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Medication Policy Manual

Policy No: dru020

Topic: Immune Globulin Replacement Therapy, (IVIG, SCIG):

Date of Origin: January 1996

- Alyglo
- Asceniv
- Bivigam
- Cutaquig
- Cuvitru
- Flebogamma DIF
- Gammagard
- Gammagard S/D
- Gammaked
- Gammaplex
- Gamunex-C
- Hizentra
- Hyqvia
- Octagam
- Panzyga
- Privigen
- Qivigy
- Xembify
- Yimmugo

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) are preparations containing antibodies purified from human blood. They are used in the treatment of many different conditions resulting from immune deficiencies or other immunologic conditions.

Policy/Criteria

Most contracts require pre-authorization approval of immune globulins prior to coverage.

I. Continuation of therapy (COT) **and** new starts (treatment-naïve patients): The use of Higher-Cost Immune Globulin Replacement Products (as listed in *Table 2*) is considered not medically necessary.

II. Continuation of therapy (COT): All other immune globulins (as listed in *Table 1*) may be considered medically necessary for COT when criteria A and B below are met.

A. One of the following (1, 2, or 3) is met:

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, *Site of Care Review*, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): All other immune globulins (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (such as chart notes) that criteria A and B below are met.

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, *Site of Care Review*, dru408].

AND

B. At least one of the following diagnostic criteria 1 through 5 below is met:

1. Immunodeficiency (primary or acquired), diagnosed by, or in consultation with an immunologist or hematologist, as defined in criterion a or b:

a. A diagnosis of one of the following and documented **hypogammaglobulinemia** (a low baseline serum IgG level):

i. Primary humoral immunodeficiency diseases (PID) (as defined in *Appendix 1*).

ii. HIV infected children (< 13 years of age) with hypogammaglobulinemia.

iii. Hematologic malignancy-related hypogammaglobulinemia.

iv. Post-allogeneic bone marrow transplant (BMT).

v. B-cell mediated cancer [e.g., chronic lymphocytic leukemia (CLL), B-cell lymphoma].

vi. Hypogammaglobulinemia in neonates, with a low birth weight (less than 1500g) or in a setting with high baseline infection rate or morbidity.

OR

b. A diagnosis of **dysgammaglobulinemia**, primary or due to multiple myeloma in patients with stable disease, and at least one of the following:

i. high risk of recurrent infections despite prophylactic antibiotic therapy.

ii. poor IgG response to the pneumococcal vaccine.

iii. low normal IgG levels during acute sepsis episodes.

OR

2. Hematologic disorders (immune-mediated), not responding to alternative therapies, or at high risk of bleeding:

a. Acquired Factor VIII inhibitor, diagnosed by, or in consultation with an immunologist or hematologist, and when conventional therapy is ineffective or not tolerated. (e.g., immunosuppressive therapy with cyclophosphamide, steroids, or azathioprine).

OR

b. **Autoimmune hemolytic anemia** (AIHA), diagnosed by, or in consultation with an immunologist or hematologist, and not responding to alternative therapies (e.g., steroids, immunosuppressive agents, plasmapheresis, rituximab and/or splenectomy).

OR

c. **Fetal (neonatal) alloimmune thrombocytopenia** (FAIT) diagnosed by, or in consultation with a neonatologist, hematologist, or obstetrician, and with documented diagnosis.

OR

d. **Idiopathic thrombocytopenia purpura**, also known as "immune thrombocytopenia," (acute; ITP), when a rapid increase in platelet count is necessary, such as in an acute bleeding episode or prior an invasive procedure (including surgery, epidural anesthesia, or Cesarean section).

OR

e. **ITP (chronic)**, diagnosed by, or in consultation with an immunologist or hematologist, and when the platelet count is dangerously low, defined as a platelet count less than 30,000 cells/mm3 in children, less than 20,000 cells/mm3 in adults, or less than 30,000 cells/mm3 along with signs/symptoms of bleeding in adults, as a bridge to an alternative chronic therapy (including, but not limited, to rituximab, a TPO mimetic, or splenectomy) OR when at least one other chronic therapy has been ineffective or all are contraindicated.

OR

f. **ITP in pregnancy**, diagnosed by, or in consultation with a neonatologist, hematologist, or obstetrician, and when at least one of the following criteria are met:

i. Platelet counts less than 20,000/mm3 in the third trimester, despite an adequate course of corticosteroids, unless use of steroids are contraindicated, or not tolerated.

OR

ii. Platelet counts less than 30,000/mm3 associated with bleeding or before vaginal delivery or C-section.

(For IVIG use in preparation for C-section or epidural anesthesia, see criteria 2.d. above)

OR

g. **Post-transfusion purpura** (hemolytic transfusion reaction) in severely affected patients.

OR

h. **Pure red cell aplasia** (PRCA, viral) diagnosed by, or in consultation with an immunologist or hematologist, and with documented parvovirus B19 infection and severe anemia.

OR

3. **Neuromuscular disorders,** diagnosed by, or in consultation with a neurologist, dermatologist or rheumatologist, AND there is clinical documentation (such as chart notes) of significant functional impairment:

a. **Guillain-Barré syndrome** (GBS), including **Acute inflammatory demyelinating polyneuropathy** (AIDP), when one of criteria i through iv below are met:

i. Deteriorating pulmonary function tests.

OR

ii. Rapid deterioration with symptoms for less than 2 weeks.

OR

iii. Rapidly deteriorating ability to ambulate.

OR

iv. Inability to walk independently for 10 meters.

OR

b. **Chronic inflammatory demyelinating polyneuropathy** (CIDP) when both criteria i and ii below are met:

i. Significant functional disability.

AND

ii. Documentation of slowing of nerve conduction velocity on electromyogram (EMG)/ nerve conduction study (NCS).

OR

c. **Acute demyelinating encephalomyelitis** (ADEM) or **anti-NMDA receptor encephalitis** when prior therapy with corticosteroids has been ineffective or not tolerated.

OR

d. **Lambert-Eaton myasthenic syndrome** (LEMS**)**.

OR

e. **Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)** when criteria i, ii, and iii below are met:

i. Patient has had at least one relapse episode or is at high risk for adverse sequelae from subsequent attack as suggested by poor recovery after acute treatment of initial event.

AND

ii. Azathioprine or mycophenolate mofetil (MMF) have been ineffective, are contraindicated, or not tolerated.

AND

iii. Rituximab has been ineffective, is contraindicated, or not tolerated.

OR

f. **Multifocal motor neuropathy** (MMN) in patients with conduction block [partial (>30%) or complete block].

OR

g. **Myasthenia gravis (MG)**, when criteria i. and ii. below are met:

i. For the treatment of acute crisis (e.g., respiratory failure, swallowing difficulties) **OR** chronic decompensation.

AND

ii. Documentation that at least one other standard MG treatment is ineffective or not tolerated [such as plasmapheresis/ plasma exchange (PLEX), pyridostigmine (generic, Mestinon), non-steroidal immunomodulating therapies (such as azathioprine, cyclosporine, mycophenolate, tacrolimus, methotrexate, or cyclophosphamide)].

OR

h. **Paraneoplastic opsoclonus ataxia syndrome** (Opsoclonus-myoclonus ataxia syndrome, OMS) in pediatric neuroblastoma patients with significant functional impairment and not responding to an adequate course of steroids (at least 3 to 7 days).

OR

i. **Pemphigoid, refractory immunobullous disease** (e.g., bullous pemphigoid, pemphigus foliaceus, pemphigus vulgaris) until conventional treatment takes effect (e.g., immunosuppressive agents and plasmapheresis).

OR

j. **Refractory myositis**, including, but not limited, to autoimmune myositis, **dermatomyositis** (adult), or polymyositis, in patients with severe active illness including muscle weakness and associated severe disability when corticosteroids or other immunosuppressants (e.g., azathioprine, methotrexate, or cyclophosphamide) have been ineffective, are contraindicated or not tolerated.

