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 page 16 for additional Important Safety Information.
Before prescribing CINRYZE, please read the Full Prescribing Information available at www.cinryze.com.
PATIENTS FACE A CONSTANT THREAT OF HEREDITARY ANGIOEDEMA (HAE) ATTACKS¹

ATTACKS CAN BE UNPREDICTABLE¹

- Attacks often occur without a known trigger and can migrate to other parts of the body during a single attack¹²
- Some triggers have been identified and may include:
  - Emotional stress²
  - Minor trauma, surgery, or a dental procedure²,³
  - Illness or infection⁴
  - Hormonal influences²
  - Mechanical pressure²
- The location and severity of HAE attacks can change over time⁵

FREQUENT, PAINFUL ATTACKS CAN HAVE A SIGNIFICANT EFFECT ON DAILY ACTIVITIES⁶,⁷

- HAE attacks can be debilitating and disfiguring¹⁴
  - Attacks cause intense swelling in the face, extremities, abdomen, and larynx, some of which may be painful and functionally disabling¹,⁴,⁸
  - Abdominal attacks may require, on average, between 24 and 50 hours of bedrest⁷
  - Extremities are the most common site affected⁹

Photographs of Heather, an HAE patient, taken at age 15 during a facial attack and at age 30.

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HAE ATTACKS CAN HAVE FAR-REACHING CONSEQUENCES

HAE ATTACKS CAN BE DEBILITATING AND LIFE-THREATENING\textsuperscript{1,10}

\begin{itemize}
\item \textbf{ABOUT 75\%} of patients experience an \textit{attack at least once a year}\textsuperscript{9}.
\item On average, an untreated patient will experience 2 to 4 attacks per month\textsuperscript{8}.
\item An HAE attack usually lasts 2 to 5 days\textsuperscript{11}.
\end{itemize}

\begin{itemize}
\item 19 to 24\% of patients undergo \textit{unnecessary procedures} as a result of misdiagnosis, including removal of appendix\textsuperscript{12,a}.
\end{itemize}

\begin{itemize}
\item \textbf{ABOUT 50\%} of HAE patients experience \textit{at least one laryngeal attack} in their lifetime\textsuperscript{9,b}.
\item Every patient with HAE, even patients who experience attacks in other locations, is still at risk for laryngeal attacks\textsuperscript{8}.
\item Untreated laryngeal attacks can result in a mortality rate as high as 30\%\textsuperscript{13}.
\end{itemize}

\textsuperscript{a}In a survey of 313 patients
\textsuperscript{b}In a survey of 221 patients
EARLY DIAGNOSIS CAN HELP ENSURE PROPER MANAGEMENT OF HAE

MANY FACTORS PLAY A KEY PART IN MAKING A CORRECT DIAGNOSIS OF HAE

- Diagnosis is made through a comprehensive evaluation:
  - Family history
  - Clinical history
  - Laboratory testing

- Proper diagnosis can provide patients with the education necessary to manage HAE during daily life, including:
  - Identification and avoidance of triggers
  - Preparation for attacks
  - Timely response to potentially lethal complications, such as airway obstruction

DIAGNOSTIC ALGORITHM FOR THE EVALUATION OF RECURRENT ANGIOEDEMA

![Diagram of diagnostic algorithm]

**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 page 16 for additional Important Safety Information.
### QUEST DIAGNOSTICS

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<td>Complement C1q, Quantitative</td>
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### NATIONAL JEWISH (ADX)

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<td>C1-Esterase Inhibitor Level (C1-INH)</td>
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<td>C1-Inhibitor (C1-INH) Function, Chromogenic Assay</td>
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<td>C1q Level</td>
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Before prescribing CINRYZE® (C1 esterase inhibitor [human]), please read the Full Prescribing information available at www.cinryze.com.
ROUTINE PROPHYLAXIS CAN HELP PATIENTS TAKE CONTROL

FREQUENCY OF ATTACKS IS NOT THE ONLY CRITERION FOR THE USE OF PROPHYLAXIS IN HAE\textsuperscript{15,16}

- Disease severity can be different for each patient\textsuperscript{17}
- Several important factors should be included in consideration of prophylactic therapy:
  - Frequency of attacks\textsuperscript{8}
  - Severity of attacks\textsuperscript{8}
  - Number of days of swelling\textsuperscript{16}
  - Past laryngeal attacks\textsuperscript{5}

US AND INTERNATIONAL GUIDELINES SUPPORT PROPHYLAXIS AS AN IMPORTANT OPTION\textsuperscript{15-17}

- Routine prophylactic therapy is appropriate for patients in whom on-demand acute treatment was inadequate to “minimize the suffering relating to the disease”\textsuperscript{16}
  - “Inadequate” was tentatively defined as greater than 12 severe attacks per year, or more than 24 days of swelling (even if mild) per year\textsuperscript{16}
- The decision to use prophylactic therapy cannot be made on rigid criteria but should reflect the needs of the individual patient\textsuperscript{17}
- Home plasma-derived C1INH self-infusion programs should be offered to patients\textsuperscript{15}

