IMMUNE GLOBULIN (IVIG and SCIG)

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Related Medical or Drug Policies:
None

Related Coverage Determination Guidelines:
None

INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

This policy refers to the following intravenous immune globulin (IVIG) drug products:
Bivigam™
Carimune® NF
Flebogamma®
Flebogamma® DIF
Gammagard® Liquid
Gammagard® S/D
Gammaked™
Gammaplex®
Gamunex®-C
Octagam®
Privigen®

And also to the following subcutaneous immune globulin (SCIG) drug products:
Gammagard® Liquid
Gammaked™

Gamunex®-C
Hizentra®

The term "IVIG" will be used in this policy where prescribing and dosing information is specific to the intravenous formulation. At all other times, the term "immune globulin" will be used.

The following information pertains to medical necessity review:

A. General Requirements (applicable to **all** medical necessity requests)**:**
1) For **initial therapy**, **both** of the following:
   a. Diagnosis
      AND
   b. Medical records documenting **both** of the following:
      1. History and physical examination documenting the severity of the condition, including frequency and severity of infections where applicable
         AND
      2. Laboratory results or diagnostic evidence supporting the indication for which immune globulin is requested
2) For **continuation of therapy, both** of the following:
   a. Documentation of positive clinical response to immune globulin therapy
      AND
   b. Statement of expected frequency and duration of proposed immune globulin treatment

B. Diagnosis-Specific Requirements
The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

Immune globulin is **proven** for:

1) Asthma (severe, persistent, high-dose steroid-dependent)[71,98,122]

   Additional information to support medical necessity review where applicable:
   Immune globulin is **medically necessary** for the treatment of severe, persistent, high-dose steroid-dependent asthma when **all** of the following criteria are met:
   A. Patient is receiving optimal conventional asthma therapy (e.g., high-dose inhaled glucocorticoids, short- and long-acting inhaled β agonists). *Refer to Benefit Considerations for specific state guidance*.
      AND
   B. Patient has required continuous oral glucocorticoid therapy for a minimum of 2 months prior to the decision to initiate immune globulin therapy. *Refer to Benefit Considerations for specific state guidance*.
      AND
   C. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

2) Autoimmune bullous diseases [pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, linear IgA bullous dermatosis][3,6,94,116,122,169]

   Additional information to support medical necessity review where applicable:
   Immune globulin is **medically necessary** for the treatment of autoimmune bullous diseases when **all** of the following criteria are met:
   A. Diagnosis of an autoimmune bullous disease
      AND
   B. Extensive and debilitating disease

AND

C. History of failure, contraindication, or intolerance to systemic corticosteroids **with concurrent** immunosuppressive treatment (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil). *Refer to Benefit Considerations for specific state guidance*.
AND

D. IVIG dose does not exceed 1,000 to 2,000 mg/kg per month divided into 3 equal doses each given over 3 consecutive days or 400 mg/kg per day given over 5 consecutive days per month. IVIG administration may be repeated monthly as needed for patients requiring maintenance therapy. Dosing interval may need to be adjusted in patients with severe comorbidities.[3]
AND

E. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

3) Autoimmune uveitis[121,122]

4) Bone marrow transplantation (BMT), prevention of acute graft vs. host disease (GVHD) after allogeneic BMT[57,122,152,158,177]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for prevention of acute GVHD after allogeneic BMT when **all** of the following criteria are met:

A. Confirmed allogeneic bone marrow transplant within the last 100 days[177]
AND

B. Documented severe hypogammaglobulinemia (IgG < 400 mg/dL)[177]
AND

C. IVIG dose does not exceed 500 mg/kg once weekly for the first 90 days of therapy, then monthly up to 360 days after transplantation

5) Bone marrow transplantation (BMT), prevention of infection after allogeneic BMT[46,57,122,152,158,177]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for prevention of infection after allogeneic BMT when **all** of the following criteria are met:

A. Confirmed allogeneic bone marrow transplant within the last 100 days[177]
AND

B. Documented severe hypogammaglobulinemia (IgG < 400 mg/dL)[177]
AND

C. IVIG dose does not exceed 500 mg/kg once weekly for the first 90 days of therapy, then monthly up to 360 days after transplantation

6) Chronic inflammatory demyelinating polyneuropathy[41,60,62,63,99,122,125,141,144,146,158,161]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of chronic inflammatory demyelinating polyneuropathy when **all** of the following criteria are met:

A. Initial treatment:
   1. Diagnosis of chronic inflammatory demyelinating polyneuropathy as confirmed by **all** of the following:
      a. Progressive symptoms present for at least 2 months[41,125,141,161]
      AND
      b. Symptomatic polyradiculoneuropathy as indicated by progressive or relapsing motor or sensory impairment of more than one limb[161]
      AND

c. Electrophysiologic findings when **three** of the following four criteria are present[99,144,146,161]:
    i. Partial conduction block of ≥ 1 motor nerve
    ii. Reduced conduction velocity of ≥ 2 motor nerves
    iii. Prolonged distal latency of ≥ 2 motor nerves
    iv. Prolonged F-wave latencies of ≥ 2 motor nerves or the absence of F waves

AND

d. **Both** of the following findings following lumbar puncture[161]:
    i. White blood cell count <10/mm^3
    ii. Elevated CSF protein

AND

2. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days administered in up to six monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.[41,47,50,60]

B. Continuation of treatment:
1. Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]
AND
2. For long-term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect[161]
AND
3. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities.[41,47,50,60]

7) Chronic lymphocytic leukemia (CLL), prevention of infection in B-cell CLL[8,58,59,115,123,158]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the prevention of infection in B-cell chronic lymphocytic leukemia when **all** of the following criteria are met:

A. Diagnosis of B-cell chronic lymphocytic leukemia (CLL)[8,58,59,115,123,158]
AND
B. **One** of the following:
1. Documented hypogammaglobulinemia (IgG < 500 mg/dL)[115,123]
2. History of bacterial infection(s) associated with B-cell CLL
AND
C. IVIG dose does not exceed 400 mg/kg every 3 to 4 weeks

8) Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants[93,122]

9) Dermatomyositis or polymyositis[41,42,47,50,122,125,141]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of dermatomyositis or polymyositis when **all** of the following criteria are met:

A. Diagnosis of dermatomyositis or polymyositis
AND
B. History of failure, contraindication, or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids, cyclophosphamide, methotrexate) *Refer to Benefit Considerations for specific state guidance*.
AND

C. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days administered as monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.
AND
D. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

10) Diabetes mellitus[73,122]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of autoimmune diabetes mellitus when **both** of the following criteria are met:
A. Patient is newly diagnosed with insulin dependent (type 1) diabetes mellitus
AND
B. Patient is not a candidate for or is refractory to insulin therapy. *Refer to Benefit Considerations for specific state guidance*.

11) Enteroviral meningoencephalitis[45,122,135]

12) Fetomaternal alloimmune thrombocytopenia[1,8,134]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of fetomaternal alloimmune thrombocytopenia when **all** of the following criteria are met:
A. For pregnant women:
1. Diagnosis of fetomaternal alloimmune thrombocytopenia
AND
2. **One** or more of the following:
a. Previously affected pregnancy
b. Family history of the disease
c. Platelet alloantibodies found on screening
AND
3. IVIG dose does not exceed 1,000 mg/kg once weekly until delivery
OR
B. For newborns:
1. Diagnosis of fetomaternal alloimmune thrombocytopenia
AND
2. Thrombocytopenia that persists after transfusion of antigen-negative compatible platelets

13) Graves' ophthalmopathy[14,122]

14) Guillain-Barré syndrome (GBS)[41,50,79,80,122,125,141,161]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of Guillain-Barré syndrome when **all** of the following criteria are met:
A. Diagnosis of Guillain-Barré Syndrome
AND
B. Severe disease requiring aid to walk
AND
C. Onset of neuropathic symptoms within the last four weeks
AND
D. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated in up to three monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.

AND

E. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

15) HIV-infection, prevention of bacterial infection in pediatric HIV[57,89,111,158,178]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the prevention of bacterial infection in pediatric HIV when **all** of the following criteria are met:

A. Diagnosis of HIV disease[57,89,111,158,178]
AND
B. Patient age ≤ 13 years[57,111,178]
AND
C. **One** of the following criteria:
1. Documented hypogammaglobulinemia (IgG < 400 mg/dL)[89]
OR
2. Functional antibody deficiency as demonstrated by either poor specific antibody titers or recurrent bacterial infections[89]
AND
D. IVIG dose does not exceed 400 mg/kg every 28 days[57,111,178]

16) Idiopathic thrombocytopenic purpura (ITP)[8,28,57,59,60,62,63,122,133,151,158]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of idiopathic thrombocytopenic purpura when **one** of the following criteria is met:

A. **All** of the following:
1. Diagnosis of **acute** thrombocytopenic purpura (ITP)[8,28,57,59,60,62,63,122,133,151,158]
AND
2. Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days)[151]
AND
3. IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days.[28,57,59-60,63,133]
OR
B. **All** of the following:
1. Diagnosis of **chronic** thrombocytopenic purpura (ITP)[8,28,57,59,60,62,63,122,133,151,158]
AND
2. **History of failure, contraindication, or intolerance to **one** of the following:
a. Corticosteroids
b. Splenectomy
AND
3. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.[28,57,59-60,63,133]

17) IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy[41,122]

18) Kawasaki disease[59,122,158,172]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of Kawasaki disease when **both** of the following criteria are met:

A. Diagnosis of Kawasaki disease
AND
B. IVIG dose does not exceed 400 mg/kg for five consecutive days or a single dose of 2,000 mg/kg

19) Lambert-Eaton myasthenic syndrome (LEMS)[41,47,50,122,125,141,181-2]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of Lambert-Eaton myasthenic syndrome when **all** of the following criteria are met:
A. Diagnosis of Lambert-Eaton myasthenic syndrome (LEMS)[41,47,50,122,125,141,181-2]
AND
B. History of failure, contraindication, or intolerance to immunomodulator monotherapy (e.g., azathioprine, corticosteroids)[181-2] *Refer to Benefit Considerations for specific state guidance*.
AND
C. Concomitant immunomodulator therapy (e.g., azathioprine, corticosteroids), unless contraindicated, will be used for long-term management of LEMS[181-2] *Refer to Benefit Considerations for specific state guidance*.
AND
D. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days.[50] IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities.
AND
E. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

20) Lennox Gastaut syndrome[47,50]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of Lennox Gastaut syndrome when **all** of the following criteria are met:
A. History of failure, contraindication or intolerance to initial treatment with traditional anti-epileptic pharmacotherapy (e.g., lamotrigine, phenytoin, valproic acid).[47] *Refer to Benefit Considerations for specific state guidance*.
AND
B. IVIG dose does not exceed 400 mg/kg/day given for 4 to 5 consecutive days. IVIG administration may be repeated monthly as needed in patients requiring maintenance therapy. Dosing interval may need to be adjusted in patients with severe comorbidities.[47]
AND
C. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

21) Lymphoproliferative disease, treatment of bacterial infections[122]

22) Monoclonal gammopathy[66,122]

23) Multifocal motor neuropathy (MMN)[41,47,50,58,122,125,183]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of multifocal motor neuropathy when **both** of the following criteria are met:
A. Initial treatment:

1. Diagnosis of multifocal motor neuropathy as confirmed by **all** of the following:[183]
   a. Weakness with slowly progressive or stepwise progressive course over at least one month
   AND
   b. Asymmetric involvement of two or more nerves
   AND
   c. Absence of motor neuron signs and bulbar signs
   AND
2. IVIG dose does not exceed 2,400 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval may need to be adjusted in patients with severe comorbidities.[41,47,50,183]

B. Continuation of treatment:
1. Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]
   AND
2. IVIG dose does not exceed 2,400 mg/kg per month given over 2 to 5 consecutive days. Dosing interval may need to be adjusted in patients with severe comorbidities.[41,47,50,183]
   AND
3. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

24) Multiple sclerosis, relapsing remitting (RRMS)[47,49,50,67,77,122,149]
NOTE: Treatment of any other type of multiple sclerosis with immune globulin is not supported by clinical evidence.

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of relapsing remitting multiple sclerosis when **all** of the following criteria are met:

A. Initial treatment:
1. Diagnosis of relapsing-remitting multiple sclerosis (RRMS)
   AND
2. Documentation of an MS exacerbation or progression (worsening) of the patient's clinical status from the visit prior to the one prompting the decision to initiate immune globulin therapy.
   AND
3. History of failure, contraindication, or intolerance to **two** of the following agents: *Refer to Benefit Considerations for specific state guidance*.
   a. Aubagio (teriflunomide)
   b. Avonex (interferon beta-1a)
   c. Betaseron (interferon beta-1b)
   d. Extavia (interferon beta-1b)
   e. Copaxone (glatiramer acetate)
   f. Gilenya (fingolimod)
   g. Rebif (interferon beta-1a)
   h. Tecfidera (dimethyl fumarate)
   i. Tysabri (natalizumab)
   AND
4. Induction, when indicated, does not exceed a dose of 400 mg/kg daily for up to five days

B. Continuation of treatment:
1. Medical records, including findings of interval examination including neurological deficits incurred and assessment of disability [e.g., Expanded

Disability Status Scale (EDSS), Functional Systems Score (FSS), Multiple Sclerosis Functional Composite (MSFC), Disease Steps (DS)]
AND
2. Stable or improved disability score (e.g., EDSS, FSS, MSFC, DS)
AND
3. Documentation of decreased number of relapses since starting immune globulin therapy
AND
4. Diagnosis continues to be the relapsing-remitting form of MS (RRMS)
AND
5. IVIG dose does not exceed 1,000 mg/kg monthly
AND
6. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

25) Myasthenic exacerbation[41,47,50,56,72,122,125]
NOTE: Evidence does not support the use of immune globulin maintenance therapy for generalized myasthenia gravis or for ocular myasthenia.

