Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 04/16/2020

## Immune Globulin Replacement Therapy Medication Use Guidelines

| Brand | Manufacturer | HCPCS | Benefit |
|---|---|---|---|
| Asceniv™ | ADMA Biologics | J1599 | Medical |
| Bivigam® | Biotest Pharmaceutical | J1556 | Medical |
| Carimune® NF | CSL Behring | J1566 | Medical |
| Cutaquig® | Octapharma | J1599 | Medical & Pharmacy |
| Cuvitru™ (SC only) | Baxalta/Shire | J1555<br>J7799 (Medicare Use)<br>J1599 (Commercial Program) | Medical & Pharmacy |
| GamaSTAN® S/D (IM) | Grifols | J1460/J1560<br>CPT /90281 | Medical |
| Gammagard® Liquid (IV & SC) | Baxter Healthcare | J1569 | Medical & Pharmacy |
| Gammagard® S/D | Baxter Healthcare | J1569 | Medical |
| Gammaked™ (IV & SC) | Grifols | J1561 | Medical & Pharmacy |
| Gammaplex® | Bio Products Laboratory | J1557 | Medical |
| Gamunex®-C (IV & SC) | Talecris | J1561 | Medical & Pharmacy |
| Hizentra® (SC only) | CSL Behring | J1559 | Medical & Pharmacy |
| HyQvia® (SC only) | Baxter | J3490 | Medical & Pharmacy |
| Octagam® | Octapharma | J1568 | Medical |
| Panzyga® | Octapharma | J1599 | Medical |
| Privigen® | CSL Behring | J1459 | Medical |
| Xembify® | Grifiols | J1558 | Medical & Pharmacy |

**Policy:**

*Requests must be supported by submission of chart notes and patient specific documentation.*

A. Coverage of the requested drug is provided when all the following are met:
   a. Requires treatment failure with or intolerance to two preferred IG products as specified in the BCBM/BCN utilization management medical drug list or BCBSM/BCN prior authorization and step therapy documents AND
   b. Coverage for Cutaquip, Cuvitru and HyQvia is provided when used for FDA-approved indications only AND

c. Requires one of the following criteria below:
    i. Acquired Factor VIII inhibitor when conventional therapy is ineffective or not tolerated. Examples of conventional therapy include, but are not limited to, immunosuppressive therapy with cyclophosphamide, steroids, or azathioprine.
    ii. Allogeneic bone marrow transplant recipients who are ≥ 20 years of age for up to 4 months following transplantation.
    iii. Autoimmune encephalitis and when patient meets all the criteria below
        1. Cerebral spinal fluid (CSF) antibody testing, electroencephalography (EEG) testing and a brain magnetic resonance image (MRI) has been done to rule out other causes.
        2. Other conditions have been ruled out.
    iv. Autoimmune hemolytic anemia (AIHA) when patient is diagnosed with warm type AIHA that does not respond to alternative therapies. Examples of alternative therapies include, but are not limited to, steroids, immunosuppressive agents, plasmapheresis, rituximab, and/or splenectomy.
    v. Dermatomyositis, documented with EMG abnormalities and/or increased CPK levels, with associated severe disability, when other interventions are ineffective or not tolerated. Other therapy interventions include, but are not limited to, corticosteroid therapy and immunosuppressive therapy with azathioprine, methotrexate, or cyclophosphamide.
    vi. Fetal alloimmune thrombocytopenia with documented diagnosis.
    vii. HIV infected children (< 13 years of age) when the CD4 cell count is greater than 200/mm3.
    viii. Hypogammaglobulinemia (acquired, secondary) associated with either chronic B-cell lymphocytic leukemia (CLL) or post allogeneic bone marrow transplant with laboratory findings (low serum IgG and/or patients with poor IgG response to the pneumococcal vaccine) and a history of recurrent infections.
    ix. Hypogammaglobulinemic neonates (infectious disease prophylaxis) with low birth weight (less than 1500g) or in a setting with high baseline infection rate or morbidity.
    x. Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome. IVIG can be used as an alternative to plasma exchange in patients who meet one of criteria 1 through 4 below:
        1. Deteriorating pulmonary function tests.
           OR
        2. Rapid deterioration with symptoms for less than 2 weeks.
           OR
        3. Rapidly deteriorating ability to ambulate.
           OR
        4. Inability to walk independently for 10 meters.
    xi. Inflammatory demyelinating polyneuropathy (chronic; CIDP) meeting all of criteria a, b, and c below:
        1. Significant functional disability.
           AND
        2. Documentation of slowing of nerve conduction velocity on EMG/NCS.
           AND
        3. Documentation of elevated spinal fluid protein on lumbar puncture or an MRI confirming the diagnosis.
    xii. Idiopathic thrombocytopenia purpura (ITP; acute), when a rapid increase in platelet count is necessary, such as in an acute bleeding episode or prior to surgery.
    xiii. ITP (chronic), when the platelet count is dangerously low (e.g., platelet count less than 30,000 cells/mm3 in children, and less than 20,000 cells/mm3 in adults) for patients concurrently receiving corticosteroids.
    xiv. ITP in pregnancy
        1. Refractory to steroids with platelet counts less than 10,000/mm3 in the third trimester.
           OR

2. Platelet counts less than 30,000/mm3 associated with bleeding before vaginal delivery or C-section.
   OR
3. Pregnant women who have developed autoimmune thrombocytopenia during a previous pregnancy.
   OR
4. Pregnant women who have platelet counts less than 50,000/mm3 during the current pregnancy.
   OR
5. Pregnant women with a past history of splenectomy.

xv. Kawasaki syndrome during the first ten days of diagnosis.

xvi. Lambert-Eaton myasthenic syndrome when other treatment options are ineffective or not tolerated. Examples of other treatment options include, but are not limited to, pyridostigmine bromide, azathioprine, and prednisone.

xvii. Multifocal motor neuropathy (MMN) in patients with conduction block and appropriate testing (example: anti-GM1 antibodies).

