NC Division of Health Benefits **Medicaid**
Outpatient Pharmacy
Prior Approval Criteria
Hereditary Angioedema (HAE) Agents **Effective Date: March 1, 2024**

Therapeutic Class Code: M0N, A7N, A7M
Therapeutic Class Description: C1 Esterase Inhibitor Agents, Plasma Kallikrein Inhibitor Agents, Small Molecule Inhibitors, Bradykinin B2 Receptor Antagonists

Medications
Prophylaxis Agents
Cinryze
Haegarda
Orladeyo
Takhzyro
Treatment Agents
Berinert
Firazyr (icatibant)
Kalbitor
Ruconest

Eligible Beneficiaries
NC Medicaid (Medicaid) beneficiaries shall be enrolled on the date of service and may have service restrictions due to their eligibility category that would make them ineligible for this service.

EPSDT Special Provision: Exception to Policy Limitations for Beneficiaries under 21 Years of Age

42 U.S.C. § 1396d(r) [1905(r) of the Social Security Act]

Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) is a federal Medicaid requirement that requires the state Medicaid agency to cover services, products, or procedures for Medicaid beneficiaries under 21 years of age **if** the service is **medically necessary health care** to correct or ameliorate a defect, physical or mental illness, or a condition [health problem] identified through a screening examination (includes any evaluation by a physician or other licensed clinician). This means EPSDT covers most of the medical or remedial care a child needs to improve or maintain his/her health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems. Medically necessary services will be provided in the most economic mode, as long as the treatment made available is similarly efficacious to the service requested by the beneficiary's physician, therapist, or other licensed practitioner; the determination process does not delay the delivery of the needed service; and the determination does not limit the beneficiary's right to a free choice of providers.
EPSDT does not require the state Medicaid agency to provide any service, product, or procedure
a. that is unsafe, ineffective, or experimental/investigational.
b. that is not medical in nature or not generally recognized as an accepted method of medical practice or treatment.

Service limitations on scope, amount, duration, frequency, location of service, and/or other specific criteria described in clinical coverage policies may be exceeded or may not apply as long as the provider's documentation shows that the requested service is medically necessary "to correct or

ameliorate a defect, physical or mental illness, or a condition" [health problem]; that is, provider

documentation shows how the service, product, or procedure meets all EPSDT criteria, including to correct or improve or maintain the beneficiary's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

EPSDT and Prior Approval Requirements

a. If the service, product, or procedure requires prior approval, the fact that the beneficiary is under 21 years of age does **NOT** eliminate the requirement for prior approval.
b. **IMPORTANT ADDITIONAL INFORMATION** about EPSDT and prior approval is found in the *Basic Medicaid Billing Guide,* sections 2 and 6, and on the EPSDT provider page. The Web addresses are specified below.

***NCTracks Provider Claims and Billing Assistance Guide*:**
https://www.nctracks.nc.gov/content/public/providers/provider-manuals.html

EPSDT provider page:
https://medicaid.ncdhhs.gov/medicaid/get-started/find-programs-and-services-right-you/medicaid-benefit-children-and-adolescents

Prophylaxis Agents:

1. Cinryze

Criteria for Initial Coverage

- Beneficiary has a diagnosis of hereditary angioedema (HAE) I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test)
    - (Note: Prophylaxis for HAE with normal C1-INH (formerly known as HAE III) is not routinely recommended and will be evaluated on a case-by-case basis)
- Request is for prophylaxis of acute HAE attacks; **AND**
- Beneficiary is at least 6 years of age; **AND**
- Not used in combination with other prophylactic therapies targeting C1 inhibitor (i.e., Haegarda, etc.) or kallikrein (i.e., Takhzyro, Orladeyo, etc.); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**
- In addition, for non-preferred products, the beneficiary must have tried and failed or experienced an insufficient response to at least two preferred products for the same indication or have a clinical reason that preferred products cannot be tried

2. Haegarda

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test)
    - (Note: Prophylaxis for HAE with normal C1-INH (formerly known as HAE III)

is not routinely recommended and will be evaluated on a case-by-case basis)

- Request is for prophylaxis of acute HAE attacks; **AND**
- Beneficiary is at least 6 years of age; **AND**
- Not used in combination with other prophylactic therapies targeting C1 inhibitor (i.e., Cinryze, etc.) or kallikrein (i.e., Takhzyro, Orladeyo, etc.); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics

3. Orladeyo

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test)
    - (Note: Prophylaxis for HAE with normal C1-INH (formerly known as HAE III) is not routinely recommended and will be evaluated on a case-by-case basis)
- Request is for prophylaxis of acute HAE attacks; **AND**
- Beneficiary is at least 12 years of age; **AND**
- Not used in combination with other prophylactic therapies targeting C1 inhibitor (i.e., Cinryze, Haegarda, etc.) or kallikrein (i.e., Takhzyro, etc.); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics

4. Takhzyro

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test)
    - (Note: Prophylaxis for HAE with normal C1-INH (formerly known as HAE III) is not routinely recommended and will be evaluated on a case-by-case basis)
- Request is for prophylaxis of acute HAE attacks; **AND**
- Beneficiary is at least 2 years of age; **AND**
- Not used in combination with other prophylactic therapies targeting C1 inhibitor (i.e., Cinryze, Haegarda, etc.) or kallikrein (i.e., Orladeyo, etc.); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**
- In addition, for non-preferred products, the beneficiary must have tried and failed or experienced an insufficient response to at least two preferred products for the same indication or have a clinical reason that preferred products cannot be tried

Procedures:

Length of therapy may be approved for up to 12 months.

