MEDICAL MUTUAL®

# Drug Policy

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| **Code(s):** | **HCPCS J1555, J1559, J1561, J1569, J1575** | **Annual Review Date: 08/16/2018** |
| **SUBJECT:** | **Immune Globulins Subcutaneous (SCIG)**<br>**•Gammagard Liquid (immune globulin infusion 10% solution – Baxter Healthcare Corporation)**<br>**•Gammaked™ (immune globulin injection 10% caprylate/chromatography purified – Kedrion Biopharma, Inc. [manufactured by Talecris Biotherapeutics] {Grifols Therapeutics Inc})**<br>**•Gamunex®-C (immune globulin injection 10% caprylate/chromatography purified – Grifols Therapeutics, Inc)**<br>**•Hizentra® (immune globulin subcutaneous 20% liquid-CSL Behring)**<br>**•HyQvia (immune globulin infusion 10% with recombinant human hyaluronidase – Baxter Healthcare Corporation)**<br>**•Cuvitru™ (immune globulin subcutaneous 20% solution – Baxalta US Inc)** | **Last Revised Date: 08/16/2018** |

**Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.**

## 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.

Cuvitru 20% (0.2 g per mL), Gammagard Liquid 10% (0.1 g per mL), Gamunex-C 10% (0.1 g per mL), Gammaked 10% (0.1 per mL), and Hizentra 20% (0.2 g per mL) are available in preservative-free single-use vials.[1-4] HyQvia is available as a dual vial unit containing one vial of 10% IG (0.1 g/mL) and one vial of 160 units of rHu hyaluronidase per mL.[5] The immunoglobulin A (IgA) content for Gammagard liquid or HyQvia is 37 mcg per mL (average),[1,5] Gamunex-C and Gammaked is 46 mcg per mL (average),[2-3] Hizentra is ≤ 50 mcg per mL,[4] and Cuvitru is 80 mcg per mL (average).[45]

## 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 Polyneruopathy (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]

In one small Phase II study, patients (n = 29) on maintenance therapy with IVIG (mean dose 0.3 g/kg/week) for CIDP were randomized to SCIG (Subcuvia® 16% product available in Europe) at a dose equivalent to their IVIG dose or to SC 0.9% sodium chloride injection given two or three times weekly for 12 weeks.[21] The isokinetic muscle strength expressed as a percentage of the pretreatment level incr

## 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

This policy involves the use of SCIG products. Prior authorization is recommended for medical benefit coverage of IG products (Cuvitru, Gammagard liquid, Gammaked, Gamunex-C, Hizentra, and HyQvia). Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing (*applies to requests under the medical benefit only*), Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the criteria for coverage of the requested medication applies to patients not currently taking the requested medication (unless continuation of therapy is addressed in the criteria for coverage). For patients already on the requested medication, follow the directions under the extended approval section (unless continuation of therapy is addressed in the criteria for coverage). **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section.

Because of the 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 to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is required for continuation of therapy.
The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.

## 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).**

**Criteria.** *The patient must meet the following criteria (A, B, and C):*

**A)** 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

**B)** The patient has ONE of the following primary humoral or combined immune deficiencies (i, ii, iii, iv, v, vi, or vii):

**i.** Common variable immunodeficiencies (CVID)[15,24,27-29] AND the patient meets the ALL of following criteria (a, b, c, d and e):

**a)** The patient is at least 2 years of age;[15,29] AND

**b)** 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

**c)** 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

**d)** 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

**e)** 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

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

**iii.** Severe combined immunodeficiencies (SCID);[15,24,35] OR

**iv.** Wiskott-Aldrich syndrome;[15,24,36-37] OR

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

**vi.** 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

**vii.** Unspecified hypogammaglobulinemia (or unspecified IgG deficiency) AND the patient meets the following criteria (a, b, c, d, and e):

