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5.20.008

Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Biologicals	**Original Policy Date:**	October 21, 2016
Subject:	SCIG	**Page:**	1 of 7

Last Review Date: March 8, 2024

SCIG Immune Globulin (subcutaneous immunoglobulin)

Description

SCIG Immune Globulin – Cutaquig, Cuvitru, Hizentra, Hyqvia, Xembify

Background
Human immune globulin therapy is used for the treatment of immunodeficiency, prophylaxis of infectious diseases, and in the management of a variety of other inflammatory and autoimmune disorders. There are two main routes of administration: intravenous (IV) and subcutaneous (SC). A third route is intramuscular (IM), although this is uncommonly used, except for hyper-immune globulins (e.g., rabies immune globulin). There are also three different methods of administering immune globulin subcutaneously: traditional, facilitated subcutaneous, and subcutaneous rapid-push. Immune globulin products from human plasma were first used in 1952 to treat immune deficiency. Subcutaneous immunoglobulin (SCIG) contains the pooled immunoglobulin G (IgG) immunoglobulins from the plasma of approximately a thousand or more blood donors (1).

Regulatory Status
FDA-approved indications:
Cutaquig, Cuvitru, Hizentra, and Xembify are indicated as replacement therapies for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (2-5).

Hizentra is also indicated for maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (3).

Hyqvia is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients two years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (6).

Limitations of Use:
Safety and efficacy of chronic use of recombinant human hyaluronidase in Hyqvia have not been established in conditions other than PI (6).

Immune globulin use is associated with increased risk of thrombosis, particularly in the elderly and patients with risk factors such as cardiovascular disease, hypercoagulopathy, those on estrogen therapy, and patients with central venous catheters. Patients should be monitored carefully for signs and symptoms of thrombosis (2-6).

Immune globulin products have also been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs (2-6).

Other potential complications to monitor include the following: (2-6)

Immunoglobulin A deficiency: People with this condition have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

Aseptic meningitis syndrome (AMS): Rare occurrences of AMS have been reported in association with immune globulin treatment. AMS usually begins within several hours to 2 days following immune globulin treatment and is characterized by symptoms including severe headache, drowsiness, fever, photophobia, painful eye movements, muscle rigidity, nausea, and vomiting. AMS may occur more frequently in association with high-dose (2 g/kg) immune globulin treatment. Discontinuation of immune globulin treatment has resulted in remission of AMS within several days without sequelae.

Bleeding complications: Bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

Severe reactions: Severe reactions, such as anaphylaxis or angioneurotic edema, have been reported in association with immune globulin immunoglobulins, even in patients not known to be sensitive to human immunoglobulins or blood products.

Related policies

Atgam, GamaSTAN, IVIG

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

SCIG may be considered **medically necessary** if the conditions indicated below are met.

SCIG may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age

2 years of age and older for **Cutaquig, Cuvitru, Hizentra** (PID), **Hyqvia,** and **Xembify**
18 years of age and older for **Hizentra** (CIDP)

Diagnoses

Patient must have **ONE** of the following:

1. Primary Immunodeficiency Disease (PID) with **ONE** of the following:
    a. Hypogammaglobulinemia, IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency with **ALL** of the following:
        i. Documented history of recurrent bacterial and viral infections
        ii. Impaired antibody response to pneumococcal vaccine
        iii. **ONE** of the following pre-treatment laboratory findings:
            1) Hypogammaglobulinemia: IgG < 500 mg/dL or ≥ 2 SD below the mean age
            2) Selective IgA deficiency: IgA level < 7 mg/dL with normal IgG and IgM levels
            3) Selective IgM deficiency: IgM level < 30 mg/dL with normal IgG and IgA levels
            4) IgG subclass deficiency: IgG1, IgG2, or IgG3 ≥ 2 SD below the mean age assessed on at least 2 occasions; normal IgG (total) and IgM levels, normal/ low IgA levels

5) Specific antibody deficiency: normal IgG, IgA and IgM levels

b. SCID (severe combined immunodeficiency disease) or agammaglobulinemia with **ONE** of the following
   i. Confirmed diagnosis by genetic or molecular testing
   ii. Pretreatment IgG level <200mg/dL
   iii. Absence or very low number of T cells (CD3 T cells< 300/microliter) or presence of maternal T cells in the circulation (SCID only)

c. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non SCID combined immunodeficiency) with **ALL** of the following:
   i. Confirmed diagnosis by genetic or molecular testing
   ii. Documented history of recurrent bacterial and viral infections
   iii. Impaired antibody response to pneumococcal vaccine

d. CVID (common variable immunodeficiency disease) with **ALL** of the following:
   i. Documented history of recurrent bacterial and viral infections
   ii. Impaired antibody response to pneumococcal vaccine
   iii. Other causes of immune deficiency have been excluded (eg, drug induced, genetic disorders, infectious diseases such as HIV, malignancy)
   iv. Pretreatment IgG level < 500mg/dL or ≥ 2 SD below the mean for the age

