MASSACHUSETTS

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Pharmacy Medical Policy
Immunoglobulins Policy

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Policy Number: 310

BCBSA Reference Number: 8.01.05

Related Policies

- RSV Immunoprophylaxis (RSV-IVIg), #422
- Medicare Advantage Part B Medical Utilization Management (Medicare IVIG), #125

☒ **Prior Authorization** ☐ **Step Therapy** ☐ **Quality Care Dosing**		**Pharmacy Operations:** Tel: 1-800-366-7778 Fax: 1-800-583-6289 Policy last updated **1/2025**
Pharmacy (Rx) or Medical (MED) benefit coverage	☒ **Rx** ☒ **MED (MPBT-2)**	**To request for coverage:** Physicians may call, fax, or mail the attached form (Formulary Exception/Prior Authorization form) to the address below. **Blue Cross Blue Shield of Massachusetts** **Pharmacy Operations Department** 25 Technology Place Hingham, MA 02043 **Individual Consideration:** Policy for requests that do not meet clinical criteria of this policy, see section labeled Individual Consideration
Policy applies to Commercial Members: • Managed Care (HMO and POS), • PPO and Indemnity • MEDEX with Rx plan • Managed Major Medical with Custom BCBSMA Formulary • Comprehensive Managed Major Medical with Custom BCBSMA Formulary • Managed Blue for Seniors with Custom BCBSMA Formulary		

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Intravenous Immunoglobulin Therapy

Intravenous immunoglobulin (IVIG) therapy may be considered **MEDICALLY NECESSARY** for the following indications:

Immunodeficiency States

Individuals with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked hyperimmunoglobulinemia M syndrome, and ataxia telangiectasia.

- Individuals with primary immunodeficiency syndromes should meet all the following criteria for treatment with immunoglobulin:
    - Laboratory evidence of immunoglobulin deficiency
    - Documented inability to mount an adequate immunologic response to inciting antigens (see Policy Guidelines section)
    - Persistent and severe infections, despite treatment with prophylactic antibiotics.
- Individuals with chronic lymphocytic leukemia who have immunoglobulin G (IgG) levels less than 400 mg/dL and persistent bacterial infections.

Infections

- Individuals (children) with HIV who have IgG levels less than 400 mg/dL to prevent opportunistic infections.
- Individuals with severe anemia associated with human parvovirus B19.
- Individuals with toxic shock syndrome.

Autoimmune and Inflammatory Conditions

- Individuals with acute, severe idiopathic thrombocytopenic purpura (see Policy Guidelines section) or chronic idiopathic thrombocytopenic purpura with a disease duration of at least 6 months, presence of symptoms, and with persistent thrombocytopenia (platelet <20,000 per microliter [adult] or 30,000 per microliter [child])-despite treatment with corticosteroids and splenectomy.
- Adults with Guillain-Barré syndrome as an equivalent alternative to plasma exchange.
- Individuals with Kawasaki syndrome.
- Individuals with Wegener granulomatosis.
- Individuals with chronic inflammatory demyelinating polyneuropathy (CIDP) with progressive symptoms for at least 2 months.
- Individuals with multifocal motor neuropathy.
- Individuals with Eaton-Lambert myasthenic syndrome who have failed to respond to anticholinesterase medications and/or corticosteroids.
- Individuals with neuromyelitis optica as an alternative for those with contraindications or lack of response to first-line treatment, particularly in children.
- Individuals with severe refractory myasthenia gravis with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
- Individuals with myasthenic exacerbation (ie, an acute episode of respiratory muscle weakness) in whom plasma exchange is contraindicated.
- Individuals with severe, progressive autoimmune mucocutaneous blistering diseases that include pemphigus, pemphigoid, pemphigus vulgaris, and pemphigus foliaceus who have failed treatment with conventional agents such as corticosteroids, azathioprine, and cyclophosphamide.
- Individuals with dermatomyositis or polymyositis that is refractory to treatment with corticosteroids; in combination with other immunosuppressive agents.

- Individuals with warm antibody hemolytic anemia who are refractory to prednisone and splenectomy.
- Individuals with catastrophic antiphospholipid syndrome.