**a)** The patient is at least 4 years of age;[15,29] AND

**b)** 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

**c)** 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

**d)** 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

**e)** 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] AND

C) Site of care medical necessity is met*

**Dosing in Primary Immune Deficiency in Adults, Children or Adolescents.** *Dosing must meet ONE the following (A, B, C, D, OR E) for Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, or Hizentra:*

**A)** The patient is transitioning from IVIG, and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly [e.g., 2 to 7 times per week]) is based on the patient's previous monthly IVIG dose;[1-4] OR

**B)** The patient is transitioning from another SCIG product, and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly) is based on the patient's previous weekly SCIG dose;[4,45] OR

**C)** The patient is initiating SCIG therapy without previous IVIG or SCIG therapy and is receiving a loading dose (e.g., 100 mg per kg once daily for 5 consecutive days) followed by once weekly (or more frequently as necessitated by volume) maintenance dosing; OR

**D)** The dose and interval between doses has been adjusted based on clinical response (e.g., frequency or severity of infections, hospitalization, days of school or work missed, failure to thrive, or to treat/prevent complications such as chronic lung disease, granulomatous infiltrative disease, or autoimmune disease) as determined by the prescribing physician; OR

**E)** Patients with primary immune deficiency and exposure to measles (rubeola) must meet ONE of the following (i or ii):[4]

**i.** In patients receiving weekly or more frequent SCIG, the total weekly dose should be a minimum of 200 mg per kg for two consecutive weeks AND if the patient has already been exposed to measles, the minimum dose should be given as soon as possible after exposure; OR

**ii.** In patients receiving SCIG every 2 weeks, one dose of a minimum of 400 mg per kg should be given, AND if the patient has already been exposed to measles, the minimum dose should be given as soon as possible after exposure.

SCIG therapy may be used in patients previously treated with IVIG; patients who are switching from one SCIG product to another; or who have not previously been treated with IG therapy. As a guide, in patients transitioning from IVIG to SCIG, SCIG is generally started 1 week after the patient's last regularly scheduled IVIG infusion. In patients receiving IVIG, the initial SCIG dose is based on the patient's monthly IVIG dose or with HyQvia, is based on a ramp-up schedule provided in the prescribing information. In patients switching from one SCIG product to another, the dose is based on the previous weekly SCIG dose. Subsequent dose adjustment is made by the prescribing physician and is based on clinical response. For SCIG products other than HyQvia, as a guide, in patients previously untreated with IG therapy, a loading dose period (e.g., 5 consecutive days) may be used followed by subsequent

weekly (or more frequent) maintenance dose as determined by the prescribing physician. Further dose adjustment is determined by the prescribing physician and based on clinical response.

Prescribing information for Cuvitru, Gammagard liquid, Gammaked, Gamunex-C, and Hizentra describes dosing in patients previously treated with IVIG. The *initial dose* of SCIG can be calculated by converting the monthly IVIG dose into a weekly equivalent and increasing (multiplying) the dose by using an adjustment factor (product specific). The adjustment factor for Gammagard liquid, Gammaked, Gamunex-C, or Hizentra is 1.37,[1-4] and is 1.30 for Cuvitru.[45] Hizentra prescribing information indicates that this product can be given from daily up to every 2 weeks.[4] More detailed information is in the Cuvitru and Hizentra prescribing information for switching to Cuvitru or Hizentra from IVIG or another SCIG product.

According to the prescribing information, the following weekly doses of Gammagard liquid and Hizentra have been used: Gammagard liquid doses have ranged from 94.2 to 293.8 mg per kg, and Hizentra median doses have ranged from 72 to 379 mg per kg (mean 213.2 mg/kg).[1,4] The prescribing information for Cuvitru indicates the mean dose was 222 mg/kg/week in one study.[45] This information is not provided in the Gamunex-C or Gammaked prescribing information. The prescribing information for HyQvia indicates that the mean volume per site was 292 mL (29.2 g per site) with a median of 1.09 monthly infusion sites.[5]

In patients who are not treated previously with IG, an initial loading dose of Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, or Hizentra may be used followed by subsequent weekly (or more frequent) maintenance dosing.[12-14]

Subsequent *dose adjustment* may be necessary to achieve the desired clinical response. A serum IgG trough level may be measured 2 or 3 months after initiating SCIG and can be used as a guide for dose adjustment; however, the patient's clinical response should be the primary consideration in dose adjustment.

