EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Subcutaneous (SCIG)

- Cuvitru™ (immune globulin subcutaneous 20% solution – Baxalta US Inc)
- Gammagard Liquid (immune globulin infusion 10% solution – Baxalta US Inc.)
- Gammaked™. (immune globulin injection 10% caprylate/chromatography purified – Kedrion Biopharma, Inc. [manufactured by Grifols Therapeutics Inc])
- Gamunex®-C (immune globulin injection 10% caprylate/chromatography purified – Grifols [manufactured by Grifols Therapeutics, Inc])
- Hizentra® (immune globulin subcutaneous 20% liquid – CSL Behring LLC [manufactured by CSL Behring GmbH])
- HyQvia (immune globulin infusion 10% with recombinant human hyaluronidase –Baxalta US Inc.)

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OVERVIEW

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors.[1-5,45] SCIG supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The exact mechanism of SCIG in primary immune deficiency is not fully understood. SCIG products are indicated for replacement therapy in patients with primary humoral immune deficiency (PID), including, but is not limited to the humoral defect in the following conditions: common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) [congenital agammaglobulinemia], Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).[1-5,45] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[4,6,46] Hizentra has an additional indication of chronic inflammatory demyelinating polyneuropathy (CIDP) via subcutaneous (SC) administration.[4] HyQvia limitation of use: safety and efficacy of chronic use of recombinant human hyaluronidase (rHu hyaluronidase) in HyQvia have not been established in conditions other than PID.[5] Safety of HyQvia has not been established in children.

Hizentra and Cuvitru are indicated as a SC infusion only, using an infusion pump.[4,45] Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous (IV) infusion for PID.[1-3] HyQvia is indicated for SC infusion only, with sequential infusion of the rHu hyaluronidase first and followed 10 minutes later with the immune globulin (IG) infusion using an infusion pump.[5] The IG infusion provides the therapeutic effect of HyQvia. The rHu hyaluronidase acts locally to increase dispersion and absorption of the IG. When administered as an IV infusion, Gamunex-C and Gammaked are also indicated for idiopathic thrombocytopenia purpura (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP).[2-3] Gammagard Liquid when given as an IV infusion is indicated for maintenance therapy in adults with multifocal motor neuropathy (MMN).[1]

Gammagard Liquid, Gammaked, or Gamunex-C are self-administered once weekly or every 2 weeks by SC infusion.[1-3] Hizentra or Cuvitru is self-administered at regular intervals from daily up to every 2 weeks.[4,45] The dose may be infused into multiple injection sites simultaneously. HyQvia is self-

administered every 3 to 4 weeks after an initial dose ramp-up.[5] The dose is infused into 1 or 2 injection sites. The volume per site with HyQvia is up to 600 mL in patients who weigh ≥ 40 kg and up to 300 mL in patients who weigh < 40 kg. The volume per injection site and flow rate is limited with any of the SCIG products and is adjusted individually. Generally, a more stable kinetic profile is noted with SCIG compared with the high peaks and low troughs noted with intravenous immune globulin (IVIG) therapy. Compared to IVIG, SCIG trough (pre-dose) levels are higher and peak serum levels are lower.

EFFICACY

Primary Humoral Immune Deficiency (PID)

Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, and Hizentra are indicated in children aged ≥ 2 years and adults when given by SC infusion.[1-4,7,45] HyQvia is indicated in adults.[5] HyQvia prescribing information notes that safety has not been established in children. Safety and efficacy of the SCIG products was established in patients with PID who were previously treated with monthly doses of IVIG[1-5,8-11] or HyQvia.[45] One week after the last dose of IVIG or HyQvia, patients were started on therapy with a SCIG product given weekly. Various methods were used for estimating the dose of SCIG and adjusting the dose to provide an adequate clinical response. Cuvitru is indicated in patients who are switching from IVIG, HyQvia, or another SCIG product.[45] Hizentra is indicated in patients who are switching from another SCIG product or from IVIG therapy.[4] HyQvia is indicated in patients who are naïve to IG therapy or who are switching from another SCIG product or from IVIG therapy.[5] An initial treatment interval and dosage ramp-up schedule is outlined in the prescribing information for initiating therapy with HyQvia. The first dose of HyQvia is given about 1 week after the last infusion of the patient's previous IG treatment and is increased to an every 3- or 4-week dose. Initiating treatment with a full monthly dose was not evaluated in the pivotal clinical trial.

