Neighborhood Health Plan OF RHODE ISLAND™
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SCIG (immune globulin SC): Hizentra®, Gammagard Liquid®, Gamunex®-C, Gammaked®, Hyqvia®, Cuvitru®, Cutaquig®, Xembify®
(Subcutaneous)

Effective Date: 01/01/2020
Review Date: 10/02/2019, 1/3/2019, 1/15/2020, 6/22/2020, 6/24/2021, 5/5/2022, 3/2/2023, 6/29/2023, 12/21/2023, 01/10/2024, 09/04/2024

Scope: Medicaid*, Commercial, Medicare-Medicaid Plan (MMP)

***(Medication only available on the Medical Benefit.)**

I. Length of Authorization

Initial coverage will be provided for 6 months and may be renewed annually thereafter.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

Drug Name	Dose/ week	Dose/28 days
Hizentra	46 g	184 g
Gamunex-C & Gammaked	42 g	168 g
Gammagard liquid	42 g	168 g
HyQvia	40 g	160 g
Cuvitru & Cutaquig	40 g	160 g
Xembify	42 g	168 g

B. Max Units (per dose and over time) [HCPCS Unit]:

Drug Name	Billable units/28 days
Hizentra	1680 (PID)
	1840 (CIDP)
Gamunex-C, Gammaked,	336
Gammagard liquid	336
HyQvia	1200
Cuvitru & Cutaquig	1600
Xembify	1680

III. Summary of Evidence

Subcutaneous Immunoglobulin (SCIG) is indicated for the treatment of primary humoral immunodeficiency (PI). Prospective, open-label, single-arm, multi-center clinical studies have been conducted to determine the efficacy of subcutaneous infusion of IVIG in subjects with PI. The annual rate of serious bacterial infections (SBIs) was the primary endpoint across the clinical studies. The results of the clinical trials conducted on SCIQ are as follows: the annual rate of acute serious bacterial infections while on Gammagard Liquid subcutaneous treatment was 0.067, with an upper 99% confidence limit of 0.133, which is lower than the minimal goal of achieving a rate of <1 bacterial infection per patient-year. No subjects experienced an SBI in the study conducted on Hizentra (upper 99% confidence limit: 0.132). The rate of serious bacterial infections (SBIs) was 0.05 events per subject-year (1 event in 20 subject-years) (upper 99% confidence limit: 0.11) during Xembify treatment. The most common adverse reactions observed are local infusion site reactions, headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, upper respiratory tract infection, rash, pruritus, vomiting, abdominal pain (upper), migraine, arthralgia, pain, fall and nasopharyngitis.

IV. Initial Approval Criteria

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

If requesting non preferred subcutaneous immune globulin formulations, such as Cuvitru, Cutaquig, Xembify, Hizentra or Hyqvia, the patient must have failure or intolerance to the following preferred formulations: Gammaked/Gamunex-C or Gammagard liquid (for patients that are currently on treatment with Cuvitru, Cutaquig, Xembify, Hizentra or Hyqvia, they can remain on treatment)

Coverage is provided in the following conditions:

Primary Immunodeficiency (PID) †

Such as: Wiskott -Aldrich syndrome, 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) [**list not all inclusive**]

- Patient is at least 2 years of age; **AND**
- Patient has an IgG level <200 mg/dL **OR**
- Patient meets **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, deep skin or organ abscesses
- Persistent thrush in mouth or fungal infection on the skin
- Need for intravenous antibiotics to clear infections
- Two or more deep-seated infections including septicemia
- Family history of PID; **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 and Hyqvia ONLY] †

- Patient is at least 18 years of age; **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 and stabilization with intravenous immunoglobulin (IVIG)§; **OR**
  - Used for re-initiation of maintenance therapy after experiencing a relapse and requiring re-induction therapy with IVIG (see Section IV for criteria)

§ Initial IVIG criteria used for determination of coverage: *(Reference Use Only)*

- Patient's disease course is progressive or relapsing and remitting for 2 months or longer; **AND**
- Patient has abnormal or absent deep tendon reflexes in upper or lower limbs; **AND**
- Electrodiagnostic testing indicating demyelination:
  - Partial motor conduction block in at least two motor nerves or in 1 nerve plus one other demyelination criterion listed here in at least 1 other nerve; **OR**
  - Distal CMAP duration increase in at least 1 nerve plus one other demyelination criterion listed here in at least 1 other nerve; **OR**
  - Abnormal temporal dispersion conduction must be present in at least 2 motor nerves; **OR**
  - Reduced conduction velocity in at least 2 motor nerves; **OR**
  - Prolonged distal motor latency in at least 2 motor nerves; **OR**
  - Absent F wave in at least two motor nerves plus one other demyelination criterion listed here in at least 1 other nerve; **OR**
  - Prolonged F wave latency in at least 2 motor nerves; **AND**
- Patient is refractory or intolerant to corticosteroids (e.g., prednisolone, prednisone, etc.) given in therapeutic doses over at least three months; **AND**
- Baseline in strength/weakness has been documented using an objective clinical measuring tool (e.g., INCAT, Medical Research Council (MRC) muscle strength, 6-MWT, Rankin, Modified Rankin, etc.)