OR

k. **Juvenile Dermatomyositis** (JDM), with muscle weakness and associated severe disability, with at least one of the following documented diagnostic criteria below:

i. Evidence of myositis, demonstrated by abnormality of muscle biopsy, MRI, OR EMG.

OR

ii. Increased muscle enzymes levels (such as CPK, AST, LDH, and/or aldolase)

OR

iii. Cutaneous changes, including heliotrope dermatitis (rash on the upper eyelids) and Gottron's papules (papules over the knuckles), not responding to oral corticosteroids, methotrexate, and/or another oral immunosuppressant.

OR

l. **Stiff-Person Syndrome** when treatment with other agents is ineffective or not tolerated. (e.g., diazepam, baclofen, clonazepam, valproic acid, and clonidine).

OR

m. **Systemic lupus erythematosus,** for severe active disease when other interventions are ineffective or not tolerated (e.g., corticosteroids and immunosuppressive agents, such as cyclophosphamide or azathioprine).

OR

4. **Transplant (solid organ), antibody (Ab)-mediated rejection,** diagnosed by, or in consultation with a transplant specialist or immunologist, and criteria a or b below are met**:**

a. **<u>Prevention</u> of antibody (Ab)-mediated rejection**: Prior to solid organ transplant and in the peri-operative period, for patients at high risk for Ab-mediated rejection, including highly sensitized patients, and those receiving an ABO-incompatible organ.

OR

b. **<u>Treatment</u> of antibody-mediated rejection (a.k.a. vascular rejection, humoral rejection)**: Following solid organ transplant and confirmed by either biopsy or presence of panel reactive antibodies (PRAs).

OR

5. **Other Miscellaneous conditions** when criteria are met:

a. **Kawasaki syndrome**, diagnosed by, or in consultation with a subspecialist (pediatrician, cardiologist, or rheumatologist), and IVIG is used during the first ten days of diagnosis.

OR

b. **Pediatric intractable epilepsy,** diagnosed by, or in consultation with a neurologist, 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. [85]

OR

c. **Post-Exposure prophylaxis against varicella-zoster** (VZV) in high-risk populations (immunocompromised individuals who lack evidence of immunity to VZV, pregnant women who lack evidence of VZV immunity, newborns of mothers who develop peri-partum varicella, or infants in the first two weeks of life), diagnosed by, or in consultation with a subspecialist (such as obstetrician, pediatrician, or infectious diseases specialist).

OR

d. **BK Viremia** (BK polyomavirus in solid organ transplantation), diagnosed by, or in consultation with a transplant or infectious diseases specialist, in patients with persistent viremia despite a sufficient reduction of immunosuppressive therapy for at least 4 **weeks.**

['Sufficient reduction' is defined as discontinuation of an antimetabolite (such as mycophenolate mofetil or azathioprine) OR a 50% dose reduction of a calcineurin inhibitor (such as tacrolimus or cyclosporine)].

OR

e. **PANDAS/PANS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections or Pediatric Acute-onset Neuropsychiatric Syndrome),** when the following (i, ii, iii, and iv) are met:

i. The patient is less than 18 years of age.

AND

Pediatric subspecialist assessment: The diagnosis is made by, or in consultation with, ONE of the following pediatric subspecialists (for an adolescent, consultation may be with an adult subspecialist): pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist.

NOTE: IVIG for adults with PANDAS/PANS is not coverable.

AND

ii. If the prescriber is not a pediatric subspecialist (e.g., primary care), clinical documentation must be provided that the pediatric subspecialist agrees with the treatment plan for IVIG [attestation].

AND

iii. Documentation of baseline evaluation, including details of neuropsychiatric symptoms, temporal relationship to the symptoms, and associated functional impairment.

NOTE: This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and post treatment to demonstrate clinically meaningful improvement (See Appendix 2).

AND

iv. Step therapy: A clinically appropriate trial of at least **two** of the following (1, 2, 3, and/or 4.) are ineffective, not tolerated, or use of all are contraindicated, and documentation stating the therapies were specifically used for PANDAS/PANS symptoms.

['Ineffective' is defined as a lack of sustained clinically meaningful improvement on a validated instrument in relation to the primary symptom complex]

1. *Antimicrobial therapy*: Short-course antibiotic therapy (such as amoxicillin, azithromycin, or penicillin) for a confirmed group A beta-hemolytic *Streptococcus* (strep) infection.

OR

2. *Anti-inflammatory therapy* with at least one of the following (criteria a, b, or c):

a. Nonsteroidal anti-inflammatory drugs (NSAIDs) for at least five days

OR

b. Systemic corticosteroids

OR

c. Plasma exchange (PLEX)

OR

3. *Psychoactive therapy* with at least one of the following (criteria a or b):

a. Selective serotonin reuptake inhibitors (SSRIs)

OR

b. Behavioral therapy (such as cognitive behavioral therapy [CBT])

OR

4. Tonsillectomy and/or adenoidectomy

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers immune globulins coverable only under the medical benefit (regardless of self- or provider-administration).

B. When pre-authorization is approved, immune globulins (as listed in *Table 1*) will be covered in the quantities and for the authorization periods outlined in *Table 3*.

C. Although the use of specific high-cost immune globulin products (as listed in *Table 2*) is considered 'not medically necessary,' if pre-authorization is approved, these immune globulins (as listed in *Table 2*) will be covered:

1. In the quantities and for the authorization periods outlined in *Table 3*.

AND

2. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

D. Subcutaneous administration of immune globulin (SCIG) is considered an alternative to intravenous administration of immune globulin (IVIG) and may be considered medically necessary when one of the coverage criteria above is met.

E. For dose requests above the policy limits (as listed in *Tables 1, 2,* and *3*):

1. **IVIG:** Higher doses may be coverable for patients who have clear clinical documentation, such as chart notes, supporting an objective improvement in symptoms or function while treated with IVIG 2 g/kg per four weeks (or equivalent), and who have maximized adjunctive therapy, but continue to have functional impairment or incomplete disease control.

2. **SCIG:** Doses of SCIG in excess of those listed in *Tables 1 and 2* are considered 'not medically necessary.'

F. The concomitant use of maintenance SCIG and IVIG is considered not medically necessary.

Table 1. Coverable Immune Globulin Replacement Products

Product Name		Route of Administration	Coverable Dose
• Flebogamma DIF • Gammagard S/D	• Octagam • Privigen	IVIG	2 grams/kg per 4 weeks (or equivalent)
• Gammagard • Gammaked	• Gamunex C	IVIG or SCIG	2 grams/kg per 4 weeks (or equivalent)
• Cutaquig • Hyqvia	• Xembify	SCIG	2 grams/kg per 4 weeks (or equivalent)
• Hizentra		SCIG	0.4 gm/kg per week (or equivalent)

Table 2. 'Not Medically Necessary' Higher-Cost Immune Globulin Replacement Products

Product Name		Route of Administration	Coverable Dose
• Alyglo • Asceniv • Bivigam • Gammaplex	• Gammaplex • Panzyga • Qivigy • Yimmugo	IVIG	2 grams/kg per 4 weeks (or equivalent)
• Cuvitru		SCIG	2 grams/kg per 4 weeks (or equivalent)

Table 3. Quantity Limits and Authorization Period

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
Replacement Therapy - Immunodeficiency [with documented hypogammaglobulinemia (low IgG levels) or poor immune response (dysgammaglobulinemia)]	
Primary humoral immunodeficiency disease (PID)	- **Initial Authorization and Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **may** be reviewed at least every 12 months. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, defined as decreased occurrence of infections or normalization of IgG levels. - IVIG doses higher than 2 g/kg per four weeks may be considered when there is documentation of continued severe infections despite IVIG doses of 2 g/kg per 4 weeks. Higher doses of SCIG are not coverable.
Hematologic malignancy-related hypogammaglobulinemia (e.g., CLL, post-BMT)	
HIV+ children with hypogammaglobulinemia	
Hypogammaglobulinemia in neonates	
Hematologic disorders (immune-mediated)	
Acquired Factor VIII Inhibitor	- **Initial Authorization and Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, defined as initial response, and continued presence of Factor VIII inhibitor.
Autoimmune hemolytic anemia, (AIHA)	- **Initial Authorization and Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, defined as initial response, and recurrence of clinically significant, symptomatic anemia.
Fetal (neonatal) alloimmune thrombocytopenia (FAIT)	- **Initial Authorization:** Up to 2 g/kg per **week** until delivery. - **Continued Authorization:** No reauthorization.
ITP (acute)	- **Initial Authorization:** Up to 2 g/kg total (authorization is for up to 28 weeks). - **Continued Authorization:** No reauthorization (please see ITP [chronic] below for ongoing therapy requests).