Other information indicates SCIG can be started in patients with PID who have not previously been treated with any IG replacement.[5,12-14]

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In addition to PID, Hizentra is also indicated for maintenance therapy in adults with CIDP. Two doses of SC immunoglobulin were studied (0.2 g/kg and 0.4 g/kg) were studied and both were efficacious and well-tolerated.[23] SC therapy should be initiated 1 week after the patient's last IVIG infusion. If symptoms worsen while on SC therapy, consideration should be given to transitioning back to an IVIG infusion.[4]

Other Uses

In contrast to IVIG, there are limited data available for off-label uses with SCIG. It is unclear if SC infusions will be effective for disorders that presumably benefit from immunomodulatory effects of peak serum IgG concentrations that result after IV infusion of high doses of IVIG for autoimmune or inflammatory diseases (see *Guidelines*).[15] There is some data, including case reports and small randomized trials, which show SCIG has been effective in diagnoses which overlap with IVIG-studied indications, such as MMN,[18-20] multiple myeloma,[21] or refractory myasthenia gravis.[22.]

GUIDELINES

According to the Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency which was sponsored and developed by three national allergy and immunology societies (the American Academy of Allergy, Asthma, and Immunology [AAAAI], the American College of Allergy, Asthma and Immunology [ACAAI], and the Joint Council of Allergy, Asthma and Immunology [JCAAI]), IG may be

given IV or SC.[24] The choice between IV and SC administration may be influenced by: problems with IV access, systemic adverse effects with IV administration, trough IgG levels, site of care (home or infusion center), and physician or patient preference.[25] Evidence-based guidelines initiated by the Canadian Blood Services and The National Advisory Committee on Blood and Blood Products echo the AAAAI/ACAAI/JCAAI practice parameter.[26]

A new consensus document providing a definition of CVID was recently published.[29] The American Academy of Allergy, Asthma & Immunology (AAAAI), the European Academy of Allergy and Clinical Immunology, the World Allergy Organization, and the American College of Allergy, Asthma & Immunology (ACAAI) on common variable immunodeficiency developed this document. CVID is a group of heterogeneous primary antibody failure syndromes that are characterized by hypogamma-globulinemia. Their recommendations are as follows. Hypogammaglobulinemia should be defined according to age-adjusted reference range for the laboratory that performs the test. IgG levels must be repeatedly low in at least two measurements > 3 weeks apart in all patients. Repeated measurement may be omitted if the level is very low (< 100 to 300 mg/dL, depending on age), other characteristics are present, and it is considered in the best interest of the patient to start immune globulin (IG) therapy as soon as possible. IgA or IgM levels must be low. All patients with an IgG level > 100 mg/dL should be studied for responses to T cell dependent and T cell independent antigens whenever possible. In these patients there must be a demonstrated impairment of response to at least one type of antigen (i.e., T cell dependent or T cell independent). Certain exceptions can be made if all other criteria are met and if the delay caused by pre-vaccination and post-vaccination antibody measurement is deleterious to the patient's health. Other causes of hypogammaglobulinemia must be excluded (e.g., drug induced, single gene and other defects, chromosomal anomalies, infectious diseases, malignancy, other systemic disorders). It is best to not confer the diagnosis of CVID before at least the age of 4 years. Some patients may not fulfill the diagnosis of CVID on initial evaluation because the serum IgA or IgM level is not low. In this case, the term unspecified hypogammaglobulinemia or unspecified IgG deficiency is used. Also the IgG and IgA levels may be low but the antigen response to vaccines appears normal. In either circumstance, patients should be assessed over time because Ig levels and antibody function may wane and the criteria for CVID will eventually be met.

