

## IMMUNE GLOBULIN (IVIG)

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**Related Medical or Drug Policies:**

None

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**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., Certificates of Coverage (COCs), Schedules of Benefits (SOBs), or Summary Plan Descriptions (SPDs)) 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 policy. Other Medical Policies, Drug Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Medical Policies, Drug Policies, and Coverage Determination Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.*

### **COVERAGE RATIONALE**

This policy provides information about immune globulin and its recommended use in hematologic (including autoimmune and immunologic related diseases), infectious disease, neurological and neuromuscular disorders, and use in the prevention of recurrent spontaneous abortion.

This policy refers to the following intravenous immune globulin drug products:

Carimune<sup>®</sup> NF

Flebogamma<sup>®</sup>

Gammagard<sup>®</sup> 5% S/D

Gammagard<sup>®</sup> 10% S/D

Gammagard<sup>®</sup> liquid

Gamunex<sup>®</sup>

Iveegam<sup>®</sup> EN

Octagam<sup>®</sup>

Privigen<sup>®</sup>

And also to the following subcutaneous immune globulin drug product:

Vivaglobin<sup>®</sup>

***Immune globulin is PROVEN for the following:***

**Autoimmune Diseases**

- Autoimmune uveitis
- Dermatomyositis and Polymyositis
- Autoimmune Diabetes mellitus (Antibodies against islet cell antigens, including glutamic acid decarboxylase II, are implicated in the autoimmune pathogenesis of insulin dependent (type 1) diabetes mellitus.)
- Fetomaternal alloimmune thrombocytopenia
- Graves ophthalmopathy
- Immune thrombocytopenic purpura (ITP)
- Severe rheumatoid arthritis

**Infectious and Infection-related Diseases**

- Bacterial infections in lymphoproliferative disease
- Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants
- Enteroviral meningoencephalitis
- Kawasaki disease
- Neonatal sepsis
- Rotaviral enterocolitis
- Staphylococcal toxic shock

**Miscellaneous Uses**

- Delayed-pressure urticaria
- Prevention of acute humoral rejection in renal transplantation
- Treatment of acute humoral rejection in renal transplantation\*
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (streptococcal infections induce exacerbation of symptoms in some children with obsessive-compulsive and tic disorders)
- Prevention of infection and acute graft vs. host disease (GVHD) after bone marrow transplantation
- Severe, persistent, high-dose, steroid-dependent asthma
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

\*Clinical evidence supporting the use of IVIG for the treatment of acute humoral rejection in renal transplantation is limited. UnitedHealthcare will continue to review clinical evidence surrounding IVIG and treatment of acute humoral rejection in renal transplantation and may modify this conclusion at a later date based upon the evolution of the published clinical evidence.

**Neuroimmunologic Disorders**

- Chronic demyelinating polyneuropathy
- Guillain-Barre syndrome (GBS)
- IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy
- Intractable childhood epilepsy
- Lambert-Eaton myasthenic syndrome (LEMS)
- Monoclonal gammopathy
- Relapsing-remitting multiple sclerosis (MS)
- Multifocal motor neuropathy (MMN)
- Myasthenia gravis (MG)
- Rasmussen syndrome
- Stiff-man syndrome

**Primary and Secondary Immune Deficiencies**

- Chronic lymphocytic leukemia with reduced IgG and history of infections

- Prevention of bacterial infection in HIV-infected children
- Prevention of neonatal sepsis
- Primary immune defects with absent B cells
- Primary immune defects with hypogammaglobulinemia and impaired specific antibody production
- Primary immune defects with normogammaglobulinemia and impaired specific antibody production

***Immune globulin is UNPROVEN for the following:***

#### **Autoimmune Diseases**

- Acquired hemophilia
- Antiphospholipid antibody syndrome (APS) in pregnancy
- Autoimmune hemolytic anemia
- Autoimmune liver disease
- Autoimmune neutropenia
- Inclusion body myositis
- Neonatal isoimmune hemolytic jaundice
- Posttransfusion purpura
- Sjogren's syndrome
- Systemic lupus erythematosus
- Vasculitides and antineutrophil antibody syndromes

#### **Infectious and Infection-related Diseases**

- Acute rheumatic fever
- Campylobacter species-induced enteritis
- Chronic fatigue syndrome
- Postoperative sepsis
- Pseudomembranous colitis
- RSV lower respiratory tract infection
- Viral load in HIV infection

