Indication
CINRYZE® (C1 esterase inhibitor [human]) is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

Important Safety Information
CINRYZE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.

Please see additional Important Safety Information throughout this booklet and on page 14.

Before prescribing CINRYZE, please read the Full Prescribing Information available at www.cinryze.com.
PATIENTS FACE A CONSTANT THREAT OF HEREDITARY ANGIOEDEMA (HAE) ATTACKS

ATTACKS CAN BE UNPREDICTABLE

- Attacks can often occur without a known trigger and can migrate to other parts of the body during a single attack
- Some triggers have been identified and include:
  - Stress
  - Physical trauma, surgery, or a dental procedure
  - Infection
  - Hormonal influences
  - Mechanical pressure
- The severity and frequency of HAE attacks vary greatly from patient to patient and can also change over time

ATTACKS CAN HAVE A SIGNIFICANT EFFECT ON DAILY ACTIVITIES

- HAE attacks can be debilitating and disfiguring
- Attacks typically cause swelling in the face, extremities, abdomen, genitals, and larynx, some of which may be painful and functionally disabling
- Untreated abdominal attacks may require, on average, between 24 and 50 hours of bedrest

*In a survey of 23 patients.

Photographs of Heather, an HAE patient, taken at age 15 during a facial attack, and at age 30.
HAE ATTACKS CAN BE DEBILITATING AND LIFE-THREATENING

UNTREATED PATIENTS HAVE A MEAN OF 27 ATTACKS PER YEAR (SD ± 43)$^8,a$

— On average, an untreated patient will experience 2 to 4 attacks per month$^2,9$
— An untreated HAE attack usually lasts 2 to 5 days$^7$

$^a$In a survey of 399 patients.

ABOUT 50% of HAE patients experience at least one laryngeal attack in their lifetime$^6,10,a$

— In the past, untreated laryngeal attacks resulted in mortality rates as high as 30%$^2$

19 to 24% of patients have undergone unnecessary procedures as a result of misdiagnosis, including removal of appendix$^{11,b}$

$^a$In a survey of 209 patients.
$^b$In a survey of 313 patients in an online survey from 2010.
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**UNDERSTANDING THE ROLE OF C1 ESTERASE INHIBITOR IN HAE**

**MOST CASES OF HAE ARE CAUSED BY A DEFICIENCY OR DYSFUNCTION OF C1 ESTERASE INHIBITOR THAT RESULTS IN THE INABILITY TO REGULATE THE KALLIKREIN-KININ SYSTEM**

- An attack is initiated when the kallikrein-kinin cascade is activated
- In response to activation, plasma kallikrein cleaves high-molecular-weight kininogen (HMWK), producing bradykinin
- Excessive bradykinin causes an increase in blood vessel permeability, which allows fluid to pass through the blood vessel walls and cause subcutaneous or submucosal swelling

[KALLIKREIN-KININ SYSTEM]

- XII (Factor XII)
- K (Kallikrein)
- HMWK (High-Molecular-Weight Kininogen)
- XIIa (Factor XIIa)
- PK (Pre-kallikrein)
- B (Bradykinin)
- Missing/dysfunctional C1 esterase inhibitor
- C1 esterase inhibitor (CINRYZE)
- Endothelial cells

Adapted from Zuraw 2008 and Kaplan 2010.
CINRYZE® WAS THE FIRST C1 ESTERASE INHIBITOR APPROVED BY THE FDA FOR ROUTINE PREVENTION OF HAE ATTACKS

CINRYZE® INCREASES PLASMA LEVELS OF C1 INHIBITOR AND HELPS PREVENT HAE ATTACKS IN ADOLESCENTS AND ADULTS

- CINRYZE® (C1 esterase inhibitor [human]) addresses the underlying cause of HAE (deficiency or dysfunction of C1 esterase inhibitor)
- CINRYZE can reduce vascular permeability by preventing the generation of bradykinin

HOW CINRYZE® WORKS

![Diagram of the Kallikrein-Kinin System](Image)

Important Safety Information

**Hypersensitivity Reactions:** Severe hypersensitivity reactions may occur during or after administration of CINRYZE. Consider treatment methods carefully, because hypersensitivity reactions and HAE attacks may have similar symptoms. In case of hypersensitivity, discontinue CINRYZE infusion and institute appropriate treatment. Have epinephrine immediately available for treatment of an acute severe hypersensitivity reaction.

