DRUG QUANTITY MANAGEMENT POLICY – PER DAYS

POLICY: Hereditary Angioedema – Berinert and Cinryze Drug Quantity Management Policy – Per Days
- Berinert® (C1 esterase inhibitor [human] intravenous infusion – CSL Behring)
- Cinryze® (C1 esterase inhibitor [human] intravenous infusion – Shire/Takeda)

REVIEW DATE: 02/19/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Berinert and Cinryze are human plasma-derived C1 esterase inhibitor (C1-INH) replacement therapies indicated for the following uses:[1,2]
- Berinert is indicated for the treatment of **acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks** in adults and pediatric patients.[1]
- Cinryze is indicated for routine **prophylaxis against HAE attacks** in patients ≥ 6 years of age.[2]

Of note, although Cinryze is labeled for use in the prophylactic setting and Berinert is labeled for use in the acute treatment setting, use of Cinryze in the acute setting and Berinert in the prophylactic setting has been reported in literature.[3,4]

Dosing

Potencies of Berinert and Cinryze are both expressed in standard units of C1-INH (equal to the mean C1-INH quantity in 1 mL of normal human plasma).[1,2] **For prophylaxis**, the maximum allowable dose in the policy comes from the Cinryze prescribing information and is applied to both Berinert and Cinryze prophylactic use requests. For a patient ≥ 12 years of age, the recommended dose is 1,000 units by intravenous (IV) route, once every 3 or 4 days.[2] If a patient does not respond adequately, doses up to 2,500 units (not to exceed 100 units/kg) once every 3 or 4 days may be considered based on individual patient response. For a patient < 12 years of age, a dose of 500 units IV once every 3 or 4 days is recommended; the dose may be adjusted up to 1,000 units once every 3 or 4 days. **For acute treatment**, dosing recommendations come from the Berinert prescribing information and are applied to both Berinert and Cinryze requests for acute use. The recommended dose is 20 units/kg for treatment of an acute HAE attack.[1]

Availability

Both Berinert and Cinryze are supplied in single-use vials containing 500 units per vial.[1,2] The Berinert vials are packaged as a part of a kit which also includes 10 mL Sterile Water for Injection, a 10 mL silicone-free syringe, an IV set and butterfly needle, a Mix2Vial filter transfer set, and alcohol swabs.[1] Cinryze, in a 500 unit single-use vial, is supplied both with and without a 5 mL vial of Sterile Water for Injection.[2]

The quantity limits provided in this policy provide sufficient quantity for a long-term prophylaxis dose of 1,000 units twice weekly plus treatment of four HAE attacks (20 units/kg per attack) for a patient weighing up to 100 kg. If the patient requires additional quantity based on higher long-term prophylactic dosing, greater body weight, or treatment of an additional HAE attack in a 28-day interval (refer to Table 1 for dosing requirements in these scenarios), exceptions will be provided in Criteria.

Table 1. Quantity Required of Berinert/Cinryze per 28 Days Based on Prophylaxis and Acute Treatment Dosing.

	Prophylaxis			Acute Treatment			Total
Weight (kg)	**Units Per Dose**	**Vials/Kits Required per Dose**	**Vials/Kits Required per 28/84 days**	**Dose Required per attack**	**Vials/Kits Required per attack**	**Vials/Kits Required per 28/84 days[a]**	**Vials/Kits per 28/84 days**
≤ 100 kg	Up to 1,000 units	2	16/48	Up to 2,000 units	4	16/48	32/96
	Up to 2,500 units for select patients[†]	5	40/120				56/168
> 100 kg to ≤ 200 kg	Up to 1,000 units	2	16/48	Up to 4,000 units	8	32/96	48/144

	Up to 2,500 units for select patients†	5	40/120				72/216

† Patient ≥ 12 years of age with inadequate response to a long-term prophylaxis dose of 1,000 units once every 3 or 4 days. ᵠ Assuming patient experiences an average of one hereditary angioedema attack per week.

