    OR
    ii. Member has had a trial and failure of, or contraindication to BOTH:
    a. Plasma Exchange AND
    b. Immunomodulator therapy (e.g., corticosteroids, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, cyclophosphamide)
AND
4. Quantity Limitation: 2000 mg/kg divided over 2 to 5 days (one course), One course per month for up to 3 months

S. MULTIFOCAL MOTOR NEUROPATHY (MMN) [IVIG ONLY]
1. Documentation of a diagnosis of ***progressive, symptomatic*** multifocal motor neuropathy (as characterized by limb weakness or motor involvement having a motor nerve distribution in at least two nerves)
AND
2. Prescriber attestation that electrophysiological findings have ruled out other possible conditions that may not respond to IVIg.
AND
3. Documentation of member's baseline strength and function documented using an objective clinical measuring tool (e.g., INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin). NOTE: Improvement in objective strength or function is required for reauthorization. [DOCUMENTATION REQUIRED]
AND
4. Quantity Limitation: 2000 mg/kg once monthly, which may be administered over 2 to 5 days

T. NEONATAL HEMOCHROMATOSIS, PROPHYLAXIS [IVIG ONLY]
1. Documentation that member is pregnant and has a history of a pregnancy ending with neonatal hemochromatosis [DOCUMENTATION REQUIRED]
AND
2. Quantity Limitation: 1000 mg/kg weekly until delivery (usually from the 18th week until the end of gestation

U. POST-TRANSFUSION PURPURA (PTP); HEMOLYTIC TRANSFUSION REACTION [IVIG ONLY]
1. Documentation of a diagnosis of post-transfusion purpura or hemolytic transfusion reaction
AND
2. Laboratory documentation of decreased platelet count (generally less than 20,000/mm3) [DOCUMENTATION REQUIRED]
AND
3. Documentation that member is 2 to 14 days post-transfusion with bleeding due to thrombocytopenia
AND
4. Quantity limit: 500 mg/kg divided for 2 to 5 days (one course) OR 1000 mg/kg daily for 2 days

V. PURE RED BLOOD CELL APLASIA (PRCA)- Secondary to Chronic (persistent) Parvovirus B19 Infection [IVIG ONLY]
1. Documentation of a diagnosis of Pure Red Blood Cell Aplasia (PRCA) secondary to parvovirus B19 infection
AND
2. Laboratory documentation of severe anemia [Hemoglobin less than 10 or Hematocrit less than 30] associated with bone marrow suppression due to CHRONIC parvovirus [DOCUMENTATION REQUIRED]
AND
3. Documentation that member has a CHRONIC immunodeficient condition (e.g., HIV infection, solid organ transplants [e.g., renal, liver], chemotherapy for hematologic malignancy)
NOTE: Chronic parvovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parvovirus and anemia may spontaneously resolve.
AND
4. Quantity Limitation: 2000-4000 mg/kg divided over up to 10 days, one course per month

W. OPSOCLONUS MYOCLONUS SYNDROME (OMS) [IVIG ONLY]
1. Documentation of a diagnosis opsoclonus myoclonus
AND
2. Documentation that member meets ONE of the following [DOCUMENTATION REQUIRED]:
    i. Member is younger than 18 years of age and has had a clinical assessment which indicates significant disability, as measured by an objective clinical score (i.e., the Cerebellar Functional System Score with a value of at least 2 points)
    NOTE: As there is no validated measure for OMS, the Cerebellar Functional System Score has been selected from the Expanded Disability Status Scale (Kurtzke 1983).
    OR
    ii. Member is 18 years of age and older and has had [BOTH]:
        a. A trial and failure of or contraindication to a standard course of corticosteroid therapy
        AND
        b. Clinical assessment which demonstrates disability, as measured by an objective clinical score (i.e. the Cerebellar Functional System Score with a value of at least 2 points)
AND
3. Quantity Limitation: Recommended dose 1000 mg/kg once monthly, which may be administered over 2 to 5 days; Maximum dose: 2000 mg/kg once monthly, which may be administered over 2 to5 days

X. RASMUSSEN SYNDROME (RS); CHRONIC FOCAL ENCEPHALITIS [IVIG ONLY]
1. Documentation that member has a diagnosis of Rasmussen Syndrome, which is also known as Rasmussen Encephalitis (RE) or Chronic Focal Encephalitis [DOCUMENTATION REQUIRED]

AND

2. Documentation that member has had intractable focal motor seizures and progressive neurologic deterioration (dementia, hemiparesis)
   AND
3. Documentation of a trial and failure of or contraindication to both antiepileptic drugs and corticosteroids
   AND
4. Prescriber attestation that IVIg has been prescribed for short-term amelioration of encephalitis prior to definitive surgical therapy
   NOTE: IVIg is not recommended for long-term therapy for Rasmussen's encephalitis as surgical treatment is the current standard of care. Requests for continuation of therapy beyond 3 months requires review and determination by a Medical Director.
   AND
5. Quantity Limitation: 2000 mg/kg once monthly, which may be administered over 2 to 5 days

Y. STIFF-PERSON SYNDROME (MOERSCH-WOLTMANN SYNDROME) [IVIG ONLY]

1. Documentation of a diagnosis of Stiff-Person Syndrome (Moersch-Woltmann Syndrome) by supportive testing including EMG findings, anti-glutamic acid decarboxylase antibodies, and/or anti- amphiphysin antibodies [DOCUMENTATION REQUIRED]
   AND
2. Documentation of member's baseline physical exam indicating that member has significant disability as measured by an objective scale: Functional Assessment ADL, Modified Rankin Score and a Distribution of Stiffness Index Score [DOCUMENTATION REQUIRED]
   NOTE: Improvement from baseline score is required for reauthorization.
   AND
3. Documentation of a history of failure, contraindication or intolerance to conventional therapy to at least two (2) of the following treatments: benzodiazepines, baclofen, phenytoin, clonidine and/or tizanidine
   AND
4. Quantity Limitation: 2000 mg/kg once monthly [typically administered in 2 or 3 infusions separated by three to five days]

Z. STAPHYLOCOCCAL OR STREPTOCOCCAL TOXIC SHOCK SYNDROME (TSS) [IVIG ONLY]

1. Documentation that member has a severe, life-threatening case of streptococcal or staphylococcal TSS [DOCUMENTATION REQUIRED]
   AND
2. Documentation that member has failed to achieve rapid improvement with antibiotic therapy and other supportive measures (fluids, inotropes, vasopressors)
   AND
3. Documentation that member meets any ONE of the following:
   i. Member has an infection that is refractory to several hours of aggressive therapy
      OR
   ii. Member has an undrainable focus
      OR
   iii. Member has persistent oliguria with pulmonary edema

   AND
4. Quantity Limitation: 2000 mg/kg administered in divided dose over 5 days

AA. SOLID ORGAN TRANSPLANT [IVIG ONLY]

NOTE: For Cytogam see Cytogam (cytomegalovirus immune globulin) MHI Policy Number C9970-A

1. Documentation that member has had or has a planned solid organ transplant meeting ONE of

the following [DOCUMENTATION REQUIRED]:

i. IVIg is prescribed PRIOR to solid organ transplant for prevention of acute rejection (pre- and peri-operative): or prevention of antibody-mediated rejection prior to solid organ transplant, or in the peri-operative period, for patients at high-risk for antibody-mediated rejection [including highly sensitized patients, and those receiving an ABO-incompatible organ]
OR

ii. IVIg is prescribed POST solid-organ transplant for the treatment of antibody-mediated (humoral) rejection following solid organ transplant confirmed by either biopsy or presence of panel reactive antibodies (PRAs), if used in combination with plasmapheresis