xviii. Multiple myeloma in patients with stable disease and a high risk of recurrent infections despite prophylactic antibiotic therapy, patients with poor IgG response to pneumococcal vaccine, or have low normal IgG levels during acute sepsis episode.

xix. Myasthenia gravis for the treatment of acute severe decompensation (e.g., respiratory failure, swallowing difficulties) or chronic decompensation, when other treatments are ineffective or not tolerated. Other treatment options include, but are not limited to, plasmapheresis, pyridostigmine, and immunosuppressive therapy such as azathioprine, cyclosporine, and cyclophosphamide.

xx. Pediatric intractable epilepsy in candidates for surgical resection or when other interventions are ineffective or not tolerated. Examples of other interventions include, but are not limited to, anticonvulsant medications, ketogenic diets, and steroids.

xxi. Polymyositis in patients with severe active illness when other interventions have been ineffective or not tolerated. Other therapy interventions include, but are not limited to, corticosteroid therapy and immunosuppressive therapy with azathioprine, methotrexate, or cyclophosphamide.

xxii. Post-transfusion purpura in severely affected patients.

xxiii. Primary humoral immunodeficiency diseases: A baseline IgG level is needed along with the laboratory findings specified below prior to the initiation of immune globulin for newly diagnosed primary humoral immunodeficiency diseases.

1. X-linked agammaglobulinemia (congenital agammaglobulinemia) diagnosis accompanied by marked deficits or absence of all five immunoglobulin classes (IgG, IgM, IgA, IgE, and IgD), decreased circulating B lymphocytes, and normal numbers of functioning T lymphocytes.
   OR
2. Hypogammaglobulinemia (a general term describing serum levels of IgG which are below the lower limits of normal).
   a) Member has low IgG levels
   b) Member has the inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax).
   c) Member has unexplained recurrent or persistent severe bacterial infections despite adequate treatment, including all of the following:
      i. Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis, etc);
      ii. Prophylactic antibiotics;
      iii. Increased vigilance and appropriate antibiotic therapy for infections

   OR
3. Common variable immunodeficiency (CVID); acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia documented with low to normal

IgG levels and the inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax).
OR

4. Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM) accompanied by very low serum concentrations of IgG, IgA, and IgE, with normal or, more frequently, greatly elevated polyclonal IgM concentrations.
OR
5. Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, accompanied by marked deficits in IgG, IgA and IgM, low lymphocyte counts, and absent or below normal levels of both B- and T- lymphocytes.

xxiv. Pure red cell aplasia with documented parvovirus B19 infection and severe anemia.

xxv. Refractory pemphigus foliaceus resistant to conventional treatments, until conventional treatment takes effect. Conventional treatments include, but are not limited to immunosuppressive agents and plasmapheresis.

xxvi. Solid organ transplant in the treatment of antibody-mediated rejection:
1. Prior to solid organ transplant, when patient is at high risk for antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ.
OR
2. Following solid organ transplant.

xxvii. Stiff-Person Syndrome when treatment with other agents is ineffective or not tolerated. Examples of other treatment options include, but are not limited to, diazepam, baclofen, clonazepam, valproic acid, and clonidine.

xxviii. Systemic lupus erythematosus for severe active disease when other interventions are ineffective or not tolerated. Other interventions include, but are not limited to corticosteroids and immunosuppressive agents, such as cyclophosphamide or azathioprine.

xxix. (For GamaSTAN only) – Prophylactic post exposure for Hepatitis A, Measles (Rubeola), Varicella, and Rubella (in early pregnancy).

B. Administration, Quantity Limits, and Authorization Period
   a. BCBSM/BCN does not consider intravenous immune globulins to be self-administered medications and is covered under the medical benefit. Subcutaneously administered immune globulin may be considered under the pharmacy benefit.
   b. When prior authorization is approved, immune globulins may be authorized for the period defined in Table 1. Please note the frequency of administration does not apply to all patients. Depending on response to therapy, there is a small set of patients that will require more frequent administrations. One treatment course where the total dose is administered over a period of more than 1 day will be allowed (ex: the usual IVIG dose of CIDP is 400 mg/kg/day for 5 days for a total of 2 g/kg/day).
   c. When prior authorization is approved immune, globulins may be authorized at the usual doses listed in Table 2. Initial dosing will be approved at the lower end of the dose range. Increase in dose and dosing interval will be authorized based on indication and literature support of the dose/dosing interval. Authorization shall be reviewed at least annually to confirm that current medical necessity criteria for the following conditions in Table 1 are met.
   d. Subcutaneous administration of immune globulin is considered an alternative to intravenous administration of immune globulin and may be considered medically necessary when one of the criteria in Section I is met.
   e. Coverage for HyQvia is authorized for an every four week dosing interval after the ramp-up period unless the four week dosing interval is ineffective or not tolerated.

C. IVIG is considered investigational when used for all other conditions, including but not limited to:
   a. Acute lymphocytic leukemia
   b. Acute renal failure

c. Adrenoleukodystrophy
d. Adult HIV infection
e. Alzheimer's disease
f. Aplastic anemia
g. Asthma
h. Atopic dermatitis
i. Autism
j. Behçet's syndrome (Behçet's disease)
k. Cardiomyopathy, recent-onset dilated
l. Chronic fatigue syndrome
m. Clostridium difficile, recurrent
n. Cystic fibrosis
o. Diabetes
p. Diamond-Blackfan anemia
q. Endotoxemia
r. Heart block, congenital
s. Hemolytic anemia
t. Hemolytic transfusion reaction
u. Hemophagocytic syndrome
v. Human T-lymphocyte virus-1 myelopathy
w. Hyper IgE syndrome
x. Immune mediated neutropenia
y. Inclusion body myositis
z. Infectious disease in high risk neonates and adults following surgery or trauma
aa. Lumbosacral plexopathy
bb. Miller-Fisher syndrome
cc. Motor neuron syndromes
dd. Multiple sclerosis
ee. Narcolepsy/cataplexy
ff. Neonatal hemochromatosis
gg. Neonatal hemolytic disease
hh. Nephropathy, membranous
ii. Nephrotic syndrome
jj. Neuromyelitis optica
kk. Nonimmune thrombocytopenia
ll. Ophthalmopathy, euthyroid
mm. Opsoclonus myoclonus
nn. Otitis media, recurrent
oo. Paraproteinemic neuropathy
pp. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
qq. Polyneuritis
rr. Post-polio syndrome
ss. Recurrent spontaneous pregnancy loss/abortion
tt. Rheumatoid arthritis
uu. Sinusitis, chronic
vv. Stevens-Johnson Syndrome
ww. Still's Disease
xx. Surgery or trauma
yy. Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)
zz. Thrombotic Thrombocytopenic Purpura, neonatal autoimmune – severe thrombocytopenia
aaa. (TTP)
bbb. Thrombotic Thrombocytopenic Purpura, refractory to platelet transfusions. (TTP)