The trough IgG level usually should be greater than or equal to 500 mg per dL (5 g per L) and varies depending on the assessment of the prescribing physician. The IgG trough level should be greater than 800 mg per dL in some patients with chronic lung and/or sinus disease to prevent serious bacterial infections. These higher trough levels may also be required to improve or prevent chronic lung disease, granulomatous infiltrative disease, or autoimmune disease in certain types of primary immune deficiency (such as CVID).

*Background information.* When starting SCIG therapy in a patient previously treated with IVIG, a serum trough level following a regularly scheduled IVIG infusion can be used to determine the initial SCIG dose of Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, or Hizentra. In patients who have not previously received IG therapy, a serum trough IgG level may be measured prior to therapy. Once therapy with SCIG is started, the IgG trough usually stabilizes after 3 months of therapy. As a general guideline, in growing children, the trough IgG level should be checked about every 3 to 6 months, and in adults, every 6 to 12 months. Once the patient is stabilized, a trough IgG level is usually measured once a year. The dose is adjusted according to clinical effectiveness as determined by the prescribing physician.

*Measles (rubeola) exposure in patients with primary immune deficiency:* In a patient who is at risk of measles exposure due to an outbreak in the US or travel to endemic areas outside the US, the total weekly dose of Hizentra

should be a minimum of 200 mg per kg for two consecutive weeks.[4] If the dose is being given every 2 weeks, one dose of a minimum of 400 mg per kg is recommended. If the patient has been exposed to measles, this minimum dose should be given as soon as possible after exposure. No dosing recommendations for SC administration are given in the prescribing information for Cuvitru, Gammagard liquid, Gammaked, Gamunex-C, or HyQvia for this indication. However, the Advisory Committee on Immunization Practices (ACIP) notes in their guidelines that IVIG and SCIG products (with no distinction among the products) provide protective levels of measles neutralizing antibody for 28 to 30 days if given at the minimum recommended dose of 0.2 g/kg.[6] For patients receiving SCIG therapy, these guidelines state that administration of ≥ 0.2 g/kg for two consecutive weeks before measles exposure should be sufficient. The ACIP guidelines include recommendations on post-exposure prophylaxis of measles using *IM IG* for infants aged < 12 months; using *IVIG* for pregnant women without evidence of measles exposure; and using *IVIG* in severely immunocompromised patients exposed to measles.

**Initial Approval/Extended Approval.**

**a)** Initial and maintenance therapy for Immunodeficiency, Primary Humoral

- **i.** *Initial Approval.* 6 months for all indications.
- **ii.** *Extended Approval.*
  - **(1)** For common variable immunodeficiencies (CVID) OR for other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect, approve for 12 months if the frequency and/or severity of infections has decreased according to the prescribing physician. Continue to approve every 12 months if the patient is responding with a decrease in frequency and/or severity of infections.
  - **(2)** For X-linked agammaglobulinemia (XLA); severe combined immunodeficiencies (SCID); hyper-IgM syndromes (X-linked or autosomal recessive); or Wiskott-Aldrich syndrome, approve for 12 months. Continue approving every 12 months.
  - **(3)** For unspecified hypogammaglobulinemia (or unspecified IgG deficiency), approve at 6-month intervals if the frequency and/or severity of infections has decreased according to the prescribing physician.

**b)** Measles exposure:

- **i.** *Initial Approval.* One or two doses of Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, or Hizentra. See Dosing in Primary Immune Deficiency in Adults, Children or Adolescents D) i or ii.
- **ii.** *Extended Approval.* Not recommended.