AND

2. Documentation of date of solid-organ transplant or anticipated transplant date
AND
3. FOR POST solid-organ transplant that are 100 days or more post-transplant, documentation of an IgG value less than 400 mg/dL or a documented CMV, EBV or RSV infection [DOCUMENTATION REQUIRED]
AND
4. For requests prior to kidney transplant only: Documentation that IVIg is prescribed for member with high levels of "anti-donor" antibodies [i.e., patients highly sensitized to the tissue of the majority of living or cadaveric donors because of "non-self" human leukocyte antigen (HLA) or ABO incompatibility].
NOTE: To reduce the risk of acute antibody-mediated rejection, IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies. A (The National Advisory Committee on Blood and Blood Products and Canadian Blood Services, 2010)
AND
5. Quantity Limitations:
Post-Transplant Acute Rejection: 2000 mg/kg (up to 140 grams in a single dose); One dose per rejection episode, 14 days
Prior to Transplant, prevention:100-500 mg/kg; Four (4) doses prior to and four (4) doses following transplant, maximum of 8 total doses (2000 mg/kg total per 8-week period). If used with plasma exchange: total maximum dose of 2000 mg/kg per 4-week period, which may be given in divided doses.

BB. ALLOGENEIC BONE MARROW TRANSPLANT (BMT)/ HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) [IVIG ONLY]
NOTE: For Cytogam see Cytogam (cytomegalovirus immune globulin) MHI Policy Number C9970-A

1. Documentation that member has had **ALLOGENEIC** (not autologous) Bone Marrow Transplant (BMT)/Hematopoietic Stem Cell Transplantation (HSCT)
NOTE: Routine use of IVIg among autologous recipients is not recommended, according to the Centers for Disease Control and Prevention.
AND
2. Documentation that IVIg is prescribed for prophylaxis of acute graft vs. host disease (GVHD) OR prophylaxis treatment against infection (i.e., cytomegalovirus)
AND
3. Documentation that member meets ONE of the following [DOCUMENTATION REQUIRED]:

i. Member in within the first 100 days post-transplant OR

ii. Member is greater than 100 days post-transplant AND has a pre-treatment serum IgG less than 400mg/dL

AND
4. Quantity limitation:

i. Less than 100 days post-transplant: 500 - 600 mg/kg/week until member reaches 90 days post-transplant
OR
ii. Greater than 100 days: 500 mg/kg/month until member reaches 360 days post- transplant

CONTINUATION OF THERAPY:

A. ALL LISTED INDICATIONS: PRIMARY IMMUNE DEFICIENCY, ALLOGENEIC BONE MARROW TRANSPLANT (BMT)/ HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT), AUTOIMMUNE HEMOLYTIC ANEMIA CHRONIC ITP, B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA, CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY, DERMATOMYOSITIS/POLYMYOSITIS, HIV-PEDIATRIC, LAMBERT- EATON MYASTHENIA SYNDROME, MULTIPLE MYELOMA, MULTIFOCAL MOTOR NEUROPATHY, MYASTHENIA GRAVIS, OPSOCLONUS MYOCLONUS SYNDROME, PURE RED BLOOD CELL APLASIA (PRCA)/PARVOVIRUS,STIFF-PERSON SYNDROME
   1. Prescriber attests to or clinical reviewer has found no evidence intolerable adverse effects or drug toxicity
      AND
   2. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms and clinical endpoints
      AND
   3. Documentation of annual review summary and/or immunological evaluation AND
   4. Prescriber attestation that the dose and frequency of immunoglobulin treatment have been titrated to the minimum dose and/or frequency to maintain the appropriate clinical outcome
      AND
   5. After 12 months of therapy and annually thereafter, prescriber attests that cessation of IVIg has been attempted and caused the condition to worsen or that cessation of therapy is medically contraindicated, or cessation of therapy is not appropriate for the disease state
      AND
   6. Documentation of weight used for dosing (ideal body weight, actual body weight, adjusted body weight) or total grams or units prescribed/requested
      NOTE: If basis for dosing weight is not provided (ideal or actual or adjusted), calculate total approved dose/units based on ideal body weight [See Appendix]
      AND
   7. CONDITION SPECIFIC REQUIREMENTS [Listed Below]

B. PRIMARY IMMUNE DEFICIENCY [IVIG or SCIG]
   1. Documentation of current IgG levels that are in the low to normal range and evidence of clinical improvement, such as reduction of the number and severity of clinical infections [DOCUMENTATION REQUIRED]

C. ALLOGENEIC BONE MARROW TRANSPLANT (BMT)/ HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) [IVIG ONLY]
   1. Documentation the member is 100 days or greater post-transplant and has a pre-treatment IgG less than 400 mg/Dl [DOCUMENTATION REQUIRED]
      AND
   2. Documentation that member is NOT beyond 360 days post-transplant

D. AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) [IVIG ONLY]
   1. Documentation of initial response and recurrence of clinically significant, symptomatic anemia [DOCUMENTATION REQUIRED]

E. B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) [IVIG ONLY]
   1. Documentation of positive clinical response as demonstrated by a reduction in the frequency of bacterial infections since the initiation of IVIG therapy [DOCUMENTATION REQUIRED]

F. CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) OR POLYRADICULOPATHY [IVIG or Hizentra SCIG ONLY]
   1. Documentation of a positive response to therapy as measures by an objective clinical measuring tool, compared to baseline: INCAT, MRC, 6-minute timed walking test, Rankin, or Modified Rankin [DOCUMENTATION REQUIRED]

G. CHRONIC ITP [IVIG ONLY]
   1. Documentation of positive clinical response to therapy as evidenced by increase in platelet count to a level sufficient to avoid clinically important bleeding, OR increase or achievement of platelet count to at least ≥ 50,000/mm^3 [DOCUMENTATION REQUIRED]

H. DERMATOMYOSITIS OR POLYMYOSITIS [IVIG]
   1. Documentation of improvement in ONE (1) objective measure, compared to baseline: serum Creatine Kinase (CK) levels, muscle strength, electromyography testing, and/or improvement in rash (for dermatomyositis indication) [DOCUMENTATION REQUIRED]

I. LAMBERT-EATON MYASTHENIA SYNDROME (LEMS) [IVIG ONLY]
   1. Documentation of improvement or stabilization in muscle function/strength as demonstrated by one of the following standard clinical scales: a. Functional scores of Activities of Daily Living (ADL) or Quantitative Muscle Scores or Medical Research Council (MRC) muscle assessment [DOCUMENTATION REQUIRED]

J. MULTIPLE MYELOMA [IVIG ONLY]
   1. Documentation that member has had an annual clinical and immunological evaluation [DOCUMENTATION REQUIRED]

K. MULTIFOCAL MOTOR NEUROPATHY (MMN) [IVIG ONLY]
   1. Documentation of clinical improvement in strength and function within three weeks of the start of the infusion period. Prescriber submit current strength and function report using an objective clinical measuring tool (e.g. INCAT, MRC, 6-minute timed walking test, Rankin, Modified Rankin) [DOCUMENTATION REQUIRED]
      AND
   2. Documentation that based on neurology evaluation that IVIg at the requested dose and interval are medically necessary and that attempts to reduce the dose, or the interval, has resulted in worsening of symptoms.