Alloimmune Processes

- Individuals with neonatal alloimmune thrombocytopenia.
- Individuals with hemolytic disease of the fetus and newborn (erythroblastosis fetalis).

Miscellaneous and BC Continuation

- Individuals with stiff-person syndrome not controlled by other therapies.
- Individuals with relapsing-remitting multiple sclerosis.
- Bone marrow transplant patients (for prevention of infection or GVH prevention)
- Multiple myeloma and immunoproliferative neoplasms
- Immune neutropenia
- Multiple myeloma without mention of remission
- Multiple myeloma in remission
- Other immunoproliferative neoplasms without mention of remission
- Other immunoproliferative neoplasms in remission
- Agranulocytosis
- Prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ
- Solid organ transplant recipients at risk for cytomegalovirus infections and pneumonia.
- Hereditary and idiopathic peripheral neuropathy
- Peroneal muscular atrophy
- Hereditary sensory neuropathy
- Idiopathic progressive polyneuropathy
- Demyelinating polyneuropathy associated with IgM paraproteinemia
- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

Subcutaneous Immunoglobulin Therapy

Preferred Agents	Non-preferred Agents
Hizentra (human immunoglobulin g liquid, subcutaneous)	**Cuvitru** ® (immune globulin subcutaneous)
Cutaquig (immunoglobulin g solution, subcutaneous)	

Subcutaneous immunoglobulin therapy (SCIG) may be considered **MEDICALLY NECESSARY** for the following indications:

- Individuals with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked agammaglobulinemia.

Other applications of SCIG therapy are considered **INVESTIGATIONAL**, including but not limited to CIDP.

Intravenous immunoglobulin (IVIG) therapy is considered INVESTIGATIONAL for the following indications:

Immunodeficiency States

- Individuals who have received solid organ transplant for prophylaxis or treatment of acute antibody-mediated rejection.
- Individuals undergoing or who have undergone hematopoietic cell transplantation who have IgG levels less than 400 mg/dL.

Infections

- Individuals with neonatal sepsis (prophylaxis or treatment).
- Individuals (adults) with sepsis.

Autoimmune and Inflammatory Conditions

- Individuals with toxic epidermal necrolysis and Stevens-Johnson syndrome.
- Individuals with inclusion body myositis.
- Individuals with systemic lupus erythematosus.
- Individuals with immune optic neuritis.
- Individuals with Crohn disease.
- Individuals with hemophagocytic lymphohistiocytosis.

Alloimmune Processes

- Individuals with recurrent spontaneous abortion.

Miscellaneous

- Individuals with autism spectrum disorder.
- Individuals with complex regional pain syndrome.
- Individuals with Alzheimer disease.
- Individuals with paraproteinemic neuropathy.
- Individuals with chronic fatigue syndrome.
- Individuals with acute myocarditis.
- Individuals with refractory recurrent pericarditis.
- Individuals with noninfectious uveitis.
- Individuals with postpolio syndrome.
- Individuals with necrotizing fasciitis.
- Individuals with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, paraneoplastic syndromes, epilepsy, chronic sinusitis, asthma, aplastic anemia, Diamond-Blackfan anemia, red cell aplasia, acquired factor VIII inhibitors, acute lymphoblastic leukemia, nonimmune thrombocytopenia, cystic fibrosis, recurrent otitis media, diabetes mellitus, Behçet syndrome, adrenoleukodystrophy, Fisher syndrome, IgG subclass deficiency, opsoclonus-myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, polyradiculoneuropathy (other than CIDP), refractory rheumatoid arthritis, other vasculitides besides Kawasaki disease, including polyarteritis nodosa, Goodpasture syndrome, and vasculitis associated with other connective tissue diseases.