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
ITP (chronic)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with a documented initial response to IVIG and: o Continued thrombocytopenia, defined as a platelet count of < 20,000 OR less than 30,000 cells/m^3 and clinically significant bleeding despite therapy with an alternative chronic therapy. **OR** o Documentation that an alternative chronic therapy has been ineffective, or not tolerated.
ITP in pregnancy	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to delivery. - **Continued Authorization:** No reauthorization (please see criteria for ITP [chronic] for ongoing therapy requests).
Post-transfusion purpura (hemolytic transfusion reaction)	- **Initial Authorization:** Up to 4 g/kg total over up to 4 weeks. - **Continued Authorization:** No reauthorization.
Pure red cell aplasia (PRCA), viral	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documentation of initial response, parvovirus, and recurrence of significant anemia.
Neuroimmunologic disorders	
GBS, Acute inflammatory demyelinating polyneuropathy (AIDP)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks. - **Continued Authorization:** No reauthorization; please see criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) for ongoing therapy requests.
Pemphigoid, refractory	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 26 weeks. - **Continued Authorization:** No reauthorization.
Paraneoplastic opsoclonus ataxia syndrome	- **Initial Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 28 weeks. - **Continued Authorization:** Up to 2 g/kg per 4 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documented functional improvement.

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
Acute demyelinating encephalomyelitis (ADEM) or anti-NMDA receptor encephalitis Chronic inflammatory demyelinating polyneuropathy (CIDP) Lambert-Eaton myasthenic syndrome (LEMS) Multifocal motor neuropathy (MMN) Myasthenia gravis (MG. acute and chronic) Myelin oligodendrocyte glycoprotein antibody disease (MOGAD) Stiff-Person syndrome	- **Initial Authorization:** Up to 2 g/kg per four weeks; up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documented functional improvement, disease stability, or reduction in relapse rates.
Dermatomyositis Myositis, including polymyositis and autoimmune myositis Systematic lupus erythematosus (SLE)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documented improvement in muscle strength and/or decreased CPK levels.
Transplant (solid organ)	
Prevention of acute rejection (pre- and peri-operative)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks total. - **Continued Authorization:** No reauthorization. Please see Treatment of antibody (Ab)-mediated (humoral) rejection. -
Treatment of antibody (Ab)-mediated (humoral) rejection	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks total. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 24 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documented improvement in symptoms or organ function.

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
Other Miscellaneous disorders	
Kawasaki syndrome	- **Initial Authorization:** Up to 4 g/kg total, authorized over an eight-week period. - **Continued Authorization:** No reauthorization
Pediatric intractable epilepsy	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documented significantly reduced frequency and/or duration of seizures.
Post-Exposure prophylaxis against varicella-zoster (VZV)	- **Initial Authorization:** 400 mg/kg as a single dose. - **Continued Authorization:** No reauthorization.
BK Viremia (BK polyomavirus in solid organ transplantation)	- **Initial Authorization:** Up to 2 g/kg total, authorized over a twelve-week period. - **Continued Authorization:** No reauthorization.
PANDAS / PANS	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks (up to 3 months). - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 12 weeks (3 months). - **Reauthorization:** Clinical documentation (such as chart notes) must be provided to confirm that the medication is effective, with documented significantly reduced severity of symptoms and improvement in functioning. This evaluation must include clinical testing with a validated instrument (see *Appendix 2*), which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.

V. Immune globulin (IVIG/SCIG) is considered investigational when used for all other conditions, including, but not limited to:

1. Acute lymphocytic leukemia
2. Acute renal failure
3. Adrenoleukodystrophy
4. Adult HIV infection
5. Alzheimer's disease
6. Aplastic anemia
7. Asthma
8. Atopic dermatitis
9. Autism
10. Cardiomyopathy, recent-onset dilated
11. Chronic fatigue syndrome
12. Clostridium difficile, recurrent

13. Combination therapy with complement inhibitors (e.g., Soliris [eculizumab, biosimilars], Ultomiris [ravulizumab], Zilbrysq or FcRn antagonists (e.g., Imaavy [nipocalimab], Rystiggo [rozanolixizumab], Vyvgart [efgartigimod alfa]) for refractory MG or CIDP.
14. Complex Regional Pain Syndrome (CRPS)
15. Cystic fibrosis
16. Diabetes
17. Diamond-Blackfan anemia
18. Encephalitis, not otherwise specified (in the coverage criteria above)
19. Endotoxemia
20. Heart block, congenital
21. Hemolytic anemia (other than autoimmune)
22. Hemophagocytic syndrome
23. Human T-lymphocyte virus-1 myelopathy
24. Hyper IgE syndrome
25. Immune mediated neutropenia
26. Inclusion body myositis
27. Infectious disease in high-risk neonates and adults following surgery or trauma
28. Lumbosacral plexopathy
29. Narcolepsy/cataplexy
30. Neonatal hemochromatosis
31. Nephropathy, membranous
32. Nephrotic syndrome
33. Neuropathy, not otherwise specified (in the coverage criteria above)
34. Ophthalmopathy, euthyroid
35. Paraproteinemic neuropathy
36. Post-polio syndrome
37. Recurrent spontaneous abortion
38. Rheumatoid arthritis
39. Small fiber neuropathy (SFN)
40. Systemic Sclerosis, diffuse cutaneous (dcSS)
41. Stevens-Johnson Syndrome
42. Still's Disease (Systemic Juvenile Immune Arthritis, SJIA)
43. Surgery or trauma
44. Thrombocytopenia, nonimmune
45. Thrombotic Thrombocytopenic Purpura, including Hemolytic Uremic Syndrome (TTP/HUS), neonatal autoimmune and transfusion refractory.
46. Tic disorder (Based on DSM Criteria)
47. Toxic epidermal necrolysis (TEN)
48. Urticaria, delayed pressure
49. Vasculitic syndromes, other systemic (not specified above), such as antineutrophil cytoplasmic antibody- (ANCA) associated vasculitis [microscopic polyangiitis (MPA)], and eosinophilic granulomatosis with polyangiitis (EGPA) [Churg-Strauss Syndrome (CSS)]
50. Von Willebrand's syndrome

Position Statement

Summary

Intravenous immune globulin (IVIG) [1 2]

- All IVIG preparations are generally considered therapeutically interchangeable.
- Minor immunoglobulin A (IgA) and immunoglobulin G (IgG) subclass differences exist. [32-34]
- IVIG preparations with low IgA content are used to minimize reactions in patients with hypogammaglobulinemia and concurrent IgA deficiency or when anti-IgA antibodies are present in a recipient.
- Differences in formulation may guide product selection (e.g., pre-mixed liquid vs. lyophilized powder, 5% vs. 10%, low sucrose, low osmolarity).
- Given that there are several available IVIG preparations that are generally considered therapeutically interchangeable, the use of significantly more expensive formulations of IVIG are considered not medically necessary and not coverable (i.e., higher-cost immune globulin replacement products as listed in *Table 2*).