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of myasthenic exacerbation when **all** of the following criteria are met:
A. Diagnosis of generalized myasthenia gravis
AND
B. Evidence of myasthenic exacerbation, defined by **one** of the following symptoms in the last month:
1. Difficulty swallowing
2. Acute respiratory failure
3. Major functional disability responsible for the discontinuation of physical activity
AND
C. Concomitant immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine), unless contraindicated, will be used for long-term management of myasthenia gravis. *Refer to Benefit Considerations for specific state guidance*.
AND
D. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days administered in up to three monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.

26) Neuromyeltis optica[81,190-191]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of neuromyelitis optica when **all** of the following criteria are met:
A. Diagnosis of neuromyelitis optica
AND
B. History of failure, contraindication, or intolerance to **two** of the following: *Refer to Benefit Considerations for specific state guidance*.
1. Azathioprine
2. Corticosteroids
3. Mycophenolate mofetil
4. Rituximab
AND

C. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days administered in up to six monthly infusions. Dosing interval may need to be adjusted in patients with severe comorbidities.

27) Paraproteinemic neuropathy[66,122]

28) Posttransfusion purpura[8,122]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of posttransfusion purpura when **both** of the following criteria are met:

A. Diagnosis of posttransfusion purpura
AND
B. IVIG dose does not exceed 1,000 mg/kg for 2 days

29) Primary immunodeficiency syndromes[8,28,51,52,57-63,76,118,122,133,158,164,173,183-9] **(list not all inclusive)**

A. Autosomal recessive agammaglobinulinemia
B. Autosomal recessive hyperimmunoglobulin M syndrome (HIM)
C. Bruton's disease
D. Combined immunodeficiency disorders
   1. Ataxia-telangiectasia
   2. DiGeorge syndrome
   3. Nijmegan breakage syndrome
   4. WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome
   5. Wiskott Aldrich syndrome
E. Common variable immunodeficiency (CVID)
F. Congenital hypogammaglobulinemia late onset, ICOS impaired
G. Congenital / X-linked agammaglobulinemia
H. Good syndrome (immunodeficiency with thymoma)
I. Hyperimmunoglobulinemia E syndrome
J. Hypogammaglobulinemia
K. ICF syndrome
L. Selective IgG subclass deficiencies (persistent absence of IgG1, IgG2, and/or IgG3)
M. Selective IgM deficiency
N. Severe combined immunodeficiency
O. Specific antibody deficiency
P. Transient hypogammaglobulinemia of infancy, short-term treatment of recurrent severe bacterial infections
Q. X-linked immunodeficiency with hyperimmunoglobulin M

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of primary immunodeficiency syndromes when **all** of the following criteria are met:

A. Diagnosis of primary immunodeficiency
AND
B. Clinically significant functional deficiency of humoral immunity as evidenced by **one** of the following:
   1) Documented failure to produce antibodies to specific antigens
   OR
   2) History of significant recurrent infections
AND
C. Initial IVIG dose is 300 to 600 mg/kg every 3 to 4 weeks and titrated based upon patient response.[28,51-2,57-61,63,76,118,133]

30) Rasmussen syndrome[50,122]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of Rasmussen syndrome when **both** of the following criteria are met:

A. Documentation that short term amelioration of encephalitis is needed prior to definitive surgical therapy
AND
B. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days. IVIG is not recommended for long-term therapy for Rasmussen's encephalitis as surgical treatment is the current standard of care.[50]

31) Renal transplantation, prevention of acute humoral rejection[30,87,104,112,122]

32) Renal transplantation, treatment of acute humoral rejection[30,87,104,112,122]

33) Rheumatoid arthritis, severe[114,122,155]

34) Rotaviral enterocolitis[68,122]

35) Staphylococcal toxic shock[122]

36) Stiff-person syndrome[41,47,50,122,179-80]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of stiff-person syndrome when **all** of the following criteria are met:

A. Diagnosis of stiff-person syndrome
AND
B. History of failure, contraindication or intolerance to GABAergic medication (e.g., baclofen, benzodiazepines)[47,50,179-80] *Refer to Benefit Considerations for specific state guidance*.
AND
C. History of failure, contraindication or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids)[179-80] *Refer to Benefit Considerations for specific state guidance*.
AND
D. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 days. IVIG administration may be repeated monthly as needed for patients requiring maintenance therapy. Dosing interval may need to be adjusted in patients with severe comorbidities.[50]
AND
E. For long term treatment, documentation of titration to the minimum dose and frequency needed to maintain a sustained clinical effect

37) Thrombocytopenia, secondary to HCV (hepatitis C virus) infection[192]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of thrombocytopenia when **one** of the following criteria is met:

A. For initial therapy, **all** of the following:
1. Diagnosis of thrombocytopenia secondary to HCV infection[192]
AND
2. **Patient is receiving concurrent antiviral therapy, unless contraindicated.[192] *Refer to Benefit Considerations for specific state guidance*.

AND

3. Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days)[151]

AND

4. IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days

OR

B. For continuation of therapy, **all** of the following:

1. Diagnosis of thrombocytopenia secondary to HCV infection[192]

AND

2. ** Patient is receiving concurrent antiviral therapy, unless contraindicated.[192] *Refer to Benefit Considerations for specific state guidance*.

AND

3. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.[28,57,59-60,63,133]

38) Thrombocytopenia, secondary to HIV (human immunodeficiency virus) infection[192]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of thrombocytopenia when **one** of the following criteria is met:

A. For initial therapy, **all** of the following:

1. Diagnosis of thrombocytopenia secondary to HIV infection[192]

AND

2. **Patient is receiving concurrent antiretroviral therapy, unless contraindicated.[192] *Refer to Benefit Considerations for specific state guidance*.

AND

3. Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days)[151]

AND

4. IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days

OR

B. For continuation of therapy, **all** of the following:

1. Diagnosis of thrombocytopenia secondary to HIV infection[192]

AND

2. ** Patient is receiving concurrent antiretroviral therapy, unless contraindicated.[192] *Refer to Benefit Considerations for specific state guidance*.

AND

3. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.[28,57,59-60,63,133]

39) Thrombocytopenia, secondary to pregnancy[192]

Additional information to support medical necessity review where applicable:
Immune globulin is **medically necessary** for the treatment of thrombocytopenia when **one** of the following criteria is met:

A. For initial therapy, **all** of the following:

1. Diagnosis of thrombocytopenia secondary to pregnancy[192]

AND

2. Documented platelet count < 50 x 10^9 / L (obtained within the past 30 days)[151]
   AND
3. IVIG dose does not exceed 1,000 mg/kg/day for 1 to 2 days

OR

B. For continuation of therapy, **both** of the following:
1. Diagnosis of thrombocytopenia secondary to pregnancy[192]
   AND
2. IVIG dose does not exceed 2,000 mg/kg per month given over 2 to 5 consecutive days. IVIG administration may be repeated monthly as needed to prevent exacerbation. Dosing interval should be adjusted depending upon response and titrated to the minimum effective dose that can be given at maximum intervals to maintain safe platelet levels.[28,57,59-60,63,133]

40) Toxic epidermal necrolysis or Stevens-Johnson syndrome[55,122]

41) Urticaria, delayed pressure[37,122]

Immune globulin is **unproven** for:

1) Acquired hemophilia
2) Acute disseminated encephalomyelitis (ADEM)
3) Adrenoleukodystrophy
4) Alzheimer's disease
5) Amyotrophic lateral sclerosis (ALS)
6) Antiphospholipid antibody syndrome (APS) in pregnancy
7) Asthma, non-steroid dependent
8) Atopic dermatitis
9) Autism spectrum disorders
10) Autoimmune hemolytic anemia
11) Autoimmune liver disease
12) Autoimmune neutropenia
13) Bone marrow transplantation (BMT), prevention of acute graft vs. host disease (GVHD) after autologous BMT
14) Bone marrow transplantation (BMT), prevention of chronic graft vs. host disease (GVHD) after either allogeneic or autologous BMT
15) Bone marrow transplantation (BMT), prevention of infection after autologous BMT
16) *Campylobacter* species-induced enteritis
17) Cerebral infarctions with antiphospholipid antibodies
18) Chronic fatigue syndrome
19) Demyelinative brain stem encephalitis
20) Demyelinating neuropathy associated with monoclonal IgM
21) Dilated cardiomyopathy
22) HIV infection, to reduce viral load
23) HTLV-1-associated myelopathy
24) Idiopathic dysautonomia, acute
25) Inclusion body myositis
26) Isolated IgA deficiency
27) Isolated IgG4 deficiency
28) Lumbosacral or brachial plexitis
29) Myocarditis, acute
30) Neonatal isoimmune hemolytic jaundice
31) Neonatal sepsis, prevention
32) Neonatal sepsis, treatment
33) Ocular myasthenia
34) Opsoclonus myoclonus
35) Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy

36) Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
37) POEMS syndrome
38) Postinfectious cerebellar ataxia
39) Postoperative sepsis
40) Pseudomembranous colitis
41) Respiratory syncytial virus (RSV) lower respiratory tract infection
42) Rheumatic fever, acute
43) Sjogren's syndrome
44) Spontaneous recurrent abortions, prevention
45) Systemic lupus erythematosus
46) Urticaria, chronic
47) Vasculitides and antineutrophil antibody syndromes

Efficacy for these conditions has not been described in adequately designed studies. The available evidence is limited to case reports or case series, anecdotal reports, and open-label trials, or the available studies have failed to demonstrate a positive treatment effect. Further well-designed studies are needed to establish the role of immune globulin in these conditions.

Centers for Medicare and Medicaid Services (CMS):
Medicare covers Intravenous Immune Globulin when criteria are met. Refer to the National Coverage Determination (NCD) for Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3) and Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine) (260.7).

Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Drugs and Biologicals: Immune Globulin Intravenous (IVIg), External Infusion Pumps, Immune Globulin Intravenous (IVIg), Immune Globulins, Intravenous Immune globulin and Intravenous Immune Globulin (IVIg).

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

(Accessed June 3, 2014)

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications when certain conditions are met. Regulations governing off-label use in the individual state must be consulted when deciding coverage. Benefit coverage for otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

BACKGROUND

Immune globulin, whether intravenous (IV) or subcutaneous (SC), is a sterile, purified preparation of human immunoglobulin derived from pooled human plasma from thousands of donors. Consisting primarily of immunoglobulin G, one of 5 classes of immunoglobulin (Ig), each batch of immune globulin (typically referred to as IVIG) provides immunomodulating peptides and

antibodies against most exogenous antigens, many normal human proteins, and Fab, the antigen-binding region of autoantibodies.[72] All currently available products contain high concentrations of IgG with subclass distribution corresponding to that of normal serum.[28,51,52,57-63,76,118,133,164]

IVIG is considered a mainstay of treatment for immunodeficiency conditions and bullous skin disorders. It has been prescribed off-label to treat a wide variety of autoimmune and inflammatory neurologic conditions.[72]

CLINICAL EVIDENCE

Proven

Autoimmune Diseases

IVIG is beneficial for treatment of a number of autoimmune diseases based upon US Food and Drug Administration (FDA) approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include immune thrombocytopenic purpura,[8,28,57,59,60,62,63,122,133,151,158] Graves' ophthalmopathy,[14,122] autoimmune uveitis,[121,122] dermatomyositis and polymyositis,[41,42,47,50,122,125,141] severe rheumatoid arthritis,[114,122,155] and autoimmune diabetes mellitus.[73,122]

IVIG is a first-line therapy for fetomaternal alloimmune thrombocytopenia.[1,8,134]

An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for hematologic conditions. Response rates in available reports of post-transfusion purpura, a rare and life-threatening condition were high.[8]

Infectious and Infection-related Diseases

IVIG is beneficial for a number of infectious and infection-related diseases based upon FDA approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include prevention of coronary artery aneurysms associated with Kawasaki syndrome,[59,122,158,172] treatment of CMV-induced pneumonitis in solid organ transplants,[93,122] treatment of rotaviral enterocolitis,[68,122] treatment of staphylococcal toxic shock,[122] treatment of enteroviral meningoencephalitis,[45,122,135] treatment of bacterial infections in lymphoproliferative diseases,[122] prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL).[8,59,115,123,158]

Neuroimmunologic Disorders

IVIG is beneficial for treatment of a number of neuroimmunologic diseases based upon FDA approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include chronic inflammatory demyelinating polyneuropathy,[41,60,62,63,99,122,125,141,144,146,158,161] Guillain-Barré syndrome,[41,50,79,80,122,125,141,162] multifocal motor neuropathy,[41,47,50,58,122,125] Lambert-Eaton myasthenic syndrome,[41,47,50,122,125,141] IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy,[122] paraproteinemic neuropathy,[66,122] stiff-person syndrome,[41,47,50,122] myasthenia gravis,[41,47,50,56,72,122,125] Lennox-Gastaut,[47,50] Rasmussen syndrome,[50,122] and monoclonal gammopathy.[66,122]

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions states that IVIG should be reserved as an option for patients with relapsing-remitting MS who fail, decline, or are not able to take standard immunomodulatory therapies. Based on consensus by the expert panel, IVIG is not recommended for treatment of primary or secondary progressive MS or for acute exacerbations of MS.[50]

In their Guidelines for the Use of Intravenous Immunoglobulin in the Treatment of Neurological Diseases, the European Federation of Neurological Societies (EFNS) states that IVIG could be considered as a second or third-line therapy in RRMS if conventional immunomodulatory therapies are not tolerated because of side effects or concomitant diseases, and in particular in pregnancy where other therapies may not be used. IVIG cannot be recommended for treatment in secondary progressive MS. IVIG does not seem to have any valuable effect as add-on therapy to methylprednisolone for acute exacerbations and cannot be recommended as treatment for chronic symptoms in MS. In clinically isolated syndromes and in primary progressive MS, the EFNS Task Force concluded that there is not sufficient evidence to make any recommendations.[47]

Similar findings were reported in a review of evidence by members of the Primary Immunodeficiency Committee of the AAAAI. The Committee concluded that IVIG might provide benefit for relapsing-remitting multiple sclerosis.[122] A meta-analysis and a review of multiple sclerosis clinical trials also found that evidence supports the use of IVIG for reduction of relapses in relapsing-remitting MS.[67,149] The use of IVIG in relapsing-remitting MS should only be considered when other established therapies have failed or cannot be utilized.