L. MYASTHENIA GRAVIS [IVIG ONLY], ACUTE myasthenic crisis, Myasthenic Exacerbation:
   1. Documentation that member has had a myasthenic exacerbation documented by at least one of the following symptoms within the recent 30 days: difficulty swallowing, acute respiratory failure, major functional disability responsible for the discontinuation of physical activity; of physical activity, disabling weakness requiring hospital admission (not an all-inclusive list) [DOCUMENTATION REQUIRED]
      - *Maintenance IVIg or plasma exchange: Periodic administration of IVIg or plasma exchange is sometimes used to maintain remission in patients with MG that is not well controlled despite the use of chronic immunomodulating drugs. There are no studies comparing this strategy with other options for refractory disease, however, maintenance IVIg has been noted as necessary and useful in some patients when other strategies have failed (Bird, SJ. 2019).*

- *There are no data from RCTs regarding the value of IVIg as maintenance therapy in MG, either alone or as add-on therapy to IS agents. IVIg has been used chronically as maintenance therapy in individual cases. (Sanders DB, et al. 2016).*
- *Hayes assigned a Rating of "B" for the use of IVIg for the treatment of adult patients with worsening or acute exacerbations of myasthenia gravis without contraindications to IVIg treatment. This Rating reflects moderate-quality evidence that IVIg is at least as efficacious as plasma exchange/plasmapheresis and superior to placebo therapy for improving muscle weakness and other clinical symptoms of MG, and that it is relatively safe for patients without contraindications (Hayes 2019).*

M. OPSOCLONUS MYOCLONUS SYNDROME (OMS) [IVIG ONLY]
1. Documentation that member has had improvement or stabilization of opsoclonus symptoms and degree of disability as measured by the Cerebellar Functional System Score [DOCUMENTATION REQUIRED]

N. PURE RED BLOOD CELL APLASIA (PRCA)- Secondary to Chronic (persistent) Parvovirus B19 Infection [IVIG ONLY]
1. Documentation that member has had an initial response to treatment, chronic parvovirus infection, and recurrence of significant anemia [DOCUMENTATION REQUIRED]

O. STIFF-PERSON SYNDROME (MOERSCH-WOLTMANN SYNDROME) [IVIG ONLY]
1. Documentation that treatment has been effective demonstrated by objective findings of improvement in symptoms of stiffness and functional improvement of disability with one of the following: Functional Assessment ADL, Modified Rankin Score and a Distribution of Stiffness Index Score (greater than the qualifying baseline scores)] [DOCUMENTATION REQUIRED] NOTE: If there has been no improvement or clinical benefits after six months of treatment, IVIg therapy will not be authorized.

P. PEDIATRIC HIV [IVIG ONLY]
1. Documentation of current IgG levels that are in the low to normal range and evidence of clinical improvement, such as reduction of the number and severity of clinical infections [DOCUMENTATION REQUIRED]

DURATION OF APPROVAL:
Initial authorization (unless specified below): 6 months, Continuation of Therapy (unless specified below): 6 months
AMBD: Initial authorization: 3 months, Continuation of Therapy: n/a
CIDP: Initial authorization: 3 months, Continuation of Therapy: 6 months
Dermatomyositis; Polymyositis: Initial authorization: 3 months, Continuation of Therapy: 6 months
HIV-associated Thrombocytopenia, Adult: One course of therapy; Continuation: n/a
FAIT: Until Delivery
ITP:
Acute ITP: One course of therapy, up to 5 days; Continuation of Therapy; n/a
ITP in Pregnancy: Until anticipated delivery date; Continuation: n/a
Guillain-Barré Syndrome (GBS): Initial authorization: One course of therapy, up to 5 days
Continuation of Therapy: n/a
Kawasaki: One course of therapy, up to 5 days; Continuation: n/a
Multiple Myeloma: Initial authorization: 3 months, Reauthorization: 3 months
Myasthenia Gravis: Initial authorization: 3 months, Continuation of Therapy: 3 months
Rasmussen Syndrome: Initial authorization: 3 months, Continuation of Therapy: n/a
NAIT: Up to 2 doses
Neonatal hemochromatosis, prophylaxis: until delivery (usually from the 18th week until the end of gestation)
Post-Transfusion Purpura: One course of therapy, up to 5 days; Continuation: n/a

Staphylococcal or Streptococcal Toxic Shock Syndrome (TSS): One course of therapy, up to 5 days; Continuation: n/a
Stiff-Person Syndrome: Initial authorization: 3 months, Continuation of Therapy: 6 months
Transplant, Solid Organ: Acute Rejection: 14 days; Prophylaxis: 8 months

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified specialist, or physician experienced in the treatment of in the management of the condition being treated. Submit consultation notes if applicable.
NOTE: Consultation notes are required with initial requests and with continuation of therapy requests, at least once annually.

Allogenic Bone Marrow Transplant (BMT)/Hematopoietic Stem Cell Transplantation (HSCT): hematologist, oncologist, or infectious diseases
Autoimmune Hemolytic Anemia: hematologist
AMBDs: dermatologist
B-cell Chronic Lymphocytic Leukemia (CLL): hematologist, oncologist, or infectious diseases
CIDP: neurologist
Dermatomyositis; Polymyositis: neurologist or rheumatologist
FAIT/ NAIT: fetal medicine, obstetrics, or hematology/transfusion
Guillain-Barré Syndrome (GBS): neurologist or specialist with experience in the diagnosis and treatment of GBS
ITP- Acute, Chronic ITP or ITP in Pregnancy: hematologist
Kawasaki Disease: cardiologist, allergist or rheumatologist
LEMS: neurologist
Multiple Myeloma: hematologist, oncologist, or infectious diseases
Multifocal Motor Neuropathy: neurologist
Myasthenia Gravis: neurologist
Neonatal hemochromatosis, prophylaxis: gastroenterologist, hematologist, and a hepatologist
Opsoclonus Myoclonus Syndrome: neurologist
Post-Transfusion Purpura: hematologist
Primary Immune Deficiency: allergist, immunologist, otolaryngologist, or infectious disease
Pure Red Blood Cell Aplasia (PRCA): Secondary to Chronic (Persistent) Parvovirus B19 Infection: infectious diseases specialist, immunologist, hematologist, or transplant specialist
Adult HIV-associated Thrombocytopenia: infectious disease or HIV specialist
Pediatric HIV: infectious disease or HIV specialist
Rasmussen Syndrome: neurologist or
neurosurgeon Stiff-Person Syndrome: neurologist
Toxic Shock Syndrome (TSS): Specialist or physician experienced in the management of TSS.
Transplant, Solid Organ: transplantation medicine specialist or physician affiliated with a transplant
Transplant, BMT or HSCT: hematologist, oncologist or infectious diseases

AGE RESTRICTIONS: [AS LISTED IN FDA LABELING]
ASCENIV: 12 years and older BIVIGAM: 6 years and older
CUTAQUIG [SC]: 2 years of age and older
CUVITRU [SC]: 2 years and older
FLEBOGAMMA DIF: 2 years and older
GAMMAGARD LIQUID (IV, SC): PID, 2 years and older; MMN: 18 years and older
GAMMAGARD S/D (IV, SC): PID, Kawasaki, CLL, 2 years and older; ITP: 18 years and older
GAMMAKED: PID (SC, IV), ITP (IV ONLY): 2 years and older; CIPD (SC, IV): 18 years and older
GAMMAPLEX [IV]: 5%, PID, ITP: 2 years and older; 10%, PID: 2 years and older, ITP: 18 years and older GAMUNEX-C: PID (SC, IV), ITP (IV ONLY): 2 years and older; CIPD (IV): 18 years and older
HIZENTRA [SC]: PID: 2 years and older; CIDP: 18 years and older
HYQVIA [SC]: PID: 18 years and older
OCTAGAM 10% [IV]: ITP: 18 years and older
OCTAGAM 5% [IV]: PID: not listed
PANZYGA [IV]: PID: 2 years and older; ITP, CIDP: 18 years and older