Subcutaneous immune globulin (SCIG) [1]

- All immune globulin products for subcutaneous (SC) use are approved for patients with primary immune deficiency (PID). They are available as 16.5% or 20% solutions for weekly SC infusion or as a 10% solution (Hyqvia) for monthly SC infusion.
- Some immune globulin products for intravenous (IV) use may also be for SC administration (see *Tables 1 and 2* above).
- Multiple injection sites (three to eight) are necessary for weekly infusion (all SCIG in *Tables 1 and 2*, excepting Hyqvia) for an average patient because of the volume that must be infused. Hyqvia 10% is formulated with hyaluronidase, to allow for larger volume infusion at a single injection site, dosed monthly.
- SCIG has a lower bioavailability than IVIG, so must be given in higher doses to achieve the same serum IgG concentrations. With exception of Hyqvia, all SCIG formulations require a dose increase versus IVIG.
- However, SC delivery may result in higher steady-state IgG levels due to less variation in IgG levels.
- Most of these products have not been approved for SC administration for any indication, other than PID. Because other diagnoses usually require larger doses (based on grams per kilogram) with a high volume per dose, SC administration is generally not feasible. Therefore, use of SCIG in excess of the doses listed in the Quantity Limits (*Tables 1 and 2*) is considered "not medically necessary." Higher doses of immune globulin replacement therapy may be given with intravenous (IVIG) products.
- Injection site swelling, redness, and itching were reported in the majority of patients.
- Given that there are several available SCIG preparations that are generally considered therapeutically interchangeable, the use of significantly more expensive formulations of SCIG are considered not medically necessary and not coverable.

Dosing Considerations and Therapeutic Levels for Replacement Therapy for Treatment of Immunodeficiency with Hypogammaglobulinemia [3]

- Dosing adjustment in replacement therapy is based on clinical response and IgG levels.
    * The trough or steady state IgG level is obtained before scheduled infusions and frequently guides immune globulin replacement therapy (IVIG/SCIG) dose selection.
    * 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 a higher IgG level for protection.
- Immune globulin replacement therapy is a blood product and by nature, in limited supply and costly to prepare and administer. Long toxicity associated with immune globulin replacement (IVIG/SCIG) therapy includes potential risk of renal toxicity and thrombotic events. As such, use of immune globulin replacement therapy should be limited to specific conditions with proven benefit, when diagnostic criteria are met, and used by, or in consultation with, appropriate subspecialists.
- Dosing of immune globulin replacement therapy for conditions other than hypogammaglobulinemia do NOT require monitoring of IgG levels. Efficacy in conditions other than hypogammaglobulinemia is based on clinical response, including improvement or resolution of disease symptoms, up to the maximum covered dose (per the Quantity Limits above).

Clinical Efficacy

IMMUNODEFICIENCY (Primary or Secondary) - Replacement Therapy for Hypogammaglobulinemia

Primary humoral immunodeficiency diseases [1 3 4]

- All available immune globulin replacement products are FDA-approved for use in primary immunodeficiency (PID).
- X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life.
- 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.
- Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, are rare, inherited syndromes.
- 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.

- Hypogammaglobulinemia in neonates [5]
    - Treatment with IVIG is usually reserved for patients with recurrent severe infections, not responding to antibiotic prophylaxis.
    - The usual IVIG dose is 400 – 600 mg/kg/month, administered as a single dose, or up to several months in duration.

Acquired Deficiencies:

- Hematologic malignancy-related hypogammaglobulinemia (including B-cell cancers, multiple myeloma, and post-bone marrow transplant (BMT). [6 7]
    - Use of immune globulin replacement in hypogammaglobulinemia patients with B-cell cancers (including CLL), multiple myeloma and post-allogeneic bone marrow transplant (BMT) is supported by guidelines.
    - IVIG therapy reduces the incidence of bacterial infections in patients with hematologic malignancies and secondary hypogammaglobulinemia.
    - Previously, use of IVIG prophylaxis post-BMT was common for prevention of graft versus host disease (GVHD); however, with improved immunosuppressant regimens, the use of routine IVIG prophylaxis is no longer supported.
    - Monthly IVIG infusions of 400 mg/kg are recommended to maintain the serum IgG level.
- HIV-infected children < 13 years of age[8]
    - Current guidelines recommend IVIG use among HIV-infected children who have hypogammaglobulinemia (IgG <400 mg/dL), to prevent serious bacterial infections (SBIs).
    - IVIG is no longer recommended for primary prevention of SBIs in children, unless hypogammaglobulinemia is present. During the pre-HAART (highly-active antiretroviral therapy) era, IVIG was shown to decrease the frequency of bacterial infections and hospitalization in children with AIDS, however only in those not receiving daily Pneumocystis carinii pneumoniae (PCP) prophylaxis.

AUTOIMMUNE (IMMUNE-MEDIATED) DISORDERS

- Pooled immune globulin (IVIG) has been studied and found to be useful in a variety of autoimmune disorders, including hematologic, neuromuscular and infectious disease-related diseases. However, given the rarity of many of these disorders, the evidence for safety and efficacy in some diagnoses is insufficient at this time.
- The mechanism of action of IVIG in autoimmune disorders is thought to include acute neutralization of circulating autoantibodies, toxins, and cytokine modulation, as well as long-term reduction of antibody production and suppression of T-cell cytokines.

Hematologic (immune-mediated) Disorders: [6]

Acquired Factor VIII inhibitor [9-14]

- 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.
- 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.

Fetal (neonatal) alloimmune thrombocytopenia (FAIT): [15 16]

- ACOG guidelines recommend IVIG as first line treatment for documented fetal thrombocytopenia.
- A trial comparing IVIG treatment with and without dexamethasone in siblings showed that:
  - IVIG treatment was associated with an increase in mean platelet count of 69,000/mm^3.
  - There were no instances of intracranial hemorrhages, although hemorrhage had occurred previously in 10 untreated siblings.
- The recommended dose of IVIG is 1 gm/kg/week, increasing to 2 gm/kg/week in refractory cases.

Idiopathic thrombocytopenia purpura (ITP) [6 17-20]

- Normal platelet count range is 115,000/mm^3 to 440,000/mm^3.
- Acute ITP
  - Acute ITP is usually seen in children and typically resolves spontaneously within 2 months.
  - Approach to management of children with observation, steroids, and/or IVIG is based on severity and type of bleeding (such as mucosal versus non-mucosal).
  - In various studies, a majority of IVIG recipients attained platelet counts greater than 100,000 cells/mm^3 within 7 days.
  - A maximum of 1 gm/kg/day for three or four doses of IVIG on alternate days is recommended.
- Chronic ITP
  - 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.
  - IVIG is not indicated for the maintenance of platelet counts in chronic ITP; however, IVIG maybe be used episodically in patients with chronic ITP, for acutely low platelet levels.
  - Steroids are considered the first-line treatment of choice for chronic ITP. Although the use of IVIG may be considered as a steroid-sparing adjunctive therapy for chronic ITP, other therapies with a more durable response should be considered, such as splenectomy, rituximab, Promacta (eltrombopag) or Nplate (romiplostim).
  - IVIG may be considered in patients with dangerously low platelet counts (less than 10,000 to 20,000 per mm^3 in adults or less than 30,000 per mm^3 in children) or patients undergoing an invasive procedure, and therefore may be at an increased risk for significant bleeding, such as intracranial hemorrhage.

    * Choosing Wisely, an evidence-based initiative to promote wise use of medical resources, states that patients with ITP should not be treated in the absence of bleeding or a very low platelet count. Only rarely should patients be treated when platelet counts are above 30,000, such a preparation of surgery or an invasive procedure. Unnecessary treatment exposes patients to potential adverse events and raises the overall cost of care, with unknown clinical benefit. [20]
    * The usual dose of IVIG is 1 to 2 gm/kg divided into equal amounts and given over 2 to 5 days.