In their review of relapse therapy and intermittent long-term therapy, the Neuromyelitis Optica Study Group (NEMOS) suggests IVIG therapy as an alternative for patients with contraindication to one of the other treatments (azathioprine and rituximab) or, particularly, in children.[81]

The use of intravenous immunoglobulin (IVIG) as treatment for acute relapses in NMO was reported in a retrospective review of 10 patients.[190] In the majority of cases, IVIG was used due to lack of response to steroids with/without plasma exchange. Improvement was noted in five of 11 (45.5%) events; the remaining had no further worsening.

In a case series of eight Spanish patients with neuromyelitis optica (NMO), positive results were observed from bimonthly IVIG treatment (0.7 g/kg body weight/day for 3 days).[191] The primary outcome measure in the study was the occurrence of serious adverse effects. Secondary outcome measures were changes in the yearly rate of attacks and in the degree of neurological disability measured with the Expanded Disability Status Scale (EDSS). All 8 patients were treated with IVIG; 5 had relapsing optic neuritis with or without myelitis and 3 had recurrent longitudinally extensive transverse myelitis (LETM). The mean age of onset was 20.5 years (range, 7-31 years) and 87.5% were female. The mean duration of the disease before beginning treatment was 9.0 years (range, 3-17 years). Following 83 infusions (range, 4-21 per patient) and a mean follow-up time of 19.3 months (range, 6-39 months), minor adverse events had occurred (headache in 3 patients and a mild cutaneous eruption in a single patient). The relapse rate decreased from 1.8 in the previous year to 0.006 during follow-up ($z = -2.5$, p=0.01). The EDSS score fell from 3.3 [SD 1.3] to 2.6 [SD 1.5] ($z = -2.0$, p=0.04). The investigators concluded that treatment with IVIG is safe and well-tolerated, and it may be used as a treatment alternative for NMO spectrum disorders.

Primary and Secondary Immune Deficiencies

IVIG is indicated as replacement therapy in primary immune deficiencies.[8,28,51,52,57-63,76,118,122,133,158,164,173]

IVIG is also beneficial in chronic lymphocytic leukemia with reduced IgG and history of infections[8,58,59,115,123,158] and prevention of bacterial infection in HIV-infected children.[57,89,111,158]

Miscellaneous Categories

Evidence supports IVIG for autoimmune bullous diseases;[3,6,94,116,122,172] toxic epidermal necrolysis and Stevens-Johnson syndrome;[55,122] severe, persistent, high-dose, steroid-dependent asthma;[71,98,122] delayed-pressure urticaria;[37,122] prevention of infection and acute GVHD after

allogeneic bone marrow transplantation;[46,57,122,152,158,177] and prevention and treatment of acute humoral rejection in renal transplantation.[30,87,104,112,122]

Unproven

Acquired hemophilia: An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for hematologic conditions. In the opinion of the expert panel, there is no convincing evidence of clinical benefit of IVIG in this disorder, and routine use is not recommended.[8]

Acute disseminated encephalomyelitis (**ADEM**): This is a nonvasculitic inflammatory demyelinating condition of brain that usually occurs following a viral infection but may appear following vaccination, bacterial or parasitic infection, or even appear spontaneously. The widely accepted first-line treatment is high doses of intravenous corticosteroids. Several case reports, but no controlled trials, have provided evidence of IVIG's successful use in ADEM. The largest by Ravaglia et al. reported that in 10 of 19 ADEM patients who had failed steroids, IVIG was effective in improving motor dysfunction. Among an additional 5 patients who received IVIG first-line due to steroid contraindications, 3 were responsive to IVIG.[136]

Adrenoleukodystrophy (ALD): This is one of a group of genetic disorders called the leukodystrophies that cause damage to the myelin sheath surrounding nerve cells in the brain and progressive dysfunction of the adrenal gland. In one very small randomized trial 6 patients received IVIG in addition to the dietary therapy while 6 received dietary therapy alone. No treatment effect of IVIG was demonstrated in this study. MRI findings and clinical status deteriorated in both groups.[27] The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that IVIG should not be used for ALD.[50]

Alzheimer's disease: An open label dose-ranging study was conducted in 8 mild Alzheimer's disease (AD) patients. IVIG was added to approved AD therapies for 6 months, discontinued, and then resumed for another 9 months. Anti-Aβ antibodies in the serum from AD patients increased in proportion to IVIG dose and had a shorter half-life than anti-hepatitis antibodies and total IgG. Plasma Aβ levels increased transiently after each infusion. Cerebrospinal fluid Aβ decreased significantly at 6 months, returned to baseline after washout and decreased again after IVIG was re-administered for an additional 9 months. Mini-mental state scores increased an average of 2.5 points after 6 months, returned to baseline during washout and remained stable during subsequent IVIG treatment. This study did not include an adequate number of AD patients to establish whether IVIG altered cognitive status.[137]

Devi et al. reported on a retrospective investigation of patients (n=10) with Alzheimer's disease treated with IVIG. Eight of the patients completed 6 months of treatment; two completed 3.5 months of treatment. Two patients developed a pruritic, maculopapular, generalized rash, resolving with appropriate treatment, but both continued with IVIG. Patients showed stability on neurocognitive scores overall, with trends toward decline on their WAIS verbal scale and full-scale intelligence scores ($p<0.1$), as well as on the WAIS information ($p<0.1$) subtest and the BNT ($p=0.1$). Patients showed trends toward improvement on the WMS logical memory II recall ($p<0.1$), WMS verbal paired associates ($p=0.15$), and the WMS auditory delayed memory test ($p=0.1$). It was found that IVIG was well tolerated and effective in this sample, with patients showing stability on neurocognitive test scores and trends toward improvement in some areas.[40]

Further studies are needed to establish efficacy, to determine the optimal dosing regimen and to confirm the safety of IVIG in the general population of AD patients.

Amyotrophic lateral sclerosis (ALS): This is a disease characterized by progressive motor neuron degeneration, which manifests as weakness, spasticity, and muscle atrophy, usually

beginning with the upper limbs. Two small-scale, uncontrolled studies (n=7,9) examined the use of IVIG for treatment of ALS; neither of these studies found a positive treatment effect. During and after treatment, all patients showed progressive deterioration at a pace similar to that observed before treatment or faster.[35,109] The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that there is no role for IVIG in the treatment of ALS.[50]

Antiphospholipid antibody syndrome (APS) in pregnancy: In their guideline for the treatment of recurrent first-trimester and second-trimester miscarriage, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends against the use of IVIG.[142] There are several reports supporting a role for IVIG in the treatment of antiphospholipid antibody syndrome (APS), including in patients with APS undergoing in vitro fertilization. However, a meta-analysis of several modes of therapy (heparin, aspirin, glucocorticosteroids, and IVIG) in this clinical setting did not support any improved outcome with IVIG and a possible association with pregnancy loss or premature birth.[48] A small randomized controlled study (n=16) demonstrated no greater benefit from IVIG (plus heparin and aspirin) than from heparin and aspirin alone.[20] Because the efficacy of IVIG has not been proved in appropriately designed studies, its use is not recommended for APS in pregnancy.[2]

Asthma, non-steroid dependent: While there have been studies done on the effect of IVIG on steroid-dependent asthma patients with efficacy shown in a trial with a subgroup that required relatively high doses of daily oral steroids, there are no clinical trials or studies to support the effect on non-steroid dependent patients.[122]

Atopic dermatitis: IVIG treatment has shown success in small, open, uncontrolled trials of patients not responding to standard therapies.[122] A small, randomized, evaluator-blinded trial (n = 10) did not support the routine use of IVIG in patients with atopic dermatitis.[126]

Autism spectrum disorders: According to the review of evidence by members of the Primary Immunodeficiency Committee of the AAAAI, there are no formal randomized studies to evaluate the use of IVIG in autism.[122] They found that two small, open-trial reports of autistic children placed on IVIG for 6 months showed no benefit.[39,131] The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that the available evidence does not support the use of IVIG in the treatment of autism.[50]

Autoimmune hemolytic anemia: Multiple anecdotal reports demonstrate benefit from the use of IVIG in the treatment of autoimmune hemolytic anemia (AIHA), but the use of IVIG should be considered only when other therapeutic modalities fail.[16,53,75,97,100] An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for hematologic conditions. They found "sparse evidence" on the use of IVIG in AIHA and despite a literal definition of response rates, those with IVIG were substantially less than accepted published response rates with other treatment alternatives. Therefore, they agreed the overall role of IVIG in AIHA is very limited.[8]

Autoimmune liver disease: In one case report of a patient with immuno-mediated chronic active hepatitis not eligible for steroids, IVIG treatment successfully normalized liver enzymes, led to undetectable circulating immune complexes, and disappearance of periportal mononuclear cell infiltrates.[29] Further studies evaluating the use of IVIG in autoimmune liver disease are needed, however, to determine the safety and efficacy of use.

Autoimmune neutropenia: Improvement in neutrophil counts has been described in several small series of patients with autoimmune neutropenia treated with IVIG,[23-25,97] and anecdotal reports also suggest utility for IVIG in post- bone marrow transplantation neutropenia, which might

be autoimmune in nature.[91,95,108] It is unclear whether IVIG offers any advantage over corticosteroid therapy for the treatment of autoimmune neutropenia. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts evidence-based practice guideline on the use of IVIG for hematologic conditions found that "the evidence to support treatment with IVIG is sparse and of poor quality. However, there was some discussion regarding its use in rare circumstances when other options (e.g. intravenous antibiotics and G-CSF) have failed.[8]

Bone marrow transplantation (BMT), prevention of acute graft-versus-host disease (GVHD) after autologous BMT: According to the Centers for Disease Control and Prevention, routine use of IVIG among autologous recipients is not recommended.[177]

Bone marrow transplantation (BMT), prevention of chronic graft-versus-host disease (GVHD) after either allogeneic or autologous BMT: The use of IVIG was studied in a randomized, double-blind, dose-effect, placebo-controlled, multicenter trial in related allogeneic marrow transplantation.[32] The trial included 200 patients receiving HLA-identical sibling marrow. IVIG-treated patients experienced no benefit versus placebo in reduction of incidence of infection, interstitial pneumonia, GVHD, transplantation-related mortality, or overall survival. There was a statistically higher incidence of grade 3 (severe) veno-occlusive disease associated with high-dose IVIG. The patients given higher doses of IVIG also had more side effects, such as fever and chills. The data does not support a recommendation for IVIG in HLA-identical sibling bone marrow transplants.[8]

Bone marrow transplantation (BMT), prevention of infection after autologous BMT: According to the Centers for Disease Control and Prevention, routine use of IVIG among autologous recipients is not recommended.[177]

***Campylobacter* species-induced enteritis:** The value of immunoglobulin therapy has been anecdotally described in *Campylobacter jejuni* infection when administered orally.[70] This uncontrolled report is insufficient to support the use for the treatment of this condition.