The American Academy of Neurology (AAN) and the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) have guidelines and consensus statements regarding the use of intravenous immunoglobulins, but have not yet addressed subcutaneous immune globulin use.[16-17]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of SCIG products (Cuvitru, Gammagard liquid, Gammaked, Gamunex-C, Hizentra, and HyQvia). Because of the specialized skills required for evaluation and diagnosis of patients treated with SCIG as well as the monitoring required for adverse events and long-term efficacy, initial approval requires SCIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, and Hizentra (all listed products except HyQvia) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Immunodeficiency, Primary Humoral (Treatment).** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy: Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):
     - **i.** SCIG is prescribed by or in consultation with one of the following physician specialists: an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies; AND
     - **ii.** The patient has ONE of the following primary humoral or combined immune deficiencies (a, b, c, d, e, f, or g):
       - **a)** Common variable immunodeficiencies (CVID)[15,24,27-29] AND the patient meets ALL of the following criteria (1, 2, 3, 4, and 5):
         - **(1)** The patient is at least 2 years of age;[15,29] AND
         - **(2)** Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present[15,24,29] according to the prescribing physician; AND
         - **(3)** The total serum IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[15,29] AND
         - **(4)** The IgA or IgM serum level is lower than the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[15,29] Note: Patients who do not have a low IgA or IgM level may be reviewed using criteria for Unspecified Hypogammaglobulinemia. AND
         - **(5)** The patient has a markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus)[15,24,29-30,32-33] OR according to the prescribing physician the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.[29] Note: In cases where impaired antibody testing would be deleterious to the patient's health, all other criteria for CVID in this section must be met.

       OR

       - **b)** X-linked agammaglobulinemia (XLA) [Bruton's agammaglobulinemia, congenital agammaglobulinemia]);[15,24,34] OR
       - **c)** Severe combined immunodeficiencies (SCID);[15,24,35] OR
       - **d)** Wiskott-Aldrich syndrome;[15,24,36-37] OR
       - **e)** Hyper-Immunoglobulin M (IgM) syndromes, X-linked (e.g., CD40 L deficiency) OR autosomal recessive (e.g., activation-induced cytidine deaminase, uracil-DNA glycosylase, CD40 deficiency);[15,25,38-39] OR
       - **f)** Other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect[15,24] (e.g., ataxia-telangiectasia,[15,24,40] hyper-Immunoglobulin E [IgE] syndrome,[15,47]STAT [signal transducer and activator of transcription]-3 deficiency,[15] STAT-1 deficiency,[15] DiGeorge syndrome,[24-25] nuclear factor κB essential modifier [NEMO] deficiency[15,24]) AND the patient has frequent and severe infections according to the prescribing physician; OR
       - **g)** Unspecified hypogammaglobulinemia (or unspecified IgG deficiency) AND the patient meets the following criteria (1, 2, 3, 4, and 5):
         - **(1)** The patient is at least 2 years of age;[15,29] AND

(2) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present[15,24,29] according to the prescribing physician; AND

(3) The total serum IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[15,29] AND

(4) The IgA or IgM serum level is in the normal range or higher (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[29] AND

(5) The patient has a markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus) [24,29-30,32-33]

B) Patients Currently Receiving SCIG (Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, and Hizentra):

i. Approve for 1 year for one of the conditions a, f, or g above (that is, CVID, other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect, or unspecified hypogammaglobulinemia) if the frequency and/or severity of infections have decreased according to the prescribing physician.

ii. Approve for 1 year for one of the conditions b, c, d, or e above (that is, XLA, SCID, Wiskott-Aldrich syndrome, or hyper-IgM syndromes).

2. Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP). Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy (with SCIG) and the patient meets both of the following (i and ii):

i. The patient is greater than or equal to 18 years of age; AND

ii. The medication has been prescribed by or in consultation with a neurologist.

B) Patients Currently Receiving SCIG: If the patient has a clinically significant improvement in neurologic symptoms (for example, improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation) as determined by the prescribing physician (a neurologist or in consultation with a neurologist).

II. Coverage of HyQvia is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Immunodeficiency, Primary Humoral (Treatment). Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy: Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. SCIG is prescribed by or in consultation with one of the following physician specialists: an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies; AND

ii. The patient is ≥ 18 years of age; AND

iii. The patient has one of the following primary humoral or combined immune deficiencies (a, b, c, d, e, f, or g):

a) Common variable immunodeficiencies (CVID)[15,24,27-29] AND the patient meets ALL of the following criteria (1, 2, 3, and 4):

(1) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present[15,24,29] according to the prescribing physician; AND

(2) The total serum IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[15,29] AND

(3) The IgA or IgM serum level is lower than the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[15,29] Note: Patients who do not have a low IgA or IgM level may be reviewed using criteria for Unspecified Hypogammaglobulinemia. AND

(4) The patient has a markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus)[15,24,29-30,32-33] OR according to the prescribing physician the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.[29] Note: In cases where impaired antibody testing would be deleterious to the patient's health, all other criteria for CVID in this section must be met.