- ITP in pregnancy (a.k.a. Pregnancy-Associated ITP) [6 15 19]
    * The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia.
    * Platelet function is typically normal, so it is not necessary to maintain platelet count in the normal range.
    * The first line of treatment is prednisone, usual dose 1-2 mg/kg/day.
    * 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.
    * For patients nearing the end of their pregnancy and preparing for use of epidural anesthesia, IVIG coverage will be considered under "ITP, acute" criteria, for use prior to an invasive procedure. Because the evidence is less useful in determining the exact threshold platelet levels needed for prevention of bleeding, the use of IVIG is generally at the discretion of the treating anesthesiologist or surgeon, and pregnant patients are managed like non-pregnant patients.
    * The American College of Obstetrics and Gynecology (ACOG) recognizes the high cost of IVIG therapy and suggests consultation from a physician experienced in the treatment of ITP when considering use of IVIG therapy.
        ▪ Guidelines recommend that, except for the delivery, treatment indications for pregnant women are similar to those currently recommended for any patient.
        ▪ At the time of delivery, management of ITP is based on an assessment of maternal bleeding risks associated with delivery, epidural anesthesia, and the minimum platelet counts recommended to undergo these procedures (80 X 10^9/L for epidural placement and 50 X 10^9/L for cesarean delivery)

<u>Post-transfusion purpura</u> (hemolytic transfusion reaction) [19 21]

- Post-transfusion purpura is a rare condition that can occur in patients undergoing blood transfusions. It typically develops approximately one-week after blood transfusion.
- IVIG may be considered first-line therapy in severely affected patients.
- The recommended dose of IVIG is 500 mg/kg/day for two consecutive days. Rapid platelet recovery has been seen within days of treatment.

Pure Red Cell Aplasia (PRCA), Viral [19 22]

- 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.
- Chronic parvovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parvovirus and anemia may spontaneously resolve.
- The usual dose of IVIG is 2-4 grams/kg, divided as 400 mg/kg/day for 5 – 10 days, 1 gm/kg/day for 3 days or 0.5 gm/kg weekly for 4 weeks. Initial treatment courses may be indicated with recurrence of anemia and increase in parvovirus B19 DNA.

Neuromuscular Disorders:

Inflammatory demyelinating polyneuropathy (IDP) [23-28]

- Guillain-Barré syndrome (GBS) and Acute IDP[22,23, 90][23-25]
    - Diagnostic criteria for GBS include all of the following:
        - Progressive weakness of the extremities, the trunk, bulbar and facial muscles, and external ophthalmoplegia.
        - Reduction or absence of deep tendon reflexes in weak limbs.
        - Presence of demyelination on electrodiagnostic studies may be present but is not required for the diagnosis of GBS.
    - IVIG appears to be effective in adult patients with Guillain-Barré syndrome when given within 2 weeks of symptom onset.
    - 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.
- Chronic IDP (CIDP)[26-28]
    - Clinical guidelines recognize the use of specific diagnostic criteria for CIDP, to exclude other causes of neuropathy and confirm the presence of peripheral nerve demyelination.
        - Objective criteria include use of electrodiagnostic (EMG) testing, along with additional studies, such as nerve biopsy or lumbar puncture (LP) to confirm elevation of CSF protein.
        - Given the lack of consensus across guidelines and need to exclude neuropathies unlikely to respond to IVIG therapy, use of objective criteria are required to support a clinical diagnosis of CIDP.
    - Treatment options include plasmapheresis, IVIG, and corticosteroids.
    - The usual IVIG dose is 400 mg/kg/day for 5 days, repeated every 6 weeks.

Autoimmune encephalitis: acute demyelinating encephalomyelitis (ADEM) or anti-NMDA receptor encephalitis

- Immune-mediated encephalitis is relatively rare and include ADEM and encephalitis syndromes associated with antibodies against neuronal tissue, such as anti-NMDA receptor encephalitis.

- The differential diagnoses list for autoimmune encephalitis is extensive and may include diagnoses considered investigational in this policy. Therefore, IVIG is considered not coverable, until the diagnosis is clarified.

Acute demyelinating encephalomyelitis (ADEM) [29]

- ADEM can be associated with various neurologic and psychiatric symptoms, including cognitive and speech dysfunction, seizures, dyskinesias, altered consciousness, and autonomic instability.
- High-dose IV corticosteroid therapy is considered the first-line treatment for ADEM, with IVIG or plasma exchange reserved for patients not responding to steroid therapy.
- The usual IVIG dose is 400 mg/kg/day for 5 days.

Anti-NMDA receptor encephalitis (anti-NMDAR)[29 30]

- Anti-NMDA receptor encephalitis is a specific type of autoimmune encephalitis, diagnosed by detection of IgG antibodies against a subunit of NMDA receptors in serum or CSF. It can be associated with various neurologic and psychiatric symptoms, including cognitive and speech dysfunction, seizures, dyskinesias, altered consciousness, and autonomic instability.
- The diagnosis of anti-NMDAR is confirmed by very specific testing, IgG antibodies to the GluN1 (also known as NR1) subunit of the NMDA receptor in CSF. However, given access to testing and delays in results, available standard diagnostic tests can support the diagnosis, including CSF, EEG, and brain MRI.
- Based on large case series and years of experience in clinical practice, use of immunosuppression therapy is the standard of care, with corticosteroids, IVIG, plasma exchange, cyclophosphamide, or rituximab. IVIG (400 mg/kg/day for 5 days) in combination with high-dose methylprednisolone or plasma exchange may be useful in treating patients with anti-NMDA receptor encephalitis in the first-line setting. Rituximab and/or cyclophosphamide may be of benefit in patients not responding to IVIG and steroids within 10 days. Children are generally managed with monotherapy (cyclophosphamide or rituximab).

Dermatomyositis (DM), adult and pediatric (juvenile)[26 31-34]

- High-dose IVIG is a safe and effective treatment for refractory dermatomyositis unresponsive to corticosteroid therapy. [26 31 32]
- For adults, abnormalities on EMG or elevations in CPK are accepted diagnostic criteria.
- Juvenile dermatomyositis (JDM) is characterized by a vasculopathy affecting both the muscle and the skin. For pediatric patients, a number of muscle enzymes, including CPK, LDH, AST or aldolase, may be used to confirm the diagnosis. Myositis may also be confirmed by an abnormal muscle biopsy, EMG or MRI. Children can also have specific skin manifestations associated with the dermatomyositis, including Gottron papules on the dorsal surface of the knuckles and heliotrope rash over the eyelids.[33]
- The recommended IVIG dose is 2 gm/kg per month.

Lambert-Eaton myasthenic syndrome (LEMS)[26 31 35]

- LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes.
- IVIG improved limb, respiratory muscle, and bulbar muscle strength in a small randomized trials. [34]
- The recommended dose of IVIG is 2 gm/kg administered over 2 – 5 days.

Multifocal motor neuropathy (MMN) [31 36-43]

- MMN is a progressive neuropathy with asymmetric, distal weakness of at least one limb, upper extremities more frequently than lower extremities.
- Small, controlled trials demonstrate significant increase in muscle strength associated with IVIG administration, long-term benefits, and safety (44 patients across four small trials of IVIG induction therapy as compared to placebo). [36-40]
- The recommended IVIG dose is 2 gm/kg/month, administered over 2 – 5 days.[31 42]

  Additionally, patients with anti-GM1 antibodies show an increased chance of response to IVIG. However, anti-GM antibodies are present in only 30-80% of patients with MMN and are not specific to MMN. In addition, patients who lack anti-GM1 antibodies may have a favorable response to IVIG; therefore, the clinical utility of monitoring anti-GM1 antibodies is uncertain. [41]

Myasthenia gravis (MG) [26 44 45]

- IVIG may be useful in treating patients with severe myasthenia gravis acutely, or as maintenance therapy for patients who fail to respond to the maximum tolerated doses of corticosteroids and/or immunosuppressants.
- Randomized trials examining short-term treatment of myasthenia gravis with IVIG have shown no difference between IVIG and plasma exchange or IVIG and methylprednisolone.
- There is no evidence to determine whether IVIG improves function or reduces steroid requirements for moderate to severe myasthenia gravis.
- The recommended dose of IVIG is 1 – 2 gm/kg/month administered over 2 – 5 days.