Other Information
Blue Cross Blue Shield of Massachusetts (BCBSMA*) members (other than Medex®; Blue MedicareRx, Medicare Advantage plans that include prescription drug coverage) will be required to fill their prescriptions for the above medications at one of the providers in our retail specialty pharmacy network, see link below:

Link to Specialty Pharmacy List

Description

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immune deficiency states and various autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G antibodies against a wide variety of bacterial and viral antigens. This evidence review addresses the use of human immunoglobulin therapy for preventing and/or treating disorders in inpatient and outpatient settings. Both intravenous immunoglobulin (IVIG) infusion and subcutaneous immunoglobulin (SCIG) infusion are addressed. However, the review only considers nonspecific pooled preparations of IVIG; it does not consider other preparations used for passive immunization to specific antigens.

Summary of Evidence

Immunodeficiency States

For individuals who have primary humoral immunodeficiency who receive intravenous immune globulin (IVIG) or subcutaneous immune globulin (SCIG) therapy, the evidence includes multiple randomized controlled trials (RCTs) and noncomparative studies. Relevant outcomes are overall survival (OS), symptoms, change in disease status, morbid events, functional outcomes, hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG and SCIG therapy improved disease-related outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing hematopoietic cell transplantation who receive IVIG therapy (prophylaxis), the evidence includes a systematic review and meta-analysis. Relevant outcomes are disease-specific survival (DSS), symptoms, change in disease status, morbid events, quality of life (QOL), hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG for routine prophylaxis of infection in patients undergoing hematopoietic cell transplantation was not associated with survival benefit or reduction in infection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are at risk of acute antibody-mediated rejection after solid organ transplants who receive IVIG therapy, the evidence consists of a systematic review, National Institutes of Health (NIH)-sponsored RCT, and nonrandomized observational studies. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. The systematic review involving variable quality studies with high to very high risk of bias concluded that there is insufficient data to support or advise against the use of IVIG prophylaxis in solid organ transplant. More adequately powered RCTs are needed. Additionally, studies have shown conflicting results that prophylaxis with IVIG in patients with high panel reactive antibody (PRA) levels prior to solid organ transplant leads to a significant reduction in PRA levels. Compared with the standard of care, IVIG

for prophylaxis of infection in patients with high PRA levels was not consistently associated with a survival benefit or reduction in infection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute antibody-mediated rejection after solid organ transplants who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG treatment for antibody-mediated rejection has shown potential benefits in retrospective or small prospective studies; however, larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic lymphocytic leukemia with recurrent bacterial infections associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for recurrent bacterial infections associated with hypogammaglobulinemia in chronic lymphocytic leukemia patients has shown reductions in minor and moderate infections without a reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Infections

For individuals who are HIV-infected children with recurrent bacterial infection associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes a single RCT. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for the prevention of opportunistic infections in HIV-infected children has shown reductions in minor and serious infections without a reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are preterm and low birth weight infants and at risk for sepsis who receive IVIG therapy (prophylaxis), the evidence includes a Cochrane review involving multiple RCTs. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection (considered of marginal clinical importance) with no improvement in any of the other clinically important outcomes, including mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are preterm and low birth weight infants with sepsis who receive IVIG therapy (treatment), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for neonatal sepsis did not differ significantly in the rates of death or major disability. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults with sepsis who receive IVIG therapy, the evidence includes a meta-analysis involving multiple RCTs. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for adult sepsis showed reductions in mortality in the meta-analysis. However, multiple factors preclude recommending the routine use of IVIG to treat sepsis. They include the preponderance of small low-quality studies, the use of heterogeneous dosing regimens, types of IVIG preparations used, and changes over time in the management of sepsis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe anemia associated with human parvovirus B19 who receive IVIG therapy, the evidence includes case series. Relevant outcomes are a change in disease status, treatment-related mortality, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefits with IVIG therapy, data are retrospective. Randomized controlled trials are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have toxic shock syndrome who receive IVIG therapy, the evidence includes a small RCT and multiple observational studies. Relevant outcomes are OS, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for toxic shock syndrome in patients has shown reductions in mortality in a small RCT and in multiple observational studies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Autoimmune and Inflammatory Conditions