Cerebral infarctions with antiphospholipid antibodies: Only single case reports were found that reported successful treatment of patients with stroke associated with antiphospholipid syndrome. Horn et al. reported that a 32-year old woman with antiphospholipid antibody syndrome who developed progressive cerebral thrombosis rapid resolution of her neurological impairment after administration of IVIG.[78] Arabshahi et al. treated a child with trisomy 21, hypothyroidism, and insulin-dependent diabetes who developed acute hemiplegia due to the antiphospholipid antibody syndrome at age four. Antiphospholipid antibodies were no longer detectable within 6 months and have continued to be negative. There was no clinical deterioration or further changes on magnetic resonance arteriography over 7 years.[9]

Chronic fatigue syndrome: Numerous anecdotal reports have shown subjective benefits of IVIG for chronic fatigue syndrome. However, a double-blind, placebo-controlled trial demonstrated IVIG was not effective in the treatment of typical chronic fatigue syndrome.[122,165]

Demyelinative brain stem encephalitis: The disease is characterized by the acute onset of neurologic deficit days to weeks after a variety of viral and bacterial infections or vaccinations. The literature search identified one case series of 2 patients with acute demyelinating brainstem encephalitis who were treated with IVIG and improved rapidly, concomitant with the course of therapy.[13]

Demyelinating neuropathy associated with monoclonal IgM: Mariette et al. conducted a 12 month multicenter, prospective, randomized, open clinical trial to compare IVIG (n=10) and interferon alpha (n=10) in the treatment of 20 patients with polyneuropathy associated with monoclonal IgM. After six months of treatment 1 out of 10 patients treated with IVIG had an improvement of neurological symptoms versus eight out of 10 patients treated with interferon

alpha. The mean functional score worsened in the IVIG group whereas it improved in the interferon group.[106]

Dilated cardiomyopathy: According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, "Case reports suggest that patients with acute myocarditis benefit from high-dose IVIG. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo. High-dose IVIG might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy.[122]

HIV infection, to reduce viral load: Although IVIG is FDA-approved for reducing the incidence of secondary infection in HIV-infected children, its use in treating HIV infection per se has not been as widely evaluated. A study examining the effect of a 2 g/kg IVIG dose on viral load found that p24 antigen levels and numbers of HIV RNA copies were significantly increased after treatment.[31] Thus IVIG might be useful for preventing bacterial infections but should not be considered an antiviral therapy in the HIV-infected patient.[122]

Human T-Lymphotrophic Virus Type 1 (HTLV-1)-associated myelopathy: HTLV-1-associated myelopathy, also known as tropical spastic paresis, is a chronic inflammatory disease of the central nervous system (CNS). The one report of IVIG usage for HTLV-1-associated myelopathy was a very small case series study (n=14) that reported a positive response to IVIG therapy in 10 (71%) patients and included an increase of 30% to 280% in muscle strength. Effects were evident beginning from day 3 to day 7 after initial IVIG treatment and were sustained for over 3 weeks in 6 patients.[96]

Idiopathic dysautonomia, acute: This is a disorder characterized by severe sympathetic and parasympathetic failure with relative preservation of motor and sensory function. There is some anecdotal evidence that IVIG is effective in this disorder. Yoshimaru et al. described a case of a 32-year old man with acute idiopathic autonomic neuropathy (AIAN) in which IVIG proved effective.[170] Smit et al. reported that a 33-year-old woman with acute idiopathic postganglionic panautonomic neuropathy experienced prompt recovery of all dysautonomic symptoms after receiving high-dose intravenous immunoglobulin therapy.[148]

Inclusion body myositis: The treatment of inclusion body myositis (IBM) with IVIG has been studied in two randomized, double-blind, placebo controlled trials. In the first study (n=19), no statistically significant treatment differences were noted between IVIG and placebo.[34] In the second study (n=22), outcome measures showed a trend towards improvement with IVIG.[167] Based on these studies, IVIG is not recommended as routine therapy for IBM due to the variability of response and expense of therapy.[41]

In an additional placebo-controlled trial (n=36), no significant changes in primary outcomes were noted from baseline at each month after treatment.[36]

IVIG for inclusion body myositis was also assessed in open-label trials, but generalized conclusions or recommendations are not presently possible.[7,122,150]

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that IVIG should not be used for the treatment of IBM.[50]

In their Guidelines for the Use of Intravenous Immunoglobulin in the Treatment of Neurological Diseases, the European Federation of Neurological Societies (EFNS) states that IVIG cannot be recommended for the treatment of sporadic IBM.[47]

In their evidence-based guideline on IVIG in the treatment of neuromuscular disorders, the American Academy of Neurology states that there is insufficient evidence to support the use of IVIG in IBM.[125]

Isolated IgA deficiency: This is the most common immunodeficiency disorder characterized by a deficiency of IgA with normal levels of other immunoglobulin classes. Isolated IgA deficiency is marked by recurrent sinusitis, bronchitis, and pneumonia, and recurrent diarrhea, although many patients have no symptoms. Management of selective IgA deficiency is limited to treating associated infections. Some advocate prophylactic daily doses of antibiotics for patients with multiple, recurrent infections. No intervention is available to either replace IgA via infusion or increase production of native IgA.[140] Selective IgA deficiency is not an indication for IVIG replacement therapy, although in some cases poor specific IgG antibody production, with or without IgG2 subclass deficiency, might coexist; in these patients IVIG might be required. Intravenous administration of IVIG can pose a risk of anaphylaxis for IgA-deficient patients who have IgE anti-IgA antibodies or reactions caused by complement activation if IgG anti-IgA antibodies are present.[122]

Isolated IgG4 deficiency: IgG4 deficiency may be found in 10-15% of the general population. The significance of isolated, or selective, IgG4 deficiency is unclear.[22,160]

Lumbosacral or brachial plexitis: Only anecdotal experience is available for assessing the treatment with IVIG for lumbar and brachial plexitis. The literature search revealed single case reports with mixed outcomes.[10,124,171]

Myocarditis, acute: According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, "Case reports suggest that patients with acute myocarditis benefit from high-dose IVIG. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo. High-dose IVIG might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy.[122]

Neonatal isoimmune hemolytic jaundice: In a 2004 Cochrane review, seven studies were identified. Three of these fulfilled the inclusion criteria and included a total of 189 infants. Term and preterm infants and infants with rhesus and ABO incompatibility were included. The use of exchange transfusion decreased significantly in the IVIG treated group (typical RR 0.28, 95% CI 0.17, 0.47; typical RD -0.37, 95% CI -0.49, -0.26; NNT 2.7). The mean number of exchange transfusions per infant was also significantly lower in the IVIG treated group (WMD -0.52, 95% CI -0.70, -0.35). None of the studies assessed long term outcomes.

Although the results show a significant reduction in the need for exchange transfusion in those treated with intravenous immunoglobulin, the applicability of the results is limited.
The number of studies and infants included is small and none of the three included studies was of high quality. The protocols of two of the studies mandated the use of early exchange transfusion, limiting the generalizability of the results. Further well designed studies are needed before routine use of intravenous immunoglobulin can be recommended for the treatment of isoimmune haemolytic jaundice.[4]

Neonatal sepsis, prevention: A recent meta-analysis found that there is insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proved neonatal infection.[120] Despite encouraging trials of IVIG as an adjunct to enhance the antibacterial defenses of premature newborn infants, there are substantial contradictory data and insufficient overall evidence to support the routine administration of IVIG in infants at risk for neonatal infection.[122]

Neonatal sepsis, treatment: In a multi-center, international, double-blind controlled trial of 3,493 infants receiving antibiotics for suspected or proven infection, subjects were randomly assigned to

receive two infusions of either polyvalent IgG immune globulin (500 mg/kg) or placebo 48 hours apart. The investigators found that there was no significant between-group difference in the rates of primary outcome which was death or major disability at the age of 2 years. The primary outcome was observed in 686 of 1,759 infants (39.0%) in the intravenous immune globulin group and in 677 of 1,734 infants (39.0%) in the placebo group (relative risk, 1.00; 95% confidence interval, 0.92 to 1.08). No significant differences in the rates of seven pre-specified secondary outcomes were observed, including the incidence of subsequent sepsis episodes and causative organisms. In follow-up of survivors at 2 years, there were no significant differences in the rates of major or non-major disability or of adverse events. The authors concluded that the use of immune globulin was not associated with significant differences in the risk of major complications or other adverse outcomes in neonates with suspected or proven sepsis.[21]

A recent meta-analysis also found that there is insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proved neonatal infection.[120]

Ocular myasthenia: Myasthenia gravis is an autoimmune disorder in which the body's own antibodies block the transmission of nerve impulses to muscles, causing fluctuating weakness and muscles that tire easily. Approximately half of patients present with purely ocular symptoms (ptosis, diplopia), so-called ocular myasthenia. Between 50% and 60% of people who have ocular myasthenia will progress to develop generalized myasthenia gravis (GMG) and weakness affecting other muscles. The aims of treatment for ocular myasthenia are to return the person to a state of clear vision and to prevent the development, or limit the severity of GMG. Treatments proposed for ocular myasthenia include drugs that suppress the immune system including corticosteroids and azathioprine, thymectomy, and acetylcholinesterase inhibitors. There are retrospective, but no prospective, data, which indicate that immunosuppressive treatment of ocular myasthenia may decrease the likelihood of developing GMG. It is not clear from these studies whether treatment actually reduces the incidence of GMG, delays its onset, or just masks its symptoms. Plasmapheresis and intravenous immune globulin are used for the short-term management of severe GMG, but available evidence does not indicate that either therapy has a role in patients with ocular myasthenia.[174-5]

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. Published evidence consists of single case reports and case series that included patients with different etiology of opsoclonus-myoclonus and different treatment approaches. Bataller et al. analyzed neurological outcomes in adult patients with idiopathic (n=10) and paraneoplastic (n=14) opsoclonus-myoclonus following IVIG treatment. The authors found that most patients with idiopathic opsoclonus-myoclonus make a good recovery that seems to be accelerated by steroids or IVIG. Among the 14 patients with paraneoplastic opsoclonus-myoclonus, eight patients whose tumors were treated showed complete or partial neurological recovery. In contrast, five of the six patients whose tumors were not treated died of the neurological syndrome despite steroids, IVIG or plasma exchange.[15]

Russo et al. conducted a retrospective case series involving 29 children diagnosed with neuroblastoma and opsoclonus-myoclonus. Patients were treated with different treatment options including ACTH (n=14), prednisone (n=12), IVIG (n=6), Imuran (n=2), and other drugs (n=2) Eighteen of 29 children (62%) had resolution of opsoclonus-myoclonus symptoms. Twenty of 29 children (69%) had persistent neurologic deficits including speech delay, cognitive deficits, motor delay, and behavioral problems. Interestingly, 6/9 children with complete recovery received chemotherapy as part of their treatment[143] Based on this case series it is difficult to assess the effectiveness of IVIG compared to other treatment options.

Improvement following the administration of IVIG has been described in abundant single cases.[65,129,130,163]

Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy: Paraneoplastic neurological syndromes are remote effects of cancer that are not caused by invasion of the tumor or its metastases. Immunologic factors appear important in their pathogenesis because antineuronal autoantibodies against nervous system antigens have been defined for many of these disorders.[38]

Uchuya et al. evaluated 22 patients with neurological paraneoplastic syndromes (paraneoplastic encephalomyelitis and sensory neuronopathy syndrome =18; paraneoplastic cerebellar degeneration =4) and found treatment with IVIG was not effective in paraneoplastic CNS syndromes associated with antineuronal antibodies. Of the 21 patients who were evaluable one patient with subacute sensory neuronopathy improved for at least 15 months, 10 remained stable, and 10 deteriorated.[157]

Keime-Guibert et al. evaluated 17 patients with paraneoplastic encephalomyelitis/sensory neuropathy (PEM/SN=10) or cerebellar degeneration (PCD=7) who received one to nine cycles of a combination of IVIG, cyclophosphamide and methylprednisolone. Of the seven patients with severe symptoms (bedridden), none improved. Of the nine patients who were still ambulatory, none improved but three stabilized.[90]

Blaes et al. reported that IVIG treatment was effective in two patients, one suffering from paraneoplastic cerebellar degeneration and the other from paraneoplastic brain stem encephalitis and polyneuropathy who started infusions within 3 weeks of the onset of neurological symptoms. However, two other patients, who had suffered from paraneoplastic neuropathy for 3 and 6 months showed no improvement with the intravenous immunoglobulin therapy.[17]

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): Streptococcal infections induce exacerbation of symptoms in some children with obsessive-compulsive and tic disorders, possibly on an autoimmune basis. The syndrome of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection is referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, IVIG might provide benefit for PANDAS. However, it should be noted that those children who do not have the autoimmune feature do not benefit from IVIG.[122] The review cited only one case-controlled, single-dose study which showed benefit from plasmapharesis and IVIG therapy.[128] Additional double-blind, placebo-controlled studies are needed before this becomes a standard of therapy.