#### **Miscellaneous Uses**

- Acute myocarditis
- Atopic dermatitis
- Autoimmune blistering skin diseases and manifestation of systemic diseases
- Autoimmune liver disease
- Autism spectrum disorders
- Chronic fatigue syndrome
- Chronic urticaria
- Dilated cardiomyopathy
- Non-steroid-dependent asthma
- Prevention of chronic GVHD after bone marrow transplantation
- Prevention of spontaneous recurrent abortions

#### **Neuroimmunologic Disorders**

- Acute disseminated encephalomyelitis
- Acute idiopathic dysautonomia
- Adrenoleukodystrophy
- Amyotrophic lateral sclerosis
- Cerebral infarctions with antiphospholipid antibodies
- Demyelinative brain stem encephalitis
- Demyelinating neuropathy associated with monoclonal IgM

- HTLV-1-associated myelopathy
- Lumbosacral or brachial plexitis
- Opsoclonus myoclonus
- Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy
- Paraproteinemic neuropathy
- POEMS syndrome
- Postinfectious cerebellar ataxia

#### **Primary and Secondary Immune Deficiencies**

- Isolated IgA Deficiency
- Isolated IgG4 Deficiency

#### **Centers for Medicare and Medicaid Services (CMS):**

Medicare covers intravenous immune globulin (IVIG) for the treatment of primary immune deficiency diseases (ICD-9 diagnosis codes 279.04, 279.05, 279.06, 279.12, and 279.2) in the home when criteria are met. See the Medicare Benefit Policy Manual (Pub. 100-2) Chapter 15 - Covered Medical and Other Health Services, Section 50.6 Coverage of Intravenous Immune Globulin for Treatment of Primary Immune Deficiency Diseases in the Home at <http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf>. (Accessed March 11, 2009)

Medicare also covers IVIG for the treatment of biopsy-proven (1) pemphigus vulgaris, (2) pemphigus foliaceus, (3) bullous pemphigoid, (4) mucous membrane pemphigoid (also known as cicatricial pemphigoid), and (5) epidermolysis bullosa acquisita when criteria are met. See the National Coverage Determinations (NCD) for Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3) at [http://www.cms.hhs.gov/mcd/viewncd.asp?ncd\\_id=250.3&ncd\\_version=1&basket=ncd%3A250%2E3%3A1%3AIntravenous+Immune+Globulin+for+the+Treatment+of+Autoimmune+Mucocutaneous+Blistering+Diseases](http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=250.3&ncd_version=1&basket=ncd%3A250%2E3%3A1%3AIntravenous+Immune+Globulin+for+the+Treatment+of+Autoimmune+Mucocutaneous+Blistering+Diseases). (Accessed March 11, 2009)

Local Coverage Determinations (LCDs) exist for Intravenous Immune Globulin and compliance with these policies is required where applicable. These LCDs are available at [http://www.cms.hhs.gov/mcd/index\\_local\\_alpha.asp?from=alphalmrp&letter=I](http://www.cms.hhs.gov/mcd/index_local_alpha.asp?from=alphalmrp&letter=I). (Accessed March 11, 2009)

## **BACKGROUND**

Immune globulin, whether intravenous (IV) or subcutaneous (SQ), 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 (Hayes, 2006a).

There are currently 7 clinical indications for which IVIG has been licensed by the United States Food and Drug Administration (FDA). These can be summarized as follows: (1) treatment of primary immunodeficiencies; (2) prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia; (3) prevention of coronary artery aneurysms in Kawasaki disease (KD); (4) prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation; (5) reduction of serious bacterial infection in children with human immunodeficiency virus (HIV); (6) increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding (Orange et al, 2006); and (7) to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in chronic inflammatory demyelinating polyneuropathy (CIDP).

IVIG has a broad range of applications and the presence of immunoglobulins has proved to be important in maintaining immune homeostasis in healthy people.

## CLINICAL EVIDENCE

### **Autoimmune diseases**

#### **Acquired Hemophilia**

IVIG may provide benefit in acquired hemophilia, a rare condition caused by development of autoantibodies against factor VIII. Its effects may be from anti-idiotypes against autoantibodies in IVIG preparations (Sultan, 1984). Efficacy has only been described in case reports (Gianella-Borradori, 1984; Bossi, 1998; Kim, 2008).

**Antiphospholipid Antibody Syndrome (APS) in Pregnancy:** There are several reports supporting a role for IVIG in the treatment of antiphospholipid antibody syndrome (APS) (Empson, 2005; Galli, 1991). Most reports focus on the use of IVIG in the obstetric complications of APS. Several patient series demonstrated that the use of IVIG resulted in successful pregnancy outcome in patients with APS with recurrent abortions. IVIG also benefited patients with APS undergoing in vitro fertilization (Galli 1991). 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 (Empson, 2005).