OR

b) X-linked agammaglobulinemia (XLA) [Bruton's agammaglobulinemia, congenital agammaglobulinemia]);[15,24,34] OR

c) Severe combined immunodeficiencies (SCID);[15,24,35] OR

d) Wiskott-Aldrich syndrome;[15,24,36-37] OR

e) Hyper-Immunoglobulin M (IgM) syndromes, X-linked (e.g., CD40 L deficiency) OR autosomal recessive (e.g., activation-induced cytidine deaminase, uracil-DNA glycosylase, CD40 deficiency);[15,25,38-39] OR

f) Other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect[15,24] (e.g., ataxia-telangiectasia,[15,24,40] hyper-Immunoglobulin E [IgE] syndrome,[15,47]STAT [signal transducer and activator of transcription]-3 deficiency,[15] STAT-1 deficiency,[15] DiGeorge syndrome,[24-25] nuclear factor κB essential modifier [NEMO] deficiency[15,24]) AND the patient has frequent and severe infections according to the prescribing physician; OR

g) Unspecified hypogammaglobulinemia (or unspecified IgG deficiency) AND the patient meets the following criteria (1, 2, 3, and 4):

(1) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present[15,24,29] according to the prescribing physician; AND

(2) The total serum IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[15,29] AND

(3) The IgA or IgM serum level is in the normal range or higher (age-adjusted and according to the normal reference range for the reporting laboratory) measured on at least two occasions more than 3 weeks apart;[29] AND

(4) The patient has a markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus).[24,29-30,32-33]

B) Patients Currently Receiving SCIG (HyQvia):

i. Approve for 1 year for one of the conditions a, f, or g above (that is, CVID, other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production

defect, or unspecified hypogammaglobulinemia) if the frequency and/or severity of infections has decreased according to the prescribing physician.

ii. Approve for 1 year for one of the conditions b, c, d, or e above (that is, XLA, SCID, Wiskott-Aldrich syndrome, or hyper-IgM syndromes).

Safety of HyQvia has not been established in pediatric patients.[5] Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, and Hizentra are indicated for primary humoral immunodeficiency in patients ≥ 2 years of age.[1-4,45] SCIG is used for replacement in primary immunodeficiency disorders where antibody production is absent or deficient to increase IgG levels and most of the time to prevent or control recurrent or unusually severe bacterial infections.[15,24,41]

Patients with PID are at high risk of developing acute and chronic bacterial infections.[24] SCIG provides a broad spectrum of IgG antibodies that help prevent or attenuate infectious diseases. The use of SCIG in IgG subclass deficiencies (e.g., deficiencies of immunoglobulin A [IgA] or immunoglobulin E [IgE] in association with reduced IgG2 or IgG4) is controversial and is recommended only in those patients who also demonstrate a deficiency in the ability to form antibodies against a variety of polysaccharide and protein antigens.[15,24,30-33]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

SCIG has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of SCIG.[15,24-25,42] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[24] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[15,24] Some of these patients with a concomitant specific antibody defect might benefit from therapy with SCIG.

2. **HyQvia in Patients < 18 years of Age.** The safety of HyQvia in pediatric patients < 18 years of age has not been established.[5] HyQvia is indicated in adults. In one prospective, open-label Phase III clinical trial, 83 patients aged 4 to 78 years with primary immunodeficiency received HyQvia.[5] Eleven of the patients were aged 2 to < 12 years and 70 patients were aged ≥ 12 years.[43-44]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gammagard Liquid 10% [prescribing information]. Westlake Village, CA: Baxalta US Inc.; June 2016.
2. Gammaked™ 10% injection [prescribing information]. Fort Lee, NJ: Kedrion Biopharma, Inc. (manufactured by Grifols Therapeutics, Inc., Research Triangle Park, NC); March 2017.
3. Gamunex®-C 10% liquid [prescribing information]. Research Triangle Park, NC: Grifols USA, LLC (manufactured by Grifols Therapeutics Inc., Research Triangle Park, NC); March 2017.
4. Hizentra® for subcutaneous infusion [prescribing information]. Kankakee, IL: CSL Behring LLC (manufactured by CSL Behring AG, Bern, Switzerland); March 2018.

