Medical Pharmacy Drug Prior Authorization Criteria

Drug Trade Name:	See Below	**Drug Generic Name:**	Subcutaneous Immune Globulins (immunoglobulin)
J Code:	See Below	**1 billable unit =**	see brand-specific information table
Original Date of Review:	12/7/2022	**Last Reviewed:**	3/13/2024
Revision Date History	12/7/2022, 3/13/2024		

Drug Trade Name (J Code); Subcutaneous*: Hizentra (J1559), Gammagard Liquid (J1569), Gamunex-C (J1561), Gammaked (J1561), HyQvia (J1575), Cuvitru (J1555), Cutaquig (J1551), Xembify (J1558)

*Intravenous immune globulin criteria listed separately

Immune globulin supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Immune globulin also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanism of action of IgG have not been fully elucidated.

Criteria:

Length of authorization:

- Initial Authorization: 6 months
- Renewal Authorizations: 12 months

Age: see below for product specific requirements

Diagnoses:

- Primary immunodeficiency (PID)/Wiskott -Aldrich syndrome
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [Hizentra ONLY]
- Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia

Quantity Limit:

Drug Name	Dose/ week	Dose/28 days
Hizentra	46 g	184 g
Gamunex-C & Gammaked	24 g	96 g
Gammagard liquid	24 g	96 g
HyQvia	17.5 g	69 g
Cuvitru	23 g	92 g
Cutaquig	24 g	96 g
Xembify	24 g	96 g

Maximum Units:

Drug Name	Billable units/28 days
Hizentra	960 (PID)
	1840 (CIDP)
Gamunex-C & Gammaked	192
Gammagard liquid	192
HyQvia	690
Cuvitru	920
Cutaquig	960
Xembify	960

Initial Approval Criteria

- **Universal Criteria**
  - Baseline values for BUN and serum creatinine obtained within 30 days of request; **AND**

- **Indication Specific Criteria**

Primary immunodeficiency (PID)/Wiskott -Aldrich syndrome

Such as: x-linked agammaglobulinemia, common variable immunodeficiency, transient hypogammaglobulinemia of infancy, IgG subclass deficiency with or without IgA deficiency, antibody deficiency with near normal immunoglobulin levels) and combined deficiencies (severe combined immunodeficiencies, ataxia-telangiectasia, x-linked lymphoproliferative syndrome) [listnot all inclusive]

- Patient is ≥ 2 years old [HyQvia ONLY: patient must be ≥ 18 years old]; **AND**
- Patient's IgG level is <200 mg/dL **OR** both of the following:
  - Patient has a history of multiple hard to treat infections as indicated by at least **one** of thefollowing:
    - Four or more ear infections within 1 year
    - Two or more serious sinus infections within 1 year
    - Two or more months of antibiotics with little effect
    - Two or more pneumonias within 1 year
    - Recurrent or deep skin abscesses
    - Need for intravenous antibiotics to clear infections
    - Two or more deep-seated infections including septicemia; **AND**
  - The patient has a deficiency in producing antibodies in response to vaccination; **AND**
    - Titers were drawn before challenging with vaccination; **AND**
    - Titers were drawn between 4 and 8 weeks of vaccination

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [Hizentra ONLY]

- Patient must be ≥ 18 years old; **AND**
- Physician has assessed baseline disease severity utilizing an objective measure/tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin,etc.); **AND**
  - Used as initial maintenance therapy for prevention of disease relapses after treatment andstabilization with intravenous immunoglobulin (IVIG); **OR**
  - Used for re-initiation of maintenance therapy after experiencing a relapse and requiring re-induction therapy with IVIG (see renewal criteria)

Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia

- Patient's IgG level is <200 mg/dL **OR** both of the following:
- Patient has a history of multiple hard to treat infections as indicated by at least **one** of the following:
  - Four or more ear infections within 1 year
  - Two or more serious sinus infections within 1 year
  - Two or more months of antibiotics with little effect
  - Two or more pneumonias within 1 year
  - Recurrent or deep skin abscesses
  - Need for intravenous antibiotics to clear infections
  - Two or more deep-seated infections including septicemia; **AND**
- The patient has a deficiency in producing antibodies in response to vaccination; **AND**
  - Titers were drawn before challenging with vaccination; **AND**
  - Titers were drawn between 4 and 8 weeks of vaccination

Note: other secondary immunodeficiencies resulting in hypogammaglobulinemia and/or B-cellaplasia will be evaluated on a case-by-case basis

Renewal Criteria

Coverage can be renewed for 1 year based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include:severe hypersensitivity/anaphylaxis, thrombosis, aseptic meningitis syndrome, hemolytic anemia, hyperproteinemia, acute lung injury, etc.; **AND**
- BUN and serum creatinine obtained within the last 6 months and the concentration and rate ofinfusion have been adjusted accordingly; **AND**

Primary immunodeficiency (PID)/Wiskott -Aldrich syndrome

- Disease response as evidenced by one or more of the following:
  - Decrease in the frequency of infection
  - Decrease in the severity of infection

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [Hizentra ONLY]

- Renewals will be authorized for patients that have demonstrated a beneficial clinical responseto maintenance therapy, without relapses, based on an objective clinical measuring tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin,etc.); **OR**
- Patient is re-initiating maintenance therapy after experiencing a relapse while on Hizentra; **AND**
  - Patient improved and stabilized on IVIG treatment: **AND**
  - Patient was NOT receiving maximum dosing of Hizentra prior to relapse

Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia

- Disease response as evidenced by one or more of the following:
  - Decrease in the frequency of infection
  - Decrease in the severity of infection; **AND**
- Patient is at a decreased risk of infection as a result of treatment necessitating continuedtherapy

Dosage/Administration

- Dosing information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.

- **Dose Calculations:**

  Dosing should be calculated using adjusted body weight if one or more of the following criteria aremet:

  - Patient's body mass index (BMI) is 30 kg/m^2 or more; **OR**
  - Patient's actual body weight is 20% higher than his or her ideal body weight (IBW)
  - Calculate the adjusted body weight using the following formulas.

Dosing Formulas
BMI = 703 x (weight in pounds/height in inches^2)
IBW (kg) for males = 50 + [2.3 (height in inches – 60)]
IBW (kg) for females = 45.5 + [2.3 x (height in inches – 60)]
Adjusted body weight = IBW + 0.5 (actual body weight – IBW)

Subcutanous Immune Globulins	
Indication	**Dose**
Chronic Inflammatory Demyelinating Polyneuropathy	**Hizentra ONLY:** ▪ Initiate therapy 1 week after the last IVIG dose ▪ The recommended subcutaneous dose is

	0.2 g/kg (1 mL/kg) body weight per week,administered in 1 or 2 sessions over 1 or 2 consecutive days. ▪ If CIDP symptoms worsen, consider increasing the dose to 0.4 g/kg (2 mL/kg) bodyweight per week, administered in 2 sessions over 1 or 2 consecutive days. If CIDP symptoms worsen on the 0.4 g/kg body weight per week dose, consider re-initiating therapy with an IVIG while discontinuing Hizentra.
Primary immune deficiency including Wiskott-Aldrich Syndrome AND Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia	**Hizentra:** ▪ Switching from IVIG o Initiate therapy 1 week after the last IVIG dose o Weekly dose: 1.37*(previous IVIG dose (g)/number of weeks between IVIGdoses) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: twice the weekly dose (using calculation above) o Frequent dosing (2-7 times per week): divide the calculated weekly dose by thedesired number of times per week ▪ Switching from SCIG o Initiate therapy 1 week after the last SCIG dose o Weekly dose (in grams) should be same as the weekly dose of prior SCIGtreatment (in grams) o Biweekly dose: multiply the calculated weekly dose by 2 Frequent dosing (2-7 times per week): divide the calculated weekly dose by thedesired number of times per week
Primary immune deficiency including Wiskott-Aldrich Syndrome AND	**Gamunex-C/Gammaked/Gammagard Liquid:** ▪ Initiate therapy 1 week after the last IVIG dose Weekly dose: 1.37*(previous IVIG dose(g)/number of weeks between IVIG doses)
	HyQvia: ▪ Naïve to IgG or switching from SCIG: 300

Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia	to 600 mg/kg at 3 to 4 week intervals after initial ramp-up* ▪ Switching from IGIV: use the same dose and frequency as the previous IV treatment after initial ramp-up* ***NOTE:*** *For patients previously on another IgG treatment, initiate therapy 1 week after the last infusion of IVIG or SCIG*
	<u>Xembify:</u> ▪ Switching from IVIG o Start treatment one week after the last IVIG infusion. o Weekly dose: 1.37*(previous monthly (or every 3- week) IVIG dose ingrams)/number of weeks between IVIG doses) ▪ Switching from SCIG Weekly dose (in grams) should be same as the weekly dose of prior SCIGtreatment (in grams)
Primary immune deficiency including Wiskott-Aldrich Syndrome AND	**<u>Cuvitru:</u>** ▪ Switching from IVIG or HyQvia o Initiate therapy 1 week after the last IVIG or Hyqvia dose o Weekly dose: 1.30*(previous IVIG or HyQvia dose (g)/number of weeksbetween IVIG or HyQvia doses) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: twice the weekly dose (using calculation above) o Frequent dosing (2-7 times per week): divide the calculated weekly dose by thedesired number of times per week ▪ Switching from SCIG o Weekly dose (in grams) should be same as the weekly dose of prior SCIGtreatment (in grams) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: multiply the calculated weekly dose by 2 o Frequent dosing (2-7 times per week): divide the calculated weekly dose by thedesired number of times per week

Acquired Immune Deficiency secondary to Chronic Lymphocytic Leukemia	**<u>Cutaquig</u>:** ***NOTE:*** *Start treatment one week after the last IVIG or SCIG infusion. Ensure that patients have received IVIG or SCIG treatment at regular intervals for at least 3 months* ▪ Switching from IVIG o Weekly dose: 1.30*(previous IVIG dose (g)/number of weeks between IVIGdoses) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: multiply the calculated weekly dose by 2 o Frequent dosing (2-7 times per week): divide the calculated weekly dose by thedesired number of times per week ▪ Switching from SCIG o Weekly dose (in grams) should be same as the weekly dose of prior SCIGtreatment (in grams) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: multiply the calculated weekly dose by 2 o Frequent dosing (2-7 times per week): divide the calculated weekly dose by thedesired number of times per week

Brand-Specific Information (Subcutaneous)						
Drug Name	**Manufacturer**	**HCPCS Code**	**1 Billable unit**	**NDC**	**IgG Grams perVial**	**Volume (mL)**
Hizentra 20% (Vials)	CSL BehringAG	J1559 – Injection, immuneglobulin (Hizentra), 100 mg	100 mg	44206-0451-01	1	5
				44206-0452-02	2	10
				44206-0454-04	4	20
				44206-0455-10	10	50
Hizentra 20% (Prefilled Syringes)	CSL BehringAG	J1559 – Injection, immuneglobulin (Hizentra), 100 mg	100 mg	44206-0456-21	1	5
				44206-0457-22	2	10
				44206-0458-24	4	20
Gammaked 10%	Grifols Therapeutics	J1561 – Injection, immune globulin, (Gamunex-C/ Gammaked), non-lyophilized (e.g., liquid), 500mg	500 mg	76125-0900-01	1	10
				76125-0900-25	2.5	25
				76125-0900-50	5	50
				76125-0900-10	10	100
				76125-0900-20	20	200
Gamunex-C 10%	Grifols Therapeutics	J1561 – Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500mg	500 mg	13533-0800-12	1	10
				13533-0800-15	2.5	25
				13533-0800-20	5	50
				13533-0800-71	10	100
				13533-0800-24	20	200
				13533-0800-40	40	400
Gammagard Liquid 10%	Baxalta US Inc.	J1569 – Injection, immuneglobulin, (Gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg	500 mg	00944-2700-02	1	10
				00944-2700-03	2.5	25
				00944-2700-04	5	50
				00944-2700-05	10	100
				00944-2700-06	20	200
				00944-2700-07	30	300
HyQvia 10%(with Recombinant Human Hyaluronidase 160 U/mL)	Baxalta US Inc.	J1575 – Injection, immuneglobulin/ hyaluronidase, (Hyqvia), 100 mg immune globulin	100 mg	00944-2510-02	2.5	25
				00944-2511-02	5	50
				00944-2512-02	10	100
				00944-2513-02	20	200
				00944-2514-02	30	300

