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Title:	Immune globulin subcutaneous		
Approved By:	UM Pharmacy Subcommittee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Immune globulin subcutaneous: History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Dosing and duration requested -Weight -Age -Medication list (current and previous) -Prescribed by or in consultation with an allergist/immunologist, otolaryngologist, pulmonologist, infectious disease physician or other specialist, as indicated -Labs/diagnostics.

BACKGROUND

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] 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,Cuvitru, and Cutaquig are indicated as a subcutaneous (SC) infusion only, using an infusion pump.[4,45,48] 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. Cutaquig's dosing

interval can be from daily up to weekly.[48] 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.

Cutaquig 16.5% (0.165 g per mL), 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] and Cutaquig ≤ 600 mcg per mL (average).[48] Gammaked and Gamunex-C have the same manufacturer and are the same product but distributed under different names by different companies.[7]

Efficacy

Primary Humoral Immune Deficiency (PID)

Cuvitru, Gammagard Liquid, Gamunex-C, and Hizentra are indicated in children aged ≥ 2 years and adults when given by SC infusion.[1-4,7,45] Cutaquig and HyQvia are indicated in adults.[5,48] 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 and Cutaquig are indicated in patients who are switching from another SCIG product or from IVIG therapy.[5] 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.

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 (Cutaquig, Cuvitru, Gammagard liquid, Gammaked, Gamunex-C, Hizentra, and HyQvia). Coverage is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by an Express Scripts clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Extended approvals are allowed if the patient continues to meet the criteria and dosing.

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, select approvals require SCIG to be prescribed by or in consultation with a physician who specializes in the condition being treated.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

I. Coverage of Cutaquig, 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. 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] 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.

B) Patients Currently Receiving SCIG (Cutaquig, 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).

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, Hizentra, or Cutaquig:*

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 Cutaquig, 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] 1.30 for Cuvitru,[45] and 1.40 for Cutaquig. 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.* 1 year
- **ii.** *Extended Approval. 1 year*

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

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

Criteria. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial therapy (with SCIG): Approve if the patient meets BOTH of the following criteria (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 (Cutaquig, Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, and Hizentra): Approve 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).

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.

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

FDA-Approved Indications

1. Immunodeficiency, Primary Humoral (Treatment).

Criteria. 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] 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.

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]

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.

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.[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]

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

SPECIAL CONSIDERATIONS
None.

LIMITATIONS/EXCLUSIONS
Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON HEALTH PROGRAM	http://chpw.org/our-plans/apple-health/

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CFR	
WAC	WAC 284-43-2050
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Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
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03/09/2018	Reassigned from UM156 to PM139	Cindy Bush
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05/22/2018	Revised	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
04/15/2019	Revised	Jennifer Farley, PharmD
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