Drug and Biologic Coverage Criteria

PRIVIGEN [IV]: PID: 3 years and older; ITP: 15 years and older, CIDP: 18 years and older
XEMBIFY [SC]: PID: 2 years and older

QUANTITY:

Allogenic Bone Marrow Transplant (BMT)/Hematopoietic Stem Cell Transplantation (HSCT): Less than 100 days post-transplant: 500 - 600 mg/kg/week until member reaches 90 days post-transplant
OR Greater than 100 days: 500 mg/kg/month until member reaches 360 days post-transplant
Autoimmune Hemolytic Anemia: 1,000 mg/kg daily for 5 days every 30 days
AMBDs: 2,000 mg/kg in divided doses (2- 5 days) every 30 days
B-cell Chronic Lymphocytic Leukemia (CLL): 600 mg/kg every 3 to 4 weeks
CIPD: Loading dose: 2,000 mg/kg in divided doses over 2 to 5 consecutive days; maintenance 1 g/kg administered in 1 or 2 infusions on consecutive days every 3 weeks; SCIG (HIZENTRA): 0.2 g/kg – 0.4 g/kg weekly
Dermatomyositis; Polymyositis: Loading dose: 2000 mg/kg; maintenance dose 500-1000 mg/kg every 30 days
FAIT: 1000 -2000 mg/kg weekly until delivery
Guillain-Barré Syndrome (GBS): 2000 mg/kg divided over 2 to 5 days
HIV:
Adult HIV-associated Thrombocytopenia: 1000 mg/kg daily for 2 days
Pediatric HIV: 400 mg/kg every 2 to 4 weeks
ITP:
Acute ITP: 2000 mg/kg divided over 2-5 days; No reauthorization
Chronic ITP: 2000 mg/kg divided over 2-5 days, every 2 to 6 weeks depending on platelet count
ITP in pregnancy: 2000 mg/kg divided over 2-5 days, every 2 to 6 weeks until anticipated delivery date, no reauthorization.
Kawasaki: 2000 mg/kg, which may be administered as a single dose or divided over 5 days
LEMS: 2000 mg/kg, which may be administered over 2 to 5 days every 4 to 8 weeks
Multiple Myeloma: 200-400 mg/kg, administered every 4 to 6 weeks
Multifocal Motor Neuropathy: 2000 mg/kg once monthly, which may be administered over 2 to 5 days
Myasthenia Gravis: 2000 mg/kg divided over 2 to 5 days (one course), One course per month
NAIT: 1000 mg/kg per dose, for up to 2 doses
Neonatal hemochromatosis, prophylaxis: 1000 mg/kg weekly until delivery (usually from the 18th week until the end of gestation)
Opsoclonus Myoclonus Syndrome: Recommended dose 1000 mg/kg once monthly, which may be administered over 2 to 5 days; Maximum dose: 2000 mg/kg once monthly, which may be administered over 2 to5 days
PID: IVIG Quantity Limitation: 300-800 mg/kg every 3 to 4 weeks; SCIG: weekly dosing in accordance with FDA labeling for product
Post-Transfusion Purpura: 500 mg/kg divided for 2 to 5 days (one course) OR 1000 mg/kg daily for 2 days (one course)
Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection: 2000-4000 mg/kg divided over up to 10 days (one course), one course per month
Rasmussen Syndrome (RS), Chronic Focal Encephalitis: 2000 mg/kg once monthly, which may be administered over 2 to 5 days
Stiff-Person Syndrome: 2000 mg/kg once monthly
Staphylococcal or Streptococcal Toxic Shock Syndrome (TSS): 2000 mg/kg, which may be administered divided over 5 days
Transplant, Solid Organ: Post-Transplant Acute Rejection: 2000 mg/kg (up to 140 grams in a single dose); One dose per rejection episode; Prior to transplant, prevention: 2000 mg/kg per 8-week period, may be given in divided doses; Four (4) doses prior to and four (4) doses following transplant, maximum of 8 total doses. If used with plasma exchange: total maximum dose of 2000 mg/kg per 4-week period which may be given in divided doses.

PLACE OF ADMINISTRATION:

Intravenous Immunoglobulin:
The recommendation is that intravenously infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Subcutaneous Immunoglobulin:
The recommendation is that subcutaneously infused medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneously infused products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.
Note: Site of Care Utilization Management Policy applies for Asceniv, Bivigam, Cutaquig, Cuvitru, Flebogamma,Gammagard, Gammaked, Gammaplex, Gamunex-C, Hizentra, HyQvia, Octagam, Privigen, Panzyga, Xembify. For information on site of care, see

Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Subcutaneous, Intravenous

DRUG CLASS:
Immune Serums

FDA-APPROVED USES:
ASCENIV: Intravenous injection indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age).

BIVIGAM: Indicated for the treatment of primary humoral immunodeficiency (PI)

CUTAQUIG: Subcutaneous infusion indicated for treatment of primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

CUVITRU: Subcutaneous infusion indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

FLEBOGAMMA DIF: Indicated in adults and pediatric patients 2 years of age and older for the treatment of primary immunodeficiency (PI), including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

GAMMAGARD LIQUID: Indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two 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. Indicated as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN).

GAMMAGARD S/D: Indicated for the treatment of primary immunodeficiency (PI) associated with defects in humoral immunity, in adults and children two years and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich

syndrome, and severe combined immunodeficiencies; Indicated for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL); Indicated for the treatment of adult chronic idiopathic thrombocytopenic purpura to increase platelet count and to prevent and/or to control bleeding; Indicated for prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients.

GAMMAKED: Indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; indicated for the treatment of adults and children with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery; indicated for the treatment of CIDP in adults to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

GAMMAPLEX 5%: Indicated for replacement therapy in 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 common variable immunodeficiency, X-linked agammaglobulinemia (XLA), congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; indicated for the treatment of chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

GAMMAPLEX 10%: Indicated for replacement therapy in 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 common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; Indicated for the treatment of chronic immune thrombocytopenic purpura (ITP) in adults to raise platelet counts.

GAMUMEX-C: Indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; indicated for the treatment of adults and children with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery; indicated for the treatment of CIDP in adults to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

HIZENTRA: Indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.

HYQVIA: Indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

OCTAGAM 10%: Indicated in Chronic Immune Thrombocytopenic Purpura to rapidly raise platelet counts to control or prevent bleeding in adults.

OCTAGAM 5%: Indicated for treatment of primary humoral immunodeficiency (PI), such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

PANZYGA: Indicated for treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable

immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; indicated for the treatment of adult patients with ITP to raise platelet counts to control or prevent bleeding; indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.

PRIVIGEN: Indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies; Indicated for the treatment of patients age 15 years and older with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts; indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.

XEMBIFY: Subcutaneous injection indicated for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older.