For individuals who have immune thrombocytopenic purpura (ITP) who receive IVIG therapy, the evidence includes multiple RCTs and noncomparative studies. Relevant outcomes are DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with corticosteroids, IVIG therapy improved platelet counts. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Guillain-Barré syndrome (GBS) who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs. Relevant outcomes are OS, DSS, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with plasma exchange or combination therapy with plasma exchange, IVIG therapy showed similar outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Kawasaki disease who receive IVIG therapy, the evidence includes a systematic review and meta-analysis of multiple RCTs. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. Compared with aspirin, IVIG therapy has shown significant decreases in new coronary artery abnormalities. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes a systematic review with a single RCT. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. The success of IVIG in Kawasaki disease has led to the investigation of IVIG therapy for other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This small trial found significantly more responders in the IVIG treatment group at 3 months, but no significant differences after 3 months, or in the frequency of relapse or use of other medications. The evidence is sufficient to determine that that the technology results in an improvement in the net health outcome.

For individuals who have chronic inflammatory demyelinating polyneuropathy (CIDP) who receive IVIG therapy, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CIDP who receive SCIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (eg, 45% of patients withdrew from the trial). The other RCT demonstrated that

the use of SCIG for the maintenance of CIDP might be effective, with relatively low adverse events, but this trial also had a number of limitations (eg, small sample, 30% dropout rate). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have multifocal motor neuropathy (MMN) who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Eaton-Lambert myasthenic syndrome who receive IVIG therapy, the evidence includes a RCT and multiple observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in outcomes assessing muscle strength and activity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have neuromyelitis optica who receive IVIG therapy, the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. Studies have shown that IVIG treatment may benefit patients who are refractory to first-line treatment with steroids or plasma exchange, particularly children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe refractory myasthenia gravis or myasthenic exacerbation who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are OS, symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. Compared with plasma exchange, IVIG therapy did not show significantly improved outcomes but was better tolerated. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have relapsing-remitting multiple sclerosis (RRMS) who receive IVIG therapy, the evidence includes a technology assessment. Relevant outcomes are OS, DSS, symptoms, change in disease status, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. According to the technology assessment, IVIG therapy is no longer considered a treatment of choice for RRMS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have autoimmune mucocutaneous blistering diseases who receive IVIG therapy, the evidence includes 2 RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. A systematic review found improvements in over 90% of patients. Randomized controlled trials have reported benefits in disease activity in the population as a whole (1 trial) or in a subgroup of patients with severe disease (1 trial). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have toxic epidural necrolysis (TEN) or Stevens-Johnson syndrome (SJS) who receive IVIG therapy, the evidence includes systematic reviews of observational studies. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. No RCTs have evaluated IVIG for TEN or SJS; most trials that have, have been uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes systematic reviews of observational studies and RCTs. Relevant outcomes are a change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. In 1 of the RCTs, compared with placebo, IVIG therapy showed significant improvements in muscle strength. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have inclusion body myositis who receive IVIG therapy, the evidence includes multiple RCTs. Relevant outcomes are a change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy failed to show improvements in muscle strength. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have systemic lupus erythematosus (SLE) who receive IVIG therapy, the evidence includes systematic reviews of multiples studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy for surrogate outcomes, data are mainly retrospective. More RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have immune optic neuritis who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show improvements in vision-related outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Crohn disease who receive IVIG therapy, the evidence includes multiple case reports of single patients summarized in a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have hemophagocytic lymphohistiocytosis who receive IVIG therapy, the evidence includes multiple case reports summarized in a systematic review and case series. Relevant outcomes are OS, DSS, change in disease status, QOL, and treatment-related mortality and morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have warm antibody autoimmune hemolytic anemia, refractory to prednisone and splenectomy, who receive IVIG therapy, the evidence includes pooled observational data and a case report. Relevant outcomes are a change in disease status, QOL, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential benefits with IVIG therapy in select patients with refractory autoimmune hemolytic anemia. Randomized controlled trials are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have antiphospholipid syndrome who receive IVIG therapy, the evidence includes pooled data from a registry. Relevant outcomes are OS, change in disease status, QOL, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested a potential mortality benefit with IVIG therapy in catastrophic antiphospholipid syndrome. Randomized controlled trials are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Alloimmune Processes