POEMS syndrome: Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome also known as Crow-Fukase syndrome or osteosclerotic myeloma is a unique multisystem disorder strongly associated with plasma cell dyscrasia. Only anecdotal experience is available for assessing IVIG as treatment for POEMS syndrome. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated there is no role for IVIG in the treatment of POEMS syndrome.[50]

Postinfectious cerebellar ataxia: Acute cerebellar ataxia in childhood is a usually a self-limited disease which occurs after viral infections.[117] Treatment with IVIG has not yet been established. Published evidence consists of isolated case reports. Daaboul et al. treated a 19 year-old man presented with acute cerebellar ataxia after a recent Epstein-Barr virus infection with IVIG. Progressive neurologic improvement occurred over two weeks.[33]

Postoperative sepsis: A meta-analysis identified six trials which enrolled surgical patients. The largest trial included 104 participants (50 received IVIG). In general, results favored IVIG versus

control, although one trial did not favor IVIG for reduction in number of deaths. Use in this setting should be evaluated in large trials in patients receiving current standard-of-care therapies.[156]

Pseudomembranous colitis: The value of IVIG therapy has been anecdotally described in pseudomembranous colitis caused by *Clostridium difficile* (*C. difficile*).[101,145] A retrospective analysis of 79 hospital-admitted patients who had a positive *C. difficile* toxin titer and severe disease included 18 patients given IVIG treatment (200-300 mg/kg) along with standard therapy. These patients were pair matched by propensity scoring with 18 patients not receiving IVIG who had the most similar characteristics and severity. There were no statistical differences in clinical outcomes as measured by all-cause mortality, colectomies, and length of stay. The investigators concluded that the use of IVIG in severe *C. difficile*-associated diarrhea remains unsubstantiated.[88]

Rheumatic fever, acute: In a prospective, double-blind trial, 59 patients with first episode of rheumatic fever, stratified by presence and severity of carditis (39 with carditis and/or migratory polyarthritis), were randomized to receive IVIG (1 g/kg on days 1 and 2 and 0.4 g/kg on days 14 and 28) or placebo. No difference in erythrocyte sedimentation rate or acute-phase proteins was found between the groups at 6 weeks. After 1 year, no difference in cardiac outcomes was found between the groups.[166]

RSV lower respiratory tract infection: The use of IVIG combined with ribavirin in the treatment of RSV-induced pneumonitis was reported in small series of immunodeficient patients.[64,168] Survival rates were encouraging and suggested that IVIG might be of benefit as an adjunct therapy to ribavirin. In a double-blind, controlled study involving 35 RSV-infected, hospitalized infants and children, IVIG 2 grams/kilogram was given over 12 to 24 hours. Therapy resulted in significant reductions in nasal RSV shedding and in improvements in transcutaneous oximetry readings. However, the mean duration of hospitalization was not reduced by IVIG treatment.[74]

Sjogren's syndrome: IVIG has shown some efficacy in Sjogren's syndrome. Most of the reports have focused on associated dysautonomia or neuropathy although they have been very small case studies.[43,69,92,110,113,153,154] One case study was of a 41 year old man with severe sympathetic and parasympathetic autonomic dysfunction as a consequence of acetylcholine receptor antibodies and Sjogren's syndrome who failed to respond to IVIG.[19] Other published literature has described IVIG use for vasculitis of the skin and central nervous system.[26,44] Larger, blinded and controlled studies of IVIG are required regarding its efficacy for Sjogren's syndrome.

Spontaneous recurrent abortions, prevention: Results of treatment with IVIG have been conflicting. While prospective studies have suggested that the use of IVIG in pregnant women with a history of recurrent abortions imparted a protective benefit, other studies suggested no benefit. The members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology assessed a review from a number of high-quality randomized, placebo-controlled, multicenter studies and found that, "Given the review of randomized trials, cumulative current evidence does not presently support the use of IVIG for the prevention of recurrent spontaneous abortions."[8]

In a Cochrane review by Porter et al., randomized trials of immunotherapies used to treat women with three or more prior miscarriages and no more than one live birth after were considered. Twenty trials of high quality were included. The various forms of immunotherapy investigated (paternal cell immunization, third party donor leukocytes, trophoblast membranes, and intravenous immune globulin) were found to provide no significant beneficial effect over placebo in improving the live birth rate.[132]

Systemic lupus erythematosus: The use of IVIG in the treatment of systemic lupus erythematosus (SLE) has been studied in a few open label trials. In the first trial, 20 patients with severe thrombocytopenia associated with SLE received IVIG 2 g/kg for 5 consecutive days each month and patients received between 1-8 treatment courses.[102] A beneficial response was noted

in 17 out of 20 patients based on either the disappearance or marked clinical improvement of the main clinical manifestation. In 9 patients who had Systemic Lupus Activity Measure (SLAM) scores before and after IVIG, there was a significant reduction in SLAM scores (19.3 ± 4.7 to 4 ± 2.9; p<0.0001). The average daily dose of prednisolone was decreased (29.7 ± 18.2 mg/day to 13.8 ± 16.7 mg/day; p=0.02) and laboratory abnormalities improved after IVIG. Two other open label studies, with 12 patients each, showed similar results.[54,147] In another trial, 14 patients with progressive lupus nephritis who had received cyclophosphamide 1 g/m^2 monthly for 6 months with 0.5 mg/kg/d of prednisone were randomized to cyclophosphamide 1 g/m^2 every 2 months for 6 months and then every 3 months for 1 year or to IVIG 400 mg/kg monthly for 18 months. The two groups were similar after randomization and at the end of follow-up.[18] In a retrospective study of 59 SLE patients, 65% of the thirty-one subjects given IVIG had clinical improvement. However, responses were transient.[11] In other case reports high-dose IVIG led to disease resolution in patients with lupus affecting specific organs. However, there is limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE.[122]

Urticaria, chronic: A report of 5 patients with common variable immunodeficiency and chronic urticaria showed improvement of urticaria in response to IVIG therapy.[5] The efficacy of IVIG (0.15 g/kg, for a minimum of 6 months and a maximum of 51 months) was also assessed in 29 outpatients (F=20, M=9) with the diagnosis of autoimmune chronic urticaria.[127] All the patients had unsatisfactory response to conventional therapy and a positive intradermal autologous serum test (AST). A clinical improvement was observed in 26 patients, with reduction of urticaria or angioedema complaints (p<0.0001) and decreasing need for oral antihistamine medication (p=0.002). The number of infusions needed to achieve clinical control showed great range between patients. In a report of delayed-pressure urticaria, a difficult-to-treat variant, 9 of 10 patients with chronic urticaria were reported to benefit from IVIG therapy, whereas, in another delayed-pressure urticaria report, no benefit was observed.[12,119] The use of IVIG in patients with delayed-pressure urticaria was reported in another open trial.[37] One third of the enrolled patients underwent a remission, another third experienced some benefit, and the rest did not respond. Due to the conflicting evidence for IVIG in patients with chronic urticaria, additional studies are needed.

Vasculitides and antineutrophil antibody syndromes: The efficacy of IVIG in the treatment of anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV) was assessed in a randomized, placebo-controlled trial.[86] Thirty four patients (24 diagnosed with Wegener's granulomatosis, 10 diagnosed with microscopic polyangiitis) were randomized to a single course of either 400 mg/kg/day IVIG or placebo for 5 days. A therapeutic response was defined as a 50% decrease in the Birmingham Vasculitis Activity Score (BVAS) at 3 months. A therapeutic response was found in 14/17 patients who received IVIG and 6/17 patients who received placebo (OR = 8.56, 95% CI = 1.74 - 42.2, p=0.015). The C-reactive protein (CRP) level decrease was significantly greater at 2 weeks and one month in the IVIG group compared to the placebo group. After 3 months, there was no difference in disease activity or CRP level between the IVIG and placebo groups. In addition, small open label trials of IVIG found some clinical benefit as an alternative therapeutic agent.[82-85,103,107,138,139] Results were reported as transient in several of these. Additional randomized controlled trials will need to be conducted to determine its place in therapy.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

There are currently eight clinical indications for which IVIG has been licensed by the United States Food and Drug Administration (FDA).[158] The indications can be summarized as follows:

1) treatment of primary immunodeficiencies such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies[28,51,52,57-63,76,118,133,164,173]
2) prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia[59]

3) prevention of coronary artery aneurysms in Kawasaki disease (KD)[59]
4) prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation[57]
5) reduction of serious bacterial infection in children with human immunodeficiency virus (HIV)[57]
6) increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding[28,57,58,60,62,63,133]
7) to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in chronic inflammatory demyelinating polyneuropathy (CIDP)[60,62,63]
8) as a maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy[58]

Subcutaneous human immune globulin products are FDA approved for the treatment of patients with primary immune deficiency.[60,63,76,164]

The FDA issued a Safety Communication dated November 13, 2012 to provide an update to their August 2002 interim statement regarding thrombotic events as a potential risk following the administration of human immunoglobulin.[159] The updated safety communication also addressed hemolysis, another risk potentially associated with the administration of human immune globulin.

In their update, the FDA issued the following recommendations regarding thrombosis:

- Care should be used when immune globulin products are given to individuals determined to be at increased risk of thrombosis.
- Patients at increased risk of thrombosis include those with acquired or hereditary hypercoagulable states, prolonged immobilization, in-dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and hyperviscosity (including cryoglobulins, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies).
- Patients at risk for thrombosis should receive immune globulin products at the slowest infusion rate practicable, and should be monitored for thrombotic complications.
- Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

The FDA also issued the following recommendations regarding hemolysis:

- Patients at increased risk for hemolysis following treatment with immune globulins include those with non-O blood group types, those who have underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days.
- Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If these occur, appropriate laboratory testing should be obtained.

The FDA issued a Safety Communication dated June 10, 2013 to report that a recent data analysis that has strengthened the association between the use of intravenous, subcutaneous and intramuscular human immune globulin products and the risk of thrombosis.[176] Because additional caution regarding the use of these products is warranted, the FDA is requiring manufacturers to add information on thrombosis to the current boxed warning in the labels of all intravenous human immune globulin products and to add a boxed warning to the labels of all subcutaneous and intramuscular human immune globulin products to highlight the risk of thrombosis and to add information on its mitigation.

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that

the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

CPT Code	Description
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each

HCPCS Code	Description
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex-C/Gammaked), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (Vivaglobin), 100 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), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg

ICD-9 Code	Description
008.61	Intestinal infection, enteritis due to rotavirus
040.82	Toxic shock syndrome
042	Human immunodeficiency virus [HIV]
048	Other enterovirus diseases of central nervous system
078.5	Cytomegaloviral disease
204.10	Chronic lymphoid leukemia, without mention of having achieved remission
204.11	Chronic lymphoid leukemia in remission
204.12	Chronic lymphoid leukemia, in relapse
238.79	Neoplasm of uncertain behavior of other and unspecified sites and tissues; other lymphatic and hematopoietic tissues
242.00	Toxic diffuse goiter without mention of thyrotoxic crisis or storm
242.01	Toxic diffuse goiter with mention of thyrotoxic crisis or storm
250.01	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
250.03	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
250.21	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled
250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled
250.31	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
250.33	Diabetes with other coma, type I [juvenile type], uncontrolled
250.41	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
250.43	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
250.51	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
250.53	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
250.61	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
250.63	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled
250.71	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as

	uncontrolled
250.73	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
250.81	Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled
250.83	Diabetes with other specified manifestations, type I [juvenile type], uncontrolled
250.91	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
250.93	Diabetes with unspecified complication, type I [juvenile type], uncontrolled
273.1	Monoclonal paraproteinemia
279.00	Unspecified hypogammaglobulinemia
279.03	Other selective immunoglobulin deficiencies
279.04	Congenital hypogammaglobulinemia
279.05	Immunodeficiency with increased IgM
279.06	Common variable immunodeficiency
279.11	DiGeorge's syndrome
279.12	Wiskott-Aldrich syndrome
279.2	Combined immunity deficiency
279.51	Acute graft-versus-host disease
279.53	Acute on chronic graft-versus-host disease
279.8	Other specified disorders involving the immune mechanism
279.9	Unspecified disorder of immune mechanism
287.31	Immune thrombocytopenic purpura
287.41	Posttransfusion purpura
287.49	Other secondary thrombocytopenia
288.09	Diseases of white blood cells; Other neutropenia
288.1	Functional disorders of polymorphonuclear neutrophils
323.01	Encephalitis and encephalomyelitis in viral diseases classified elsewhere
323.02	Myelitis in viral diseases classified elsewhere
323.81	Other causes of encephalitis and encephalomylitis
323.9	Unspecified cause of encephalitis, myelitis, and encephalomyelitis
333.91	Stiff-man syndrome
334.8	Other spinocerebellar diseases
340	Multiple sclerosis
341.0	Neuromyelitis optica
345.00	Generalized nonconvulsive epilepsy, w/o mention of intractable epilepsy
345.01	Generalized nonconvulsive epilepsy, w/intractable epilepsy
345.10	Generalized convulsive epilepsy, w/o mention of intractable epilepsy
345.11	Generalized convulsive epilepsy, w/intractable epilepsy
355.9	Mononeuritis of unspecified site
357.0	Acute infective polyneuritis
357.4	Polyneuropathy in other diseases classified elsewhere
357.81	Chronic inflammatory demyelinating polyneuritis
357.9	Inflammatory and toxic neuropathy; Unspecified
358.01	Myasthenia gravis with (acute) exacerbation
358.1	Myasthenic syndromes in diseases classified elsewhere
358.30	Lambert-Eaton syndrome, unspecified
358.31	Lambert-Eaton syndrome in neoplastic disease
358.39	Lambert-Eaton syndrome in other diseases classified elsewhere
364.00	Unspecified acute and subacute iridocyclitis
364.01	Primary iridocyclitis
364.02	Recurrent iridocyclitis
364.04	Secondary iridocyclitis, noninfectious
446.1	Acute febrile mucocutaneous lymph node syndrome (MCLS)
448.0	Hereditary hemorrhagic telangiectasia
484.1	Pneumonia in cytomegalic inclusion disease