Please see additional Important Safety Information throughout this booklet and on page 14.
Patients have received CINRYZE® (C1 esterase inhibitor [human])

Doses of CINRYZE have been distributed

Physicians have prescribed CINRYZE for their HAE patients

Physicians and patients have attended more than 150 CINRYZE speaker programs

Important Safety Information

Thromboembolic Events: Serious arterial and venous thromboembolic (TE) events have been reported at the recommended dose of C1 Esterase Inhibitor (Human) products, including CINRYZE, following administration in patients with HAE. Risk factors may include presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives, certain androgens, morbid obesity, and immobility. Benefits of CINRYZE for routine prophylaxis of HAE attacks should be weighed against the risks of TE events in patients with underlying risk factors. Monitor patients with known risk factors for TE events during and after CINRYZE administration.

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PREVENTION WITH CINRYZE® IS PROVEN TO HELP REDUCE THE BURDEN OF HAE ATTACKS

CINRYZE® HAS BEEN PROVEN TO REDUCE THE FREQUENCY, SEVERITY, AND DURATION OF ATTACKS, AND THE NUMBER OF DAYS OF SWELLING

The primary endpoint in the CINRYZE® (C1 esterase inhibitor [human]) pivotal study was the number of HAE attacks during the 12-week treatment period with CINRYZE compared to the number of attacks during the 12-week placebo treatment period.

CINRYZE significantly reduced the mean number of HAE attacks vs placebo ($p<0.0001$)

- Number of HAE attacks (standard deviation [SD]): CINRYZE 6.1 (5.4)
  vs placebo 12.7 (4.8)

Study design
Randomized, double-blind, placebo-controlled, multicenter, crossover study designed to establish the safety ($n=24$) and efficacy ($n=22$) of CINRYZE prophylaxis in patients with a history of at least 2 HAE attacks per month. In addition to the primary efficacy analysis of attack frequency, secondary endpoints included the duration and severity of attacks and the number of days of swelling.

Important Safety Information
Transmissible Infectious Agents: Because CINRYZE is made from human blood, it may carry a risk of transmitting infectious agents e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by CINRYZE should be reported to Shire Medical Information at 1-800-828-2088.

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CINRYZE® HAS BEEN PROVEN TO REDUCE THE FREQUENCY OF HAE ATTACKS

CINRYZE® REDUCED ATTACK FREQUENCY IN 20 OF 22 PATIENTS

The effectiveness of CINRYZE® (C1 esterase inhibitor [human]) prophylaxis in reducing the number of HAE attacks was variable among 22 subjects in a controlled clinical trial.

20 patients experienced a reduction in attack frequency — Ranging from a 100% to 1% reduction in number of attacks
— 4 patients experienced no attacks during a 12-week period

2 patients experienced an increase in attack frequency — One patient showed an 8% increase in attacks
— One patient showed an 85% increase in attacks

Important Safety Information

Adverse Reactions: The only serious adverse reaction observed in clinical studies of CINRYZE was cerebrovascular accident. The most common adverse reactions observed were headache, nausea, rash, and vomiting. Postmarketing adverse reactions include local infusion site reactions and hypersensitivity. Postmarketing thromboembolic events have been reported, including catheter-related and deep venous thromboses, transient ischemic attack, and stroke.
Not every day is perfect, but I believe that every day has the potential to be what I choose to make it. I’m fortunate that I’ve found a treatment that works for me.