COMPENDIAL APPROVED OFF-LABELED USES:
UpToDate, Micromedex, AHFS or Clinical Pharmacology

APPENDIX

APPENDIX:

BRAND NAME	ROUTE	PID	ITP	CLL	CIDP	KD	MMN
Intravenous							
Asceniv (FDA-approved April	IV	X					
Bivigam	IV	X					
Flebogamma 5% DIF	IV	X					
Flebogamma 10% DIF	IV	X	X				
Gammagard S/D (5% or 10% when reconstituted)	IV	X	X	X		X	
Gammaplex 5% or 10%	IV	X	X				
Octagam 5%	IV	X					
Octagam 10%	IV		X				
Panzyga 10%	IV	X	X				
Privigen 10%	IV	X	X		X		
Intravenous OR Subcutaneous							
*Gammagard Liquid 10%	IV/SC	X					X
*Gammaked 10%	IV/SC	X	X		X		
*Gamunex-C 10%	IV/SC	X	X		X		
Subcutaneous Immune Globulin (SCIg)							
Hizentra 20%	SQ	X			X		
HyQvia 10%	SQ	X					
	SQ	X					
Cuvitru 20%	SQ	X					
Xembify 20%	SQ	X					

PI: Primary Immunodeficiency; ITP: Immune Thrombocytopenia; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CLL: Chronic Lymphocytic Leukemia; KD: Kawasaki Disease; MMN: Multifocal Motor Neuropathy

*Gammaked, Gamunex-C, and Gammagard Liquid are approved for both intravenous and subcutaneous use for treatment of PID and when administered subcutaneously, are FDA-approved for the treatment of PID only. NOTE: Gammagard Liquid, Gammaked and Gamunex-C are not approved for SQ use in patients with ITP or CIDP.

[§]The following products do not contain sucrose: Gammaplex, Bivigam, Octagam 10%, Gamunex-C, Gammagard Liquid, Gammagard S/D, Gammaked, Flebogamma 5% DIF, Flebogamma 10% DIF, Privigen, and Hizentra

Dosage Forms Considerations

- Cutaquig and Octagam contains maltose.
- Gammagard S/D may contain a significant amount of sodium and also contains glucose.
- Hyqvia Kit is supplied with a Hyaluronidase (Human Recombinant) component intended for injection prior to Immune Globulin administration to improve dispersion and absorption of the Immune Globulin.

Each product varies with FDA-approved indications.

- Currently there are six (6) indications that are FDA approved for specific Ig products:
  - Primary Immunodeficiency Diseases (PID) [includes, but are not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies]; All available immune globulin replacement products are FDA-approved for use in primary immunodeficiency (PID).
  - Idiopathic thrombocytopenic purpura (ITP)
  - B-cell chronic lymphocytic leukemia (CLL)
  - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
  - Kawasaki Disease (KD)
  - Multifocal Motor Neuropath (MMN)
- SCIg products are currently only FDA approved for the treatment of PID and CIDP (Hizentra only)
  - Hizentra is the first and only SCIg approved for the treatment of CIDP (March 2018)
- All conditions are FDA approved for the intravenous route
- IVIg products will not be approved for subcutaneous use unless FDA approved for that route of administration.

Subcutaneous immune globulin:

Subcutaneous immune globulin (SCIg) is a protein solution that contains at least 98% immunoglobulin G(IgG). It is used in the treatment of primary immunoglobulin deficiency (PID). For individuals with immunodeficiencies, both IVIg and SCIg are effective. Use of SCIg for the treatment of primary immunodeficiencies was approved by the FDA based on an open-label, nonrandomized, prospective, multicenter study.

SCIg products are indicated for replacement therapy in patients with PID, including but not limited to the humoral defect in the following conditions: common variable immunodeficiency (CVID), X-lined agammaglobulinemia (XLA), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).[Clinical Pharmacology, 2019]. The exact mechanism of SCIg in PID is not fully understood.

Immune globulin may be administered subcutaneously by three methods which differ in the frequency and how the SCIG is given: traditional, facilitated subcutaneous, and subcutaneous rapid push.

- Traditional: uses infusion pumps to give predominantly weekly infusions
- Rapid-push SC: administered using only a syringe and butterfly needle at frequencies from several times per week to daily
- Hyaluronidase-facilitated SCIg (fSCIg): A two-step delivery system of recombinant human hyaluronidase (rHuPH20) and a 10% immune globulin preparation, human hyaluronidase (rHuPH20)given immediately before the immune globulin, to allow up to a full monthly dose to be given in a

  single SC infusion. The hyaluronidase is drawn up into a separate single syringe and infused alone by manual push from the syringe before the SCIG is given. Generally administered every three to four weeks

SCIg has a lower bioavailability than IVIg, so must be given in higher doses to achieve the same serum IgG concentrations. However, subcutaneous delivery may result in higher steady-state IgG levels due to less variation in IgG levels.

Comparison of SCIg with IVIg:
Immune globulin products specifically intended for subcutaneous (SC) and intramuscular (IM) administration are generally more concentrated than those designed for intravenous (IV) use, allowing more immune globulin to be administered in lower volumes. Generally, many 10% IVIg solutions can be administered subcutaneously or intravenously, but more concentrated products (e.g., 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse events and provides more stable serum IgG levels. In contrast, SCIG has not been studied as extensively in autoimmune and inflammatory disorders. IVIg infusions may be preferable for patients who require faster increase of trough level at initiation. SCIg is associated with more stable serum Ig concentrations and advantageous for patients with poor venous access due to no need for indwelling venous catheter, particularly in patients with poor venous access. There are no head-to-head studies comparing concentrated SCIg to IVIg in PID and no evidence-based reviews demonstrating that SCIg is more effective than IVIg to improve and maintain immunoglobulin levels. **Therefore, unless contraindicated, a trial of IVIg is required before SCIg products will be considered for authorization.**

Black Box Warnings
Thrombosis may occur with immune globulin products. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Renal dysfunction and acute renal failure (excluding Cuvitru, Hizentra, HyQvia, and GamaSTAN S/D) may occur in predisposed patients with immune globulin intravenous IV products. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving immune globulin IV products containing sucrose. (Note: The following products do not contain sucrose: Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam 5%, Octagam 10%, Panzyga, and Privigen) For patients at risk of renal dysfunction or acute renal failure, administer immune globulin IV products at the minimum concentration dose and infusion rate practicable. Ensure adequate hydration in patients before administration.

Objective Testing Information:

<u>Cerebellar Functional System Score</u>
The cerebellar functional system score was chosen to demonstrate initial disability and response.
Values of the cerebellar functional system score are:

0. Normal: no evidence of cerebellar dysfunction
1. Abnormal signs without disability
2. Mild ataxia
3. Moderate ataxia
4. Severe ataxia (all limbs or gait)

5. Unable to perform coordinated movements due to ataxia

Changes in opsoclonus symptoms will be rated as:

i. Deterioration in symptoms
ii. Symptoms stable
iii. Mild improvement
iv. Moderate improvement
v. Significant improvement

Inflammatory Neuropathy Cause and Treatment (INCAT)

The Inflammatory Neuropathy Cause and Treatment (INCAT) scale is used to access functional disability of both upper and lower extremity components in chronic inflammatory demyelinating polyneuropathy (CIDP). The INCAT scale has upper and lower extremity components, with a maximum of 5 points for the upper extremity (arm disability) and a maximum of 5 points for the lower extremity (leg disability), which add up to a maximum of 10 points (where 0 is normal and 10 is severely incapacitated). The INCAT scores may be used to evaluate the effectiveness and need for IVIG. IVIG may be discontinued when there is a lack of clear clinical improvement (i.e., a decline in INCAT disability score or failure to improve by 1 point at 6 weeks following the initial infusion or return to baseline at any time following initial improvement of 1 point).