493.01	Extrinsic asthma with status asthmaticus
493.11	Intrinsic asthma with status asthmaticus
493.21	Chronic obstructive asthma with status asthmaticus
646.80	Other specified complication of pregnancy, unspecified as to episode of care
646.81	Other specified complication of pregnancy, with delivery
646.82	Other specified complications of pregnancy, with delivery, with current postpartum complication
646.83	Other specified complication, antepartum
646.84	Other specified complications of pregnancy, postpartum condition or complication
647.60	Other maternal viral disease complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care
647.61	Other maternal viral disease with delivery
647.63	Other maternal viral disease, antepartum
647.64	Other maternal viral diseases complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication
678.00	Fetal hematologic conditions, unspecified as to episode of care or not applicable
678.03	Fetal hematologic conditions, antepartum condition or complication
694.4	Pemphigus
694.5	Pemphigoid
694.60	Benign mucous membrane pemphigoid without mention of ocular involvement
694.61	Benign mucous membrane pemphigoid with ocular involvement
694.8	Other specified bullous dermatosis
695.13	Stevens-Johnson syndrome
695.14	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
695.15	Toxic epidermal necrolysis
708.5	Cholinergic urticaria
708.8	Other specified urticaria
710.3	Dermatomyositis
710.4	Polymyositis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.30	Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
714.31	Polyarticular juvenile rheumatoid arthritis, acute
714.32	Pauciarticular juvenile rheumatoid arthritis
714.33	Monoarticular juvenile rheumatoid arthritis
757.39	Other specified anomalies of skin; Other
773.2	Hemolytic disease due to other and unspecified isoimmunization of fetus or newborn
776.1	Transient neonatal thrombocytopenia
776.8	Hematological disorders of newborn; Other specified transient hematological disorders
776.9	Hematological disorders of newborn; Unspecified hematological disorder specific to newborn
996.81	Complications of transplanted organ; kidney
996.85	Complications of transplanted organ; bone marrow
V42.81	Bone marrow replaced by transplant
V42.82	Peripheral stem cells replaced by transplant

ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2015***, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. **The effective date for ICD-10 code set implementation is subject to change.*

ICD-10 Diagnosis Code (Effective 10/01/15)	Description
A08.0	Rotaviral enteritis
A48.3	Toxic shock syndrome
A52.15	Late syphilitic neuropathy
A88.0	Enteroviral exanthematous fever [Boston xanthema]
B20	Human immunodeficiency virus [HIV] disease
B25.0	Cytomegaloviral pneumonitis
B25.1	Cytomegaloviral hepatitis
B25.2	Cytomegaloviral pancreatitis
B25.8	Other cytomegaloviral diseases
B25.9	Cytomegaloviral disease, unspecified
C88.8	Other malignant immunoproliferative diseases
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.90	Lymphoid leukemia, unspecified not having achieved remission
C94.40	Acute panmyelosis with myelofibrosis not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.6	Myelodysplastic disease, not classified
D47.1	Chronic myeloproliferative disease
D47.2	Monoclonal gammopathy
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D69.3	Immune thrombocytopenic purpura
D69.51	Posttransfusion purpura
D69.59	Other secondary thrombocytopenia
D70.8	Other neutropenia
D71	Functional disorders of polymorphonuclear neutrophils
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	Di George's syndrome
D82.8	Immunodeficiency associated with other specified major defects
D82.9	Immunodeficiency associated with major defect, unspecified
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified

D89.2	Hypergammaglobulinemia, unspecified
D89.810	Acute graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified
D89.9	Disorder involving the immune mechanism, unspecified
E05.00	Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm
E05.01	Thyrotoxicosis with diffuse goiter with thyrotoxic crisis or storm
E10.10	Type 1 diabetes mellitus with ketoacidosis without coma
E10.11	Type 1 diabetes mellitus with ketoacidosis with coma
E10.21	Type 1 diabetes mellitus with diabetic nephropathy
E10.22	Type 1 diabetes mellitus with diabetic chronic kidney disease
E10.29	Type 1 diabetes mellitus with other diabetic kidney complication
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E10.321	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E10.329	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E10.331	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.339	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E10.341	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.349	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E10.351	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.359	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E10.36	Type 1 diabetes mellitus with diabetic cataract
E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E10.52	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E10.59	Type 1 diabetes mellitus with other circulatory complications
E10.610	Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E10.618	Type 1 diabetes mellitus with other diabetic arthropathy
E10.620	Type 1 diabetes mellitus with diabetic dermatitis
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E10.628	Type 1 diabetes mellitus with other skin complications
E10.630	Type 1 diabetes mellitus with periodontal disease
E10.638	Type 1 diabetes mellitus with other oral complications
E10.641	Type 1 diabetes mellitus with hypoglycemia with coma
E10.649	Type 1 diabetes mellitus with hypoglycemia without coma
E10.65	Type 1 diabetes mellitus with hyperglycemia
E10.69	Type 1 diabetes mellitus with other specified complication
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications
G04.81	Other encephalitis and encephalomyelitis
G04.90	Encephalitis and encephalomyelitis, unspecified

G04.91	Myelitis, unspecified
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere
G05.4	Myelitis in diseases classified elsewhere
G11.3	Cerebellar ataxia with defective DNA repair
G25.82	Stiff-man syndrome
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
G37.4	Subacute necrotizing myelitis of central nervous system
G40.309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.311	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus
G40.319	Generalized idiopathic epilepsy and epileptic syndromes, intractable, without status epilepticus
G40.409	Other generalized epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.411	Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus
G58.8	Other specified mononeuropathies
G58.9	Mononeuropathy, unspecified
G59	Mononeuropathy in diseases classified elsewhere
G61.0	Guillain-Barré syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.9	Inflammatory polyneuropathy, unspecified
G62.9	Polyneuropathy, unspecified
G63	Polyneuropathy in diseases classified elsewhere
G65.0	Sequelae of Guillain-Barré syndrome
G65.1	Sequelae of other inflammatory polyneuropathy
G65.2	Sequelae of toxic polyneuropathy
G70.01	Myasthenia gravis with (acute) exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
G73.1	Lambert-Eaton syndrome in neoplastic disease
G73.3	Myasthenic syndromes in other diseases classified elsewhere
H20.00	Unspecified acute and subacute iridocyclitis
H20.011	Primary iridocyclitis, right eye
H20.012	Primary iridocyclitis, left eye
H20.013	Primary iridocyclitis, bilateral
H20.019	Primary iridocyclitis, unspecified eye
H20.021	Recurrent acute iridocyclitis, right eye
H20.022	Recurrent acute iridocyclitis, left eye
H20.023	Recurrent acute iridocyclitis, bilateral
H20.029	Recurrent acute iridocyclitis, unspecified eye
H20.041	Secondary noninfectious iridocyclitis, right eye
H20.042	Secondary noninfectious iridocyclitis, left eye
H20.043	Secondary noninfectious iridocyclitis, bilateral
H20.049	Secondary noninfectious iridocyclitis, unspecified eye
I78.0	Hereditary hemorrhagic telangiectasia
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
J45.20	Mild intermittent asthma, uncomplicated
J45.22	Mild intermittent asthma with status asthmaticus
J45.30	Mild persistent asthma, uncomplicated
J45.32	Mild persistent asthma with status asthmaticus
J45.40	Moderate persistent asthma, uncomplicated
J45.42	Moderate persistent asthma with status asthmaticus

J45.50	Severe persistent asthma, uncomplicated
J45.52	Severe persistent asthma with status asthmaticus
J45.902	Unspecified asthma with status asthmaticus
J45.909	Unspecified asthma, uncomplicated
L10.0	Pemphigus vulgaris
L10.1	Pemphigus vegetans
L10.2	Pemphigus foliaceous
L10.3	Brazilian pemphigus [fogo selvagem]
L10.4	Pemphigus erythematosus
L10.5	Drug-induced pemphigus
L10.81	Paraneoplastic pemphigus
L10.89	Other pemphigus
L10.9	Pemphigus, unspecified
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.30	Acquired epidermolysis bullosa, unspecified
L12.31	Epidermolysis bullosa due to drug
L12.35	Other acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified
L13.8	Other specified bullous disorders
L14.	Bullous disorders in diseases classified elsewhere
L50.5	Cholinergic urticaria
L50.6	Contact urticaria
L50.8	Other urticaria
L51.1	Stevens-Johnson syndrome
L51.2	Toxic epidermal necrolysis [Lyell]
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M05.00	Felty's syndrome, unspecified site
M05.011	Felty's syndrome, right shoulder
M05.012	Felty's syndrome, left shoulder
M05.019	Felty's syndrome, unspecified shoulder
M05.021	Felty's syndrome, right elbow
M05.022	Felty's syndrome, left elbow
M05.029	Felty's syndrome, unspecified elbow
M05.031	Felty's syndrome, right wrist
M05.032	Felty's syndrome, left wrist
M05.039	Felty's syndrome, unspecified wrist
M05.041	Felty's syndrome, right hand
M05.042	Felty's syndrome, left hand
M05.049	Felty's syndrome, unspecified hand
M05.051	Felty's syndrome, right hip
M05.052	Felty's syndrome, left hip
M05.059	Felty's syndrome, unspecified hip
M05.061	Felty's syndrome, right knee
M05.062	Felty's syndrome, left knee
M05.069	Felty's syndrome, unspecified knee
M05.071	Felty's syndrome, right ankle and foot
M05.072	Felty's syndrome, left ankle and foot
M05.079	Felty's syndrome, unspecified ankle and foot
M05.09	Felty's syndrome, multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder

M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip
M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist

M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems

M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement
M05.721	Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement
M05.722	Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement
M05.729	Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems involvement
M05.731	Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement
M05.732	Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement
M05.739	Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems involvement
M05.741	Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement
M05.742	Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement
M05.749	Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems involvement
M05.751	Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement
M05.752	Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement
M05.759	Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement
M05.761	Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement
M05.762	Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement
M05.769	Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems involvement
M05.771	Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems involvement
M05.772	Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement
M05.779	Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems involvement
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement

M05.80	Other rheumatoid arthritis with rheumatoid factor of unspecified site
M05.811	Other rheumatoid arthritis with rheumatoid factor of right shoulder
M05.812	Other rheumatoid arthritis with rheumatoid factor of left shoulder
M05.819	Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder
M05.821	Other rheumatoid arthritis with rheumatoid factor of right elbow
M05.822	Other rheumatoid arthritis with rheumatoid factor of left elbow
M05.829	Other rheumatoid arthritis with rheumatoid factor of unspecified elbow
M05.831	Other rheumatoid arthritis with rheumatoid factor of right wrist
M05.832	Other rheumatoid arthritis with rheumatoid factor of left wrist
M05.839	Other rheumatoid arthritis with rheumatoid factor of unspecified wrist
M05.841	Other rheumatoid arthritis with rheumatoid factor of right hand
M05.842	Other rheumatoid arthritis with rheumatoid factor of left hand
M05.849	Other rheumatoid arthritis with rheumatoid factor of unspecified hand
M05.851	Other rheumatoid arthritis with rheumatoid factor of right hip
M05.852	Other rheumatoid arthritis with rheumatoid factor of left hip
M05.859	Other rheumatoid arthritis with rheumatoid factor of unspecified hip
M05.861	Other rheumatoid arthritis with rheumatoid factor of right knee
M05.862	Other rheumatoid arthritis with rheumatoid factor of left knee
M05.869	Other rheumatoid arthritis with rheumatoid factor of unspecified knee
M05.871	Other rheumatoid arthritis with rheumatoid factor of right ankle and foot
M05.872	Other rheumatoid arthritis with rheumatoid factor of left ankle and foot
M05.879	Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot
M05.89	Other rheumatoid arthritis with rheumatoid factor of multiple sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00	Rheumatoid arthritis without rheumatoid factor, unspecified site
M06.011	Rheumatoid arthritis without rheumatoid factor, right shoulder
M06.012	Rheumatoid arthritis without rheumatoid factor, left shoulder
M06.019	Rheumatoid arthritis without rheumatoid factor, unspecified shoulder
M06.021	Rheumatoid arthritis without rheumatoid factor, right elbow
M06.022	Rheumatoid arthritis without rheumatoid factor, left elbow
M06.029	Rheumatoid arthritis without rheumatoid factor, unspecified elbow
M06.031	Rheumatoid arthritis without rheumatoid factor, right wrist
M06.032	Rheumatoid arthritis without rheumatoid factor, left wrist
M06.039	Rheumatoid arthritis without rheumatoid factor, unspecified wrist
M06.041	Rheumatoid arthritis without rheumatoid factor, right hand
M06.042	Rheumatoid arthritis without rheumatoid factor, left hand
M06.049	Rheumatoid arthritis without rheumatoid factor, unspecified hand
M06.051	Rheumatoid arthritis without rheumatoid factor, right hip
M06.052	Rheumatoid arthritis without rheumatoid factor, left hip
M06.059	Rheumatoid arthritis without rheumatoid factor, unspecified hip
M06.061	Rheumatoid arthritis without rheumatoid factor, right knee
M06.062	Rheumatoid arthritis without rheumatoid factor, left knee
M06.069	Rheumatoid arthritis without rheumatoid factor, unspecified knee
M06.071	Rheumatoid arthritis without rheumatoid factor, right ankle and foot
M06.072	Rheumatoid arthritis without rheumatoid factor, left ankle and foot
M06.079	Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot
M06.08	Rheumatoid arthritis without rheumatoid factor, vertebrae
M06.09	Rheumatoid arthritis without rheumatoid factor, multiple sites
M06.1	Adult-onset Still's disease
M06.20	Rheumatoid bursitis, unspecified site
M06.211	Rheumatoid bursitis, right shoulder
M06.212	Rheumatoid bursitis, left shoulder
M06.219	Rheumatoid bursitis, unspecified shoulder