Brand-Specific Information (Subcutaneous)						
Drug Name	**Manufacturer**	**HCPCS Code**	**1 Billable unit**	**NDC**	**IgG Grams per Vial**	**Volume (mL)**
Cuvitru 20%	Baxalta US Inc.	J1555 – Injection, immuneglobulin (Cuvitru), 100 mg	100 mg	00944-2850-01	1	5
				00944-2850-03	2	10
				00944-2850-05	4	20
				00944-2850-07	8	40
				00944-2850-09	10	50
Cutaquig 16.5%	Octapharma	J1551 – Injection, immune globulin (cutaquig), 100 mg *(Effective 07/01/2022)*	100 mg	00069-1061-01	1	6
				00069-1802-01	1.65	10
				00069-1476-01	2	12
				00069-1960-01	3.3	20
Xembify 20%	Grifols	J1558 – Injection, immuneglobulin (Xembify), 100 mg	100 mg	13533-0810-05	1	5
				13533-0810-10	2	10
				13533-0810-20	4	20
				13533-0810-50	10	50
Immune Globulin, Human, Subcutaneous	N/A	J3590 – unclassified biologics C9399 – unclassified drugsor biologicals	N/A	N/A	N/A	N/A

References:

1. Xembify [package insert]. Research Triangle Park, NC; Grifols Therapeutics, LLC; August 2020. Accessed September 2021.
2. Cutaquig [package insert]. Vienna, Austria; Octapharma; October 2021. Accessed October 2021.
3. Hizentra [package insert]. Bern, Switzerland; CSL Behring AG; April 2021. Accessed September 2021.
4. HyQvia [package insert]. Lexington, MA; Baxalta US Inc.; March 2021. Accessed September 2021.
5. Cuvitru [package insert]. Lexington, MA; Baxalta US Inc.; September 2021. Accessed September 2021.
6. Gammagard Liquid [package insert]. Lexington, MA; Baxalta US Inc.; March 2021. Accessed September 2021.
7. Gamunex®-C [package insert]. Research Triangle Park, NC; Grifols Therapeutics, LLC; January 2020. Accessed September 2021.