Myelin oligodendrocyte glycoprotein antibody disease (MOGAD)[46]

- Myelin oligodendrocyte glycoprotein antibody disease (MOGAD) is an autoimmune disorder where the immune system mistakenly attacks the protective covering of nerves in the central nervous system, leading to symptoms like vision loss, weakness, and coordination problems.
- Not all patients have recurring episodes (relapsing). Identifying those who are at risk for relapse is crucial to avoid unnecessary treatment.
- According to the European Union pediatric MOG consortium consensus, for patients who do not recover well from their initial event (such as those with transverse myelitis or optic neuritis), new disease activity can be catastrophic, potentially leading to severe disability, such as being wheelchair-bound or blind. In these cases, maintenance treatment should be considered 1-3 months after initial treatment if the patient has not shown significant improvement, as indicated by an Expanded Disability Status Scale (EDSS) score of 3.0 or higher, a modified Rankin Scale (mRS) score of 3 or higher, and/or

a visual acuity of 1/3 (0.3) or worse, in an attempt to prevent a first relapse.

- The evidence for the use of intravenous immunoglobulin (IVIG) in MOG antibody disease (MOGAD) is primarily based on retrospective and case studies.
- IV methylprednisolone is used for acute attacks up to a maximum of three months. IVIG and plasmapheresis constitute second-line therapies for acute attacks. Standard of care for maintenance include azathioprine, mycophenolate mofetil (MMF), rituximab and IVIG.

Opsoclonus-myoclonus ataxia (OMA)

- Opsoclonus-myoclonus ataxia (OMA) is a rare neurological syndrome characterized by an unsteady gait, brief shock-like muscle spasms, and irregular rapid eye movements and can be a paraneoplastic (e.g., with neuroblastoma) or non-paraneoplastic syndrome.

  Evidence supporting the use of IVIG for OMA consists mainly of retrospective chart reviews and case reports in children and adults. [47]
- However, one randomized phase 3 placebo-controlled trial for the use of IVIG for children with opsoclonus-myoclonus associated with neuroblastomas found a reduction in OMA in the IVIG-treated group as compared to placebo (81 versus 41%). All patients received steroids and chemotherapy. IVIG was dosed 1 gm/kg on days 0 and 1 of each 28-day cycle.[49]

Pemphigoid bullous (e.g., pemphigus foliaceus, pemphigus vulgaris) [34 50]

- IVIG is typically given in refractory disease, in combination with conventional treatments, such as immunosuppressive agents and plasmapheresis, and is discontinued once conventional treatment (such as corticosteroids, azathioprine, cyclophosphamide, etc.) takes effect. IVIG is not considered a maintenance therapy for pemphigus foliaceus, pemphigus vulgaris or other autoimmune mucocutaneous blistering diseases.
- The usual dose of IVIG is 1-2 gm/kg administered over 3 days. This regimen may be repeated every 3-4 weeks.

Polymyositis 24, 25, 32[26 31 32]

- 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.
- IVIG may be considered for patients not responding to first-line immunosuppression.
- The recommended dose of IVIG is 2 gm/kg/month administered over 2 – 5 days.

Stiff Person Syndrome 24, 44 [26 51]

- Sixteen patients were randomized to IVIG or placebo for 3 months, and 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.
- The usual dose of IVIG is 400 mg/kg/day for 3 – 5 days.

Systemic Lupus Erythematosus

- Small case series suggest some benefit from treatment with IVIG when compared to cyclophosphamide.
- The usual dose of IVIG is 400 mg/kg/day for 5 days.

Transplant (Solid Organ):

Antibody-mediated rejection (AMR) [45-47] [52-54]

- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, AMR).
- The standard for diagnosis of rejection is a transplant biopsy. [53]
- Pre-treatment with IVIG (desensitization) may reduce the risk of AMR in "highly sensitized" renal and/or heart transplant patients, also referred to as "with donor specific antibodies (DSAs)" [53 54]
- 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. [52]
- Acute humoral rejection (AHR) is also an AMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy. The goal of therapy is early antibody elimination with IVIG, pheresis, or a combination of modalities.
- A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant. [53 54]
- The American Heart Association (AHA) guidelines indicate that the significance of isolated appearance or increase in DSA without clinical manifestations or pathological evidence of AMR is unclear. Often, the decision to discontinue IVIG is based on the patient's overall clinical status, the stability of graft function, and the absence of signs of rejection. If the patient remains stable without evidence of AMR, the clinician may opt to discontinue IVIG to avoid unnecessary treatment and potential side effects.

Once DSAs are undetectable and rejection is inactive, the risk of AMR drops significantly, rendering the continued use of IVIG largely unnecessary.

Other Miscellaneous Disorders:

Kawasaki syndrome[55 56]

- IVIG in conjunction with aspirin given within the first 10 days of illness can reduce the incidence of coronary artery abnormalities, compared with treatment with aspirin alone. IVIG is not effective if more than ten days have elapsed from onset of symptoms.
- The usual dose of IVIG is 2 gm/kg as a single dose but may be repeated if the patient fails to defervesce.

BK viremia (BK polyomavirus in solid organ transplantation) [57-60]

- The American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP) recommends a stepwise reduction of immunosuppressive therapy until serum BK levels are no longer detectable. Although there are no randomized controlled

trials, this approach is supported by a meta-analysis and a number of large prospective observational studies reporting successful clearance BK virus in 80% to 100% of cases.

- Reduction of immunosuppressants is often done in a stepwise fashion:
  * Immunosuppressants for solid organ transplants include calcineurin inhibitors (such as cyclosporine and tacrolimus), antimetabolites (such as azathioprine and mycophenolate), and steroids (prednisone).
  * Immunosuppression reduction may begin with a reduction of either the calcineurin inhibitor or antimetabolite by 50%, eventually leading to a discontinuation of the antimetabolite.
- The highest IVIG dose studied in BK viremia was 2g/kg, given over several days to weeks. The optimum dose, frequency, and duration for IVIG use in BK viremia varies greatly and needs further evaluation. However, there is no evidence to support higher, longer, or repeated doses of IVIG.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) / Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) [61-65]

* PANDAS/PANS are syndromes with an abrupt onset of symptoms and associated temporally with a Group A beta-hemolytic streptococcal infection. The symptoms generally are abnormal behavioral (neurologic and psychiatric in nature) and may include obsessive-compulsive disorder (OCD), tic disorders (verbal or motor), and cognitive issues. Other symptoms may include emotional symptoms (e.g., anxiety, emotional lability, irritability, aggression, oppositional behaviors), reduced performance in school (related to deficits in attention and memory, hyperactivity, and cognitive changes), sensory or motor abnormalities, and somatic symptoms (sleep disturbance, enuresis, or urinary frequency). [65]
* There is currently insufficient evidence that IVIG is more effective than any other approach for treatment of for PANS/ PANDAS. Case series and case reports, as well as initial low-quality studies in small numbers of subjects, have suggested that IVIG may be efficacious in PANS/PANDAS. However, good quality, randomized, double-blinded trials have failed to show any significant difference between IVIG and placebo during the blinded study period. [62 64] Any recommendation for treatment is based on very low-quality evidence, including expert opinion and lower-quality observational data.[65]
* *Guidelines*: Until December 2024, there were no clinical guidelines for the use of IVIG for PANDAS.
  - Previously, the use was based on a consensus statement from the PANS Research Consortium (2018), which indicated that IVIG has been used in clinical practice for PANS/PANDAS, despite a lack of high-quality evidence in this area. [61 63]
  - More recently (2024), the American Academy of Pediatrics (AAP) Clinical Report recommended against the use of IVIG except in "rare cases," given the lack of demonstrated efficacy and significant safety risks with the use of IVIG. Their report cited the systematic review by Sigra, 2018 (discussed above). [62] Noted significant risks included

immunocompromise, severe headaches, anaphylaxis, aseptic meningitis, thromboembolic phenomena, hemolysis, renal failure, among other serious reactions. In rare cases where IVIG is a thorough workup and consultation with a team including pediatric neurologists, immunologists, and rheumatologists is required. [66]