ccc. Tic disorder (DSM-IV)
ddd. Toxic epidermal necrolysis
eee. Urticaria, delayed pressure
fff. Uveitis
ggg. Vasculitic syndromes, systemic
hhh. Von Willebrand's syndrome
iii. Wegener's granulomatosis

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

| Table 1.Indications | Frequency | Authorization Duration | | | | Reauthorization | |
|---|---|---|---|---|---|---|---|
| | IVIG may be given no more frequently than: | 2 weeks | 3 months | 6 months | 1 year | Yes/ No | Criteria |
| Acquired Factor VIII inhibitor | One treatment per month | | | X | | Yes | Documented initial response to IVIG and presence of Factor VIII inhibitor |
| Allogeneic bone marrow transplant | On days 7 and 2 prior to transplant, then once weekly for up to 90 days (total therapy duration of 97 days) | | | X | | Yes | Reauthorization may be considered under hypogammaglobulinemia criteria |
| Autoimmune encephalitis | One treatment per month | | | X | | | Documentation of clinical improvement |
| Autoimmune hemolytic anemia (warm type) | One treatment per month | | | X | | Yes | Documented initial response to IVIG and recurrence of clinically significant, symptomatic anemia |
| Dermatomyositis | One treatment per month | | X | | | Yes | Objective evidence of efficacy of initial three-month treatment, such as improvement in muscle strength or decreased CPK levels |
| Fetal alloimmune thrombocytopenia (FAIT) | One treatment per month | | | X | | Yes | Documented previous history of FAIT. Treatment not to exceed the duration of pregnancy |
| HIV + children (< 13 years) | One treatment per month | | | | X | Yes | Documentation of clinical improvement |
| Hypogammaglobuline mia, acquired, associated with chronic B-cell lymphocytic leukemia or post allogeneic bone marrow transplant | One treatment per month | | | | X | Yes | Documentation of clinical improvement and current IgG levels that are in the low to normal range. Consideration of up to 1 year of therapy based on clinical benefit |
| Hypogammaglobuline mic neonates (infectious disease prophylaxis) | One treatment per month | | | X | | Yes | Documentation of clinical improvement and current IgG levels that are in the low to normal range |
| Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome | One treatment per month | | X | | | No | Reauthorization may be considered under chronic IDP criteria |
| Inflammatory demyelinating polyneuropathy (chronic; CIDP) | One treatment per month | | | X | | Yes | Documented initial response to IVIG and evidence of functional improvement |
| ITP (acute) | Up to 4 doses given every other day | | | X | | No | Reauthorization may be considered under chronic ITP criteria |

| Indication | Frequency | Authorization Duration | | | | Reauthorization | |
|---|---|---|---|---|---|---|---|
| | IVIG may be given no more frequently than: | 2 week | 3 months | 6 month | 1 year | Yes/ No | Criteria |
| ITP (chronic) | One treatment per month | | | X | | Yes | Platelet count equal to or greater than 30,000/ mm3 but no more than 150,000/$mm^3$, OR less than 30,000/$mm^3$ but platelets have increased from base-line accompanied by resolution of previous bleeding. IVIG treatment only covered until conventional therapy takes effect |
| ITP in pregnancy | One treatment per month | | X | | | Yes | Platelet count (see policy criteria). Treatment is not to exceed the duration of pregnancy . |
| Kawasaki syndrome | One treatment given within 10 days of symptom onset. | X | | | | No | No further authorization shall be given. |
| Lambert-Eaton myasthenic syndrome | One treatment per month | | | X | | Yes | Documented initial response to IVIG and measurable improvement in muscle function/strength. |
| Multifocal motor neuropathy | One treatment per month | | | X | | Yes | Documented initial response to IVIG and measurable improvement in muscle function/strength. |
| Multiple myeloma | One treatment per month | | | | X | Yes | Documentation of clinical improvement and current IgG levels that are in the low to normal range. |
| Myasthenia gravis (acute and chronic) | One treatment per month | | | X | | Yes | Documented initial response to IVIG and measurable improvement in muscle function/strength. |
| Pediatric intractable epilepsy | One treatment per month | | | X | | Yes | Documented initial response to IVIG and significantly reduced frequency and/or duration of seizures |
| Polymyositis | One treatment per month | | X | | | Yes | Objective evidence of the efficacy of initial 3-month treatment, such as improvement in muscle strength and/or decreased CPK levels. |
| Post-transfusion purpura | One or two treatments | X | | | | No | No further authorization shall be given. |
| Primary humoral immunodeficiency diseases | One treatment per month | | | | X | Yes | Documented initial response to IVIG, current IgG levels that are in the low to normal range and evidence of clinical improvement, such as decreased occurrence of infections |
| Pure red cell aplasia | One treatment per month | | | X | | Yes | Documentation of initial response to IVIG, parvovirus, and recurrence of significant anemia. |
| Refractory pemphigus foliaceus | One treatment per month | | | X | | No | No further authorization shall be given beyond 6 months. Approval may be granted until conventional therapy takes effect. |

