VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Subcutaneous (SCIG)

- Cutaquig® (immune globulin subcutaneous [human] 16.5% solution – Octapharma USA, Inc.)
- 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.)
- Xembify® (immune globulin subcutaneous [human] 20% solution – Grifols Therapeutics LLC)

TAC APPROVAL DATE: 7/31/2019

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.[1-5,7,12,13] 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).[1-5,7,12,13] 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.[4,6,13,29] 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, Cuvitru, Xembify, and Cutaquig are indicated as a SC infusion only, using an infusion pump.[4,7,12,13] 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, Cuvitru, or Xembify can be administered weekly or at more frequent intervals.[4,7,12] Cutaquig's dosing interval can be from daily up to weekly.[13] 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, Hizentra, and Xembify are indicated in children aged ≥ 2 years and adults when given by SC infusion.[1-4,7,12] HyQvia and Cutaquig are indicated in adults.[5,13] 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.[12] 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.[12] Hizentra, Cutaquig, and Xembify are indicated in patients who are switching from another SCIG product or from IVIG therapy.[4,7,13] 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.[5,14]

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]

A consensus document providing a definition of CVID was published in 2016.[26] 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.

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

FDA-Approved Indications

1. Primary Immunodeficiencies (PID). 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, 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 meets ONE of the following (a, b, or c):

NOTE: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) The patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) The patient has a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):
- **(1)** The patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
- **(2)** The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR
- **(3)** The patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency or a diagnosis of selective antibody deficiency (SAD) and meets the following (1 and 2):
- **(1)** The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
- **(2)** The patient has recurrent infections.

B) Patients Currently Receiving SCIG (Cutaquig, Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, and Xembify): Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product (e.g., increased IgG levels, preventing or controlling infections).

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, ii, and iii):
- 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; AND
- iii. Electrodiagnostic studies support the diagnosis of CIDP.

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 prescriber (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. Primary Immunodeficiencies (PID). 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 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 meets ONE of the following (a, b, or c):

  NOTE: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.
  - **a)** The patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndromes, an

IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) The patient has a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):
- **(1)** The patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
- **(2)** The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR
- **(3)** The patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency or a diagnosis of selective antibody deficiency (SAD) and meets the following (1 and 2):
- **(1)** The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
- **(2)** The patient has recurrent infections.

B) Patients Currently Receiving SCIG (HyQvia): Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product (e.g., increased IgG levels, preventing or controlling infections).

Safety of HyQvia has not been established in pediatric patients.[5] Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, and Xembify are indicated for primary humoral immunodeficiency in patients ≥ 2 years of age.[1-4,7,12] 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]

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] 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.[27,28]

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

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
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

Selected revision	Cutaquig was added to the policy with the same criteria that applies to the other products with the exception of HyQvia. Immunodeficiency, Primary Humoral (Treatment): For the unspecified hypogammaglobulinemia diagnosis in the criterion that requires that the patient has markedly impaired antibody response to protein testing with polysaccharide antigen (pneumococcus), the option of "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" was added.	01/16/2019
Annual revision	• Xembify was added to the policy with the same criteria that applies to the other products with the exception of HyQvia. • Immunodeficiency, Primary Humoral (Treatment) was updated to Primary Immunodeficiencies (PID). Criteria for PID was updated to the following: approval if (along with prescribing by a physician specialist) the patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndrome, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing. For a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia, approval if (along with prescribing physician specialist) the patients pretreatment IgG level is below the normal range AND either an impaired antibody response or recurrent infections. For a diagnosis of IgG subclass deficiency or selective antibody deficiency, approval if (along with prescribing physician specialist) the patient has an impaired antibody response and has recurrent infections. Criteria for patients currently receiving subcutaneous immune globulin for this diagnosis were updated to approve if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product. • Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP): the criterion, electrodiagnostic studies to support the diagnosis of CIDP, was added. Wording in reference to "determined by the prescribing physician" was changed to "determined by the prescriber."	07/31/2019

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.