Scott, a real HAE patient

Indication
CINRYZE® (C1 esterase inhibitor [human]) is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

Important Safety Information
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Please see additional Important Safety Information throughout this booklet and on page 14.
CINRYZE® REDUCED ATTACK DURATION\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{reduction_in_mean_duration_of_attacks}
\caption{Reduction in Mean Duration of Attacks}
\end{figure}

\begin{itemize}
\item CINRYZE® (C1 esterase inhibitor [human]) significantly reduced the mean duration of HAE attacks vs placebo ($p<0.01$)\textsuperscript{16}
\item Mean duration of HAE attacks (days) (SD): CINRYZE 2.1 (1.13) vs placebo 3.4 (1.4)
\item Mean treatment effect (placebo minus CINRYZE) was 1.23 (95% CI, 0.49, 1.96)
\end{itemize}

CINRYZE® REDUCED THE NUMBER OF DAYS OF SWELLING\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{reduction_in_days_of_swelling_over_12_weeks}
\caption{Reduction in Days of Swelling Over 12 Weeks}
\end{figure}

\begin{itemize}
\item CINRYZE significantly reduced the mean number of days of swelling vs placebo ($p<0.01$)\textsuperscript{16}
\item Days of swelling (SD): CINRYZE 10.1 (10.73) vs placebo 29.6 (16.9)
\item Mean treatment effect (placebo minus CINRYZE) was 19.5 (95% CI, 11.94, 27.06)
\end{itemize}

Important Safety Information

Hypersensitivity Reactions: Severe hypersensitivity reactions may occur during or after administration of CINRYZE. Consider treatment methods carefully, because hypersensitivity reactions and HAE attacks may have similar symptoms. In case of hypersensitivity, discontinue CINRYZE infusion and institute appropriate treatment. Have epinephrine immediately available for treatment of an acute severe hypersensitivity reaction.

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ADMINISTRATION OPTIONS PUT PROVEN PREVENTION IN PATIENTS’ HANDS

CONSIDER SELF-ADMINISTRATION FOR ALL OF YOUR CINRYZE® PATIENTS

Physicians and patients can work together to choose between self-administration and infusion by a healthcare professional or trained caregiver.

THE PATH TO INDEPENDENCE™ PROGRAM OFFERS HANDS-ON SELF-ADMINISTRATION TRAINING

- For appropriate patients who are receiving therapy with CINRYZE® (C1 esterase inhibitor [human]), this complimentary program provides self-administration training from specially trained infusion nurses at no cost to the patient.

- Hands-on training includes:
  - Proper reconstitution and administration techniques
  - Appropriate practices for how to store, handle, and dispose of CINRYZE
  - Instruction on when to reorder medication and infusion supplies, and on the procedure for contacting a Specialty Pharmacy

- Shire advises the patient to receive training from a healthcare professional prior to self-administration.

“

OnePath® arranged for an infusion nurse to train me on how to properly self-infuse in the comfort of my own home...plus, they arranged for both my husband and mom to be trained to give me my CINRYZE infusions as well.

Jenny, a real HAE patient

“
PRODUCT SUPPORT SERVICES THROUGH ONEPATH®

OnePath is designed to be a helpful resource for your patients with HAE. Upon enrollment in OnePath, your patient is assigned a dedicated Patient Support Manager who will help your patient with access to therapy.

OnePath Patient Support Managers assist your patients by:

- Facilitating insurance benefits investigation to verify coverage
- Providing information about financial assistance options
- Working with specialty pharmacies to facilitate treatment access
- Setting up infusion or injection training and services, if requested
- Informing patients about additional resources available to them

In addition to OnePath Patient Support Managers, Patient Access Managers (PAMs) are available as a resource. PAMs can help to address insurance or access challenges and provide information on reimbursement to you and your patients.

“Through OnePath product support services, I have my own Patient Support Manager who has been a great help.”