Hizentra **ONLY**

2. Chronic inflammatory demyelinating polyneuropathy (CIDP)
   a. 18 years of age or older
   b. Previous treatment with immunoglobulin therapy (IVIG)
   c. Prescriber agrees to initiate Hizentra one week after the last infusion of IVIG
   d. Patient had significant improvement in disability and has maintained improvement while on previous immunoglobulin therapy (IVIG)

AND ALL of the following for **ALL** indications:
a. Patients or caregivers have been instructed on how to monitor for signs and symptoms of thrombosis when self-administering the medication
b. **NO** dual therapy with other immune globulin medications

Prior – Approval *Renewal* Requirements

Age

2 years of age and older for **Cutaquig, Cuvitru, Hizentra** (PID), **Hyqvia,** and **Xembify**
18 years of age and older for **Hizentra** (CIDP)

Diagnoses

Patient must have **ONE** of the following:

1. Primary Immunodeficiency Disease (PID)
    a. Patient has **ONE** of the following:
        i. Hypogammaglobulinemia, IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency
        ii. SCID (severe combined immunodeficiency disease) or Agammaglobulinemia
        iii. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non SCID combined immunodeficiency)
        iv. CVID (common variable Immunodeficiency disease)

AND ALL of the following:

a. Documented reduction in frequency of bacterial and viral infections since initiation
b. IgG trough levels are monitored at least yearly and maintained at or above the lower range of normal for age
c. The prescriber will re-evaluate the dose of the SCIG and reconsider a dose adjustment
d. Patients or caregivers have been instructed on how to monitor for signs and symptoms of thrombosis when self-administering the medication
e. **NO** dual therapy with other immune globulin medications

Hizentra **ONLY**

2. Chronic inflammatory demyelinating polyneuropathy (CIDP)
    a. 18 years of age and older
    b. CIDP symptoms have remained stable or improved since changing from previous immunoglobulin therapy (intravenous immunoglobulin)
    c. The prescriber will re-evaluate the dose of the SCIG and reconsider a dose adjustment
    d. Patients or caregivers have been instructed on how to monitor for signs and

symptoms of thrombosis when self-administering the medication

e. **NO** dual therapy with other immune globulin medications

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Human immune globulin therapy is used for the treatment of immunodeficiency, prophylaxis of infectious diseases, and in the management of a variety of other inflammatory and autoimmune disorders. Cutaquig, Cuvitru, Hizentra, and Xembify are subcutaneous immunoglobulin (SCIG) indicated as replacement therapies for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older. Hizentra is also indicated for maintenance therapy in adults with chronic inflammatory demyelinating polyneuropathy (CIDP). Hyqvia is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients two years of age and older (1-6).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use SCIG while maintaining optimal therapeutic outcomes.

References

1. UpToDate. Subcutaneous and intramuscular immune globulin therapy. Accessed on January 31, 2024.
2. Cuvitru [package insert]. Lexington, MA: Baxalta US Inc.; September 2021.
3. Hizentra [package insert]. Kankakee, IL: CSL Behring LLC; April 2021.
4. Xembify [package insert]. Research Triangle Park, NC: Grifols Therapeutics LLC; August 2020.
5. Cutaquig [package insert]. Hoboken, NJ: Octapharma USA, Inc.; November 2021.

6. HyQvia [package insert]. Lexington, MA: Takeda Pharmaceuticals USA, Inc.; April 2023.

Policy History

Date	Action
October 2016	Addition of Cuvitru to PA and the addition of Hyqvia and Hizentra to this PA
December 2016	Annual review
March 2017	Annual review
December 2017	Annual editorial review and reference update Addition of no dual therapy to criteria
April 2018	Addition of the diagnosis of CIDP to addition and continuation criteria for Hizentra only
June 2018	Annual review and reference update
November 2018	Annual review and reference update
March 2019	Annual editorial review and reference update. Updated CVID requirements per SME
June 2019	Addition of Cutaquig
September 2019	Annual review. Added references for PID diagnostic criteria per SME
October 2019	Addition of Xembify
December 2019	Annual review
March 2020	Annual review and reference update. Gammagard, Gamunex-C, and Gammaked to be kept on IVIG policy only per FEP
June 2020	Annual review
May 2021	Removal of the following CIDP renewal requirements: reduction of infections since initiation of therapy, and chronically stable patients having to taper and or withdraw treatment to determine if continued therapy is necessary
September 2021	Annual review
April 2022	Decreased age requirement for Cutaquig from 18 and older to 2 and older per PI update
June 2022	Annual review and reference update
March 2023	Annual review and reference update. Changed policy number to 5.20.008
August 2023	Per PI update, decreased age requirement for Hyqvia to 2 and older
December 2023	Annual review and reference update
March 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.