Most experts recognize APS as a treatable cause of recurrent pregnancy loss. Administration of maternal heparin or low molecular weight (LMW) heparin, with or without low-dose aspirin, is the treatment of choice. The use of steroids is associated with maternal and fetal morbidity and is not recommended (Royal College of Obstetricians and Gynaecologists (RCOG), 2003).

**Autoimmune hemolytic anemia:** Multiple anecdotal reports demonstrate benefit from the use of IVIG in the treatment of autoimmune hemolytic anemia, (Kurtzberg, 1987; Besa, 1988; Hilgartner, 1987) but the use of IVIG should be considered only when other therapeutic modalities fail (Flores, 1993). IVIG might decrease the need for exchange transfusion in neonates with isoimmune hemojaundice (Alpay, 2000; Rubo, 1992).

**Autoimmune neutropenia:** There are no published clinical trials of IVIG in patients with autoimmune neutropenia. Clinical responses (in neutrophil counts) have been described in several small series of patients with autoimmune neutropenia who were treated with IVIG (Bux, 1998; Kurtzberg, 1987). It is unclear whether the beneficial effects are due to the ability of IVIG to induce neutrophil egress from the bone marrow or to prolong the survival of neutrophils. Because corticosteroids are also an effective therapy for this disorder, it is unclear whether IVIG offers any advantage over corticosteroid therapy. Anecdotal reports also suggest utility for IVIG in post-bone marrow transplantation neutropenia, which might be autoimmune in nature (Mascarin, 1993; Klumpp, 1993). As stated in a more recent article by Anderson et al., (2007) the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services convened a panel of national experts to develop an evidence-based practice guideline on the use of IVIG for hematologic conditions. The mandate of the expert panel was to review evidence regarding use of IVIG for 18 hematologic conditions and formulate recommendations on IVIG use for each. They concluded that for most hematologic conditions reviewed by the expert panel, routine use of IVIG was not recommended.

**Inclusion body myositis:** The treatment of inclusion body myositis with IVIG has been studied in two randomized, double-blind, placebo controlled trials (Dalakas, 1997; Walter, 2000). In the first trial, 19 patients were randomized to receive either 1 g/kg/d of IVIG (n=9) for 2 days or placebo (n=10) once per month for 3 months (Dalakas, 1997). After a one month washout period, patients had the option to crossover to the other therapy for an additional 3 months. Changes in muscle strength, measured using the Medical Research Council (MRC) scores, was the primary outcome

measure. In the initial phase of the study, there was a small increase in MRC scores for the IVIG group (MRC increased 4.2 points) and a small decline in the placebo group (MRC decreased by 2.7 points). The difference was not statistically significant. During the crossover portion of the trial the same trend towards an increase in strength with IVIG and decrease with placebo was found. Again this was not statistically significant. In a post hoc analysis, a significant increase in muscle strength in the lower extremities of some patients (39%) receiving IVIG occurred, while there was no increase in strength in patients receiving placebo ( $p < 0.05$ ). Of interest, in the same limb, some muscles had an increase in strength while other muscles had a decrease in strength. In the second study, 22 patients were randomly assigned to IVIG 2 g/kg per month or placebo for 6 months and then crossed over to the alternative therapy (Walter, 2000). Outcomes were measured in a similar manner to the previous trial. Patients receiving IVIG had a mild and significant improvement (11%) when measured with the Neuromuscular System Score (NSS), otherwise other measures showed a trend towards improvement with IVIG.

An additional placebo-controlled trial (Dalakas 2001) assessed IVIG ( $n=19$ ) vs. placebo ( $n=17$ ) monthly for 3 months. However, both groups also received high dose prednisone before infusions. Primary outcomes were differences in the Quantitative Muscle Strength (QMT) testing and modified MRC scores. No significant change in QMT and MRC was noted from baseline at each month after treatment between the two groups.

IVIG for inclusion body myositis was also assessed in two open-label trials. Four patients were treated with high-dose IVIG. After 2 monthly infusions of IVIG 2 gms/kg/month, muscle strength improved or normalized in proximal and less atrophied muscle groups in 3 of the 4 patients. The improvement last for 2 to 4 months (Soueidan, 1993). Another open-label, uncontrolled trial ( $n=9$ ) failed to demonstrate objective improvement in those treated with IVIG (Amato, 1994).