5. HyQvia immune globulin infusion 10% with recombinant human hyaluronidase [prescribing information]. Westlake Village, CA: Baxalta US Inc.; September 2016.
6. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62:1-34.
7. Kedrion United States. Gammaked® frequently asked questions. Available at: http://www.gammaked.com/main/faqs/ Accessed on June 4, 2018.
8. Ochs HD, Gupta S, Kiessling P, et al; Subcutaneous IgG Study Group. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol.* 2006;26:265-273.
9. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. *J Clin Immunol.* 2006;26:177-185.
10. Berger M, Murphy E, Riley P and Bergman GE and the VIRTUE Trial Investigators. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. *South Med J.* 2010;103:856-863.
11. McCormak PL. Immune globulin subcutaneous (human) 20%: in primary immunodeficiency disorders. *Drugs.* 2012;72:1087-1097.
12. Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. *Arch Dis Child.* 1998;79:48-51.
13. Gardulf A, Hammarstrom L, Smith CI. Home treatment of hypogammaglobulinemia with subcutaneous gammaglobulin by rapid infusion. *Lancet.* 1991;338:162-166.
14. Berger M. Subcutaneous administration of IgG. *Immunol Allergy Clin North Am.* 2008;28:779-802, viii.
15. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017;139(3S):S1-S46. Available at: http://www.jacionline.org/article/S0091-6749(16)31141-1/pdf. Accessed on June 4, 2018.
16. Donofrio PD, Berger A, Brannagan TH 3rd, et al. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. *Muscle Nerve.* 2009;40:890-900.
17. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2012;78(13): 1009-15. Available at: http://n.neurology.org/content/78/13/1009.full. Accessed on June 12, 2018.
18. Harbo T, Andersen H, Hess A, et al. Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: a randomized, single-blinded cross-over trial. *Eur J Neurol.* 2009;16:631-638.
19. Eftimov F, Vermeulen M, de Hann RJ, et al. Subcutaneous immunoglobulin therapy for multifocal motor neuropathy. *J Peripher Nerv Syst.* 2009;14:93-100.
20. Harbo T, Anderson H and Jakobsen J. Long-term therapy with high doses of subcutaneous immunoglobulin in multifocal motor neuropathy. *Neurology*. 2010;75:1377-1380.
21. Vacca A, Melaccio A, Sportelli A, et al. Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial. *Clin Immunol.* 2018; 191: 110-115.
22. Kovacs E, Dando K, Nagy-Vince M, et al. Long-term treatment of refractory myasthenia gravis with subcutaneous immunoglobulin. *Ther Adv Neurol Disord*. 2017; 10(11):363-366.
23. van Schaik IN, Bril V, van Geloven N, et al; PATH study group. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2018;17(1):35-46.
24. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015;136:1186-1205.e1-78.
25. Immune Deficiency Foundation. Patient & Family Handbook for Primary Immunodeficiency diseases. 5th edition. 2015. Available at: http://primaryimmune.org/wp-content/uploads/2016/03/IDF-Patient-Family-Handbook-5th-Edition-2015-Reprint-Web.pdf, Accessed on June 4, 2018.
26. Shehata N, Palda V, Bowen T, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: An evidence-based practice guideline. *Transfus Med Rev.* 2010;24(Suppl 1); S28-S50.
27. Deane S, Selmi C, Naguwa SM, et al. Common variable immunodeficiency: etiological and treatment issues. *Int Arch Allergy Immunol.* 2009;150:311-324.
28. Jolles S. The variable in common variable immunodeficiency: a disease of complex phenotypes. *J Allergy Clin Immunol Pract.* 2013;1:545-556.
29. Bonilla FA, Barlan I, Chapel H, et al. International Consensus Document (ICON): Common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract*. 2016;4(1):38-59.
30. Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? *Curr Allergy Asthma Reports.* 2002;2:356-360.
31. Herrod HG. Management of the patient with IgG subclass deficiency and/or selective antibody deficiency. *Ann Allergy.* 1993;70:3-8.