- Of note, there is a lack of consensus among experts that PANDAS is an autoimmune disorder. As such, use of immunomodulators is not universally recommended and some experts caution against their use. [64]

* Because the safety and efficacy of IVIG remains inconclusive, the use of IVIG is coverable for PANS/PANDAS only when: [65]
  - PANS/PANDAS is diagnosed by a subspecialist (such as a pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist) and
  - IVIG use is endorsed by the primary care provider (such as a family physician or pediatrician) and
  - An appropriate clinical trial of less intensive treatments is ineffective for sustained reduction in symptoms. Less intensive treatments investigated for management of PANDAS/PANS include antimicrobials, anti-inflammatories, and psychoactive therapies:
    * Antimicrobials: short-course antibiotic therapy for confirmed Group A beta-hemolytic strep infection (14-day course, minimum).
    * Anti-inflammatory therapies: initial therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) for 5-7 days. Corticosteroids may be used if suboptimal response to NSAIDs (sufficient course).
    * Psychoactive therapies: selective serotonin reuptake inhibitors (SSRIs) and/or behavioral therapy [such as cognitive behavioral therapy (CBT), or
    * Given lack of clearly recommended specific treatments by guidelines among a large variety of available of less intensive treatment options available, IVIG is coverable only when <u>at least</u> two of these listed above are ineffective, as detailed in the coverage criteria.
    * Plasma exchange (PLEX), tonsillectomy, and adenoidectomy are also treatment options in this setting, which are not required but may be considered valid prior step therapies.
  - A baseline evaluation is completed and includes detailed documentation of neuropsychiatric symptoms and associated functional impairment. Clinical testing with a validated instrument must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement (see *Appendix 2*). Use of non-validated instruments are not sufficient (see *Appendix 3*).

INVESTIGATIONAL CONDITIONS

- The University Hospital Consortium (UHC), an alliance of 68 academic health centers, performed a critical assessment of off-label IVIG uses.
- The UHC determined published data to be inadequate to support the use of IVIG in various conditions. [67]
- Asthma: 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. [68-71]
- HIV (adults): The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes. [72]
- Multiple sclerosis, progressive: There is not substantial evidence to support IVIG in the treatment of chronic progressive multiple sclerosis. [73 74]
- Multiple sclerosis; relapsing-remitting type (RRMS): IVIG may provide some benefit in reducing the acute exacerbation rate in relapsing-remitting multiple sclerosis.[75]
    * Trials are generally limited to small numbers of patients and have lacked complete data on clinical outcomes.
    * Current evidence suggests little benefit with regard to slowing disease progression.
    * The American Academy of Neurology does not consider IVIG to be a first-line therapy in the treatment of relapsing-remitting multiple sclerosis. Instead, disease modifying therapies (DMTs) should be initiated (see *Medications for Multiple Sclerosis Policy* in *Cross Reference*s for more information).
- Neuropathy, other (not listed in the criteria): Other neuropathies, such as small fiber neuropathy (SFN) and autonomic autoimmune neuropathy NOS
    * The differential diagnoses list for neuropathy is extensive and may include diagnoses considered investigational in this policy.
    * Therefore, IVIG is not coverable until the diagnosis is clarified, for evaluation versus coverage criteria.
    * *Specific to SFN*: The available literature for the use of IVIG for SFN is limited to case reports/case series,[76] along with two small double-blind, placebo-controlled trials in patients with SFN, one with painful idiopathic SFN (I-SFN)[77] and a more recent trial with SFN associated with two autoantibodies, trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor receptor 3 (FGFR-3). [78]
        - Available case reports/ case series reported inconsistent and transient results. [76]
        - The trial in idiopathic SFN reported no significant effect on pain in patients with painful I-SFN with use of IVIG. It would require 10 patients to be treated for a single person to have a 1-point change in an 11-point pain scale. Disease modification effect was not measured. [77]
        - The trial in SFN and autoantibodies to TS-HDS and FGFR-3 did not find a benefit with use of IVIG versus placebo.[78]

        - Therefore, given that lack of meaningful benefit, the use of IVIG for small fiber neuropathy is considered investigational and not coverable.
        - The underlying cause needs to be treated (such as sarcoid, diabetes, Sjogren).
        - Pain treatment options include antidepressants (tricyclics [TCAs], serotonergic norepinephrine reuptake inhibitors [SNRIs)], anticonvulsants, corticosteroids, topical pain cream, analgesics, and tramadol.
    * *Specific to autoimmune neuropathy* (i.e., immune-mediated neuropathy): [79-81]
        - The diagnosis of autoimmune neuropathy, including autoimmune autonomic neuropathy, requires exclusion of other immune-mediated neuropathy causes, such as Guillain-Barre Syndrome (GBS), demyelinating polyneuropathy, and multifocal motor neuropathy (MMN).
        - For autoimmune neuropathy associated with systemic autoimmune disease (such as vasculitis, rheumatoid arthritis, lupus, Sjogren syndrome), the underlying cause needs to be treated.
        - The available literature for the use of IVIG for autoimmune autonomic neuropathy is limited to case reports/case series and one recent small RCT in chronic residual peripheral neuropathy in microscopic polyangiitis (no clear benefit of IVIG).[81] Other reported treatment options include mycophenolate, prednisone, azathioprine, and rituximab alone or in combination. Additional evidence is needed to establish the benefit of IVIG.
    * *Paraproteinemic neuropathy:* neuropathies associated with a monoclonal gammopathy or paraprotein, including IgG or IgA paraproteinemic neuropathy. Insufficient evidence is available to establish benefit from IVIG. [82]
- Optic neuritis (ON): There is insufficient evidence for the use of IVIG for optic neuritis.[83 84]
    * Optic neuritis is characterized by acute monocular visual loss. Demyelinating optic neuritis is a frequent condition in patients with a diagnosis of multiple sclerosis. Optic neuropathies due to other conditions are numerous and addressed elsewhere.
    * The use of IVIG for optic neuritis is not supported by available evidence. One small RCT (n=32) failed to demonstrate a statistically significant benefit in improvement of the primary endpoint of logarithm of the minimum angle of resolution (logMAR), a measure of visual acuity as compared to IV methylprednisolone ("steroid pulse") for steroid-resistant ON.[83]
    * At this time, the standard of care treatment for steroid-resistant ON in patients with abnormal brain MRIs is initiation of disease-modifying therapies (DMTs) for clinically isolated syndromes (CIS) suggestive of MS.
- Post-Polio: Trials of IVIG for post-polio syndrome failed to demonstrate a statistically significant benefit in improvement of muscle strength. [85]

- Recurrent pregnancy loss, or recurrent spontaneous abortion (due to anti-phospholipid or anti-cardiolipin antibodies): [86-89]
    * 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.
    * 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. [86]
    * 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. [87]
    * 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. [88]
    * A randomized controlled trial in 82 women with a history of idiopathic secondary miscarriage compared live birth rates in those who received IVIG versus placebo infusion (saline). There was no statistical difference between treatment groups. [[86]
    * ACOG recommendations state:[89]
        - 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.
        - IVIG is not effective in preventing recurrent pregnancy loss.
- 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*, complex regional pain syndrome (CRPS), narcolepsy/cataplexy, combination therapy with complement inhibitors or FcRn antagonists for refractory MG or CIDP, neonatal hemochromatosis, chronic sinusitis, tic disorder, delayed pressure urticaria, systemic sclerosis (diffuse cutaneous, dcSS) and toxic epidermal necrolysis[90-100]

Appendix 1: Primary Humoral Immunodeficiencies, as defined by the following diagnostic criteria:
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). **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.