Although IVIG might be useful in other inflammatory myopathies, generalized conclusions or recommendations are not presently possible.

**Neonatal isoimmune hemolytic jaundice:** In a 2004 Cochran 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 immunoglobulin 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 immunoglobulin 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 (Alcock, 2002).

**Posttransfusion purpura:** Intravenous immunoglobulin (IVIG) is used to treat immune thrombocytopenia resulting from a variety of autoimmune and nonautoimmune diseases such as idiopathic thrombocytopenic purpura (ITP), heparin-induced thrombocytopenia, and posttransfusion purpura. IVIG is a limited resource and although considered safe, may nevertheless carry some risk of transferring disease. Its high cost makes monoclonal antibodies, capable of mimicking the clinical effects of IVIG, highly desirable. In a 2003 study by Song et al. (2003), it was concluded that monoclonal IgG with specificity for a circulating cellular target antigen may provide an alternative therapeutic approach to treating immune thrombocytopenia. It may also be less expensive to produce, in more abundant supply, and less susceptible to transmission of viral diseases than the human-derived product.

### **Sjogren's Syndrome**

IVIg has shown some efficacy in Sjogren's syndrome. Most of the reports have focused on associated dysautonomia (Dupond, 1999) or neuropathy (Mochizuki, 2002; Takahashi, 2003; Taguchi, 2004; Kizawa, 2006; Hagiwara, 2008; Morozumi, 2009), although they have been very small case studies. One case study (Bourcier, 2008) 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. Other published literature has described IVIg use for vasculitis of the skin (Durez, 1998) and central nervous system (Canhao, 2000). Complete resolution of middle cerebral artery stenosis was observed following IVIg use in 49 year old woman with neuromyelitis optica coexisting with Sjogren's (Li, 2008). Larger, blinded and controlled studies of IVIg are required regarding its efficacy for Sjogren's syndrome.

**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 SLE received IVIg 2g/kg for 5 consecutive days each month and patients received between 1-8 treatment courses (Levy, 1999a). 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 ( $19.3 \pm 4.7$  to  $4 \pm 2.9$ ;  $p < 0.0001$ ). The average daily dose of prednisolone was decreased ( $29.7 \pm 18.2$  mg/day to  $13.8 \pm 16.7$  mg/day;  $p = 0.02$ ) and laboratory abnormalities improved after IVIg. Two other open label studies, with 12 patients each, showed similar results (Francioni, 1994; Schroeder, 1996). In another trial, 14 patients with progressive lupus nephritis who had received cyclophosphamide 1 gm/m<sup>2</sup> monthly for 6 months with 0.5 mg/kg/d of prednisone were randomized to cyclophosphamide 1 gm/m<sup>2</sup> 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 (Boletis, 1999). In a retrospective study (Arnal, 2002) of 59 SLE patients, 65% of the thirty-one subjects given IVIg had clinical improvement. However, responses were transient. 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 prothrombotic effects and possible IVIg-associated azotemia in SLE (Orange, 2006).

**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 (Jayne, 2000). 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 in the treatment of systemic vasculitis found some clinical benefit as an alternative therapeutic agent (Jayne, 1991; Jayne, 1993a; Jayne, 1993b; Richter, 1993; Richter, 1995; Jayne, 1996; Levy, 1999b). Results were reported as transient in several of these (Jayne, 1991; Jayne, 1993a; Jayne, 1993b; Jayne, 1996). Additional randomized controlled trials will need to be conducted to determine its place in therapy.

### **Infectious and Infection-related Diseases**

**Acute rheumatic fever:** A single randomized trial did not demonstrate benefit of IVIg for the prevention of cardiac sequelae of acute rheumatic fever (Voss, 2001).

**Campylobacter species-induced enteritis:** The value of immunoglobulin therapy has been anecdotally described in Campylobacter jejuni infection when administered orally

(Hammarstrom, 1993). This uncontrolled report is insufficient to support the use for the treatment of this condition.

**Chronic fatigue syndrome:** This is a clinically defined disorder that has been associated with mild immune dysfunction. There have been numerous anecdotal reports of IVIG use having subjective benefits; however, IVIG has not been found to be effective in the treatment of typical chronic fatigue syndrome, as demonstrated in a double-blind, placebo-controlled trial (Orange, 2006; Vollmer-Conna, 1997).