32. Agarwal S, Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. *Ann Allergy Asthma Immunol.* 2007;99:281-283.
33. Paris K, Sorensen RU. Assessment and clinical interpretation of polysaccharide antibody responses. *Ann Allergy Asthma Immunol.* 2007;99:462-464.
34. Smith CIE, Berglöf A. X-Linked Agammaglobulinemia. 2001 Apr 5 [Updated 2106 Aug 4]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1453/. Accessed on June 4, 2018.
35. Allenspach E, Rawlings DJ, Scharenberg AM. X-Linked Severe Combined Immunodeficiency. 2003 Aug 26 [Updated 2016 Apr 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1410/. Accessed on June 4, 2018.
36. Chandra S, Bronicki L, Nagaraj CB, Zhang K. WAS-Related Disorders. 2004 Sep 30 [Updated 2016 Sep 22]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1178/ Accessed on June 4, 2018.
37. Ochs HD, Filipovich AH, Veys P, et al. Wiskott-Aldrich syndrome: diagnosis, clinical and laboratory manifestations, and treatment. *Biol Blood Marrow Transplant.* 2009;15(1 Suppl):84-90.
38. Ochs HD. Patients with abnormal IgM levels: assessment, clinical interpretation, and treatment. *Ann Allergy Asthma Immunol.* 2008;100:509-511.
39. Johnson J, Filipovich AH, Zhang K. X-Linked Hyper IgM Syndrome. 2007 May 31 [Updated 2013 Jan 24]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1402/. Accessed June 4, 2018.
40. Gatti R, Perlman S. Ataxia-Telangiectasia. 1999 Mar 19 [Updated 2016 Oct 27]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26468/ Accessed on June 4, 2018.
41. Stein MR, Nelson RP, Church JA, et al. Safety and efficacy of Privigen, a novel 10% liquid immunoglobulin preparation for intravenous use, in patients with primary immunodeficiencies. *J Clin Immunol.* 2009;29:137-144.
42. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. *Clin Microbiol Rev.* 2009;22:396-414.
43. Wasserman RL, Melamed I, Stein MR, et al; the IGSC, 10% with rHuPH20 Study Group. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J Allergy Clin Immunol.* 2012;130:951-957.
44. Sanford M. Human immunoglobulin 10 % with recombinant human hyaluronidase: replacement therapy in patients with primary immunodeficiency disorders. *BioDrugs.* 2014;28:411-420.
45. Cuvitru™ subcutaneous 20% solution [prescribing information]. Westlake Village, CA: Baxalta US Inc.; September 2016.
46. Lejeune A, Martin L, Santibanez S, et al. Postexposure prophylaxis with intravenous immunoglobulin G prevents infants from getting measles. *Acta Paediatr*. 2017;106(1):174-177.
47. Hsu AP, Davis J, Puck JM, et al. Autosomal dominant yyper IgE syndrome (Synonyms: AD-HIES, Job's Syndrome, STAT3-deficient hyper IgE syndrome, STAT3 deficiency)**.** 2010 Feb 23 [Updated 2012 Jun 7]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK25507/ Accessed on June 4, 2018.

OTHER REFERENCES UTILIZED

- Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol.* 2004;112:1-7.
- Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. *Immunol Allergy Clin North Am.* 2008;28:413-437.
- Berger M. Subcutaneous IgG in neurologic diseases. *Immunotherapy.* 2014;6:71-83.
- Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. *J Allergy Clin Immunol.* 2008;122:210-212.
- Conley ME, Saragoussi D, Notarangelo L, et al; PAGID; ESID. An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. *Clin Immunol.* 2003;109:272-277.
- Durandy A, Wahn V, Petteway S, et al. Immunoglobulin replacement therapy in primary antibody deficiency diseases--maximizing success. *Int Arch Allergy Immunol.* 2005;136:217-229.
- Fasth A, Nyström J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. *Acta Paediatr.* 2007;96:1474-1478.
- Gardulf A, Nicolay U, Math D, et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. *J Allergy Clin Immunol.* 2004;114:936-942.
- Haddad E, Berger M, Wang EC, et al. Higher doses of subcutaneous IgG reduce resource utilization in patients with primary immunodeficiency. *J Clin Immunol.* 2012;32:281-289.