| Indication | Frequency | Authorization Duration | | | | Reauthorization | |
|---|---|---|---|---|---|---|---|
| | IVIG may be given no more frequently than: | 2 weeks | 3 months | 6 months | 1 year | Yes/ No | Criteria |
| Solid organ transplant | Up to 4 doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant. | | X | | | No | No further authorization shall be given. |
| Stiff-Person Syndrome | One treatment per month | | X | | | Yes | Objective evidence of the efficacy of initial 3-month treatment, such as improvement in mobility, ability to perform work-related or household tasks, and decreased fall frequency. |
| Systemic lupus erythematosus | One treatment per month | | | X | | Yes | Documentation of initial response to IVIG and evidence of clinical improvement. |
| GamaSTAN Only-Prophylactic Post Exposure-Medicare Only | | | | | | | |
| Hepatitis A | Once for < 3month stay in endemic region. Repeat every 4 to 6 months for > 3 month stay in endemic region | | | | X | Yes | Recommended for persons who plan to travel in areas where hepatitis A is common. |
| Measles (Rubeola) | Once post suspected exposure if fewer than 6 days previously | | | | X | Yes | Prevention or to modify measles in a susceptible person exposed fewer than 6 days previously. |
| Varicella | Once immediately post exposure | | | | X | Yes | When VZIG is unavailable, given promptly post exposure. |
| Rubella (in early pregnancy) | Once | | | | X | Yes | Exposed women who will not consider a therapeutic abortion. |

**Table 2. Dosing per Indication***

| Indication | Dose |
|---|---|
| Acquired Factor VIII inhibitor | 1000 mg/kg for 2 days OR 400 mg/kg for 5 days |
| Allogeneic bone marrow transplant | 500 mg/kg on day 7 and day 2 prior to transplantation and then once weekly thereafter for 90 days after transplantation |
| Autoimmune encephalitis | 400 mg/kg/day for 5 days |
| Autoimmune hemolytic anemia (warm type) | 400 mg/kg/day for 5 days |
| Dermatomyositis | 2000 mg/kg every month |
| Fetal alloimmune thrombocytopenia (FAIT) | 1000 mg/kg every week, 2gm/kg/week in refractory cases |
| HIV + children (< 13 years) | 400 mg/kg every 4 weeks |
| Hypogammaglobulinemia, acquired, associated with chronic B-cell lymphocytic leukemia or post allogeneic bone marrow transplant | 400 mg/kg IV every 4 weeks |
| Hypogammaglobulinemic neonates (infectious disease prophylaxis) | 400 – 600 mg/kg/month, administered as a single dose, or up to several months in duration |
| Inflammatory demyelinating polyneuropathy (acute), including Guillain-Barré syndrome | 400 mg/kg/day for 5 days |
| Inflammatory demyelinating polyneuropathy (chronic; CIDP) | *Loading dose:* 2000 mg/kg, given in divided doses over 2 to 4 consecutive days<br>*Maintenance dose:* 1000 mg/kg every 3 weeks OR 500 mg/kg/day, for 2 consecutive days every 3 weeks 400 mg/kg/5 days, repeated every 6 weeks |
| ITP (acute) | 1000 mg/kg/day for 2 consecutive days OR 400 mg/kg once daily for 2- 5 consecutive days |
| ITP (chronic) | 1 – 2 gm/kg as a single dose or divided into equal amounts and given over 2-5 days |
| ITP in pregnancy | 400 mg/kg/day for 5 days |
| Kawasaki syndrome | 2000 mg/kg as a single dose OR 400 mg/kg/day for 4 days |
| Lambert-Eaton myasthenic syndrome | 2000 mg/kg administered over 2-5 days |
| Multifocal motor neuropathy | 2000 mg/kg/month, administered over 2-5 days |
| Multiple myeloma | 400 mg/kg every month |
| Myasthenia gravis (acute and chronic) | 1-2 gm/kg/month IV, given over 2 to 5 days |
| Pediatric intractable epilepsy | 2000 mg/kg over 4 days followed by 1000 mg/kg over 2 days every month for 6 months |
| Polymyositis | 2000 mg/kg/month given over 2 to 5 days |
| Post-transfusion purpura | 500 mg/kg/day for 2 consecutive days |
| Primary humoral immunodeficiency diseases | 100 – 800 mg/kg /month |
| Pure red cell aplasia | 400 mg/kg/day for 5-10 days OR 1000 mg/kg/day for 3 days |
| Refractory pemphigus foliaceus | 1-2 gm/kg over 3 days every 4 weeks |
| Solid organ transplant | 2000 mg/kg/month for 4 months |
| Stiff-Person Syndrome | 400 mg/kg/day for 3 - 5 days |
| Systemic lupus erythematosus | 400 mg/kg/day for 5 days |

* Dosing must be based on ideal body weight (IBW) unless the patient's BMI is ≥ 30 kg/m$^2$ or actual body weight is greater than ideal body weight (IBW) by 20% or more, then adjusted body weight (adjBW) must be used.

**Therapeutic considerations:**

A. **FDA approved indication / Diagnosis**
   a. Primary humoral immunodeficiency diseases
   b. HIV-infected children < 13 years of age
   c. Allogenic bone marrow transplant (BMT)
   d. Chronic B-Cell Lymphocytic Leukemia (CLL)
   e. Idiopathic thrombocytopenia purpura (ITP)
   f. Kawasaki syndrome
   g. Multifocal motor neuropathy