**Postoperative sepsis:** Specific uses for which IVIG preparations have been evaluated and might be useful include postoperative sepsis. Of the complete list, neonatal sepsis has been the most extensively evaluated (Jenson, 1998). However, indications for IVIG therapy in this setting require more precise definition. For example, one study found no improvement in outcome when IVIG therapy was initiated early for suspected sepsis before obtaining results of cultures (Ohlsson, 2001).

**Pseudomembranous colitis:** The value of immunoglobulin therapy has also been only anecdotally described in pseudomembranous colitis caused by *Clostridium difficile*. (Salcedo, 1997; Leung, 1991).

**RSV lower respiratory tract infection:** The treatment of RSV-induced pneumonitis in a small series of immunodeficient patients has also been reported with IVIG (Whimbey, 1995; Ghosh, 2000) combined with ribavirin. Survival rates in this series compared with those expected on the basis of historical cohorts were encouraging and suggest that IVIG might be of benefit as an adjunct therapy to ribavirin.

**Viral load in HIV infection:** Although the use is approved and there is evidence of efficacy IVIG 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 single study that examined 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 (Church, 1999). Thus IVIG might be useful for preventing bacterial infections but should not be considered an antiviral therapy in the HIV-infected patient (Orange, 2006).

#### **Miscellaneous Categories**

**Acute myocarditis and dilated cardiomyopathy:** Treatment for acute myocarditis and dilated cardiomyopathy is not readily available. 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 (Orange, 2006).

**Atopic dermatitis** does not respond to standard therapeutic intervention regimens in a small percentage of patients. IVIG treatment has been tried in those patients and had success in small, open uncontrolled trials. (Orange, 2006). A single small, randomized, evaluator-blinded trial (n = 10) did not support the routine use of IVIG in patients with atopic dermatitis (Paul, 2002).

**Autoimmune blistering skin diseases and manifestation of systemic diseases** includes a number of distinct entities. Pemphigoid is an autoimmune, vesiculobullous, erosive disease that can affect the mucosa. Treatment regimens include prolonged courses of immunosuppressive therapies. An estimated 25% of patients with bullous pemphigoid do not respond to standard treatment. Pemphigus is a group of autoimmune blistering diseases that involve the skin and mucous membranes. The pathognomonic feature of these is acantholysis, which likely results from an autoimmune response to desmoglein. Conventional therapy of pemphigus is immune suppression, although not all patients respond. Open uncontrolled trials in which IVIG was used as a last resort for the treatment of bullous pemphigoid showed some benefit. IVIG therapy was

also found to provide therapeutic benefit for both pemphigus foliaceus and pemphigus vulgaris. Other autoimmune blistering diseases reported to benefit from IVIG therapy are epidermolysis bullosa acquisita and linear IgA disease. All the publications related to the subject are prospective open-label studies or case reports. No controlled studies have yet been conducted to substantiate its benefits compared with other therapeutic modalities. IVIG therapy should be considered only as a last resort in the treatment of patients with this category of disorders (Orange, 2006).

**Autoimmune liver disease:** In one case report of a patient with autoimmune chronic active hepatitis, IVIG treatment was used with a successful outcome. Specifically, liver enzymes normalized, circulating immune complexes were no longer detectable, and periportal mononuclear cell infiltrates improved after treatment (Orange, 2006). Further studies, evaluating the use of IVIG in autoimmune liver disease, are needed however to determine the safety and efficacy of use.

**Autism spectrum disorders:** Children in this spectrum reportedly can have mild abnormalities in their immune systems, suggesting immunologic involvement in the pathophysiology of the disease. Increased immunoglobulin levels and autoimmune antibodies against neural antigens might be found in subsets of these patients. There are no formal randomized studies to evaluate the use of IVIG in the treatment of autism. Two reports (Plioplys, 1998; DelGiudice-Ash, 1999) of open trials including a total of 15 autistic children placed on IVIG for 6 months showed no benefit from the infusions (Orange et al 2006).

**Chronic fatigue syndrome:** This is a clinically defined disorder that has been associated with mild immune dysfunction. There have been numerous anecdotal reports of IVIG use having subjective benefits; however, IVIG is not effective in the treatment of typical chronic fatigue syndrome, as demonstrated in a double-blind, placebo-controlled trial (Orange et al 2006; Vollmer-Conna, 1997).