Guidelines

US HAE Medical Advisory Board guidelines (2020) recommend that all patients with laboratory confirmed HAE should have access to at least two standard doses of an approved on-demand medication for treatment of acute attacks.[5] On-demand treatment of attacks is most effective when administered early after attack onset. Short-term prophylaxis may be indicated before invasive medical, surgical, or dental procedures. A single dose of 20 units/kg of plasma-derived C1-INH can be given 1 to 12 hours before the stressor.

POLICY STATEMENT

This Drug Quantity Management program has been developed to promote the safe, effective, and economic use of Berinert and Cinryze. If the Drug Quantity Management rule is not met for the requested medication at the point of service, coverage will be determined by the Criteria below. All approvals are provided for 1 year in duration. "One-time" approvals are provided for 30 days in duration.

Drug Quantity Limits

Product	Package Size	Retail Maximum Quantity per 28 Days	Home Delivery Maximum Quantity per 84 Days
Berinert® (C1 esterase inhibitor [human] IV infusion)	500 unit kit	32 kits*	96 kits*
Cinryze® (C1 esterase inhibitor [human] IV infusion)	500 unit vial	32 vials*	96 vials*
	500 unit vial, co-packaged with diluent	32 vials*	96 vials*

IV – Intravenous; * Provides a quantity sufficient for prophylaxis of hereditary angioedema attacks at a dose of 1,000 units twice weekly (16 vials/kits); PLUS an additional 8,000 units (16 vials/kits), which would provide four doses per 28 days of 20 units/kg for a patient weighing up to 100 kg.

Hereditary Angioedema – Berinert and Cinryze Drug Quantity Management Policy – Per Days product(s) is(are) covered as medically necessary when the following criteria is(are) met. Any other exception is considered not medically necessary.

CRITERIA

Berinert 500 unit kit

1. If the patient weighs > 100 kg, approve 48 kits per 28 days at retail or 144 kits per 84 days at home delivery.

2. If the patient is ≥ 12 years of age, weighs ≤ 100 kg, and requires a dose > 1,000 units twice weekly for long-term prophylaxis of hereditary angioedema attacks, approve 56 kits per 28 days at retail or 168 kits per 84 days at home delivery.

3. If the patient is ≥ 12 years of age, weighs > 100 kg, and requires a dose > 1,000 units twice weekly for long-term prophylaxis of hereditary angioedema attacks, approve 72 kits per 28 days at retail or 216 kits per 84 days.

4. If the patient weighs ≤ 100 kg and requires an additional dose of Berinert to treat a subsequent hereditary angioedema attack or requires use of Berinert as short-term (procedural) prophylaxis, approve a one-time override for the requested quantity, not to exceed 16 additional kits at retail and home delivery. Note: At retail, the approval quantity should be the number of kits of Berinert the patient has received in the past 28 days plus 16 kits. At home delivery, the approval quantity should be the number of kits of Berinert the patient has received in the past 84 days plus 16 kits. ONE override may be approved ONCE every 30 days.

5. If the patient weighs > 100 kg and requires an additional dose of Berinert to treat a subsequent HAE attack or requires use of Berinert as short-term (procedural) prophylaxis, approve a one-time override for the requested quantity, not to exceed 32 additional kits at retail or home delivery. Note: At retail, the approval quantity should be the number of kits of Berinert the patient has received in the past 28 days plus 32 kits. At home delivery, the approval quantity should be the number of kits of Berinert the patient has received in the past 84 days plus 32 kits. ONE override may be approved ONCE every 30 days.

Cinryze 500 unit vial and 500 unit vial co-packaged with diluent

1. If the patient weighs > 100 kg, approve 48 vials per 28 days at retail or 144 vials per 84 days.

2. If the patient is ≥ 12 years of age, weighs ≤ 100 kg, and requires a dose > 1,000 units twice weekly for long-term prophylaxis of hereditary angioedema attacks, approve 56 vials per 28 days at retail or 168 kits per 84 days at home delivery.

3. If the patient is ≥ 12 years of age, weighs > 100 kg, and requires a Cinryze dose of > 1,000 units twice weekly for long-term prophylaxis of hereditary angioedema attacks, approve 72 vials per 28 days at retail or 216 vials per 84 days at home delivery.

