VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Immune Globulin Subcutaneous Utilization Management Medical Policy

- Cutaquig® (immune globulin subcutaneous 16.5% solution – Octapharma)
- Cuvitru™ (immune globulin subcutaneous 20% solution – Baxalta)
- Gammagard Liquid (immune globulin infusion 10% solution – Baxalta)
- Gammaked™ (immune globulin injection 10% caprylate/chromatography purified – Kedrion Biopharma)
- Gamunex®-C (immune globulin injection 10% caprylate/chromatography purified – Grifols)
- Hizentra® (immune globulin subcutaneous 20% liquid – CSL Behring)
- HyQvia (immune globulin infusion 10% with recombinant human hyaluronidase – Baxalta)
- Xembify® (immune globulin subcutaneous 20% solution – Grifols)

REVIEW DATE: 9/15/2021; selected revision 10/13/2021

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. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy,** for maintenance therapy in adults.[4]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-5,7-9] 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.[2-4,6,9]

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only.[4,7-9] 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 recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion.[5] The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the IG. HyQvia has a Limitation of Use that the safety and efficacy of chronic use of recombinant human hyaluronidase in HyQvia have not been established in conditions other than PID. The safety of HyQvia has also not been established in children.[5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of SCIG products. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. 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.

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

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

A) Initial Therapy. Approve if the patient meets BOTH of the following (i and ii):

i. 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) 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, 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) Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):

(1) 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) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR

(3) Patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following (1 and 2):

(1) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND

(2) Patient has recurrent infections; AND

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

B) Patient is Currently Receiving Immune Globulin. Approve if the patient has been diagnosed with a primary immunodeficiency and, according to the prescriber, the patient is continuing to receive benefit from the product.

Note: Examples of continued benefit with the product includes increased IgG levels or, prevention and/or controlling of infections.

Dosing. Approve the following dosing regimens (A, B, C, D, or E):

A) The patient is transitioning from immune globulin intravenous (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; OR

B) The patient is transitioning from another immune globulin subcutaneous (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; OR

C) The patient is initiating SCIG therapy without previous IVIG or SCIG therapy and is receiving a loading dose (e.g., 100 mg/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, as determined by the prescriber; OR
E) For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

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2. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy . Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Electrodiagnostic studies support the diagnosis of CIDP; AND
iii. The medication has been prescribed by or in consultation with a neurologist.
B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurological symptoms as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved for stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

Dosing. Approve the following dosing regimens (A or B):
A) The dose is either 0.2 g/kg or 0.4 g/kg per week administered in one or two sessions over 1 or 2 consecutive days; OR
B) The dose and interval between doses has been titrated and adjusted based on clinical response as determined by the prescriber.

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

FDA-Approved Indications

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1. Primary Immunodeficiencies. Approve for 1 year if the patient meets the ONE of the following (A or B):
A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. 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) 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, 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) Patient has a diagnosis of common variable immunodeficiency, unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):
(1) 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) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR
(3) Patient has recurrent infections; OR

c) Patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following (1 and 2):
(1) Patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
(2) Patient has recurrent infections; AND

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

B) Patient is Currently Receiving Immune Globulin. Approve if the patient meets BOTH of the following (i and ii):
i. Patient is ≥ 18 years of age; AND
ii. Patient has been diagnosed with a primary immunodeficiency and, according to the prescriber, is continuing to receive benefit from the product.
Note: Examples of receiving benefit with the product includes increased IgG levels or, prevention and/or controlling of infections.

Dosing. Approve the following dosing regimens for HyQvia (A, B, or C):

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 immune globulin intravenous (IVIG) or from another SCIG product OR the patient may be naïve to immune globulin 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, or iii):
i. The dose is 300 mg/kg 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 as determine by the prescribing physician.

C) For a patient with primary immune deficiency and exposure to measles (previous exposure or risk of future measles exposure), the minimum dose has been determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin subcutaneous is not recommended in the following situations:

1. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of immune globulin.[15,24] 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. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gammagard Liquid 10% [prescribing information]. Lexington, MA: Baxalta US; March 2021.
2. Gammaked™ 10% injection [prescribing information]. Fort Lee, NJ: Kedrion Biopharma, Inc.; January 2020.
3. Gamunex®-C 10% liquid [prescribing information]. Research Triangle Park, NC: Grifols USA, LLC; January 2020.
4. Hizentra® for subcutaneous infusion [prescribing information]. Kankakee, IL: CSL Behring LLC; April 2021.
5. HyQvia immune globulin infusion 10% with recombinant human hyaluronidase [prescribing information]. Lexington, MA: Baxalta US Inc.; March 2021.
6. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62:1-34.
7. Xembify 20% solution [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics LLC; August 202019.
8. Cuvitru subcutaneous 20% solution [prescribing information]. Lexington, MA: Baxalta US Inc.; March 2021.
9. Cutaquig 16.5% solution [prescribing information]. Paramus, NJ: Octapharma USA, Inc.; July 2020.
10. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. Available at: http://www.jacionline.org/article/S0091-6749(16)31141-1/pdf. Accessed on August 9, 2021.
11. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015;136:1186-1205.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Primary Immunodeficiencies (PID)**: In Initial Therapy, the wording of "or another confirmed primary immunodeficiency" was added. For Continuation Therapy, the examples of benefits from the product were moved to a Note and the wording "according to the prescriber" was added. In **Dosing**, the examples of clinical response were removed. In Dosing related to patients with primary immunodeficiency and exposure to measles, the wording of "previous exposure or risk of future measles exposure" was added. The specific measles dosing regimens were removed and the wording that the minimum dose has been determined by the prescriber was added. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy**: For Continuation Therapy, moved examples of a clinically significant improvement to a note. Removed a neurologist or in consultation with a neurologist for continuation criteria. Dosing criteria- added the wording "and interval between doses" has been titrated "and adjusted based on clinical response as determined by the prescriber". **Removed the following condition not recommended for approval**: HyQvia in Patients < 18 years of Age. Age is already addressed in the HyQvia criteria.	08/19/2020
Selected Revision	For continuation criteria, removed the wording "subcutaneous."	09/02/2020
Annual Revision	**Primary Immunodeficiencies:** The prescriber's specialty of allergist/immunologist was updated to allergist (immunologist is listed separately). Reworded continuation of treatment criteria to match the wording in other policies with similar criteria. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy:** The initial approval duration was changed to 3 months (previously was 1 year) to align with other policies with similar criteria. **HyQvia:** Dosing was added for patients with primary immune deficiency and exposure to measles.	09/15/2021
Selected Revision	HyQvia: Patients ≥ 18 years of age was added to the continuation criteria.	10/13/2021