**Chronic urticaria:** This is a disorder that is often difficult to treat. One third of patients with chronic urticaria appear to have an autoimmune disease. A single report of 5 patients with CVID (common variable immunodeficiency) with chronic urticaria documents amelioration of the urticaria in response to IVIG therapy (Altschul, 2002). Delayed-pressure urticaria is a variant of chronic urticaria that is also difficult to treat. In one report (O'Donnell, 1998) 9 of 10 patients with chronic urticaria were reported to benefit from IVIG therapy, and in another no benefit was observed. The use of IVIG in patients with delayed-pressure urticaria was conducted as an open trial; one third of the enrolled patients underwent a remission, another third experienced some benefit, and the rest did not respond. Because there is not clear evidence that the use of IVIG benefits patients with chronic urticaria, additional studies are needed. Patients with pressure urticaria who fail other therapeutic modalities, however, might benefit from high-dose IVIG (Orange, 2006).

**Non-steroid-dependent asthma:** 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 as to the effect on non-steroid dependent patients (Orange, 2006).

**Prevention of chronic graft-versus-host disease (GVHD) after bone marrow transplantation:** The use of IVIG was studied in a randomized, double-blind, dose-effect, placebo-controlled, multicenter trial in related allogeneic marrow transplantation (Cordonnier, 2003). The 200 patients studied were from 19 different centers; all received HLA-identical sibling marrow. IVIG-treated patients experienced no benefit over those receiving placebo in terms 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, and patients given higher doses of IVIG had more side effects, such as fever and chills. The data provide no basis to recommend IVIG for HLA-identical sibling bone marrow transplants (Orange, 2006).

**Prevention of spontaneous recurrent abortions:** 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. To address this potential benefit, the publications reporting a number of high-quality randomized, placebo-controlled, multicenter studies were reviewed, and these found that IVIG did not provide benefit. Given the review of randomized trials, cumulative current evidence does not presently support the use of IVIG for the prevention of recurrent spontaneous abortions (Orange, 2006).

### **Neuroimmunologic Disorders**

**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. No controlled clinical trials have been conducted on ADEM treatment. Ravaglia et al. (2007) reported that in 10 of 19 ADEM patients who had failed steroids IVIG was effective in improving motor dysfunction. Among steroid-free patients, three of five were responsive to IVIG. Similar results were reported by Marchioni et al. (2002) and Sahlas et al. (2000) who treated 5 and 2 ADEM patients successfully with IVIG after steroid treatment failure.

**Acute idiopathic dysautonomia:** 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. (2006) described a case of a 32-year old man with acute idiopathic autonomic neuropathy (AIAN) in which intravenous administration of immunoglobulin (IVIG) proved effective. Smit et al. (1997) 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.

**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. (Cappa, 1994)

**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. (Dalakas, 1994; Meucci, 1996)

**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. (2004) 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. Arabshahi et al. (2007) 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.

**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. (Assa, 1999)

**Demyelinating neuropathy associated with monoclonal IgM:** Mariette et al. (1997) 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.

**Human T-Lymphotropic 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. (Kuroda, 1991)

**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. Ardolino et al. (2003) successfully treated a child with hereditary recurrent brachial plexus neuropathy while Park et al. (2005) reported dramatic resolution of motor weakness and pain in an adult with acute lumbosacral plexopathy after IVIG. Zochodne et al. (2003) reported that two patients with diabetic lumbosacral plexopathy progressed while receiving IVIG.

**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. (2001) analyzed neurological outcomes in adult patients with idiopathic (n=10) and paraneoplastic 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. Russo et al. (1997) 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), immuran (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. 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 (Petruzzi and de Alarcon, 1995; Veneselli, 1998; Pless, 1996; Glatz, 2003)

**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 (de Beukelaar, 2006). Uchuya et al. (1996) 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. Keime-Gilbert et al. (2000) 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. Blaes et al (1999) 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.

**Paraproteinemic neuropathy:** The occurrence of a peripheral neuropathy in association with a monoclonal gammopathy is quite common and suggests that monoclonal proteins may play a pathogenic role in peripheral nervous system damage. No randomized controlled studies were found for paraproteinemic neuropathy other than associated with monoclonal IgM. Gorson et al. (2002) reported their experience with IVIG in 20 patients with IgG monoclonal gammopathy of undetermined significance polyneuropathy. IVIG therapy was beneficial in 8 (40%) of 20 patients with polyneuropathy and IgG monoclonal gammopathy of undetermined significance. Proximal leg weakness, short duration of symptoms, and demyelinating features on electrodiagnostic studies were associated with a response to IVIG 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. Chang et al. (1996) reported a case of POEM syndrome that did not respond to IVIG.