† FDA Approved Indication(s)

V. Renewal Criteria

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

- Patient continues to meet criteria identified in section III; **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 of infusion have been adjusted accordingly; **AND**

Primary Immunodeficiency (PID)

- 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 and HyqviaONLY]

- Renewals will be authorized for patients that have demonstrated a beneficial clinical response to 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 or Hyqvia**; AND**
    - Patient improved and stabilized on IVIG treatment: **AND**
    - Patient was NOT receiving maximum dosing of Hizentra or Hyqvia prior to relapse

VI. Dosage/Administration

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

- 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)

Use the following dosing formulas to calculate the adjusted body weight (round dose to nearest 5 gram increment in adult patients)
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)

This 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.

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td>Chronic Inflammatory Demyelinating Polyneuropathy (CIPD)</td><td>
<u>Hizentra:</u>

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) body weight 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.

<u>HyQqvia:</u>

Patients must be on stable doses of IVIG prior to starting HyQvia.
Before initiating therapy with Hyqvia, calculate the weekly equivalent dose to plan for the ramp-up schedule (see table below): previous IVIG dose (g)/number of weeks between IVIG doses
The sStarting dose and dosing frequency of Hyqvia is the same as the patient's previous IVGIGV treatment.
The typical dosing interval range in the clinical trial for Hyvia was 4 weeks. For patients with less frequent IVGIGV dosing (greater than 4 weeks), the dosing interval can be converted to 3 or 4 weeks while maintaining the same monthly equivalent IgG dose.
Administer the calculated one-week dose (1st infusion) 2 weeks after the last IVGIGV infusion. One week after the first Hyqvia dose, administer another weekly equivalent dose (2nd infusion).
A ramp-up period can take up to 9 weeks, depending on the dosing interval and tolerability (see table below)

<table>
<tr><th colspan="3">HyQvia Dose Ramp-up Schedule</th></tr>
<tr><th>Week*</th><th>Infusion Number</th><th>Dose Interval</th></tr>
<tr><td>1</td><td>No infusion</td><td>Not applicable</td></tr>
<tr><td>2</td><td>1st infusion</td><td>1-week-doseDose in Grams X 0.67</td></tr>
<tr><td>3</td><td>2nd infusion</td><td>1-week-doseTotal Dose in Grams</td></tr>
<tr><td>4</td><td>3rd infusion</td><td>2-week-doseTotal Dose in Grams</td></tr>
<tr><td>5</td><td>No infusion</td><td>Not applicable</td></tr>
<tr><td>6</td><td>4th infusion</td><td>3-week-dose</td></tr>
<tr><td>7</td><td>No infusion</td><td>Not applicable</td></tr>
<tr><td>8</td><td>No infusion</td><td>Not applicable</td></tr>
<tr><td>9</td><td>5th infusion</td><td>4-week-dose</td></tr>
</table>
– *Clock starts one week after the last IVIG IV dose is administered. Week 1 is the week that starts one week after the last IVIG IV dose.
</td></tr>
</table>

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td rowspan="4">Primary immune deficiency (PID)</td><td>
<u>Hizentra:</u>

Switching from IVIG

Initiate therapy 1 to 2 weeks after the last IVIG dose
Weekly dose: 1.37*(previous IVIG dose (g)/number of weeks between IVIG doses)
May be administered from daily up to every two weeks (biweekly)
Biweekly dose: twice the weekly dose (using calculation above)
Frequent dosing (2-7 times per week): divide the calculated weekly dose by the desired number of times per week

Switching from SCIG

Initiate therapy 1 week after the last SCIG dose
Weekly dose (in grams) should be same as the weekly dose of prior SCIG treatment (in grams)
Biweekly dose: multiply the prior weekly dose by 2

Frequent dosing (2-7 times per week): divide the prior weekly dose by the desired number of times per week

</td></tr>
<tr><td>
<u>Gamunex-C/Gammaked/Gammagard Liquid:</u>

Switching from IVIG

Initiate therapy 1 week after the last IVIG doseWeekly dose: 1.37*(previous IVIG dose(g)/number of weeks between IVIG doses)

</td></tr>
<tr><td>
<u>HyQvia</u>:

Naïve to IgG or switching from SCIG: 300 to 600 mg/kg at 3 to 4 week intervals after initial ramp-up (see table below)
Switching from IVIG: use the same dose and frequency as the previous IV treatment after initial ramp-up (see table below)