Medical Research Council (MRC)

The Medical Research Council (MRC) scale is used to grade muscle strength. Scale: 0 = no muscle movement; 1 = flicker of muscle movement; 2 = trace movement but not able to fully overcome gravity; 3 = just able to overcome gravity, but not against resistance; 4 = moves against resistance, but weak; 5 = full strength against resistance.

Dosing Considerations

- If TBW is less than IBW, TBW should be used for calculating the dose.
- If BMI is ≥30 kg/m^2 or if TBW is greater than 20%-30% over IBW, adjBW should be used for calculating the dose.

Suggested calculations for determining IBW and adjBW:

- IBW male: 50 kg + (2.3 x inches over 5 feet)
- IBW female: 45.5 kg + (2.3 x inches over 5 feet)
- AdjBW = IBW + 0.4 (TBW-IBW)

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Autoimmune Hemolytic Anemia (AIHA): AIHA is a relatively uncommon disorder caused by antibodies directed against autologous red blood cells. AIHA is classified as warm, cold (which includes cold hemagglutinin disease (CAD) and paroxysmal cold hemoglobinuria) or mixed, according to the thermal range of the autoantibody. AIHA due to the presence of warm agglutinins is almost always due to the presence of IgG antibodies that react with protein antigens on the RBC surface at body temperature.

Autoimmune Mucocutaneous Blistering Diseases (AMBDs): AMBDs are a group of rare, debilitating and possibly fatal disorders caused by antibodies directed against components of the skin. The diseases are characterized by the formation of extensive blisters evolving to painful erosions on the skin and mucous membranes.

B-Cell Chronic Lymphocytic Leukemia (CLL): CLL is a blood and marrow disorder characterized by increased numbers of CD5-positive B cells. The underlying cause of CLL is unknown, although it is thought to be genetically linked.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy: CIDP is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. Chronic Inflammatory Demyelinating Polyneuropathy (CIPD) is an immune mediated disorder which affects the peripheral nervous system. The classical presentation has symmetric proximal and distal sensory and motor involvement which develops over 8 weeks. This 8 week development time and persistence greater than 8 weeks helps to distinguish CIPD from Guillain-Barre. For CIPD the typically IVIg is administered as an initial induction dose of 2 g/kg over 2 to 5 days, followed by a maintenance dose of 0.4 g/kg (0.2 to 1 g/kg) every 3 to 4 weeks.[18,19] **Dermatomyositis; Polymyositis:** Dermatomyositis is an idiopathic inflammatory myopathy that most commonly affects the skin and muscles and may impact joints. Polymyositis is an idiopathic inflammatory myopathy causing muscle weakness, elevated muscle enzyme levels and is similar to dermatomyositis.

Fetal or Natal Alloimmune Thrombocytopenia (FAIT/ NAIT): FAIT/ NAIT is the most common cause of severe thrombocytopenia in the fetus and in otherwise healthy newborn. The mother produces antibodies (IgG) against fetal HPA antigens inherited from the father. These alloantibodies (IgG) can cross the placenta, destroy fetal thrombocytes and may induce severe thrombocytopenia. It is most commonly caused by the HPA-1a antigen (80%).

Guillain-Barré Syndrome (GBS) [also referred to as Acute Inflammatory Demyelinating Polyneuropathy (AIDP)]: GBS is an acquired acute peripheral neuropathy causing limb weakness that progresses over a period of days to weeks. The syndrome typically presents with rapidly progressive, relatively symmetrical ascending limb weakness consistent with a polyradiculoneuropathy and often with associated cranial nerve involvement. Motor signs and symptoms usually predominate over sensory signs and symptoms. Major complications include respiratory failure and autonomic dysfunction. The disease is monophasic, reaching its nadir usually within two weeks, although arbitrary definition accepts a limit of four weeks. A plateau phase of variable duration follows the nadir before gradual recovery.

Immune or Idiopathic Thrombocytopenic Purpura (ITP): ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. ITP is divided into chronic and acute forms. The goal of medical care for ITP is to increase the platelet count to a safe level, permitting patients to live normal lives while awaiting spontaneous or treatment-induced remission. Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. The goal is to maintain platelet count at a level that prevents spontaneous bleeding or bruising.

Neonatal hemochromatosis, prophylaxis: Neonatal hemochromatosis is a rare gestational condition in which iron accumulates in the fetal tissues in a distribution like that seen in hereditary hemochromatosis. Extensive liver damage is the dominant clinical feature, with late fetal loss or early neonatal death.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome): Kawasaki disease is an acute, febrile, multi-system disease of children and young infants often involving the coronary arteries. Coronary artery aneurysms may occur from the second week of illness during the convalescent stage. The cause of the condition is unknown but there is evidence that the characteristic vasculitis results from an immune reaction characterized by T-cell and macrophage activation to an unknown antigen, secretion of cytokines, polyclonal B-cell hyperactivity, and the formation of autoantibodies to endothelial cells and smooth muscle cells. It is likely that in genetically susceptible individuals,
one or more uncharacterized common infectious agents, possibly with super-antigen activity, may trigger the disease.

Lambert-Eaton Myasthenia Syndrome (LEMS): LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes. The primary goal of treatment for LEMS is to identify and treat any tumors or other underlying disorders.

Multiple Myeloma (MM): MM is a malignant tumor of plasma cells associated with impaired

function of immunoglobulins, which are an essential component of the immune system. Patients with MM are at increased risk of infection, due to a combination of several factors, including immunoparesis and physical factors.

Myasthenia Gravis: Myasthenia gravis is an autoimmune disease characterized by autoantibodies directed against the acetylcholine receptors of the muscle end plate that induce muscle weakness and pronounced fatigability. Initial treatment focuses on the use of cholinesterase inhibitors to overcome the post-synaptic blockade.

Multifocal Motor Neuropathy (MMN): MMN is a rare neurological disorder characterized by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern.

Post-Transfusion Purpura (PTP) [Hemolytic Transfusion Reaction]: PTP is a rare bleeding disorder caused by alloantibodies specific to platelet antigens. PTP is characterized by the development of severe, sudden and self-limiting thrombocytopenia occurring 5-10 days after a blood transfusion.

Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection: Parvovirus B19 infects and lyses red cell precursors, which can cause pure red cell aplasia. IVIg therapy is usually reserved for patients with chronic parvovirus infection and chronic anemia.

Opsoclonus Myoclonus Syndrome (OMS): Opsoclonus myoclonus is a rare neurological disorder that may occur in association with tumors (paraneoplastic) or viral infections and is characterized by an unsteady, trembling gait, myoclonus and opsoclonus (irregular, rapid eye movements). It is more common in children.

Rasmussen Syndrome (RS) [also known as Rasmussen Encephalitis (RE) or Chronic Focal Encephalitis]: RS/RE is a rare neurological, progressive, focal encephalitis that is commonly accompanied by focal seizures, hemiparesis and cognitive decline. It is generally considered to be a disease of childhood, with most cases occurring in children younger than 10 years, although adult onset cases do occur. The precise etiology of RE remains unknown, but immune-mediated injury is considered central in the pathogenesis.

Stiff-Person Syndrome (Moersch-Woltmann Syndrome): Stiff-person syndrome is a chronic disorder with features of an autoimmune disease involving painful muscle spasms and rigidity. SPS treatments are aimed at symptom relief and/or modulation of the underlying aberrant immune process.