**Postinfectious cerebellar ataxia:** Acute cerebellar ataxia in childhood is usually a self-limited disease which occurs after viral infections. (Nussinovitch, 2003) Treatment with IVIG has not yet been established. Published evidence consists of isolated case reports. Daaboul et al. (1998) 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.

#### **Primary and Secondary Immune Deficiencies**

**Isolated IgA deficiency:** This is the most common immunodeficiency disorder characterized by a deficiency of IgA with normal levels of other immunoglobulin classes and normal cellular immunity. Isolated IgA deficiency is marked by recurrent sinusitis, bronchitis, and pneumonia, and recurrent diarrhea. 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 (Rose, 2006). 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 (Orange, 2006).

**Isolated IgG4 deficiency:** This most often occurs in association with IgG2 deficiency. The significance of isolated, or selective, IgG4 deficiency is unclear at this time (Vafaie, 2005). Many experts debate the clinical relevance of IgG subclass deficiency and the use of IVIG to treat it. In a prospective, randomized placebo-controlled crossover study of 43 adult patients with

symptomatic IgG subclass deficiency, treatment with IVIG was associated with significantly fewer days of infection. However, no other studies have been conducted to confirm these findings (Rose, 2006).

## 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

HCPCS Code	Description
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex), 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

ICD-9 Code	Description
<b>Proven Codes</b>	
008.61	Intestinal infection, enteritis due to rotavirus
038.10	Unspecified staphylococcal septicemia
040.82	Toxic shock syndrome
042	Human immunodeficiency virus [HIV]
048	Other enterovirus diseases of central nervous system
078.5	Cytomegaloviral disease
204.00	Acute lymphoid leukemia, without mention of having achieved remission
204.10	Chronic lymphoid leukemia, without mention of having achieved remission
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
279.00	Unspecified hypogammaglobulinemia
279.02	Selective IgM immunodeficiency
279.03	Other selective immunoglobulin deficiencies
279.04	Congenital hypogammaglobulinemia
279.05	Immunodeficiency with increased IgM
279.06	Common variable immunodeficiency
279.12	Wiskott-Aldrich syndrome
279.2	Combined immunity deficiency
287.31	Immune thrombocytopenic purpura
287.33	Congenital and hereditary thrombocytopenic purpura
333.91	Stiff-man syndrome
340	Multiple sclerosis
356.9	Unspecified hereditary and idiopathic peripheral neuropathy
357.0	Acute infective polyneuritis
357.4	Polyneuropathy in other diseases classified elsewhere
357.81	Chronic inflammatory demyelinating polyneuritis
358.00	Myasthenia gravis without (acute) exacerbation
358.01	Myasthenia gravis with (acute) exacerbation
358.1	Myasthenic syndromes in 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)
446.6	Thrombotic microangiopathy
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
714.4	Chronic postrheumatic arthropathy
771.81	Septicemia (sepsis) of newborn
776.1	Transient neonatal thrombocytopenia
V42.81	Bone marrow replaced by transplant
V42.82	Peripheral stem cells replaced by transplant
<b>Unproven Codes</b>	
008.43	Intestinal infections due to campylobacter
008.45	Intestinal infections due to clostridium difficile
047.0	Meningitis due to coxsackie virus
047.1	Meningitis due to ECHO virus
047.8	Other specified viral meningitis
047.9	Unspecified viral meningitis