For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple RCTs, a large observational study, and a systematic review. Relevant outcomes are DSS, change in disease status, and treatment-related mortality and morbidity. Compared with combination use with corticosteroids, IVIG alone did not show any additional increases in platelet counts. Multiple trials have demonstrated increased platelet counts with IVIG therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a recurrent spontaneous abortion who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are DSS, treatment-related mortality, and treatment-related morbidity. In multiple RCTs, compared with placebo, IVIG therapy alone did not show any beneficial effects in preventing spontaneous abortions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Miscellaneous Indications

For individuals who have pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related mortality and morbidity. The trials had mixed findings and both had small sample sizes and short intervention duration. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have autism spectrum disorder who receive IVIG therapy, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Although improvements were observed in 1 case series, the other 2 reported negative findings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have complex regional pain syndrome (CRPS) who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related mortality and morbidity. In 1 trial, compared with placebo, IVIG therapy was associated with improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from data on 13 patients. In the other RCT, low-dose IVIG was ineffective in relieving pain in CRPS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Alzheimer disease who receive IVIG therapy, the evidence includes 3 RCTs. Relevant outcomes are OS, DSS, symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. With the exception of a few subgroup analyses using mild cognitive impairment (MCI) status, IVIG therapy was not significantly better than a placebo for outcomes such as brain atrophy, level of plasma amyloid β 1-40, or cognition and function. Studies differed by treatment protocols, outcomes assessed, and 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have paraproteinemic neuropathy who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are a change in disease status, QOL and treatment-related mortality and morbidity. Compared with placebo, IVIG showed mild and transitory improvements in 1 trial but failed to show any improvement in another. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes a RCT and anecdotal reports. Relevant outcomes are symptoms, QOL, and treatment-related mortality and

morbidity. Compared with placebo, IVIG therapy has shown no therapeutic benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes a meta-analysis, RCTs, and a retrospective study. Results from a Cochrane review concluded that, after pooling the available data, there was uncertain evidence of the effect of IVIG in preventing deaths. More RCT evidence is required before IVIG can be routinely recommended in the setting of myocarditis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have refractory recurrent pericarditis who receive IVIG therapy, the evidence includes a systematic review of multiple case reports and case series. Relevant outcomes are OS, change in disease status, QOL, and treatment-related mortality and morbidity. Although improvements were observed in some patients, controlled trials are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have stiff-person syndrome who receive IVIG therapy, the evidence includes a small randomized crossover study. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown decreases in stiffness scores and improvements in functional outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. The case series reported measurable improvements in visual acuity after IVIG therapy, but controlled studies are needed to draw conclusions about the efficacy of IVIG for this population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have postpolio syndrome who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs and nonrandomized prospective studies. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show reductions in the severity of pain and fatigue or improvements in muscle strength. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes a RCT. Relevant outcomes are OS, symptoms, functional outcomes, and treatment-related mortality and morbidity. The RCT found that, compared with placebo, IVIG therapy did not significantly improve functional outcomes, mortality rates, or other outcomes (eg, the use of life support in the intensive care unit). Additional controlled studies are needed to draw conclusions about the efficacy of IVIG for treating necrotizing fasciitis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Prior Authorization Information

<table>
<tr><td colspan="2">☒ Prior Authorization
☐ Step Therapy
☐ Quality Care Dosing</td><td>Pharmacy Operations:
Tel: 1-800-366-7778
Fax: 1-800-583-6289
Policy last updated | 9/2024</td></tr>
<tr><td>Pharmacy (Rx) or Medical (MED) benefit coverage</td><td>☒ Rx
☒ MED (MPBT-2)</td><td>To request for coverage: Physicians may call, fax, or mail the attached form (Formulary Exception/Prior Authorization form) to the address below.</td></tr>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

HCPCS Codes

HCPCS codes:	Code Description
C9072	Injection, immune globulin Asceniv , 500 mg
J0850	Injection, cytomegalovirus immune globulin intravenous (human), per vial [Cytogam]
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1554	Injection, immune globulin (Asceniv), 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin Bivigam , 500 mg
J1557	Injection, immune globulin, Gammaplex, intravenous, nonlyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin Xembify, 100 mg
J1559	Injection, immune globulin Hizentra, 100 mg
J1561	Injection, immune globulin, Gamunex / Gamunex-C / Gammaked , nonlyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), 500 mg [Carimune, Panglobulin]
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

J1575	Injection, immune globulin/hyaluronidase, Hyqvia, 100 mg immunoglobulin
J1576	Injection, immune globulin (Panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg
J3590	Unclassified biologics (e.g. Alyglo)

Other Information
Preferred Home Infusion Therapy Network
Referring providers are encouraged to use these preferred Home Infusion providers to obtain these medications.