Staphylococcal or Streptococcal Toxic Shock Syndrome (TSS): TSS is an acute, multi-system, toxin-mediated illness which may typically result in shock and multi-organ failure early in its clinical course. Causes include toxin-producing strains of Staphylococcus aureus and Invasive Group A Streptococcus (e.g. Streptococcus pyogenes). IVIg is recommended as an adjunctive therapy in children with severe toxin-related infection showing failure to improve despite best standard care.

Solid Organ Transplantation: Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common antibody-mediated rejection reaction (AbMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AbMR does not, and, as such, has also been referred to as “steroid-resistant rejection.”

- The risk of AbMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a panel reactive antibody (PRA) screen, which combines the recipient’s serum with samples of antigen containing cells taken from 60

individuals, representative of the potential donor pool.

- The percentage of PRA is the percentage of positive reactions. Those with a PRA greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of ABMR.
- As an immunomodulatory agent, IVIg has been widely used in the prevention and management of AbMR, often in conjunction with plasma exchange. For instance, in patients at high risk for AbMR, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AbMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AbMR develops.

Treatment

- The aim of immunosuppression in clinical practice is to control an undesirable immune response while avoiding, if possible, the complications of immunodeficiency. The effect can be achieved by ablation (i.e., irreversibly damaging immune tissue); by altering lymphocyte location and traffic; by altering lymphocyte or dendritic cell function; or by affecting lymphokines. These interventions may be physical (i.e., by irradiation, plasmapheresis, photopheresis) or pharmacological (i.e., IVIg).
- Patients with high levels of "anti-donor" antibodies often have very high rejection rates after transplant, especially in kidney transplant. Rejection risks are very high for a patient whose immune system has been exposed to "non-self" human leukocyte antigens (HLA). Exposure to HLAs may occur in a number of ways, including prior organ transplant or blood transfusions.
- IVIg increases a highly sensitized patient's chance of successful transplant. IVIg is a new immune-modulating therapy that can reduce high antibody levels and improve transplant rates. IVIg helps by modifying the immune system rather than suppressing it.
- IVIg is given while a highly sensitized patient waits for transplant, with the goal of decreasing their overall level of sensitization and therefore increasing the possibility that a donor kidney would be acceptable to their immune system.

POSITION STATEMENTS

A position statement from the American Academy of Asthma, Allergy and Immunology (Orange, et al., 2005) states that "the decision to administer IVIg to patients with primary deficiencies in antibody production should be based on: 1) abnormalities of serum immunoglobulin concentrations; 2) clinical history of infections; and, when appropriate, 3) the demonstrated inability to produce antibody normally following antigenic stimulation."

Guidelines from the American Academy of Asthma, Allergy & Immunology (Orange, et al., 2006) state; "Reduced levels of serum immunoglobulin in patients with recurrent bacterial infections coupled with a lack of response to protein or polysaccharide vaccine challenges (i.e., patients who cannot make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both) is a clear indication for IgG replacement.

CLINICAL PRACTICE GUIDELINES

American Academy of Neurology

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 (AAN 2012)

AAN’s evidence-based guideline on “Intravenous immunoglobulin in the treatment of neuromuscular

disorders" (Patwa et al, 2012) states the following:

- IVIg is as efficacious as plasmapheresis and should be offered for treating Guillain-Barré syndrome (GBS) in adults (Level A)
- IVIg is effective and should be offered in the long-term treatment of chronic inflammatory demyelinating polyneuropathy (Level A)
- IVIg is probably effective and should be considered for treating moderate-to-severe myasthenia gravis and multifocal motor neuropathy (Level B)
- IVIg is possibly effective and may be considered for treating non- responsive dermatomyositis in adults and Lambert-Eaton myasthenic syndrome (Level C)
- Evidence is insufficient to support or refute use of IVIG in the treatment of immunoglobulin M paraprotein-associated neuropathy, inclusion body myositis, polymyositis, diabetic radiculoplexoneuropathy, or Miller Fisher syndrome, or in the routine treatment of post-polio syndrome or in children with GBS (Level U)
- IVIg combined with plasmapheresis should not be considered for treating GBS (Level B). More data are needed regarding IVIG efficacy as compared with other treatments/treatment combinations.

The Immune Deficiency Foundation (IDF) Guidelines

In 2011, the Immune Deficiency Foundation (IDF) published guidelines on diagnosis and clinical care for primary immunodeficiency diseases. The guidelines support clinicians determine the possible type of PI and the screening diagnostic tests that should be ordered based on the site of infection. Although there are several different types of PI, the types that result in antibody production defects are those that are eligible for IgG therapy.

- The IDF recommends regular IgG therapy for patients with identified antibody deficiency disorders.
- The guidelines state the IVIG product should be dosed every 2-4 weeks and SCIG should be given every 1-14 days.
- It is recommended that an immunologist should participate in the determination of the proper dose and interval for IgG therapy in each patient.
- Should IgG treatment be required IV or SC administration are both recommended, and one product is not preferentially recommended over any other product.

Canadian Blood Services and Canada's National Advisory Committee Guidelines

The Canadian Blood Services and Canada's National Advisory Committee on Blood and Blood Products led a joint initiative to create guidelines for treatment of PI with immunoglobulin therapy. While the guidelines are primarily intended for health care professionals in Canada, many of their recommendations may be applied in other parts of the world, including the United States.

The National Advisory Committee on Blood and Blood Products and Canadian Blood Services issued practice guidelines on the use of IVIg in primary immune deficiency in 2010. The recommendations were based on interpretation of available evidence and where evidence was lacking, consensus of expert clinical opinion. The guidelines were constructed from an expert panel consisting of physicians from large pediatric and adult tertiary care centers who frequently cared for patients with primary immune deficiency, methodology experts, and members from the National Advisory Committee on Blood and Blood Products. The levels of evidence and grades used for each recommendation were adapted from the Canadian Task Force on Preventative Health Care. The levels of evidence describe the methodological rigor of the study, and the grades of recommendation comprise the level of evidence and clinical expertise. Relevant recommendations include the following:

- Give immunoglobulin to patients with primary antibody deficiency to reduce infections. (Level of evidence: I, Grade of recommendation: A)
- Give immunoglobulin to reduce hospitalization and organ damage. (I, A)
- Give immunoglobulin to improve survival and quality of life. (III, A)
- With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one manufacturer of IG over another for currently available products. (I to II-2, I)
- With respect to clinical efficacy for reducing infections, IVIG and SCIG preparations should be considered equivalent. (I and II, B)
- Do not give IMIG for replacement therapy for primary immune deficiency. (I, D)
- Start IVIG at a dose of 400 to 600 mg/kg per 4 weeks or SCIG at a dose of 100 to 150 mg/kg per week in most patients. (III, B)
- Patient and practitioners should be aware that patients with primary immune deficiency may require immunoglobulin replacement therapy indefinitely. (II-3, A)