**Please refer to most recent prescribing information.*

B. **Background Information**
   a. Primary humoral immunodeficiency diseases
      i. X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life.
      ii. Common variable immunodeficiency (CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia) is characterized by low to normal IgG levels and inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax). Most patients experience severe recurrent and/or chronic infections.
      iii. Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, are rare, inherited syndromes.
      iv. Immunoglobulin reference ranges vary depending on the age of the patient and the particular assay method used. The usual immune globulin maintenance dose is 100- 800mg/kg/month and therapy is usually life-long.
      v. A serum IgG level should be drawn every 3 months, before infusion, and IVIG dose adjusted accordingly.
      vi. Serum trough levels should be maintained at 400 – 600 mg/dL. Documentation of the rationale should be provided in the event that a trough level greater than 600 mg/dL is required. [Medicare]
      vii. HyQvia has not been studied for use in indications other than primary immunodeficiency in adults. Safety has not been established in children.
      viii. Cuvitru has not been studied for use in indications other than primary immunodeficiency in adults and pediatric patients two years of age and older.
      ix. When IGHy (HyQvia) or IVIG was administered at 3- or 4-week treatment intervals, serum IgG trough levels were similar, regardless of the administration route (IGHy or IGIV) or patient age.
   b. HIV-infected children < 13 years of age
      i. IVIG has been shown to decrease the frequency of bacterial infections, increase the time free from serious bacterial infections, and decrease the frequency of hospitalization in children with AIDS.
      ii. There is no evidence to suggest that IVIG gives incremental benefit to antiretroviral therapy and prophylactic antibiotics.
      iii. In children with advanced HIV disease who are receiving zidovudine, IVIG decreases the risk of serious bacterial infections. However, this benefit is apparent only in children who are not receiving co-trimoxazole as prophylaxis and for children with a CD4 count of greater than 200 to 400 per mm3.
      iv. The recommended dose is 400 mg/kg/month to maintain the serum IgG level.
   c. Allogenic bone marrow transplant (BMT)
      i. IVIG is safe and effective in reducing the incidence and severity of infections and graft-vs.-host disease in allogeneic BMT recipients greater than 20 years old.
      ii. Mortality after 100 days is unaffected by IVIG.
      iii. Little to no benefit is apparent among younger patients or in autologous transplants.

iv. The usual dosage is 500 mg/kg administered on day 7 and day 2 prior to transplantation and then once weekly thereafter. Therapy generally continues for 90 days after the transplant.

d. Chronic B-Cell Lymphocytic Leukemia (CLL) with hypogammaglobulinemia
    i. IVIG therapy reduces the incidence of bacterial infections to approximately 50% of the incidence without IVIG administration.
    ii. Monthly IVIG infusions of 400 mg/kg are recommended to maintain the serum IgG level.

e. Idiopathic thrombocytopenia purpura (ITP)
    i. Normal platelet count range is 115,000/mm3 to 440,000/mm3.
    ii. Acute ITP
        1. In various studies, 64% to 100% of IVIG recipients attained platelet counts greater than 100,000 cells/mm3 within 7 days.
        2. A maximum of 1 gm/kg/day for three or four doses of IVIG on alternate days is recommended. Acute ITP is usually seen in children and typically resolves spontaneously within 2 months.
    iii. Chronic ITP
        1. Current evidence does not support that IVIG alters the natural course of chronic ITP, affects long-term morbidity/mortality, or increases the rate of long-term remission.
        2. IVIG is not indicated for the maintenance of platelet counts in chronic ITP.
        3. Steroids and/or splenectomy are considered the first-line treatment of choice for chronic ITP.
        4. IVIG may be considered in patients with dangerously low platelet counts (less than 10,000 to 20,000 per mm3 in adults or less than 30,000 per mm3 in children), and therefore may be at an increased risk for significant bleeding, such as intracranial hemorrhage.
        5. The usual dose of IVIG is 1 to 2 gm/kg divided into equal amounts and given over 2 to 5 days.

f. Kawasaki syndrome
    i. IVIG in conjunction with aspirin given within the first 10 days of illness can reduce the incidence of coronary artery abnormalities by 65% - 78%, compared with treatment with aspirin alone. IVIG is not effective if more than ten days have elapsed from onset of symptoms.
    ii. The usual dose of IVIG is 2 gm/kg as a single dose, or 400 mg/kg daily for 4 days.

g. Multifocal motor neuropathy
    i. Small controlled trials demonstrate significant increase in muscle strength associated with IVIG administration, long-term benefits, and safety.
    ii. Baxter International's Gammagard Liquid is the first immunoglobulin treatment FDA approved for MMN patients in the United States, June 2012.
    iii. The recommended IVIG dose is 2 gm/kg/month, administered over 2 – 5 days.

C. **Off-Label Indications**

a. Acquired Factor VIII inhibitor
    i. A sufficient treatment course is usually 6-12 weeks before attempting a different immunosuppressive agent. Patients are generally treated until remission (elimination of the inhibitor) occurs, which may take several months.
    ii. Treatment regimens of 1 gm/kg for 2 days or 400 mg/kg for 5 days have been studied. In one study, only 6 of 19 patients responded to IVIG within 40 days of treatment.

b. Autoimmune encephalitis
    i. Evidence for the effectiveness of IVIG in autoimmune encephalitis comes from one large systematic review by Nosadini et al 2015.
    ii. IVIG when used in combination with other immunomodulatory treatments has better outcomes compared to patients with no immunotherapy.
    iii. The usual dose of IVIG is 0.4 gm/kg/day for 5 days and subsequent replacement of IVIG is usually considered at 3 to 4 weeks.