Preferred Home Infusion Therapy Provider Contact Information:
Accredo Health Group Phone: 1 866-759-1557 For Hemophilia therapies only, 1-866-712-5007 Website: www.accredo.com
Caremark, LLC. Phone: 1-866-846-3096 Website: www.caremark.com
Coram™ Specialty Infusion Services Phone: 1-800-678-3442 For Hemophilia therapies only, 1-888-699-7440 Website: www.coramhc.com

Individual Consideration

Our medical policies are written for most people with a given condition. Each policy is based on peer reviewed clinical evidence. We also take into consideration the needs of atypical patient populations and diagnoses.

If the coverage criteria outlined is unlikely to be clinically effective for the prescribed purpose, the health care provider may request an exception to cover the requested medication based on an individual's unique clinical circumstances. This is also referred to as "individual consideration" or an "exception request."

Some reasons why you may need us to make an exception include: therapeutic contraindications; history of adverse effects; expected to be ineffective or likely to cause harm (physical, mental, or adverse reaction).

To facilitate a thorough and prompt review of an exception request, we encourage the provider to include additional supporting clinical documentation with their request. This may include:

- Clinical notes or supporting clinical statements.
- The name and strength of formulary alternatives tried and failed (if alternatives were tried) and specifics regarding the treatment failure, if applicable.
- Clinical literature from reputable peer reviewed journals.
- References from nationally recognized and approved drug compendia such as American Hospital Formulary Service® Drug Information (AHFS-DI), Lexi-Drug, Clinical Pharmacology, Micromedex or Drugdex®; and
- References from consensus documents and/or nationally sanctioned guidelines.

Providers may call, fax or mail relevant clinical information, including clinical references for individual patient consideration, to:

Blue Cross Blue Shield of Massachusetts
Pharmacy Operations Department
25 Technology Place
Hingham, MA 02043
Phone: 1-800-366-7778
Fax: 1-800-583-6289

We may also use prescription claims records to establish prior use of formulary alternatives or to show if step therapy criteria has been met. We will require the provider to share additional information when prescription claims data is either not available or the medication fill history fails to establish use of preferred formulary medications or that step therapy criteria has been met.

Policy History

Date	Action
1/2025	Updated to add a preferred section to SubQ IG section of the policy.
8/2024	Clarified policy with Association
4/2024	Updated to add Alyglo to Medical UM.
11/2023	Updated criteria for Myasthenia Gravis and updated IC to align with 118E MGL § 51A.
7/2023	Reformatted Policy.
4/2023	Clarified not covering Organ Rejection.
7/2022	Renamed policy to be inclusive of IV and SubQ products.
12/2021	BCBSA National medical policy review. No changes to policy statements. New references added.
2/2021	Updated to add PANDAS & PANS in line with state mandate.
1/2021	Coding information clarified.
12/2020	BCBSA National medical policy review. No changes to policy statements. New references added.
10/2020	Clarified coding information
4/2020	Updated to add Asceniv to the policy.
11/2019	Updated to add Xembify to the policy.
7/2019	Updated to add Cutaquig to the policy.
1/2019	Clarified coding information.
8/2018	Updated to include Association coverage statement for Neuromyelitis Optica & Blistering disease.
10/2017	Clarified coding information plus updated to change Walgreens Specialty Name.
7/2017	Updated to add AllCare to Pharmacy Specialty list.
6/2017	Updated address for Pharmacy Operations.
1/2016	Updated to add new HCPCS code J1575.
10/2015	Updated to included revised language for Pharmacy only medications.
7/2015	Update to include Retail billing.
6/2015	Updated to include Bivigam, Cytogam, Gammaplex, Hizentra and HyQvia and to align ICD codes.
2/2015	Updated to include a couple HCPCS codes and one ICD code.
7/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
1/2014	Updated ExpressPAth Language.
1/2013	Updated 1/2013 to include new FDA products Gammaked ™ and Gamunex ®-C.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/2012	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.