M06.221	Rheumatoid bursitis, right elbow
M06.222	Rheumatoid bursitis, left elbow
M06.229	Rheumatoid bursitis, unspecified elbow
M06.231	Rheumatoid bursitis, right wrist
M06.232	Rheumatoid bursitis, left wrist
M06.239	Rheumatoid bursitis, unspecified wrist
M06.241	Rheumatoid bursitis, right hand
M06.242	Rheumatoid bursitis, left hand
M06.249	Rheumatoid bursitis, unspecified hand
M06.251	Rheumatoid bursitis, right hip
M06.252	Rheumatoid bursitis, left hip
M06.259	Rheumatoid bursitis, unspecified hip
M06.261	Rheumatoid bursitis, right knee
M06.262	Rheumatoid bursitis, left knee
M06.269	Rheumatoid bursitis, unspecified knee
M06.271	Rheumatoid bursitis, right ankle and foot
M06.272	Rheumatoid bursitis, left ankle and foot
M06.279	Rheumatoid bursitis, unspecified ankle and foot
M06.28	Rheumatoid bursitis, vertebrae
M06.29	Rheumatoid bursitis, multiple sites
M06.30	Rheumatoid nodule, unspecified site
M06.311	Rheumatoid nodule, right shoulder
M06.312	Rheumatoid nodule, left shoulder
M06.319	Rheumatoid nodule, unspecified shoulder
M06.321	Rheumatoid nodule, right elbow
M06.322	Rheumatoid nodule, left elbow
M06.329	Rheumatoid nodule, unspecified elbow
M06.331	Rheumatoid nodule, right wrist
M06.332	Rheumatoid nodule, left wrist
M06.339	Rheumatoid nodule, unspecified wrist
M06.341	Rheumatoid nodule, right hand
M06.342	Rheumatoid nodule, left hand
M06.349	Rheumatoid nodule, unspecified hand
M06.351	Rheumatoid nodule, right hip
M06.352	Rheumatoid nodule, left hip
M06.359	Rheumatoid nodule, unspecified hip
M06.361	Rheumatoid nodule, right knee
M06.362	Rheumatoid nodule, left knee
M06.369	Rheumatoid nodule, unspecified knee
M06.371	Rheumatoid nodule, right ankle and foot
M06.372	Rheumatoid nodule, left ankle and foot
M06.379	Rheumatoid nodule, unspecified ankle and foot
M06.38	Rheumatoid nodule, vertebrae
M06.39	Rheumatoid nodule, multiple sites
M06.80	Other specified rheumatoid arthritis, unspecified site
M06.811	Other specified rheumatoid arthritis, right shoulder
M06.812	Other specified rheumatoid arthritis, left shoulder
M06.819	Other specified rheumatoid arthritis, unspecified shoulder
M06.821	Other specified rheumatoid arthritis, right elbow
M06.822	Other specified rheumatoid arthritis, left elbow
M06.829	Other specified rheumatoid arthritis, unspecified elbow
M06.831	Other specified rheumatoid arthritis, right wrist
M06.832	Other specified rheumatoid arthritis, left wrist

M06.839	Other specified rheumatoid arthritis, unspecified wrist
M06.841	Other specified rheumatoid arthritis, right hand
M06.842	Other specified rheumatoid arthritis, left hand
M06.849	Other specified rheumatoid arthritis, unspecified hand
M06.851	Other specified rheumatoid arthritis, right hip
M06.852	Other specified rheumatoid arthritis, left hip
M06.859	Other specified rheumatoid arthritis, unspecified hip
M06.861	Other specified rheumatoid arthritis, right knee
M06.862	Other specified rheumatoid arthritis, left knee
M06.869	Other specified rheumatoid arthritis, unspecified knee
M06.871	Other specified rheumatoid arthritis, right ankle and foot
M06.872	Other specified rheumatoid arthritis, left ankle and foot
M06.879	Other specified rheumatoid arthritis, unspecified ankle and foot
M06.88	Other specified rheumatoid arthritis, vertebrae
M06.89	Other specified rheumatoid arthritis, multiple sites
M06.9	Rheumatoid arthritis, unspecified
M08.00	Unspecified juvenile rheumatoid arthritis of unspecified site
M08.011	Unspecified juvenile rheumatoid arthritis, right shoulder
M08.012	Unspecified juvenile rheumatoid arthritis, left shoulder
M08.019	Unspecified juvenile rheumatoid arthritis, unspecified shoulder
M08.021	Unspecified juvenile rheumatoid arthritis, right elbow
M08.022	Unspecified juvenile rheumatoid arthritis, left elbow
M08.029	Unspecified juvenile rheumatoid arthritis, unspecified elbow
M08.031	Unspecified juvenile rheumatoid arthritis, right wrist
M08.032	Unspecified juvenile rheumatoid arthritis, left wrist
M08.039	Unspecified juvenile rheumatoid arthritis, unspecified wrist
M08.041	Unspecified juvenile rheumatoid arthritis, right hand
M08.042	Unspecified juvenile rheumatoid arthritis, left hand
M08.049	Unspecified juvenile rheumatoid arthritis, unspecified hand
M08.051	Unspecified juvenile rheumatoid arthritis, right hip
M08.052	Unspecified juvenile rheumatoid arthritis, left hip
M08.059	Unspecified juvenile rheumatoid arthritis, unspecified hip
M08.061	Unspecified juvenile rheumatoid arthritis, right knee
M08.062	Unspecified juvenile rheumatoid arthritis, left knee
M08.069	Unspecified juvenile rheumatoid arthritis, unspecified knee
M08.071	Unspecified juvenile rheumatoid arthritis, right ankle and foot
M08.072	Unspecified juvenile rheumatoid arthritis, left ankle and foot
M08.079	Unspecified juvenile rheumatoid arthritis, unspecified ankle and foot
M08.08	Unspecified juvenile rheumatoid arthritis, vertebrae
M08.09	Unspecified juvenile rheumatoid arthritis, multiple sites
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site
M08.211	Juvenile rheumatoid arthritis with systemic onset, right shoulder
M08.212	Juvenile rheumatoid arthritis with systemic onset, left shoulder
M08.219	Juvenile rheumatoid arthritis with systemic onset, unspecified shoulder
M08.221	Juvenile rheumatoid arthritis with systemic onset, right elbow
M08.222	Juvenile rheumatoid arthritis with systemic onset, left elbow
M08.229	Juvenile rheumatoid arthritis with systemic onset, unspecified elbow
M08.231	Juvenile rheumatoid arthritis with systemic onset, right wrist
M08.232	Juvenile rheumatoid arthritis with systemic onset, left wrist
M08.239	Juvenile rheumatoid arthritis with systemic onset, unspecified wrist
M08.241	Juvenile rheumatoid arthritis with systemic onset, right hand
M08.242	Juvenile rheumatoid arthritis with systemic onset, left hand
M08.249	Juvenile rheumatoid arthritis with systemic onset, unspecified hand

M08.251	Juvenile rheumatoid arthritis with systemic onset, right hip
M08.252	Juvenile rheumatoid arthritis with systemic onset, left hip
M08.259	Juvenile rheumatoid arthritis with systemic onset, unspecified hip
M08.261	Juvenile rheumatoid arthritis with systemic onset, right knee
M08.262	Juvenile rheumatoid arthritis with systemic onset, left knee
M08.269	Juvenile rheumatoid arthritis with systemic onset, unspecified knee
M08.271	Juvenile rheumatoid arthritis with systemic onset, right ankle and foot
M08.272	Juvenile rheumatoid arthritis with systemic onset, left ankle and foot
M08.279	Juvenile rheumatoid arthritis with systemic onset, unspecified ankle and foot
M08.28	Juvenile rheumatoid arthritis with systemic onset, vertebrae
M08.29	Juvenile rheumatoid arthritis with systemic onset, multiple sites
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.40	Pauciarticular juvenile rheumatoid arthritis, unspecified site
M08.411	Pauciarticular juvenile rheumatoid arthritis, right shoulder
M08.412	Pauciarticular juvenile rheumatoid arthritis, left shoulder
M08.419	Pauciarticular juvenile rheumatoid arthritis, unspecified shoulder
M08.421	Pauciarticular juvenile rheumatoid arthritis, right elbow
M08.422	Pauciarticular juvenile rheumatoid arthritis, left elbow
M08.429	Pauciarticular juvenile rheumatoid arthritis, unspecified elbow
M08.431	Pauciarticular juvenile rheumatoid arthritis, right wrist
M08.432	Pauciarticular juvenile rheumatoid arthritis, left wrist
M08.439	Pauciarticular juvenile rheumatoid arthritis, unspecified wrist
M08.441	Pauciarticular juvenile rheumatoid arthritis, right hand
M08.442	Pauciarticular juvenile rheumatoid arthritis, left hand
M08.449	Pauciarticular juvenile rheumatoid arthritis, unspecified hand
M08.451	Pauciarticular juvenile rheumatoid arthritis, right hip
M08.452	Pauciarticular juvenile rheumatoid arthritis, left hip
M08.459	Pauciarticular juvenile rheumatoid arthritis, unspecified hip
M08.461	Pauciarticular juvenile rheumatoid arthritis, right knee
M08.462	Pauciarticular juvenile rheumatoid arthritis, left knee
M08.469	Pauciarticular juvenile rheumatoid arthritis, unspecified knee
M08.471	Pauciarticular juvenile rheumatoid arthritis, right ankle and foot
M08.472	Pauciarticular juvenile rheumatoid arthritis, left ankle and foot
M08.479	Pauciarticular juvenile rheumatoid arthritis, unspecified ankle and foot
M08.48	Pauciarticular juvenile rheumatoid arthritis, vertebrae
M08.80	Other juvenile arthritis, unspecified site
M08.811	Other juvenile arthritis, right shoulder
M08.812	Other juvenile arthritis, left shoulder
M08.819	Other juvenile arthritis, unspecified shoulder
M08.821	Other juvenile arthritis, right elbow
M08.822	Other juvenile arthritis, left elbow
M08.829	Other juvenile arthritis, unspecified elbow
M08.831	Other juvenile arthritis, right wrist
M08.832	Other juvenile arthritis, left wrist
M08.839	Other juvenile arthritis, unspecified wrist
M08.841	Other juvenile arthritis, right hand
M08.842	Other juvenile arthritis, left hand
M08.849	Other juvenile arthritis, unspecified hand
M08.851	Other juvenile arthritis, right hip
M08.852	Other juvenile arthritis, left hip
M08.859	Other juvenile arthritis, unspecified hip
M08.861	Other juvenile arthritis, right knee
M08.862	Other juvenile arthritis, left knee

M08.869	Other juvenile arthritis, unspecified knee
M08.871	Other juvenile arthritis, right ankle and foot
M08.872	Other juvenile arthritis, left ankle and foot
M08.879	Other juvenile arthritis, unspecified ankle and foot
M08.88	Other juvenile arthritis, vertebrae
M08.89	Other juvenile arthritis, multiple sites
M08.90	Juvenile arthritis, unspecified, unspecified site
M08.911	Juvenile arthritis, unspecified, right shoulder
M08.912	Juvenile arthritis, unspecified, left shoulder
M08.919	Juvenile arthritis, unspecified, unspecified shoulder
M08.921	Juvenile arthritis, unspecified, right elbow
M08.922	Juvenile arthritis, unspecified, left elbow
M08.929	Juvenile arthritis, unspecified, unspecified elbow
M08.931	Juvenile arthritis, unspecified, right wrist
M08.932	Juvenile arthritis, unspecified, left wrist
M08.939	Juvenile arthritis, unspecified, unspecified wrist
M08.941	Juvenile arthritis, unspecified, right hand
M08.942	Juvenile arthritis, unspecified, left hand
M08.949	Juvenile arthritis, unspecified, unspecified hand
M08.951	Juvenile arthritis, unspecified, right hip
M08.952	Juvenile arthritis, unspecified, left hip
M08.959	Juvenile arthritis, unspecified, unspecified hip
M08.961	Juvenile arthritis, unspecified, right knee
M08.962	Juvenile arthritis, unspecified, left knee
M08.969	Juvenile arthritis, unspecified, unspecified knee
M08.971	Juvenile arthritis, unspecified, right ankle and foot
M08.972	Juvenile arthritis, unspecified, left ankle and foot
M08.979	Juvenile arthritis, unspecified, unspecified ankle and foot
M08.98	Juvenile arthritis, unspecified, vertebrae
M08.99	Juvenile arthritis, unspecified, multiple sites
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.00	Juvenile dermatopolymyositis, organ involvement unspecified
M33.01	Juvenile dermatopolymyositis with respiratory involvement
M33.02	Juvenile dermatopolymyositis with myopathy
M33.09	Juvenile dermatopolymyositis with other organ involvement
M33.10	Other dermatopolymyositis, organ involvement unspecified
M33.11	Other dermatopolymyositis with respiratory involvement
M33.12	Other dermatopolymyositis with myopathy
M33.19	Other dermatopolymyositis with other organ involvement
M33.20	Polymyositis, organ involvement unspecified
M33.21	Polymyositis with respiratory involvement
M33.22	Polymyositis with myopathy
M33.29	Polymyositis with other organ involvement
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.91	Dermatopolymyositis, unspecified with respiratory involvement
M33.92	Dermatopolymyositis, unspecified with myopathy
M33.99	Dermatopolymyositis, unspecified with other organ involvement
M34.83	Systemic sclerosis with polyneuropathy
M35.9	Systemic involvement of connective tissue, unspecified
M36.0	Dermato(poly)myositis in neoplastic disease
O26.40	Herpes gestationis, unspecified trimester
O26.41	Herpes gestationis, first trimester
O26.42	Herpes gestationis, second trimester