c. Autoimmune hemolytic anemia
    i. In a retrospective study of 73 patients, a response was observed in 40% of cases, only 15% achieving hemoglobin levels of 10 g/dL or greater; children were more likely to respond (54%).
    ii. In a recent guideline, high-dose immunoglobulin was not recommended for use in AIHA, except under certain life-threatening circumstances.
d. Dermatomyositis
    i. High-dose IVIG is a safe and effective treatment for refractory dermatomyositis unresponsive to corticosteroid therapy.
    ii. The recommended IVIG dose is 2 gm/kg per month.
e. Fetal alloimmune thrombocytopenia
    i. ACOG guidelines recommend IVIG as first line treatment for documented fetal thrombocytopenia.
    ii. A trial comparing IVIG treatment with and without dexamethasone in siblings showed that:
        1. IVIG treatment was associated with an increase in mean platelet count of 69,000/$mm^3$.
        2. There were no instances of intracranial hemorrhages, although hemorrhage had occurred previously in 10 untreated siblings.
    iii. The recommended dose of IVIG is 1 gm/kg/week, increasing to 2 gm/kg/week in refractory cases.
f. Hypogammaglobulinemic neonates
    i. Treatment with IVIG is usually reserved for patients with recurrent severe infections, not responding to antibiotic prophylaxis.
    ii. The usual IVIG dose is 400 – 600 mg/kg/month, administered as a single dose, or up to several months in duration.
g. Inflammatory demyelinating polyneuropathy (IDP)
    i. Acute IDP, including Guillain-Barré syndrome
        1. The American Academy of Neurology recommends the use of IVIG in non-ambulant adult patients with Guillain-Barré syndrome within 2–4 weeks of neuropathic symptom onset.
        2. The recommended IVIG dose is 400 mg/kg/day for 5 days. If relapse occurs within 1-2 weeks of initial therapy, an additional treatment course of IVIG may be effective. Further treatment does not improve outcomes and is not recommended.
    ii. Chronic IDP
        1. Treatment options include plasmapheresis, IVIG, and corticosteroids.
        2. The usual IVIG dose is 400 mg/kg/day for 5 days, repeated every 6 weeks.
h. ITP in pregnancy
    i. The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia.
    ii. Platelet function is typically normal so it is not necessary to maintain platelet count in the normal range.
    iii. The first line of treatment is prednisone, usual dose 1-2mg/kg/day.
    iv. IVIG is useful in cases that are resistant to steroids and when a rapid rise in platelets is necessary. A response typically occurs within 6–72 hours of IVIG treatment.
i. Lambert-Eaton myasthenic syndrome (LEMS)
    i. LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes.
    ii. Patients reported improved limb, respiratory muscle, and bulbar muscle strength with IVIG, compared to placebo in a small randomized crossover trial (n = 9).
    iii. The recommended dose of IVIG is 2 gm/kg administered over 2–5 days.
j. Myasthenia gravis
    i. Randomized trials examining short-term treatment of myasthenia gravis with IVIG have shown no difference between IVIG and plasma exchange or IVIG and methylprednisolone.
    ii. IVIG may be useful in treating patients with severe myasthenia gravis who fail to respond to the maximum tolerated doses of corticosteroids and/or immunosuppressants.
    iii. There is no evidence to determine whether IVIG improves function or reduces steroid requirements for moderate to severe myasthenia gravis.
    iv. The recommended dose of IVIG is 1 – 2 gm/kg/month administered over 2–5 days.

k. Pediatric epilepsy
    i. The efficacy was evaluated in a retrospective, multicenter study comprising 64 consecutive patients treated with immunoglobulins for either epileptic encephalopathy or refractory epilepsy.
    ii. Nine patients (14%) demonstrated complete resolution and 10 (15.6%) exhibited partial improvement. Of these 19 responders (29.7%), eight relapsed.
    iii. Although intravenous immunoglobulin is not suitable for all cases of epilepsy, it may prove efficacious for specific epileptic syndromes.
l. Polymyositis
    i. Polymyositis is an inflammatory myopathy with no unique clinical features. It is typically a diagnosis of exclusion in patients with slowly progressive muscle weakness. Traditional therapies include immunosuppressive medications or steroids.
    ii. The recommended dose of IVIG is 2 gm/kg/month administered over 2–5 days.
m. Post-transfusion purpura
    i. Post-transfusion purpura is a rare condition that can occur in patients undergoing blood transfusions. It typically develops approximately one-week after blood transfusion.
    ii. IVIG may be considered first-line therapy in severely affected patients.
    iii. The recommended dose of IVIG is 500 mg/kg/day for two consecutive days. Rapid platelet recovery has been seen within days of treatment.
n. Pure red cell aplasia
    i. Parvovirus B19 infects and lyses red cell precursors, which can cause pure red cell aplasia. IVIG therapy is usually reserved for patients with chronic parvovirus infection and chronic anemia.
    ii. Chronic parvovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parvovirus and anemia may spontaneously resolve.
    iii. The usual dose of IVIG is 400 mg/kg/day for 5–10 days or 1 gm/kg/day for 3 days. Initial treatment courses may be indicated with recurrence of anemia and increase in parvovirus B19 DNA.
o. Refractory pemphigus foliaceus
    i. IVIG is typically given in combination with conventional treatments, such as immunosuppressive agents and plasmapheresis, and is discontinued once conventional treatment takes effect. IVIG is not considered a maintenance therapy for pemphigus foliaceus.
    ii. The usual dose of IVIG is 1-2 gm/kg administered over 3 days. This regimen may be repeated every 3-4 weeks.
p. Solid organ transplant
    i. Antibody-mediated rejection (AMR) is a potential cause of acute organ rejection after transplant. Pre-treatment with IVIG (desensitization) may reduce the risk of AMR.
    ii. A randomized, double-blind trial comparing IVIG to placebo in 101 highly sensitized renal transplant candidates concluded that IVIG is better than placebo in improving transplantation rates.
    iii. A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant.
q. Stiff Person Syndrome
    i. Sixteen patients were randomized to IVIG or placebo for 3 months, then crossed over to the alternate treatment after a 1 month washout period. IVIG patients demonstrated decreased stiffness scores, decreased frequency of falls, ability to walk more easily without assistance, and improved ability to perform work-related tasks. Benefits lasted 6 weeks to 1 year without additional treatment.
    ii. The usual dose of IVIG is 400 mg/kg/day for 3 – 5 days.
r. Systemic Lupus Erythematosus
    i. Small case series suggest some benefit from treatment with IVIG when compared to cyclophosphamide.
    ii. The usual dose of IVIG is 400 mg/kg/day for 5 days.