Renewal Criteria for Prophylaxis Agents:

- Beneficiary continues to meet initial criteria; **AND**
- Significant improvement in frequency, severity and duration of attacks have been achieved and sustained; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe hypersensitivity reactions, thromboembolic events, etc

Procedures:

Length of therapy may be approved for up to 12 months.

Treatment Agents:

1. Berinert

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test), **OR**
- Beneficiary has a diagnosis of HAE with normal C1-INH (formerly known as HAE III); **AND**
    - Patient has a known HAE-causing mutation (e.g., mutation of coagulation factor XII gene [F12 mutation], mutation in the angiopoietin-1 gene, mutation in the plasminogen gene, mutation in the kininogen 1 gene, mutation in the myoferlin gene, mutation in the heparan sulfate 3-O sulfotransferase 6 gene, etc.); OR
    - Patient has a family history of HAE; **AND**
- Request is for treatment of acute abdominal, facial, or laryngeal attacks of HAE; **AND**
- Not used in combination with, other approved treatments for acute HAE attacks (e.g. Firazyr, Ruconest, and Kalbitor); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics

2. Firazyr (icatibant)

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test), **OR**
- Beneficiary has a diagnosis of HAE with normal C1-INH (formerly known as HAE III); **AND**
    - Patient has a known HAE-causing mutation (e.g., mutation of coagulation factor XII gene [F12 mutation], mutation in the angiopoietin-1 gene, mutation in the plasminogen gene, mutation in the kininogen 1 gene, mutation in the myoferlin gene, mutation in the heparan sulfate 3-O sulfotransferase 6 gene, etc.); OR
    - Patient has a family history of HAE; **AND**
- Request is for treatment of acute abdominal, facial, or laryngeal attacks of HAE; **AND**
- Beneficiary is at least 18 years of age; **AND**
- Not used in combination with, other approved treatments for acute HAE attacks (e.g. Berinert,

Ruconest, and Kalbitor); **AND**

- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**
- In addition, for non-preferred products, the beneficiary must have tried and failed or experienced an insufficient response to at least two preferred products or have a clinical reason that preferred products cannot be tried

3. Kalbitor

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test), **OR**
- Beneficiary has a diagnosis of HAE with normal C1-INH (formerly known as HAE III); **AND**
    - Patient has a known HAE-causing mutation (e.g., mutation of coagulation factor XII gene [F12 mutation], mutation in the angiopoietin-1 gene, mutation in the plasminogen gene, mutation in the kininogen 1 gene, mutation in the myoferlin gene, mutation in the heparan sulfate 3-O sulfotransferase 6 gene, etc.); OR
    - Patient has a family history of HAE; **AND**
- Request is for treatment of acute abdominal, facial, or laryngeal attacks of HAE; **AND**
- Beneficiary is at least 12 years of age; **AND**
- Not used in combination with, other approved treatments for acute HAE attacks (e.g. Berinert, Firazyr, and Ruconest); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics

4. Ruconest

Criteria for Initial Coverage

- Beneficiary has a diagnosis of HAE I or II; **AND**
    - Low C4 level (C4 below the lower limit of normal as defined by the laboratory performing the test), **OR**
- Beneficiary has a diagnosis of HAE with normal C1-INH (formerly known as HAE III); **AND**
    - Patient has a known HAE-causing mutation (e.g., mutation of coagulation factor XII gene [F12 mutation], mutation in the angiopoietin-1 gene, mutation in the plasminogen gene, mutation in the kininogen 1 gene, mutation in the myoferlin gene, mutation in the heparan sulfate 3-O sulfotransferase 6 gene, etc.); OR
    - Patient has a family history of HAE; **AND**
- Request is for treatment of acute abdominal or facial attacks of HAE; **AND**
- Not used in combination with, other approved treatments for acute HAE attacks (e.g. Berinert, Firazyr, and Ruconest); **AND**
- Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**

- In addition, for non-preferred products, the beneficiary must have tried and failed or experienced an insufficient response to at least two preferred products for the same indication or have a clinical reason that preferred products cannot be tried

Procedures:

Length of therapy may be approved for up to 12 months.

Renewal Criteria for Treatment Agents:

- Beneficiary continues to meet initial criteria; **AND**
- Significant improvement in severity and duration of attacks have been achieved and sustained; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe hypersensitivity reactions, thromboembolic events, etc

Procedures:

Length of therapy may be approved for up to 12 months.

Quantity Limits:

Cinryze	24 vials per 34 days
Haegarda	Haegarda 2000 IU single-dose vial kit: 20 kits per 34 days Haegarda 3000 IU single-dose vial kit: 10 kits per 34 days
Orladeyo	1 capsule/day (34 capsules/34 days)
Takhzyro	Takhzyro 150 mg/mL single-dose prefilled syringe: 1 unit every 14 days Takhzyro 300 mg/2 mL single-dose vial and prefilled syringe: 1 unit every 14 days
Berinert	24 kits/30 days
Firazyr (icatibant)	24 syringes/30 days
Kalbitor	48 vials/30 days
Ruconest	16 vials/30 days

References

1. Orladeyo [package insert]. Durham, NC; BioCryst; March 2022.
2. Cinryze [package insert]. Lexington, MA; ViroPharma; April 2022.
3. Haegarda [package insert]. Kankakee, IL; CSL Behring; January 2022.
4. Takhzyro [package insert]. Lexington, MA; Takeda; February 2022.
5. Kalbitor [package insert]. Lexington, MA; Takeda; November 2021.
6. Firazyr [package insert]. Lexington, MA; Shire; October 2021.
7. Berinert [package insert]. Kankakee, IL; CSL Behring; September 2021.
8. Ruconest [package insert]. Warren, NJ; Pharming; April 2020.

Criteria Change Log

03/01/2024	Criteria effective date