Dariela, a real HAE patient

Before prescribing CINRYZE® (C1 esterase inhibitor [human]), please read the Full Prescribing Information available at www.cinryze.com.
### EXAMPLES OF HAE LABORATORY TESTS BY PROVIDER

Current as of December 2017

#### LabCorp® 1-800-845-6167

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Laboratory Code</th>
<th>CPT Code</th>
<th>ICD-10-CM Code</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Angioedema (HAE) (Panel includes all tests below)</td>
<td>123020</td>
<td>86160 (x2)</td>
<td>D84.1</td>
<td>See below</td>
</tr>
<tr>
<td>Complement C4, Serum</td>
<td>001834</td>
<td>86160</td>
<td></td>
<td>13–44 mg/dL</td>
</tr>
<tr>
<td>Complement C1 Esterase Inhibitor, Serum</td>
<td>004648</td>
<td>86160</td>
<td></td>
<td>21–39 mg/dL</td>
</tr>
</tbody>
</table>
| Complement C1 Esterase Inhibitor, Functional | 120220 | 86161 |  | Normal: >67%  
Equivocal: 41–67%  
Abnormal: <41% |
| Complement C1q, Quantitative | 016824 | 86160 |  | Male: 11.8–23.8 mg/dL  
Female: 11.8–24.4 mg/dL |

#### National Jewish Health (ADx)® 1-800-550-6627

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Laboratory Code</th>
<th>CPT Code</th>
<th>ICD-10-CM Code</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4 Level</td>
<td>C4</td>
<td>86160</td>
<td>D84.1</td>
<td>13–52 mg/dL (depending on age)</td>
</tr>
</tbody>
</table>
| Ratio of C4d to C4 | C4RAT | 86160 (x2) |  | Male/Female:  
C4: 0.112–0.441 mg/mL  
C4d: 0.52–7.88 mcg/mL  
Ratio <25 |
| C1-Esterase Inhibitor Level (C1-INH) | CEIQ | 86160 |  | 20–37 mg/dL |
| C1-Inhibitor (C1-INH) Function, Chromogenic Assay | CEICHR | 86161 |  | Units for CEICHR 74–147% of Normal |
| C1q Level | C1Q | 86160 |  | 83–125 mcg/mL |

#### Quest Diagnostics® 1-800-222-0446

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Laboratory Code</th>
<th>CPT Code</th>
<th>ICD-10-CM Code</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema Panel, Hereditary, Comprehensive (Panel includes all tests below)</td>
<td>17706</td>
<td>86160 (x2), 86161</td>
<td>D84.1</td>
<td>See below</td>
</tr>
<tr>
<td>Complement Component C4c</td>
<td>353</td>
<td>86160</td>
<td></td>
<td>Adults: 16–47 mg/dL</td>
</tr>
<tr>
<td>C1 Esterase Inhibitor, Protein</td>
<td>298</td>
<td>86160</td>
<td></td>
<td>21–39 mg/dL</td>
</tr>
</tbody>
</table>
| C1 Inhibitor, Functional | 297 | 86161 |  | Normal: ≥68%  
Equivocal: 41–67%  
Abnormal: ≤40% |
| Complement Component C1q | 981 | 86160 |  | 5.0–8.6 mg/dL |

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*aLaboratory Corporation of America® Holdings  
*Advanced Diagnostic Laboratories, National Jewish Health—Affiliated with the University of Colorado, Denver  
*Quest Diagnostics Incorporated
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REFERENCES


16. CINRYZE® (C1 esterase inhibitor [human]) Prescribing Information. Shire.

ROUTINE PROPHYLAXIS HELPS PATIENTS TAKE CONTROL

- CINRYZE® (C1 esterase inhibitor [human]) is the first C1 esterase inhibitor approved by the FDA for routine prevention against angioedema attacks in adolescent and adult patients with HAE16
- CINRYZE has been proven to reduce the burden of HAE attacks, including attack frequency, severity, duration, and days of swelling in most patients16
- Consider self-administration for all of your CINRYZE patients

SUPPORT YOUR PATIENTS TAKING CINRYZE®

- Set up a treatment schedule to keep patients on track
- Empower your patients to take charge by following the infusion schedule you provide
- Remind your patients that CINRYZE is administered every 3 or 4 days for routine prophylaxis against attacks in HAE patients16

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