DOSING CONSIDERATIONS

Although there is no clearly defined standard approach to dosing of immune globulin in obese patients, there is substantial evidence to support dosing using adjusted or ideal body weight. According to published data, both options provide comparable drug exposure without altering the clinical outcomes of immune globulin treatment. Immune globulin is a relatively polar molecule with a small volume of distribution – it does not distribute into fat tissue and is only present in the intravascular space and extracellular fluids. The use of adjBW, rather than IBW or lean body weight (LBW) is based on the presumption that extracellular fluid is increased in patients with increased adipose tissue. Dosing immune globulin using a patient's adjBW or IBW rather than TBW has been demonstrated to have similar clinical outcomes as using TBW. Ultimately, regardless of dosing, immune globulin efficacy should be monitored by clinical outcome. Also consider, If TBW is less than IBW, TBW should be used
for calculating the dose. If BMI is ≥30 kg/m2 or if TBW is greater than 20%-30% over IBW, adjBW should be used for calculating the dose.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of immune globulin are considered experimental/investigational and
therefore, will follow Molina's Off- Label policy. Contraindications to Contraindications to Asceniv, Bivigam, Cutaquig, Cuvitru, Flebogamma, Gammagard, Gammagard S/D, Gammaplex, Gamunex-C, Octagam, Panzyga(immune globulin) include: History of anaphylactic or severe systemic reactions to human immunoglobulin, IgA deficient patients with antibodies against IgA and a history of hypersensitivity; Contraindications to Hizentra (immune globulin): Anaphylactic or severe systemic reaction to human immune globulin or inactive ingredients of Hizentra, such as polysorbate 80; Hyperprolinemia Type I or II (HIZENTRA contains stabilizer L-proline); IgA-deficient patients with antibodies against IgA and a history of hypersensitivity. Contraindications to Hyqvia (immune globulin)include: History of anaphylactic or severe systemic hypersensitivity reactions to Immune Globulin (Human); IgA deficient patients with antibodies against IgA and a history of hypersensitivity; Known systemic hypersensitivity to hyaluronidase including Recombinant Human Hyaluronidase of HYQVIA;
Known systemic hypersensitivity to human albumin (in the hyaluronidase solution). Contraindications to Privigen (immune globulin) include: History of anaphylactic or severe systemic reaction to human immuneglobulin; Hyperprolinemia (PRIVIGEN contains the stabilizer L-proline); IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

Applications of Subcutaneous Immune Globulin (SCIg) for conditions other than primary immunodeficiencies and Chronic Inflammatory Demyelinating Polyneuropathy are considered investigational.

OTHER SPECIAL CONSIDERATIONS:

Drug shortages In August 2019, FDA released a statement addressing the issues of product shortages along with a list of the products with limited availability. IG products with a supply that is not able to keep pace as the reason for the shortages. Its recommendations for healthcare providers are to develop a system to determine which patients should receive priority treatment and to consider adding additional products to their formularies to use during times of shortages.

One or more forms of this drug may be in short supply or unavailable. Refer to the following for additional information: ASHP FDA

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J1459	Injection, immune globulin (privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1551	Injection, immune globulin (cutaquig), 100 mg
J1554	Injection, immune globulin (asceniv), 500 mg
J1555	Injection, immune globulin (cuvitru), 100 mg
J1556	Injection, Immune Globulin (bivigam) Intravenous, Non-Lyophilized (e.g., Liquid), 500mg
J1557	Injection, immune globulin, (gammaplex), intravenous, non-hyphenlyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (xembify), 100 mg
J1559	Injection, immune globulin (hizentra), 100 mg
J1561	Injection, immune globulin, (gamunex-hyphenc/gammaked), nonlyophilized (e.g. liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (octagam), intravenous, nonlyophilized (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
J1572	Injection, immune globulin, intravenous, non-lyophilized (e.g, liquid), not otherwise specified, 500 mg

AVAILABLE DOSAGE FORMS:
Asceniv (immune globulin intravenous, human) 10% 50 mL
Bivigam Immune Globulin Intravenous (Human), 10% Liquid 5g, 50 mL; 10g, 100 mL
CUTAQUIG® (Immune Globulin Subcutaneous (Human) - hipp), 16.5% solution: 1g, 1.65g, 2g, 3.3g, 4g, 8g vials
CUVITRU, Immune Globulin Subcutaneous (Human), 20% Solution: 5mL (1g), 10 mL (2g), 20 mL (4g), 40 mL (8g), 50 mL (10g)
FLEBOGAMMA 5% DIF (immune globulin intravenous [human]), solution: 0.5g, 2.5g, 5g, 10g, 20g
GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution: 1g, 2.5g, 5g, 10g, 20g, 30g
GAMMAGARD S/D Immune Globulin Intravenous (Human)
IgA less than 1 microgram per mL in a 5% Solution: 5g, 10g
GAMMAKED, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified]: 1g, 2.5g, 5g, 10g, 20g GAMMAPLEX 5% Immune Globulin Intravenous (Human), 5% Liquid: 5g, 10g, 20g
GAMMAPLEX 10% Immune Globulin Intravenous (Human), 5% Liquid: 5g, 10g, 20g
GAMUNEX-C [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified]: 1g, 2.5g, 5g, 10g, 20g, 40g
HIZENTRA®*, Immune Globulin Subcutaneous (Human), 20% Liquid: Vials 1g, 2g, 4g, 10g; Prefilled Syringe: 1g, 2g, 4g
HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] Solution: 2.5g, 5g, 10g, 20g, 30g
Octagam 10% [Immune Globulin Intravenous (Human)] liquid solution for intravenous administration: 2g, 5g, 10g
Octagam [Immune Globulin Intravenous (Human)] 5% Liquid Preparation: 1g, 2.5g, 5g, 10g, 25g
PANZYGA, (immune globulin intravenous, human - ifas) 10% Liquid Preparation: 1g, 2.5g, 5g, 10g, 20g, 30g
PRIVIGEN Immune Globulin Intravenous (Human), 10% Liquid: 5g, 10g, 20g, 40g

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1. ASCENIV (immune globulin intravenous, human – slra) 10% liquid package insert. Boca Raton, FL: ADMA Biologics, April 2019
2. BIVIGAM (immune globulin intravenous, human) 10% liquid package insert. Boca Raton, FL: ADMA Biologics, July 2019
3. CUTAQUIG® (Immune Globulin Subcutaneous (Human) - hipp),16.5% solution package insert. Paramus, NJ: Octapharma USA, Inc., October 2021
4. CUVITRU, Immune Globulin Subcutaneous (Human), 20% Solution package insert. Lexington, MA: Baxalta US Inc., Inc, September 2021
5. FLEBOGAMMA 5% DIF (immune globulin intravenous [human]), solution package insert. Barcelona, Spain: GRIFOLS US LLC., September 2019
6. GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% solution package insert. Lexington, MA: Baxalta US Inc., March 2021
7. GAMMAGARD S/D, Immune Globulin Intravenous (Human) IgA less than 1 microgram per mL in a 5% Solution package insert. Lexington, MA: Baxalta US Inc., March 2021
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9. GAMMAPLEX 5% Immune Globulin Intravenous (Human), 5% Liquid Package Insert, Durham, NC: BPL Inc., September 2019
10. GAMMAPLEX 10% Immune Globulin Intravenous (Human), 10% Liquid Package Insert, Durham, NC: BPL Inc., September 2019
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12. HIZENTRA®, Immune Globulin Subcutaneous (Human), 20% Liquid package insert, Kankakee, IL: CSL Behring LLC, April 2022

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14. Octagam 10% [Immune Globulin Intravenous (Human)] liquid solution for intravenous administration package insert, Hoboken, NJ: Octapharma USA Inc. July 2021
15. Octagam [Immune Globulin Intravenous (Human)] 5% Liquid Preparation package insert, Hoboken, NJ: Octapharma USA Inc., March 2022
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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Age Restrictions Quantity Appendix Background Coding/Billing Information Available Dosage Forms References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file