BlueCross BlueShield
Federal Employee Program

IVIG (intravenous Immunoglobulin)
Asceniv, Alyglo, Bivigam, Flebogamma, Gammagard, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, Privigen

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Immune globulin products from human plasma were first used in the 1950s and 60s to treat immune deficiency. These initial preparations were given either intramuscularly or subcutaneously to avoid the severe shock-like reactions from intravenous administration. In the early 1980s chemical and enzymatic modifications of the pooled plasma provided a preparation suitable for intravenous administration. Intravenous immunoglobulin (IVIG) products are prepared from pooled donations exceeding 10,000 liters (1).

IVIG is used to treat various autoimmune, infectious, and idiopathic diseases (1).

Regulatory Status

FDA-approved indications: The immune globulins addressed by this policy are FDA-approved for use in one or more of the following conditions: (2-13)

- Primary immune deficiency (PID)
- Acute and Chronic Thrombocytopenic Purpura (ITP)
- Prevention of bacterial and viral infections in patients with hypogammaglobulinemia and/or recurrent bacterial and viral infections associated with B-cell Chronic Lymphocytic Leukemia (CLL)
- Prevention of coronary artery aneurysms associated with Kawasaki syndrome
- Multifocal Motor Neuropathy (MMN)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Off-Label Uses: (14-31)

1. Prophylaxis of bacterial and viral infections in pediatric human immunodeficiency virus (HIV) infection
2. Prophylaxis of bacterial and viral infections in bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) recipients
3. Dermatomyositis
4. Polymyositis

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5. Myasthenia gravis
6. Guillain-Barre syndrome
7. Lambert-Eaton myasthenic syndrome
8. Fetal/neonatal alloimmune thrombocytopenia
9. Parvovirus B19-induced pure red cell aplasia
10. Stiff-person syndrome
11. End-stage renal disease (ESRD) to improve the chances of successful kidney transplantation
12. Peripheral blood progenitor cell (PBPC) collection
13. Umbilical Cord Stem Cell Transplantation
14. Inclusion-body myositis
15. Multiple sclerosis
16. Secondary immunosuppression associated with hematological malignancy
17. Autoimmune encephalitis

Use of immune globulin to treat immunosuppression secondary to hematological malignancy is supported by data from several clinical trials. This acquired hypogammaglobulinemia is thought to occur, in part, due to the use of therapies targeting B-cells, and due to the clonal proliferation of abnormal B-cells as part of the hematological malignancy's disease process. The decision to supplement with exogenous IVIG should be made after review of patient's physical history and IgG serum concentrations indicating hypogammaglobulinemia (serum IgG < 500 mg/dL or ≥ 2 standard deviations below the mean concentration for age) (1, 30).

There are various types of immune-mediated encephalopathy, including anti-NMDA encephalitis, VGKG-associated limbic encephalopathies, and Hu and Ma2-mediated encephalitis. These have been seen in patients both with cancer and cancer-free of all ages, notably in young adults and children. First-line treatment, showing moderate success, includes the use of IVIGs (15-16).

Immune globulin use is associated with increased risk of thrombosis, particularly in the elderly and patients with risk factors such as cardiovascular disease, hypercoagulopathy, those on estrogen therapy, and patients with central venous catheters. Patients should be monitored carefully for signs and symptoms of thrombosis both at the time of infusion and after infusion. For those patients who will

be self-administering the medication, practitioners need to instruct the patients and caregivers on how to monitor for signs and symptoms of thrombosis. Thrombosis may occur regardless of the route of administration (2-13).

IVIG products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, > 65 years of age, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs (2-13).

Other potential complications to monitor include the following (2-13):
Immunoglobulin A deficiency: People with this condition have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

Aseptic meningitis syndrome (AMS): Rare occurrences of AMS have been reported in association with IVIG treatment. AMS usually begins within several hours to 2 days following IVIG treatment and is characterized by symptoms including severe headache, drowsiness, fever, photophobia, painful eye movements, muscle rigidity, nausea, and vomiting. AMS may occur more frequently in association with high-dose (2 g/kg) IVIG treatment. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.

Bleeding complications: Bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

Severe reactions: Severe reactions, such as anaphylaxis or angioneurotic edema, have been reported in association with IV immunoglobulins, even in patients not known to be sensitive to human immunoglobulins or blood products.

Summary
Immune globulin products are primarily used to treat immune deficiency. They are also used off-label to treat other conditions such as myasthenia gravis and multiple sclerosis. The IVIG products differ in

the preparation method, viral inactivation steps, stabilizing agent, osmolality, and IgA content (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of IVIG while maintaining optimal therapeutic outcomes.

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