**Duration of Therapy in Primary Immune Deficiency or Other Immunodeficiency States:** Indefinite or until definitive correction of the underlying disorder (such as hematopoietic stem cell transplant (HCT), gene therapy). Some patients continue to require IG supplementation after HCT because of failure of B-cell engraftment.[15,24]

**Labs/Diagnostics.** In CVID or unspecified hypogammaglobulinemia total IgG levels, and either IgA and/or IgM levels AND antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen [pneumococcus] are required as part of the diagnosis.

**2. Chronic Inflammatory Demyelinating Polyneurapthy or Polyradiculoneurpathy (CIDP).**

**Criteria.** *The patient must meet the following criteria (A OR B AND C):*

**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 neurological 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); AND

**C) Site of care medical necessity is met***

**Dosing in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).** *Dosing must meet the following (A or B):*

**A)** The dose is either 0.2 g/kg or 0.4 g/kg per week administered in 1 or 2 sessions over 1 or 2 consecutive days;[4] OR

**B)** The dose has been titrated according to clinical response.

**Approval/Extended Approval.**

**A)** Initial and maintenance therapy for Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneurapthy (CIDP)

*Initial and Extended Approval.* 1 year

**Duration of Therapy in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):** SCIG was studied for up to 18 months in maintenance therapy for CIDP. Therapy beyond should be individualized based on the patient's response and need for continued therapy.[4]

**Labs/Diagnostics.** None required.

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

**FDA-Approved Indications**

**1. Immunodeficiency, Primary Humoral (Treatment).**

**Criteria.** *The patient must meet the ALL of following criteria (A, B, C and D):*

**A)** 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

**B)** The patient is ≥ 18 years of age; AND

**C)** The patient has ONE of the following primary humoral or combined immune deficiencies (i, ii, iii, iv, v, vi, or vii):

**i.** Common variable immunodeficiencies (CVID)[15,24,27-29] AND the patient meets the following criteria (a, b, c, and d):
- **a)** 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
- **b)** 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
- **c)** 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
- **d)** 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

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

**iii.** Severe combined immunodeficiencies (SCID);[15,24,35] OR

**iv.** Wiskott-Aldrich syndrome;[15,24,36-37] OR

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

**vi.** 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

**vii.** Unspecified hypogammaglobulinemia (or unspecified IgG deficiency) AND the patient meets the following criteria (a, b, c, and d):
- **a)** 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
- **b)** 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
- **c)** 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

**d)** 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]

D) Site of care medical necessity is met*

Safety of HyQvia has not been established in pediatric patients.[5] Cuvitru, Gammagard Liquid, Gamunex-C, and Hizentra are indicated for primary humoral immunodeficiency in patients ≥ 2 years of age.[1,3-4,45] Safety and efficacy of SC administration of Gammaked for primary humoral immunodeficiency have not been established in pediatric patients, but safety and efficacy are established in pediatric patient when these products are given IV for primary humoral immunodeficiency and ITP.[2] 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]

**Dosing in Primary Immune Deficiency in <u>Adults</u>.** *<u>Dosing must meet ONE of the following (A OR B) for HyQvia:</u>*

**A)** The patient is starting HyQvia and the dose and interval is being ramped-up to determine tolerability; OR

Note: The patient may be switching from IVIG OR from another SCIG product OR the patient may be naïve to IG therapy. See prescribing information for ramp-up schedule.

**B)** The patient has already been started on HyQvia after the initial dose ramp-up and ONE of the following applies (i, ii, <u>or</u> iii):

- **i.** The dose is 300 to 600 mg/kg given at 3 to 4 week intervals; OR
- **ii.** The dose and frequency is the same as previously used when receiving IVIG; OR
- **iii.** The dose and interval between doses has been adjusted based on clinical response (e.g., frequency or severity of infections, hospitalization, days of school or work missed, failure to thrive, or to treat/prevent complications such as chronic lung disease, granulomatous infiltrative disease, or autoimmune disease) as determined by the prescribing physician.