Appendix 2: Validated Neuropsychological Tests for PANS/PANDAS[65]	
Assessment of:	**Validated Test**
Motor and vocal tics, obsession and compulsion	• Children's Yale–Brown Obsessive Compulsive Scale (CY- BOCS) for presence and severity of motor and vocal tics • Yale Global Tic Severity Scale (YGTSS) for presence and severity of child's obsession and compulsion
Anxiety	Multidimensional Anxiety Scale for Children (MASC) for the presence and types of child's anxiety symptoms for ages 8 to 19 years.
Short-term memory and attention	• Digit Span subtest Wechsler Intelligence Scale for Children for verbal short-term memory for ages 6 to 16 years • Coding subtest Wechsler Intelligence Scale for Children for visual-motor dexterity and nonverbal short-term memory for ages 6 to 16 years; and • Symbol Search subtest Wechsler Intelligence Scale for Children for accuracy, attention and concentration for ages 6 to 16 years.
Processing speed	Processing Speed Index Wechsler Intelligence Scale for Children (WISC III-IV) for speed of cognitive processes and response output on visual-motor tasks for ages 6 to 16 years
General	Global Impairment Score scale to measure impairment in children and adolescents

Appendix 3: Other Neuropsychological Tests (non-validated) [65]	
Assessment of:	**Test**
General	• Achenbach System of Empirically Based Assessment (ASEBA),19 Mini international neuropsychiatric interview (M.I.N.I.- KID) or equivalent - general assessment of psychiatric conditions • Child and Adolescent Trauma Screen (CATS) for trauma screening • Children's Global Assessment Scale (C- GAS) for general functioning • Clinical Global Impression- Severity Scale (CGI- S) for severity of the patient's illness at time of assessment • Pediatric Quality of Life Inventory (PedsQL) for quality of life • Work and Social Adjustment Scale (WSAS) 2 for impaired functioning • KIDSCREEN for subjective health and well- being
Anxiety	The Screen for Child Anxiety Related Disorders (SCARED)
Executive Function	Behavior Rating Inventory of Executive Function (BRIEF)
Screening for psychiatric diagnoses	Kiddie Schedule for Affective Disorders and Schizophrenia (Kiddie- SADS)
Inattention, hyperactivity and impulsivity	ADHD rating scale (ADHD- RS)

Cross References
Immunoglobulin Therapy, BlueCross BlueShield Association (BCBSA) Medical Policy, MPRM 8.01.05 [November 2025]
Medications for thrombocytopenia, Medication Policy Manual, Policy No. dru648
Medications for multiple sclerosis, Medication Policy Manual, Policy No. dru753
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description (Injection, immune globulin)
HCPCS	J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1460	Injection, gamma globulin, intramuscular, 1 cc
HCPCS	J1551	Injection, immune globulin (Cutaquig), 100 mg
HCPCS	J1552	Injection, immune globulin (Alyglo), intravenous, 100 mg
HCPCS	J1554	Injection, immune globulin (Asceniv), 500 mg
HCPCS	J1555	Injection, immune globulin (Cuvitru), 100 mg
HCPCS	J1556	Injection, immune globulin (Bivigam), 500 mg
HCPCS	J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1558	Injection, immune globulin (Xembify), 100 mg
HCPCS	J1559	Injection, immune globulin (Hizentra), 100 mg
HCPCS	J1561	Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1562	Injection, immune globulin (Vivaglobin), 100 mg
HCPCS	J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
HCPCS	J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1569	Injection, immune globulin, (Gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg
HCPCS	J1572	Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1576	Immune globulin intravenous, human - ifas (Panzyga)
HCPCS	J1575	Injection, immune globulin/hyaluronidase, (HYQVIA), 100 mg immune globulin
HCPCS	J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg

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Revision History

Revision Date	Revision Summary
4/2/2026	• Added new IVIG products, Qivigy (immune globulin intravenous, human-kthm) and Yimmugo (immune globulin intravenous, human-dira), to policy as not medically necessary due to higher cost. • Added small fiber neuropathy (SFN) as investigational. • Added combination treatment with complement inhibitors or FcRn antagonists for refractory myasthenia gravis or CIDP as investigational.
4/3/2025	• Added coverage criteria for myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD). • Reauthorization criteria for antibody (Ab)-mediated (humoral) rejection simplified to allow continued coverage if improvement in symptoms or organ function.
9/19/2024	Effective 1/1/2025, moved Hyqvia from Table 2 ('Not Medically Necessary' Higher-Cost Immune Globulin Replacement Products) to Table 1 (Coverable Immune Globulin Replacement Products).
6/20/2024	New IVIG product, Alyglo (immune globulin intravenous, human-stwk), added to policy as medically necessary.

3/21/2024	Effective 3/21/2024: • Clarification of the following criteria: - Multifocal motor neuropathy (MMN) diagnostic criteria, for operational consistency. - Myasthenia gravis (MG) step therapy criteria, to align with other medication policies for MG for administrative consistency (no change to intent of coverage criterion). - PANDAS/PANS step therapy criteria (from three to two step-therapies), as required by Oregon State DFR 11/14/2023 Notice of Coverage Requirement). • Correction of the products considered not medically necessary in the Continuation of Therapy (COT) criteria. Changed criteria I. to refer to the products listed in *Table 2*. • Removed Carimune from the policy (no longer commercially available). • Renamed *Table 2* to specify "High-Cost". • Corrected coverable dose in *Table 1* and *Table 2* to match Dosing Schedule in *Table 3*.
9/14/2023	Effective 1/1/2024: • Added coverage criteria for PANDAS/PANS. • Clarified "diagnosis by, or in consultation with" subspecialist throughout the diagnostic criteria. No change to intent of criteria. • Moved following products to "not medically necessary," for both Continuation of therapy (COT) and New Starts: - IVIG: Bivigam, Gammaplex, Panzyga - SCIG: Cuvitru, Hyqvia
3/16/2023	Clarified Guillain-Barré syndrome (GBS) criteria to include, but not be limited to acute inflammatory demyelinating polyneuropathy (AIDP).
6/17/2022	Moved Asceniv to "not medically necessary," for both Continuation of therapy (COT) and New Starts.
4/21/2021	• Coverage criteria and quantity limit for use in BK viremia added. • Continuation of therapy (COT) language updated (no change to intent).
10/28/2020	• Clarified policy quantity limits and intent. • Added coverage for postexposure VZV prophylaxis.
4/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).

7/24/2019	• Add Asceniv (IVIG), Xembify (SCIG) and Cutaquig (SCIG) to policy (new products) • Clarified coverage criteria for ADEM and anti-NMDA receptor encephalitis are specific to those two specific diagnoses. ADEM and anti-NMDA receptor encephalitis are types of autoimmune encephalitis. Autoimmune encephalitis (not otherwise specified) is considered a non-specific diagnosis and is not coverable. • Broadened coverage criteria for: - ITP of pregnancy (align platelet count to guidelines; 20,000) - LEMS (remove step therapy) • Investigational Uses: - Added PANDAS/PANS - Removed Behçet's syndrome, Neonatal hemolytic disease, Multiple Sclerosis, Uveitis and Wegener's granulomatosis. • Clarified Quantity Limits (QL): - Added QL per dose (and month) for SCIG and IVIG products. - Modified QL for treatment of immune-mediated rejection to allow up to six months if re-transplant is the treatment plan. • Update HCPCS Codes.
8/17/2018	• Added Panzyga to policy. • Added investigational use: Complex Regional Pain Syndrome • Updates HCPCS Codes
1/18/2018	Add Gammaked to policy.
4/14/2017	• Clarify coverage criteria for CIDP • Add coverage criteria for refractory acute demyelinating encephalomyelitis (ADEM) and anti-NMDA encephalitis • Clarify re-authorization period for Immunodeficiency (Replacement Therapy)
11/11/2016	Removed site of care language from the individual drug policy; however, requirements still apply. Reference to *Site of Care Review*, dru408 is provided as part of criterion IA.
9/15/2016	Add Cuvitru to policy.
4/8/2016	• Reworded coverage criteria for Polymyositis to Refractory Myositis. Move Dermatomyositis (juvenile) criteria, to follow after Refractory Myositis. • Delete requirement for IgG levels for reauthorization for hypogammaglobulinemia in re-authorization table (typographical error).

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