D. **Investigational Conditions**

a. The University Hospital Consortium (UHC), an alliance of 68 academic health centers, performed a critical assessment of off-label IVIG uses.
b. The UHC determined published data to be inadequate to support the use of IVIG in various conditions.
c. Asthma:
    i. Further trials in asthma patients are necessary to delineate patient subsets that would best benefit from IVIG therapy, and define optimal dosing in this condition.
d. HIV
    i. The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes.
e. Multiple sclerosis
    i. Progressive: There is not substantial evidence to support IVIG in the treatment of chronic progressive multiple sclerosis.
    ii. Relapsing-remitting type: IVIG may provide some benefit in reducing the acute exacerbation rate in relapsing-remitting multiple sclerosis.
    iii. Trials are generally limited to small numbers of patients and have lacked complete data on clinical outcomes.
    iv. Current evidence suggests little benefit with regard to slowing disease progression.
    v. The American Academy of Neurology does not consider IVIG to be a first-line therapy in the treatment of relapsing-remitting multiple sclerosis.
f. Opsoclonus-myoclonus
    i. A rare neurological syndrome characterized by an unsteady gait, brief shock- like muscle spasms, and irregular rapid eye movements
    ii. Evidence supporting the use of IVIG in this condition consists of retrospective chart reviews and case reports. However, a randomized phase II trial is currently investigating the use of IVIG in treating children with opsoclonus-myoclonus associated with neuroblastomas.
g. Post-Polio
    i. Two published trials of post-polio syndrome failed to demonstrate a statistically significant benefit compared to placebo in improvement of muscle strength.
h. Recurrent pregnancy loss or recurrent spontaneous abortion: due to anti-phospholipid or anti-cardiolipin antibodies
    i. Recurrent pregnancy loss is defined as three or more pregnancies resulting in spontaneous abortion prior to 20 weeks of gestational age. These women often have immunologic abnormalities, particularly antiphospholipid antibodies.
    ii. IVIG has not been established as a safe or effective therapy to prevent recurrent spontaneous abortion in women with immunologic abnormalities, such as elevated natural killer cells, defective cytokines, or defective growth factors.
    iii. One randomized controlled trial comparing IVIG to thyroid replacement therapy for the prevention of miscarriages found IVIG to be less effective. There was a statistically significant higher rate of live birth among women treated with thyroid replacement therapy.
    iv. A small randomized controlled trial in 85 women with a history of three or more spontaneous abortions before 10 weeks of gestation compared low molecular heparin (LMW) plus aspirin with IVIG therapy. The percentage of live births in the LMW plus aspirin versus the IVIG treatment group was 72.5% and 39.5%, respectively.
    v. A randomized controlled trial in 82 women with a history of idiopathic secondary miscarriage compared live birth rates in those who received intravenous immune globulin versus placebo infusion (saline). There was no statistical difference between treatment groups.
    vi. ACOG recommendations state:
        1. If results are positive for the same antibody on two consecutive tests 6 to 8 weeks apart, initiate heparin and low-dose aspirin with next pregnancy attempt.
        2. IVIG is not effective in preventing recurrent pregnancy loss.

i. Alzheimer's Disease
    i. A small sample of four patients received intravenous immune globulin (IVIG) treatment at a dose of 0.4 g/kg every two weeks and showed no further cognitive decline in patients with Alzheimer's disease.

j. Additional conditions for which published data is determined to be inconclusive or inadequate to support the use of IVIG include Alzheimer's disease, atopic dermatitis, recurrent *C. difficile*, narcolepsy/cataplexy, neonatal hemochromatosis, chronic sinusitis, tic disorder, delayed pressure urticaria, and toxic epidermal necrolysis.

E. **Dosing and administration**

a. A plasma IgG level of 200 mg/dL is often a common minimum target for patients being considered for IVIG replacement therapy.
b. In patients with mild to moderate IgG deficiency with levels of 300 mg/dL-400mg/dL, the decisions to treat are based on clinical symptoms and antigenic challenge.
c. Dosing adjustment in replacement therapy is based on clinical response and IgG levels.
d. The minimum serum concentration of IgG necessary for protection has not been firmly established. However, maintenance of serum trough IgG levels above 500 mg/dL has been considered a sufficient target to prevent most systemic infections. Some patients may require an IgG level of 400-500 mg/dL above their baseline value for protection.
e. In patients with severe hypogammaglobulinemia or agammaglobulinemia, IgG levels (trough) should be checked every three to six months in growing children and every six to twelve months in adults.
f. The trough or steady state IgG level is obtained before scheduled infusions and frequently guides IVIG dose selection.

F. **Efficacy**

**Please refer to most recent prescribing information.*

G. **Medication Safety Considerations**

Black Box Warning: Yes

**Please refer to most recent prescribing information.*

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| Policy History | | |
|---|---|---|
| # | Date | Change Description |
| 2.6 | Effective Date: 4/16/2020 | Updated weight based dosing changes and cost table |
| 2.5 | Effective Date: 02/03/2020 | PA added to BCNA and MAPPO for Cuvitru and Panzyga |
| 2.4 | Effective Date: 11/7/2019 | Removed Flebogamma DIF and updated weight based dosing requirements |
| 2.3 | Effective Date: 10/01/2019 | PA added to BCNA and MAPPO for Asceniv |
| 2.2 | Effective Date: 08/15/2019 | PA added to BCBSM and BCN for Xembify<br><br>Added Xembify and Gammaked |
| 2.1 | Effective Date: 06/01/2019 | PA added to BCBSM and BCN for Asceniv |
| 2.0 | Effective Date: 02/14/2019 | Added Cutaquig |
| 1.9 | Effective Date: 12/06/2018 | Added Panzyga |
| 1.8 | Effective Date: 11/01/2018 | Reviewed policy for new Hizentra indication but no changes required.<br>Updated criteria for hypogammaglobulinemia – added IgG levels, removed necessity for immunization after no response to vaccines. |
| 1.7 | Effective Date: 05/03/2018 | Added criteria for autoimmune encephalitis and PANDAS was placed under investigational use |
| 1.6 | Effective Date: 08/10/2017 | Updated CIDP criteria. |
| 1.5 | Effective Date: 02/09/2017 | Added Cuvitru (new product) and GamaSTAN.<br>Updated criteria for MMN. |
| 1.4 | Effective Date: 11/10/2016 | Annual Review of Policies |
| 1.3 | Effective Date: 02/12/2015 | Updated criteria – Require 2 vs. 1 preferred IG products;<br>Added HyQvia (new product) |
| 1.2 | Effective Date: 05/08/2014 | Updated criteria - include preferred product |
| 1.1 | Effective Date: 05/02/2013 | Added Bivigam (new product) |