11/2011	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology. No changes to policy statements.
10/2011	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
9/2011	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.
1/2011	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
12/2010	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology. No changes to policy statements.
11/2010	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
10/2010	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
1/2010	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
12/2009	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology. No changes to policy statements.
11/2009	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
10/2009	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.
9/2009	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
10/2009	Updated to reflect UM requirements.
1/2009	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
12/2008	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology. No changes to policy statements.
11/2008	Reviewed - Medical Policy Group - Gastroenterology, Nutrition and Organ Transplantation. No changes to policy statements.
10/2008	Reviewed - Medical Policy Group - Urology and Obstetrics/Gynecology. No changes to policy statements.
10/2008	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
1/2008	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
9/2007	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
1/2007	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.

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Endnotes

1. Revised 9/95 based on TEC (Technology Evaluation Center) 6/95 assessment of medical literature from 1991 to 1995 addressing IVIg for SLE-related cytopenia, vasculitis, pericarditis, and pleural effusions in patients who were not controlled by immunosuppressives or cytotoxic agents.
2. Revised 9/95 to include the 2/95 TEC evaluation of medical literature from 1991-4/95 assessing IVIg to improve the functional status of patients with inclusion body myositis who have not responded to prednisone or other immunosuppressives.
3. Revised 10/95 based on 1994 TEC evaluation of medical literature from 1991-1994 assessing IVIG to stop progression of muscle weakness or to decrease frequency or severity of relapses in MS..
4. Revised 10/95 based on a 1994 TEC evaluation of medical literature from 1991-1994 assessing IVIg to improve functional capacity or to reduce pain in patients with RA refractory to NSAIDS and either cytotoxic or disease-modifying antirheumatic drugs.
5. Revised 10/95 based on a 1994 TEC evaluation of medical literature from 1991-1994 assessing IVIG to improve neurologic function in CIDP, either as first-line therapy, or for acute exacerbations in patients refractory or intolerant of prednisone or azathioprine.
6. Revised 10/95 based on a 1994 TEC evaluation of medical literature assessing IVIG to reduce fetal loss in women with recurrent fetal loss (sequence of 3 or more miscarriages), with or without antiphospholipid antibodies.
7. Revised 3/96 to include CMS (Centers for Medicare and Medicaid services) regulations published in the February/March 1996 issue of the Medicare Health Resources.
8. Revised 2/97 to include CMS (Centers for Medicare and Medicaid services) regulations published in the February/March 1997 issue of the Medicare Health Resources.
9. Revised 9/97 to include CMS regulations (Centers for Medicare and Medicaid services) published in the June/July 1997 Medicare B Health Resources.
10. Added based on recommendations made by the Massachusetts Neurological Society.
11. Based on the July 1998 TEC (Technology Evaluation Center) analysis of the literature on IVIg for MS. Health outcomes considered by TEC included prevention of disease progress and disability, improving baseline neuro disability, and reducing acute relapse.
    Also see the July/August 1997 ACP Journal Club commentary:
    http://www.acponline.org/journals/acpjc/julaug97
    Regarding the article: Fazekas F et al., Austrian Immunoglobulin in Multiple Sclerosis Study Group. Randomized placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Lancet. 1997 Mar 1;349:589-93.
12. FDA-approved uses as of July, 1998.
13. Off-label use in the treatment of AIDS and HIV as required by law.
14. Label use based on National Blue Cross Blue Shield policy 8.01.05, issued 12/15/98.
15. Off-label use based on National Blue Cross Blue Shield policy 8.01.05, issued 12/15/98.
16. Investigational use based on National Blue Cross Blue Shield policy 8.01.05, issued 12/15/98.
17. Based on recommendations from Walt Kagan, MD, Massachusetts Society of Clinical Oncologists.
18. Based upon a September 1999 Medicare B HealthResource Newsletter.
19. Medicare policy is developed separately from BCBSMA policy. While BCBSMA policy is based upon scientific evidence, Medicare policy incorporates scientific evidence with local expert opinion, and governmental regulations from CMS (Centers for Medicare and Medicaid Services) and the U.S Congress. While BCBSMA and Medicare policies may differ, our Medicare HMO Blue and Medicare PPO Blue members must be offered the same services as Medicare offers. In many instances, BCBSMA policies offer more benefits than does Medicare policy.
20. Based on recommendations from David Weinberg, MD, Massachusetts Neurologic Association, 1/2000 MPG Neurology meeting.
21. Medical Policy Group, August 2000.
22. Previous criteria summarized in the current form: vital capacity less than 1L; dysphagia associated with aspiration; inability to ambulate 100 feet without assistance.