079.51	Human t-cell lymphotropic virus, type I (HTLV-I), in conditions classified elsewhere and of unspecified site
079.52	Human t-cell lymphotropic virus, type II (HTLV-II), in conditions classified elsewhere and of unspecified site
283.0	Autoimmune hemolytic anemias
286.9	Other and unspecified coagulation defects
287.4	Secondary thrombocytopenia
288.00	Neutropenia, unspecified
299.00	Autistic disorder, current or active state
299.01	Autistic disorder, residual state
323.01	Encephalitis and encephalomyelitis in viral diseases classified elsewhere
323.02	Myelitis in viral diseases classified elsewhere
323.1	Encephalitis, myelitis, and encephalomyelitis in rickettsial diseases classified elsewhere
323.2	Encephalitis, myelitis, and encephalomyelitis in protozoal diseases classified elsewhere
323.41	Other encephalitis and encephalomyelitis due to infection classified elsewhere
323.42	Other myelitis due to infection classified elsewhere
323.51	Encephalitis and encephalomyelitis following immunization procedures
323.52	Myelitis following immunization procedures
323.61	Infectious acute disseminated encephalomyelitis [ADEM]
323.62	Other postinfectious encephalitis and encephalomyelitis
323.63	Postinfectious myelitis
323.71	Toxic encephalitis and encephalomyelitis
323.72	Toxic myelitis
323.81	Other causes of encephalitis and encephalomyelitis
323.82	Other causes of myelitis
323.9	Unspecified causes of encephalitis, myelitis, and encephalomyelitis
333.2	Myoclonus
334.4	Cerebellar ataxia in diseases classified elsewhere
335.20	Amyotrophic lateral sclerosis
337.9	Unspecified disorder of autonomic nervous system
341.0	Neuromyelitis optica
341.1	Schilder's disease
353.0	Brachial plexus lesions
357.89	Other inflammatory and toxic neuropathy
390	Rheumatic fever without mention of heart involvement
391.0	Acute rheumatic pericarditis
391.1	Acute rheumatic endocarditis
391.2	Acute rheumatic myocarditis
391.8	Other acute rheumatic heart disease
391.9	Unspecified acute rheumatic heart disease
422.0	Acute myocarditis in diseases classified elsewhere
422.90	Unspecified acute myocarditis
422.91	Idiopathic myocarditis
422.92	Septic myocarditis
422.93	Toxic myocarditis
422.99	Other acute myocarditis
425.0	Endomyocardial fibrosis
425.1	Hypertrophic obstructive cardiomyopathy
425.2	Obscure cardiomyopathy of Africa
425.3	Endocardial fibroelastosis
425.4	Other primary cardiomyopathies
425.5	Alcoholic cardiomyopathy

425.7	Nutritional and metabolic cardiomyopathy
425.8	Cardiomyopathy in other diseases classified elsewhere
425.9	Unspecified secondary cardiomyopathy
493.90	Asthma, unspecified, unspecified
493.91	Unspecified asthma, with status asthmaticus
493.92	Asthma, unspecified, with (acute) exacerbation
634.00	Unspecified spontaneous abortion complicated by genital tract and pelvic infection
634.01	Incomplete spontaneous abortion complicated by genital tract and pelvic infection
634.02	Complete spontaneous abortion complicated by genital tract and pelvic infection
634.10	Unspecified spontaneous abortion complicated by delayed or excessive hemorrhage
634.11	Incomplete spontaneous abortion complicated by delayed or excessive hemorrhage
634.12	Complete spontaneous abortion complicated by delayed or excessive hemorrhage
634.20	Unspecified spontaneous abortion complicated by damage to pelvic organs or tissues
634.21	Incomplete spontaneous abortion complicated by damage to pelvic organs or tissues
634.22	Complete spontaneous abortion complicated by damage to pelvic organs or tissues
634.30	Unspecified spontaneous abortion complicated by renal failure
634.31	Incomplete spontaneous abortion complicated by renal failure
634.32	Complete spontaneous abortion complicated by renal failure
634.40	Unspecified spontaneous abortion complicated by metabolic disorder
634.41	Incomplete spontaneous abortion complicated by metabolic disorder
634.42	Complete spontaneous abortion complicated by metabolic disorder
634.50	Unspecified spontaneous abortion complicated by shock
634.51	Incomplete spontaneous abortion complicated by shock
634.52	Complete spontaneous abortion complicated by shock
634.60	Unspecified spontaneous abortion complicated by embolism
634.61	Incomplete spontaneous abortion complicated by embolism
634.62	Complete spontaneous abortion complicated by embolism
634.70	Unspecified spontaneous abortion with other specified complications
634.71	Incomplete spontaneous abortion with other specified complications
634.72	Complete spontaneous abortion with other specified complications
634.80	Unspecified spontaneous abortion with unspecified complication
634.81	Incomplete spontaneous abortion with unspecified complication
634.82	Complete spontaneous abortion with unspecified complication
634.90	Unspecified spontaneous abortion without mention of complication
634.91	Incomplete spontaneous abortion without mention of complication
634.92	Complete spontaneous abortion without mention of complication
691.8	Other atopic dermatitis and related conditions
694.0	Dermatitis herpetiformis
694.4	Pemphigus
694.5	Pemphigoid
694.60	Benign mucous membrane pemphigoid without mention of ocular involvement
710.0	Systemic lupus erythematosus
728.87	Muscle weakness (generalized)
773.0	Hemolytic disease due to Rh isoimmunization of fetus or newborn
780.71	Chronic fatigue syndrome
780.79	Other malaise and fatigue
780.8	Generalized hyperhidrosis

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#### **POLICY HISTORY/REVISION INFORMATION**

<b>Date</b>	<b>Action/Description</b>
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, 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.