4. If the patient weighs ≤ 100 kg and requires an additional dose of Cinryze to treat a subsequent hereditary angioedema attack or requires use of Cinryze as

short-term (procedural) prophylaxis, approve a one-time override for 16 additional vials at retail or home delivery.
Note: At retail, the approval quantity should be the number of vials of Cinryze the patient has received in the past 28 days plus 16vials. At home delivery, the approval quantity should be the number of vials of Cinryze the patient has received in the past 84 days plus 16 vials. ONE override may be approved ONCE every 30 days.

5. If the patient weighs > 100 kg and requires an additional dose of Cinryze to treat a subsequent hereditary angioedema attack or requires use of Cinryze as short-term (procedural) prophylaxis, approve a one-time override for 32 additional vials at retail or home delivery.
Note: At retail, the approval quantity should be the number of vials of Cinryze the patient has received in the past 28 days plus 32 vials. At home delivery, the approval quantity should be the number of vials of Cinryze the patient has received in the past 84 days plus 32 vials. ONE override may be approved ONCE every 30 days.

REFERENCES

1. Berinert® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2021.
2. Cinryze® intravenous infusion [prescribing information]. Lexington, MA: Takeda; November 2024.
3. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.
4. Craig T, Shapiro R, Vegh A, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017 Mar 1;8(1):13-19.
5. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/18/2023
Annual Revision	No criteria changes.	02/09/2024
Annual Revision	Policy statement was updated to note that "one-time" approvals are provided for 30 days in duration. **Berinert 500 unit kit:** For a patient weighing ≤ 100 kg, the override was updated to approve a one-time override for 16 additional vials if the patient requires additional doses of Berinert to treat a subsequent attack of hereditary angioedema. Previously, criteria approved 4 additional vials at retail and 12 additional vials at home delivery. Criteria Note was updated to clarify, "At retail, the approval quantity should be the number of kits of Berinert the patient has received in the past 28 days plus 16 kits. At home delivery, the approval quantity should be the number of kits of Berinert the patient has received in the past 84 days plus 16 kits. ONE override may be approved ONCE every 30 days." For a patient	02/19/2025

	weighing > 100 kg, the override was updated to approve a one-time override for 32 additional vials if the patient requires additional doses of Berinert to treat a subsequent attack of hereditary angioedema. Previously, criteria approved 8 additional vials at retail and 24 additional vials at home delivery. Criteria Note was updated to clarify, "At retail, the approval quantity should be the number of kits of Berinert the patient has received in the past 28 days plus 32 kits. At home delivery, the approval quantity should be the number of kits of Berinert the patient has received in the past 84 days plus 32 kits. ONE override may be approved ONCE every 30 days." **Cinryze 500 unit vial and 500 unit vial co-packaged with diluent:** For a patient weighing ≤ 100 kg, the override was updated to approve a one-time override for 16 additional vials if the patient requires additional doses of Cinryze to treat a subsequent attack of hereditary angioedema. Previously, criteria approved 4 additional vials at retail and 12 additional vials at home delivery. Criteria Note was updated to clarify, "At retail, the approval quantity should be the number of kits of Cinryze the patient has received in the past 28 days plus 16 kits. At home delivery, the approval quantity should be the number of kits of Cinryze the patient has received in the past 84 days plus 16 kits. ONE override may be approved ONCE every 30 days." For a patient weighing > 100 kg, the override was updated to approve a one-time override for 32 additional vials if the patient requires additional doses of Cinryze to treat a subsequent attack of hereditary angioedema. Previously, criteria approved 8 additional vials at retail and 24 additional vials at home delivery. Criteria Note was updated to clarify, "At retail, the approval quantity should be the number of kits of Cinryze the patient has received in the past 28 days plus 32 kits. At home delivery, the approval quantity should be the number of kits of Cinryze the patient has received in the past 84 days plus 32 kits. ONE override may be approved ONCE every 30 days."	