SCIG therapy may be used in patients previously treated with IVIG; patients who are switching from one SCIG product to another; or who have not previously been treated with IG therapy. As a guide, in patients transitioning from IVIG to SCIG, SCIG is generally started 1 week after the patient's last regularly scheduled IVIG infusion. In patients receiving IVIG, the initial SCIG dose is based on the patient's monthly IVIG dose or with HyQvia, is based on a ramp-up schedule provided in the prescribing information. In patients switching from one SCIG product to another, the dose is based on the previous weekly SCIG dose. Subsequent dose adjustment is made by the prescribing physician and is based on clinical response. For SCIG products other than HyQvia, as a guide, in patients previously untreated with IG therapy, a loading dose period (e.g., 5 consecutive days) may be used followed by subsequent weekly (or more frequent) maintenance dose as determined by the prescribing physician. Further dose adjustment is determined by the prescribing physician and based on clinical response. For HyQvia, in patients switching from

IVIG, the dose and frequency of HyQvia is the same as the previous IV therapy, after giving the initial dose ramp up. In patients who are naïve to IG therapy or switching from another SCIG product, HyQvia 300 to 600 mg/kg at 3- to 4-week intervals is given after the initial ramp-up. The prescribing information has details on adjusting the dose, based on the patient's body weight and desired change in IgG trough level. The dose of HyQvia should be adjusted if needed based on clinical response. The full therapeutic dose of HyQvia can be given in one site up to every 4 weeks. The frequency and number of infusion sites is adjusted considering the volume, total infusion time, and tolerability. Evaluate the use of a second site or infusing at shorter intervals when the volume of HyQvia is > 600 mL. The volume per site is up to 600 mL in patients ≥ 40 kg and up to 300 mL per site for patients < 40 kg.

**Initial Approval/Extended Approval.**
Initial and maintenance therapy for Immunodeficiency, Primary Humoral

- **i.** *Initial Approval.* 6 months for all indications.
- **ii.** *Extended Approval.*
  - **a)** For common variable immunodeficiencies (CVID) OR for other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect, approve for 12 months if the frequency and/or severity of infections has decreased according to the prescribing physician. Continue to approve every 12 months if the patient is responding with a decrease in frequency and/or severity of infections.
  - **b)** For X-linked agammaglobulinemia (XLA); severe combined immunodeficiencies (SCID); hyper-IgM syndromes (X-linked or autosomal recessive); or Wiskott-Aldrich syndrome, approve for 12 months. Continue approving every 12 months.
  - **c)** For unspecified hypogammaglobulinemia (or unspecified IgG deficiency), approve at 6-month intervals if the frequency and/or severity of infections has decreased according to the prescribing physician.

**Duration of Therapy in Primary Immune Deficiency or Other Immunodeficiency States:** Indefinite or until definitive correction of the underlying disorder (such as hematopoietic stem cell transplant (HCT), gene therapy). Some patients continue to require IG supplementation after HCT because of failure of B-cell engraftment.[15,24]

**Labs/Diagnostics.** In CVID or unspecified hypogammaglobulinemia total IgG levels, and either IgA and/or IgM levels AND antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen [pneumococcus] are required as part of the diagnosis.

## Other Uses with Supportive Evidence

**Hypogammaglobulinemia after Car-T infusion.**

Approve in patients who meeting the following criteria (A, B, and C):

A) Patient is diagnosed with Hypogammaglobulinemia or IgG agammaglobulinemia after infusion with CAR-T Therapy [examples of Car-T therapy are as follows: Kymriah (tisagenlecleucel)]; AND
B) SCIG is prescribed by or in consultation with an infectious diseases physician, hematologist or an oncologist; AND
C) site of care medical necessity is met*.