<table>
<tr><th colspan="4">HyQvia Initial Treatment Interval/Dosage Ramp-up Schedule</th></tr>
<tr><th>Week</th><th>Infusion Number</th><th>3-week treatment interval</th><th>4-week treatment interval</th></tr>
<tr><td>1</td><td>1st infusion</td><td>Dose in Grams X 0.33</td><td>Dose in Grams X 0.25</td></tr>
<tr><td>2</td><td>2nd infusion</td><td>Dose in Grams X 0.67</td><td>Dose in Grams X 0.50</td></tr>
<tr><td>4</td><td>3rd infusion</td><td>Total Dose in Grams</td><td>Dose in Grams X 0.75</td></tr>
<tr><td>7</td><td>4th infusion</td><td>Total Dose in Grams</td><td>Total Dose in Grams</td></tr>
</table>
</td></tr>
<tr><td>
<u>Xembify:</u>

Switching from IVIG :

Start treatment one week after the last IVIG infusion.
Weekly dose: 1.37*(previous monthly (or every 3- week) IVIG dose in grams)/number of weeks between IVIG doses)

To convert the dose in grams to mL, multiply the calculated initial SQ dose (in grams) by 5

</td></tr>
</table>

Indication	Dose
	– Provided the total weekly dose is maintained, any dosing interval from daily up to weekly will achieve similar systemic IgG exposure when administered regularly at steady-state. ▪ Switching from SCIG o Weekly dose (in grams) should be same as the weekly dose of prior SCIG treatment (in grams)
	<u>Cuvitru:</u> Switching from IVIG or HyQvia: o Initiate therapy 1 week after the last IVIG dose o o Weekly dose: 1.30*(previous IVIG or HyQvia dose (g)/number of weeks between 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 the desired number of times per week ▪ Switching from SCIG o Weekly dose (in grams) should be same as the weekly dose of prior SCIG treatment (in grams) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: multiply the prior weekly dose by 2 o Frequent dosing (2-7 times per week): divide the calculated weekly dose by the desired number of times per week
	<u>Cutaquig</u>: (*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 IVIG doses) 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 the desired number of times per week ▪ Switching from SCIG o Weekly dose (in grams) should be same as the weekly dose of prior SCIG treatment (in grams) o May be administered from daily up to every two weeks (biweekly) o Biweekly dose: multiply the prior weekly dose by 2 ▪ Frequent dosing (2-7 times per week): divide the prior weekly dose by the desired number of times per

Dosing for immunoglobulin products is highly variable depending on numerous patient specific factors, indication(s), and the specific product selected. For specific dosing regimens refer to current prescribing literature.

VII. Billing Code/Availability Information

HCPCS code & NDC:

Drug Name	Manufacturer	HCPCS Code or CPT Code	1 Billable unit	NDC	IgG (grams) per SDV	Volume (mL)
Hizentra 20%	CSL Behring AG	J1559 – Injection, immune globulin (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
Gammaked 10%	Kedrion Biopharma, Inc.	J1561 Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g. liquid), 500 mg	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), 500 mg	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%	Baxter Healthcare Corporation	J1569 – Injection, immune globulin, (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)	Baxter Healthcare Corporation	J1575 – Injection, immune globulin/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
Cuvitru 20%	Baxalta US Inc.	J1555 – Injection, immune globulin (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
Cutaquig 16.5%	Octapharma	J1551	N/A	68892-0810-01	1	6

Drug Name	Manufacturer	HCPCS Code or CPT Code	1 Billable unit	NDC	IgG (grams) per SDV	Volume (mL)
				68892-0810-02	1.65	10
				68892-0810-03	2	12
				68892-0810-04	3.3	20
				68892-0810-05	4	24
				68892-0810-06	8	48
Xembify 20%	Grifols	90284; J1558	N/A	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 biologic; C9399 – unclassified drug or biological	N/A	N/A	N/A	N/A
		90284 – immune globulin (SCIg), human, for use in subcutaneous infusions				

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32. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2023. National Comprehensive Cancer Network, 2023. 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 October 2023.
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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
B20	Human immunodeficiency virus [HIV] disease
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
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

ICD-10	ICD-10 Description
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
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.89	Other inflammatory polyneuropathies
G62.89	Other specified polyneuropathies

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations.		
Jurisdiction	**NCD/LCA/LCD Document (s)**	**Contractor**
H, L	A56786	Novitas Solutions, Inc.
N	A57778	First Coast Service Options, Inc.
5, 8	A57554	Wisconsin Physicians Service Insurance Corporation (WPS)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale:

Hizentra, Gammagard Liquid, Gamunex-C, Gammaked, Hyqvia, Cuvitru, Cutaquig, and Xembify were reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Hizentra, Gammagard Liquid, Gamunex-C, Gammaked, Hyqvia, Cuvitru, Cutaquig, and Xembify according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.