<table>
<tr>
<td>1.0</td>
<td>Effective Date:<br>11/2012</td>
<td>Initial Dose changed to Usual Doses Investigational indications updated: Add:<br>• Atopic dermatitis<br>• Autism<br>• Hemolytic anemia<br>• Hyper IgE syndrome<br>• Miller-Fisher syndrome<br>• Neuromyelitis optica<br>• Steven's Johnson syndrome<br>• Wegener's granulomatosis<br><br>
<table>
<tr><th>Line of Business</th><th>PA Required (Yes/No)</th></tr>
<tr><td>BCBS</td><td>Yes</td></tr>
<tr><td>BCN</td><td>Yes</td></tr>
<tr><td>MAPPO</td><td>Yes</td></tr>
<tr><td>BCNA</td><td>Yes</td></tr>
</table>
</td>
</tr>
</table>

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or [http://dailymed.nlm.nih.gov/dailymed/index.cfm](http://dailymed.nlm.nih.gov/dailymed/index.cfm).*

# Blue Cross Blue Shield/Blue Care Network of Michigan
# Medication Authorization Request Form

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

**Immune Globulin Replacement Therapy -** Bivigam® (J1556), Carimune NF® (J1566), Cuvitru™ (J1555), Flebogamma® (J1572), Gammagard® (J1569), Gammaplex® (J1557), Gamunex® (J1561), Gammaked (J1561), Hizentra® (J1559), HyQvia® (J1575), Octagam® (J1568), Privigen® (J1459), Ig NOS (J1599) Panzyga® (J1599), Cutaquig® (J1599), Asceniv™ (J1599), Xembify (J1599)

This form is to be used by participating physicians to obtain coverage for immune globulin products. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

| PATIENT INFORMATION | PHYSICIAN INFORMATION |
|---|---|
| **Name** | **Name** |
| **ID Number** | **Specialty** |
| **D.O.B.** ☐Male ☐Female | **Address** |
| **Diagnosis** | **City /State/Zip** |
| **Drug Name** | **Phone/Fax: P**: ( ) - **F**: ( ) - |
| **Dose and Quantity** | **NPI** |
| **Directions** | **Contact Person** |
| **Date of Service(s)** | **Contact Person Phone / Ext.** |

**STEP 1: DISEASE STATE INFORMATION**

1) **Initial or Continuation of therapy?** ☐ Initial ☐ Continuation ***Original Start date:*** _____

2) **How administered?** ☐ Self-administered ☐ Health care professional administered

3) Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
☐ Hospital outpatient facility (go to #4) *Reason for Hospital Outpatient:* _____

4) Please specify location of administration if hospital outpatient infusion? _____

5) Please provide the member's current weight (in kilograms) and height (in inches): _____

6) **Indication:** ☐ Primary Humoral Immunodeficiency Diseases Type: _____ ☐ Acute IDP (Guillain Barre)
☐ Chronic Inflammatory Demyelinating Polyneuropathy (IDP) ☐ Multifocal Motor Neuropathy
☐ Solid Organ Transplant ☐ Dermatomyositis ☐ Multiple myeloma ☐ Hypogammaglobulinemia
☐ Idiopathic Thrombocytopenic Purpura (ITP) ☐Chronic ☐ Acute ☐ Pregnancy ☐ HIV ☐ Bone Marrow Transplant
☐ Myasthenia Gravis ☐ Systemic Lupus Erythematosus ☐ Polymyositis ☐ Other_____

7) **Please fill out what pertains to patient AND give level:**

| Test | Response | Levels | Date | Test | Response | Levels | Date |
|---|---|---|---|---|---|---|---|
| IgG | ☐ low ☐ normal ☐ high | _____ | _____ | IgD | ☐ low ☐ normal ☐ high | _____ | _____ |
| IgM | ☐ low ☐ normal ☐ high | _____ | _____ | B cells | ☐ low ☐ normal ☐ high | _____ | _____ |
| IgA | ☐ low ☐ normal ☐ high | _____ | _____ | T cells | ☐ low ☐ normal ☐ high | _____ | _____ |
| IgE | ☐ low ☐ normal ☐ high | _____ | _____ | Platelet count _____/mm$^3$ Date: _____ | | | |

8) **Please check which boxes pertain to patient:** ☐ Unable to produce response to: ☐ protein antigen ☐carbohydrate antigen
☐ Recurrent infections ☐ Prophylactic Antibiotics ☐ Immunization with conjugate vaccine

9) **Please list past trials and failures of other conventional therapies:**

| Prior Therapy | Dates of Therapy | Outcome/Reason for D/C |
|---|---|---|
| _____ | _____ to _____ | ☐ Not tolerated ☐ Failure Explain: _____ |
| _____ | _____ to _____ | ☐ Not tolerated ☐ Failure Explain: _____ |
| _____ | _____ to _____ | ☐ Not tolerated ☐ Failure Explain: _____ |

10) **For continuation, check all that applies to response to therapy (please provide and attach applicable lab values)**
☐ Improved Please describe: _____
☐ Stable Please describe: _____
☐ Worse Please describe: _____
☐ No assessment available on file; Explain: _____

***Chart notes are required for the processing of all requests. Please add any other supporting medical information.***

**Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.**

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

**Physician's Name** **Physician Signature** **Date**

| | | |
|---|---|---|
| **Step 2:** Checklist | ☐ Form Completely Filled Out<br>☐ Attached Chart Notes | ☐ Concurrent Medical Problems<br>☐ Prior Therapies |
| **Step 3:** Submit | **By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979** | **By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320** |



Created 6/6/14; Updated; 7/22/14; 12/2/14; 11/20/2015; 9/21/2016; 11/29/2017;10/11/2018; 1/2/2019; 1/24/2019; 5/24/2019; 7/23/2019

Created 6/6/14; Updated; 7/22/14; 12/2/14; 11/20/2015; 9/21/2016; 11/29/2017;10/11/2018; 1/2/2019; 1/24/2019; 5/24/2019; 7/23/2019