Hypogammaglobulinemia and IgG agammaglobulinemia may occur in patients with a complete remission (CR) after tisagenlecleucel infusion. Because B-cell aplasia is an on-target effect of tisagenlecleucel, hypogammaglobulinemia may persist as long as tisagenlecleucel persists. Monitor immunoglobulin levels after tisagenlecleucel treatment. Manage hypogammaglobulinemia with infection precautions, antibiotic prophylaxis and immunoglobulin treatment (per standard replacement guidelines). Pregnant women who have received tisagenlecleucel may have hypogammaglobulinemia; assess immunoglobulin levels in newborns of mothers treated with tisagenlecleucel.

**Dosing in Hypogammaglobulinemia after CAR-T infusion in Adults, Children or Adolescents.** *Dosing must meet ONE the following (a, b, c, OR d) for Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, or Hizentra,:*

**a)** The patient is transitioning from IVIG, and the maintenance dose (given once weekly, every 2 weeks, or more frequently than once weekly [e.g., 2 to 7 times per week]) is based on the patient's monthly IVIG dose;[1-5] OR
**b)** The patient is initiating SCIG therapy without previous IVIG therapy and is receiving a loading dose (e.g., 100 mg per kg once daily for 5 consecutive days) followed by once weekly (or more frequently as necessitated by volume) maintenance dosing;[13] OR
**c)** The dose and interval between doses has been adjusted based on clinical response (e.g., frequency or severity of infections, hospitalization, days of school or work missed, failure to thrive, or to treat/prevent complications such as chronic lung disease, granulomatous infiltrative disease, or autoimmune disease) as determined by the prescribing physician; OR
**d)** Patients with hypogammaglobulinemia and exposure to measles (rubeola) must meet ONE of the following (i or ii):[4]

**i.** In patients receiving weekly or more frequent SCIG, the total weekly dose should be a minimum of 200 mg per kg for two consecutive weeks AND if the patient has already been exposed to measles, the minimum dose should be given as soon as possible after exposure; OR
**ii.** In patients receiving SCIG every 2 weeks, one dose of a minimum of 400 mg per kg should be given, AND if the patient has already been exposed to measles, the minimum dose should be given as soon as possible after exposure.

**Initial Approval/Extended Approval.**
*Initial Approval:* Initial approval is for 6 months of therapy.
*Extended Approval:* Approve at additional 6-month intervals.

**Duration of Therapy in Hypogammaglobulinemia after Car-T infusion.** Continue to maintain IgG to prevent bacterial infections.

**Labs/Diagnostics.** Baseline IgG is required. Dose and interval are adjusted to maintain trough (pre-dose) IgG levels.

**Waste Management for All Indications.** Vials of SCIG are available in many sizes and concentrations. The dose should be calculated and the number of vials needed assessed.

## 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.[14,18,39,44] 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.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit 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.[6] HyQvia is indicated in adults. In one prospective, open-label Phase III clinical trial, eighty three patients aged 4 to 78 years with primary immunodeficiency received HyQvia.[6] Eleven of the patients were aged 2 to < 12 years, and seventy patients were aged ≥ 12 years).[45-46]

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

**Documentation Requirements:**

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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**FOR MEDICAL BENEFIT COVERAGE REQUESTS:**

***MMO Site of Care Medical Necessity Criteria:**

- Medications listed in this policy will be administered in a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met†:

    1. Age less than 21 years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

No initial doses are allowed in a hospital based outpatient facility without other above criteria being met.

†This criterion does not apply to Medicare or Medicare Advantage members.

**Prior approval is required for HCPCS Codes J1555, J1559, J1561, J1569, J1575**

| HCPCS Code(s): | |
|---|---|
| J1555 | Injection, immune globulin (Cuvitru), 100 mg |
| J1559 | Injection, immune globulin (Hizentra), 100 mg |
| J1561 | Injection, immune globulin, Gamunex/Gamunex-c/Gammaked), non-lyophilized (e.g. liquid), 500 mg |
| J1569 | Injection, immune globulin, (Gammagard liquid), intravenous, non-lyophilized, (e.g. liquid), 500 mg |
| J1575 | Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immunoglobulin |