23. Medical Policy Group, January 2000.
24. Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for the American Society of Hematology
25. See the 1998 ASRM (American Society of Reproductive Medicine) Practice Committee Report on Intravenous Immunoglobulin and Spontaneous Pregnancy Loss.
26. Based on the June 2002 Medicare B Resource Newsletter. See also the CMS /Medicare websites at www.cms.gov and www medicare.gov.
27. Based upon the 2002 Blue Cross Blue Shield Association policy 8.01.05. IVIG for myasthenic crisis is considered medically necessary. Myasthenic crisis is an off-label indication.
28. Based upon the 2002 Blue Cross Blue Shield Association National policy 8.01.05.
29. Based upon the 2004 Blue Cross Blue Shield Association policy 2.01.01.
30. Based upon the 2004 Blue Cross Blue Shield Association National policy 8.01.05.
31. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol.2003;139:1051-1059.
32. Based upon the 2004 BCBSA National Policy 8.01.05. Bone marrow transplant patients (for prevention of infection or GVH prevention.)
    - Cordonnier C, Chevret S, Legrand M et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled multicenter trial. Ann Intern Med 2003;139(1):8-18.
33. Based upon the 2004 BCBSA National Policy 8.01.05. Recurrent Spontanous Abortion.
34. Based on Blue Cross Blue Shield National policy 8.01.05 Intravenous Immune Globulin Therapy issued 4/06.

Forms

To request prior authorization using the Massachusetts Standard Form for Medication Prior Authorization Requests (eForm), click the link below:

https://www.bluecrossma.org/medical-policies/sites/g/files/csphws2091/files/acquiadam-assets/023%20E%20Form%20medication%20prior%20auth%20instruction%20prn.pdf

OR

Print and fax, Massachusetts Standard Form for Medication Prior Authorization Requests #434

Home Infusion Therapy
Prior Authorization Form

Please complete and fax with the physician's prescription to: (888) 641-5355. If the patient is a BCBSMA employee, please fax the form to: (617)246-4013.

Company name:		Contact Name:			
Phone #:		Provider #:			
Fax#		Address:			
Patient name:		Address:			
Patient_ID#:		DOB:____/____/____		Diagnosis:	
Prescribing Physician/addr:	_____			Telephone:	
PCP name/address:	_____			Telephone:	

Is this fax number 'secure' for PHI receipt/transmission per HIPAA requirements? (circle one) Yes No

Place of Service ☐ **Home** ☐ **SNF** ☐ **MD office** ☐ **other (specify)**_____

Primary Therapy

Primary drug name: _____ Approximate duration: ____/____/____ to ____/____/____

Dose: _____

Frequency: _____ Route of Administration: pump: Y N

Other Therapy

Other drug name: _____ Approximate duration: ____/____/____ to ____/____/____

Dose: _____

Frequency _____ Route of Administration: pump: Y N

☐ If this is a "drug only" authorization request, indicate other services the nursing agency is providing:

_____

Nursing provided by: _____ Contact: _____

Phone: _____ Fax: _____

Request for 7 Day Coverage : Date of occurrence: _____ request dates:_____

Occurrence type: ☐ Hospitalization ☐ Death ☐ Change of Therapy

Physician signature:_____ **Date:**_____