8. Gammaked [package insert]. Research Triangle Park, NC; Grifols Therapeutics, LLC; January 2020. Accessed September 2021.
9. Jeffrey Modell Foundation Medical Advisory Board, 2013. 10 Warning Signs of Primary Immunodeficiency. Jeffrey Modell Foundation, New York, NY
10. Orange J, Hossny E, Weiler C, et al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117(4 Suppl): S525-53.
11. Orange JS, Ballow M, Stiehm, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol Vol 130 (3).
12. Bonilla FA, Khan DA, Ballas ZK, et al. Practice Parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015 Nov;136(5):1186-205.e1-78.
13. Emerson GG, Herndon CN, Sreih AG. Thrombotic complications after intravenous immunoglobulin therapy in two patients. Pharmacotherapy. 2002;22:1638-1641.
14. Department of Health (London). Clinical Guidelines for Immunoglobulin Use: Update to Second Edition. August, 2011.
15. Provan, Drew, et al. "Clinical guidelines for immunoglobulin use." Department of Health Publication, London (2008).
16. Dantal J. Intravenous Immunoglobulins: In-Depth Review of Excipients and Acute Kidney Injury Risk. Am J Nephrol 2013;38:275-284.
17. Immune Deficiency Foundation. Diagnostic & Clinical Care Guidelines for Primary Immunodeficiency Diseases. 3rd Ed. 2015. Available at:https://primaryimmune.org/sites/default/files/publications/2015-Diagnostic-and-Clinical-Care- Guidelines-for-PI_1.pdf.
18. 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 Mar;139(3S):S1-S46.
19. Alonso W, Vandeberg P, Lang J, et al. Immune globulin subcutaneous, human 20% solution (Xembify®), a new high concentration immunoglobulin product for subcutaneous administration. Biologicals. 2020;64:34-40.
20. Kobayashi RH, Gupta S, Melamed I, et al. Clinical Efficacy, Safety and Tolerability of a New Subcutaneous Immunoglobulin 16.5% (octanorm [cutaquig®]) in the Treatment of Patients with Primary Immunodeficiencies. Front Immunol. February 2019 | Volume 10 | Article 40.
21. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (CIDP), a multicenter randomised double-blind placebo-controlled trial: the PATH Study. Lancet Neurol. 2017;17(1):35-46.
22. Hagan JB, Fasano MB, Spector S, et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol. 2010;30(5):734-745.
23. Jolles S, Borte M, Nelson R, et al. Long-term efficacy, safety, and tolerability of Hizentra for treatment of primary immunodeficiency disease. Clin Immunol. 2014;150(2):161-169.
24. Wasserman RL, Melamed I, Nelson RP Jr, et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin Pharmacokinet. 2011;50(6):405-414.
25. Wasserman RL, Melamed I, Kobrynski L, et al. Efficacy, Safety, and Pharmacokinetics of a 10% Liquid Immune Globulin Preparation (GAMMAGARD LIQUID, 10%) Administered Subcutaneously in Subjects with Primary Immunodeficiency Disease. J Clin Immunol. 2011 Mar 22. [Epub ahead of print]

26. Food and Drug Administration. Safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency. https://www.fda.gov/regulatory-information/search-fda-guidance- documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human. Accessed May 28, 2019
27. Wasserman RL, Melamed I, Stein MR, et al; and IGSC, 10% with rHuPH20 Study Group. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J Allergy Clin Immunol. 2012;130(4):951-957.
28. Suez D, Stein M, Gupta S, et al. Efficacy, safety, and pharmacokinetics of a novel human immune globulin subcutaneous, 20% in patients with primary immunodeficiency diseases in North America. J Clin Immunol. 2016;36(7):700-712.
29. Roifman CM, Schroeder H, Berger M, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency: a randomized double-blind trial. Int Immunopharmacol. 2003;3(9):1325-1333.
30. Roifman CM, Schroeder H, Berger M, et al, and the IGIV-C in PID Study Group. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency: a randomized double-blind trial. Int Immunopharmacol. 2003;3:1325-1333.
31. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2022. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2021.
32. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol 1994 Sep;88(1):209- 12. doi: 10.1111/j.1365-2141.1994.tb05002.x.

Appendix 1 – Covered Diagnosis Codes (All Products)

ICD-10	ICD-10 Description
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.2	Selective deficiency of immunoglobulin A [IgA]
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.7	Transient hypogammaglobulinemia of infancy
D80.8	Other immunodeficiencies with predominantly antibody defects
D80.9	Immunodeficiency with predominantly antibody defects, unspecified
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
D84.9	Immunodeficiency, unspecified

Appendix 2 – Covered Diagnosis Codes (Hizentra ONLY)

ICD-10	ICD-10 Description
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.89	Other inflammatory polyneuropathies
G62.89	Other specified polyneuropathies