- Hadden RD, Marreno F. Switch from intravenous to subcutaneous immunoglobulin in CIDP and MMN: improved tolerability and patient satisfaction. *Ther Adv Neurol Disord.* 2015;8:14-19.
- Hagan JB, Fasano MB, Spector S, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. *J Clin Immunol*. 2010;30:734-745.
- Immune Deficiency Foundation. IDF Diagnostic & Clinical Care Guidelines for Primary Immunodeficiency diseases. 2nd Edition. 2008, 2009. Available at: http://primaryimmune.org/?attachment_id=379. Accessed June 4, 2018.
- Jolles S, Bernatowska E, de Gracia J, et al. Efficacy and safety of Hizentra(®) in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. *Clin Immunol.* 2011;141:90-102.
- Litzman J, Jones A, Hann I, et al. Intravenous immunoglobulin, splenectomy, and antibiotic prophylaxis in Wiskott-Aldrich syndrome. *Arch Dis Child.* 1996;75:436-439.
- Misbah S, Sturzenegger MH, Borte M, et al. Subcutaneous immunoglobulin: opportunities and outlook. *Clin Exp Immunol.* 2009;158(Suppl 1): 51-59.
- Rajabally YA. Subcutaneous immunoglobulin therapy for inflammatory neuropathy: current evidence base and future prospects. *J Neurol Neurosurg Psychiatry.* 2014;85:631-637.
- Rosengren S, Dychter SS, Printz MA, et al. Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. *AAPS J*. 2015;17:1144-1156.
- Wasserman RL, Irani AM, Tracy J, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. *Clin Exp Immunol.* 2010;161:518-526.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	Vivaglobin removed from list of products. No criteria changes.	03/09/2016
Selected revision by DEU	Cuvitru added 09/21/2016.	NA
Annual revision	Immunodeficiencies, Primary Humoral: For CVID the requirement for a documented history of significant recurrent or persistent, severe bacterial infections and that infections are responding inadequately to treatment with antibiotics and/or appropriate prophylaxis with antibiotics or the patient has multiple antibiotic hypersensitivities were removed. The patient is at least 4 years of age was added. Previously the criteria required that at least one of three criteria be met. Of these, the option for reduced IgG1 and IgG3 subclass levels or IgG1 alone was deleted. The total IgG level was revised to add that it is below the normal range and measured at least two times more than 3 weeks apart (IgG level is age adjusted and according to the reference lab is still required). Criteria for an antibody response to protein antigen or polysaccharide antigen were revised to add an exception if the physician believes the delay for this testing would be deleterious. Criteria were added requiring that IgA or IgM serum level is lower than the normal range. Similar revisions were made to the Unspecified hypogammaglobulinemia criteria. One difference is that the IgA or IgM levels are in the normal range or higher. See policy for details.	06/14/2017
Selected revision	Immunodeficiencies, Primary Humoral: Initial approval is for 1 year (previous duration was 3 years). Criteria were added for patients currently receiving SCIG to approve for 1 year for CVID, other combined immunodeficiencies, or unspecified hypogammaglobulinemia if the frequency and/or severity of infections have decreased according to the prescribing physician. The conditions of XLA, SCID, Wiskott-Aldrich syndrome, or hyper-IgM syndromes are approved for 1 year.	02/07/2018
Selected revision	Immunodeficiencies, Primary Humoral (Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, and Hizentra [all listed products except HyQvia]): Age in patients with CVID or Unspecified hypogammaglobulinemia revised to be at least 2 years of age. Previously the age was at least 4 years.	03/14/2018
Annual revision	Added criteria for the diagnosis chronic inflammatory demyelinating polyneuropathy (CIDP).	07/11/2018

TAC – Therapeutic Assessment Committee**;** DEU – Drug Evaluation Unit. CVID – common variable immunodeficiencies; IgG – Immunoglobulin G; IgA – Immunoglobulin A; IgM – Immunoglobulin M; XLA – X-linked agammaglobulinemia; SCID – severe combined

immunodeficiencies; CIDP – chronic inflammatory demyelinating polyneuropathy. * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.