O26.43	Herpes gestationis, third trimester
O36.8210	Fetal anemia and thrombocytopenia, first trimester, not applicable or unspecified
O36.8211	Fetal anemia and thrombocytopenia, first trimester, fetus 1
O36.8212	Fetal anemia and thrombocytopenia, first trimester, fetus 2
O36.8213	Fetal anemia and thrombocytopenia, first trimester, fetus 4
O36.8214	Fetal anemia and thrombocytopenia, first trimester, fetus 4
O36.8215	Fetal anemia and thrombocytopenia, first trimester, fetus 5
O36.8219	Fetal anemia and thrombocytopenia, first trimester, other fetus
O36.8220	Fetal anemia and thrombocytopenia, second trimester, not applicable or unspecified
O36.8221	Fetal anemia and thrombocytopenia, second trimester, fetus 1
O36.8222	Fetal anemia and thrombocytopenia, second trimester, fetus 2
O36.8223	Fetal anemia and thrombocytopenia, second trimester, fetus 3
O36.8224	Fetal anemia and thrombocytopenia, second trimester, fetus 4
O36.8225	Fetal anemia and thrombocytopenia, second trimester, fetus 5
O36.8229	Fetal anemia and thrombocytopenia, second trimester, other fetus
O36.8230	Fetal anemia and thrombocytopenia, third trimester, not applicable or unspecified
O36.8231	Fetal anemia and thrombocytopenia, third trimester, fetus
O36.8232	Fetal anemia and thrombocytopenia, third trimester, fetus 2
O36.8233	Fetal anemia and thrombocytopenia, third trimester, fetus 3
O36.8234	Fetal anemia and thrombocytopenia, third trimester, fetus 4
O36.8235	Fetal anemia and thrombocytopenia, third trimester, fetus
O36.8239	Fetal anemia and thrombocytopenia, third trimester, other fetus
O36.8290	Fetal anemia and thrombocytopenia, unspecified trimester, not applicable or unspecified
O36.8291	Fetal anemia and thrombocytopenia, unspecified trimester, fetus 1
O36.8292	Fetal anemia and thrombocytopenia, unspecified trimester, fetus 2
O36.8293	Fetal anemia and thrombocytopenia, unspecified trimester, fetus 3
O36.8294	Fetal anemia and thrombocytopenia, unspecified trimester, fetus 4
O36.8295	Fetal anemia and thrombocytopenia, unspecified trimester, fetus 5
O36.8299	Fetal anemia and thrombocytopenia, unspecified trimester, other fetus
O98.411	Viral hepatitis complicating pregnancy, first trimester
O98.412	Viral hepatitis complicating pregnancy, second trimester
O98.413	Viral hepatitis complicating pregnancy, third trimester
O98.419	Viral hepatitis complicating pregnancy, unspecified trimester
O98.42	Viral hepatitis complicating childbirth
O98.43	Viral hepatitis complicating the puerperium
O98.711	Human immunodeficiency virus [HIV] disease complicating pregnancy, first trimester
O98.712	Human immunodeficiency virus [HIV] disease complicating pregnancy, second trimester
O98.713	Human immunodeficiency virus [HIV] disease complicating pregnancy, third trimester
O98.72	Human immunodeficiency virus [HIV] disease complicating childbirth
O99.355	Diseases of the nervous system complicating the puerperium
P61.0	Transient neonatal thrombocytopenia
P61.8	Other specified perinatal hematological disorders
P61.9	Perinatal hematological disorder, unspecified
Q81.8	Other epidermolysis bullosa
Q81.9	Epidermolysis bullosa, unspecified
T86.00	Unspecified complication of bone marrow transplant
T86.01	Bone marrow transplant rejection
T86.02	Bone marrow transplant failure
T86.03	Bone marrow transplant infection
T86.09	Other complications of bone marrow transplant
T86.10	Unspecified complication of kidney transplant
T86.11	Kidney transplant rejection
T86.12	Kidney transplant failure

T86.13	Kidney transplant infection
T86.19	Other complication of kidney transplant
T86.90	Unspecified complication of unspecified transplanted organ and tissue
T86.91	Unspecified transplanted organ and tissue rejection
T86.92	Unspecified transplanted organ and tissue failure
T86.93	Unspecified transplanted organ and tissue infection
T86.99	Other complications of unspecified transplanted organ and tissue
Z48.290	Encounter for aftercare following bone marrow transplant
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
9/1/2014	Added NMO and secondary thrombocytopenia as proven uses. Updated medical

	necessity criteria for ITP. Clarified examples of PID subtypes. Updated clinical evidence and references. Updated list of ICD-9 codes (added 204.11, 287.49, 341.0, 647.60, 647.61, 647.63, and 647.64) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 7/8/2014. Policy 2014D0035N archived.
4/1/2014	Clarified General Criteria for Medical Necessity Review. Revised dosing criteria for ITP and PID. Added dose titration criterion to asthma, autoimmune bullous diseases, CIDP, dermatomyositis, polymyositis, Guillain-Barré syndrome, LEMS, Lennox Gastaut syndrome, MMN, MS, and stiff person syndrome. Removed concomitant immunomodulator requirement from continuation of therapy criteria for CIDP and MMN. Updated clinical evidence and references. Updated list of ICD-9 codes (added 334.8 and 448.0) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 2/18/2014. Policy 2013D0035M archived.
1/1/2014	Policy updated with code J1556, effective on 1/1/2014.
N/A	Added product selection criteria. Approved by the National Pharmacy & Therapeutics Committee on 11/12/2013.
12/1/2013	Full policy review. Removed Gamunex from list of products. Changed “myasthenia gravis, acute exacerbation” to “myasthenic exacerbation,” and revised medical necessity criteria for this indication. Revised medical necessity criteria for CIDP, dermatomyositis and polymyositis, GBS, LEMS, MMN, MS, and stiff-person syndrome. Specified that IVIG is proven in allogeneic BMT. Added treatment of acute GVHD after autologous BMT, prevention of infection after autologous BMT, and ocular myasthenia to the list of unproven uses. Added FDA Safety Communication. Updated clinical evidence and references. Updated list of ICD-9 codes (added 355.9) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 10/8/2013. Policy 2013D0035L archived.
6/1/2013	Revised dosing for prevention of infection and prevention of GVHD after BMT and for fetomaternal alloimmune thrombocytopenia. Approved by the National Pharmacy & Therapeutics Committee on 4/9/2013. Policy 2013D0035K archived.
4/1/2013	Policy updated. Added Bivigam to list of products. Updated list of ICD-9 codes (added 242.00 and 242.01, and removed 242.0, 287.33, 337.00, 337.09, 356.9, 358.00, 714.4, and 776.7) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 2/19/2013.
4/1/2013	Annual policy review. Removed Vivaglobin from list of products. Added Alzheimer’s disease to the list of unproven uses. Revised paraproteinemic neuropathy from unproven to proven use. Reformatted list of proven and unproven uses to appear in alphabetical order. Added medical necessity criteria. Updated clinical evidence and references. Added FDA Safety Communication. Added CPT codes 90283 and 90284 to the policy. Updated list of ICD-9 codes (added 204.12, 279.11, 279.8, 279.9, 288.09, 288.1, 323.01, 323.02, 323.9, 357.9, 484.1, 646.80, 646.81, 646.82, 646.83, 646.84, 678.00, 678.03, 757.39, 776.8, and 776.9, and removed 038.10, 041.01, 279.02, 337.01, 694.0, 772.10, 772.11, 772.12, 772.13, 772.14, 995.91, and 995.92) and applicable ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 11/13/2012. Modifications to policy based upon societal input approved by the National Pharmacy & Therapeutics Committee on 12/14/2012. Policy 2012D0035J archived.
11/1/2012	Policy updated. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) revised to unproven use. Updated FDA section to list multifocal motor neuropathy as a new indication for Gammagard. Updated clinical evidence and references. Updated list of ICD-9 codes (added 337.00, 337.01, 337.09, 772.10, 772.11, 772.12, 772.13, 772.14, and 773.2, and removed 337.0, 493, 772.1, and 996.8). Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/14. Approved by the National Pharmacy & Therapeutics Committee on 7/10/2012. Policy 2012D0035I archived.
3/1/2012	Policy updated. Added Gammaked to list of products. Approved by the National Pharmacy & Therapeutics Committee on 1/10/2012. Policy 2012D0035H archived.
2/1/2012	Policy updated. Gammagard Liquid added to list of subcutaneous products. Prevention

	and treatment of neonatal sepsis revised to unproven status. Addition of Clinical Evidence related to treatment and prevention of neonatal sepsis. Updated list of proven ICD-9 codes (removed 771.81). Added code J1557, which became effective on 1/1/2012. Approved by the National Pharmacy & Therapeutics Committee on 11/8/2011. Policy 2012D0035G archived.
1/1/2012	Policy updated with code J1557, effective on 1/1/2012. Policy 2011D0035F archived.
10/1/2011	Policy updated with addition of ICD-9 codes 358.30, 358.31, and 358.39, which became effective on 10/1/2011. Incomplete ICD-9 code 041.0 updated to 041.01. Policy 2011D0035E archived.
9/1/2011	Annual policy review. Added Flebogamma DIF and Gamunex-C to list of products. Autoimmune blistering skin diseases revised to proven use. Revised proven status and evidence for intractable childhood epilepsy to be specific to Lennox Gastaut syndrome. Updated list of proven ICD-9 codes (added 041.0, 238.79, 242.0, 273.1 279.51, 279.53, 323.81, 337.0, 345.00, 345.01, 345.10, 345.11, 493, 493.01, 493.11, 493.21, 694.0, 694.4, 694.5, 694.60, 694.61, 694.8, 695.13, 695.14, 695.15, 708.5, 708.8, 772.1, 776.7, 995.91, 995.92, 996.8, 996.81, and 996.85, and removed 204.00 and 446.6). Removed all unproven ICD-9 codes from the policy because standard policy format is to list only proven ICD-9 codes. Approved by the National Pharmacy & Therapeutics Committee on 7/12/2011. Policy 2010D0035D archived.
1/5/2011	Policy updated with addition of codes J1559 and J1599, which became effective on 1/1/2011.
11/14/2010	Removed 287.4 from and added 287.41 to list of proven ICD-9 codes.
8/16/2010	Policy revised per annual review. Posttransfusion purpura revised to proven use. Clinical evidence and references revised. Switched ICD-9 287.4 to proven. Approved by the National Pharmacy & Therapeutics Committee on 5/11/2010. Added Gammaplex to list of products and information to Background section regarding product IgG content. Approved by the National Pharmacy & Therapeutics Committee on 8/11/2010. Policy 2009D0035C archived.
11/16/2009	Updated list of proven indications for immune globulin (IVIG) to add fetomaternal alloimmune thrombocytopenia; enteroviral meningoencephalitis; staphylococcal toxic shock; treatment of acute humoral rejection in renal transplantation; and primary immune defects with normogammaglobulinemia and impaired specific antibody production. Revised coverage rationale to indicate the use of IVIG for the treatment of diabetes mellitus is proven for autoimmune, type 1 diabetes mellitus only and the use of IVIG for the treatment of multiple sclerosis (MS) is proven for relapsing-remitting multiple sclerosis only. Updated the list of unproven indications to include Sjogren's syndrome. Updated list of proven ICD-9 codes (added 038.10, 040.82, 048, 279.12, and 776.1 and removed 249.00-249.91, 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, 279.01 and 694.60). Approved by National Pharmacy & Therapeutics Committee on 6/9/2009. Policy 2008D0035B archived.
7/7/2009	Policy updated with separation of monoclonal gammopathy and multiple sclerosis (MS) diagnoses in neuroimmunologic disorders section.
1/2/2009	Policy updated with deletion of codes G0332 and Q4097 and addition of code J1459. Policy 2008D0035A archived.
11/7/2008	New ICD9 code added 90283.
9/17/2008	New ICD9 Codes for Diabetes added as Proven.
9/16/2008	Diagnosis codes 279.01 and 279.02 added as Proven.
8/18/2008	Diagnosis codes 279.00 and 279.03 added to Proven Diagnosis Code list per National Pharmacy & Therapeutics Committee.
6/30/2008	Proven diagnosis code list updated per Manager, Coding and Integrity.
6/30/2008	Diagnosis code 279.00 removed and 358.1 added to Proven Diagnosis Code list per Manger, Coding and Integrity.
4/22/2008	Diagnosis codes 279.05 and 279.06 removed from Unproven Diagnosis Codes per Manager, Coding and Integrity.

4/10/2008	Immune Globulin (IVIG)2008D0035A replaces the previous policies, Intravenous Immune Serum Globulin (IVIG) for Recurrent Spontaneous Abortion 2006D0009B; Intravenous Immune Globulin (IVIg) Use in Rheumatological Disorders 2005D0015C; Intravenous Immune Globulin (IVIg) Use in Neurological and Neuromuscular Disorders 2005D0014C; Intravenous Immune Globulin (IVIg) Use in Infectious Disease 2005D2019C; Intravenous Immune Globulin (IVIg) Use in Miscellaneous Disorders 2007D0020D; Intravenous Immune Globulin (IVIg) Use in Hematological Disorders 2005D0018C. Previous policies were archived.