COLLABORATIVE TREATMENT DECISIONS BETWEEN PHYSICIANS AND PATIENTS ARE CRITICAL\textsuperscript{17}

- Patient input is important in determining overall disease burden
- Working together to design individualized treatment plans to help facilitate successful compliance\textsuperscript{17}
- Discussions can include:
  - Administration options of therapy
  - Potential risks and physical benefits of prophylaxis

\textit{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
CINRYZE® IS THE ONLY FDA-APPROVED C1 ESTERASE INHIBITOR FOR ROUTINE PROPHYLAXIS

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

- C1 esterase inhibitor regulates the contact, fibrinolytic, and complement systems.  
- 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

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 page 16 for additional Important Safety Information.
CINRYZE® REDUCED ATTACK FREQUENCY IN 20 OUT OF 22 PATIENTS

PREVENTION OF HAE ATTACKS—CLINICAL TRIAL RESULTS BY SUBJECT

Primary endpoint analysis

The efficacy of CINRYZE® (C1 esterase inhibitor [human]) in preventing HAE attacks was evaluated based on the number of HAE attacks during the 12-week treatment period with CINRYZE compared with the number of attacks during the 12-week placebo treatment period.

The effectiveness of CINRYZE prophylaxis in reducing the number of HAE attacks was variable among the 22 subjects in a controlled clinical trial.

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

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

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

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.

Please see page 16 for additional Important Safety Information.

Before prescribing CINRYZE® (C1 esterase inhibitor [human]), please read the Full Prescribing Information available at www.cinryze.com.
CINRYZE® HAS BEEN PROVEN TO REDUCE THE FREQUENCY OF HAE ATTACKS

PRIMARY EFFICACY OUTCOME

Study design
Randomized, double-blind, placebo-controlled, multicenter, crossover study designed to establish the safety (n=24) and efficacy (n=22) of CINRYZE® (C1 esterase inhibitor [human]) 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 1-866-888-0660.
PREVENTION WITH CINRYZE® HELPED REDUCE THE SEVERITY AND DURATION OF HAE ATTACKS

CINRYZE® REDUCED ATTACK SEVERITY

CINRYZE® (C1 esterase inhibitor [human]) significantly reduced the mean severity of HAE attacks vs placebo ($p<0.01$)

- Mean severity of HAE attacks (SD): CINRYZE 1.3 (0.85) vs placebo 1.9 (0.36)
- Mean treatment effect (placebo minus CINRYZE) was 0.58 (95% CI, 0.19, 0.97)

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.

My doctor and I are pleased with how CINRYZE has helped to reduce the frequency and severity of my HAE attacks.

Andrea, a real HAE patient
**CINRYZE® REDUCED ATTACK DURATION**

![Graph showing reduction in mean duration of HAE attacks](image)

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

**CINRYZE® REDUCED THE NUMBER OF DAYS OF SWELLING**

![Graph showing reduction in mean number of days of swelling](image)

- CINRYZE significantly reduced the mean number of days of swelling vs placebo ($p<0.01$)
  - Days of swelling (SD): CINRYZE 10.1 (10.73) vs placebo 29.6 (16.9)
  - Mean treatment effect (placebo minus CINRYZE) was 19.5 (95% CI, 11.94, 27.06)

**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.
CINRYZE® IS PURIFIED TO REDUCE RISK OF VIRAL TRANSMISSION

MORE THAN 14,000 DOSES OF CINRYZE® HAVE BEEN ADMINISTERED TO MORE THAN 260 PATIENTS IN ALL COMPLETED CLINICAL STUDIES

▷ All patients who were evaluated were found negative for seroconversion to parvovirus B19, hepatitis B, hepatitis C, and HIV
▷ CINRYZE® (C1 esterase inhibitor [human]) is purified through a multistep process that includes pasteurization and nanofiltration to minimize a wide range of potential pathogens
▷ CINRYZE is derived from natural human plasma collected from US source donors prescreened to rule out infection with human immunodeficiency virus (HIV-1/HIV-2), hepatitis B virus, or hepatitis C virus

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 1-866-888-0660.

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# AN OVERVIEW OF THERAPIES APPROVED FOR PROPHYLAXIS IN HAE

<table>
<thead>
<tr>
<th>Indication</th>
<th>CINRYZE® (C1 esterase inhibitor [human])</th>
<th>Danocrine (danazol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indicated for</strong></td>
<td>Indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE).</td>
<td>Indicated for the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females.</td>
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<tr>
<td><strong>Contraindications</strong></td>
<td>Contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.</td>
<td>Should not be administered to patients with: undiagnosed abnormal genital bleeding; markedly impaired hepatic, renal, or cardiac function; pregnancy; breast-feeding; porphyria—Danocrine can induce aminolevulinic acid (ALA) synthetase activity and hence porphyrin metabolism. Androgen-dependent tumor; active thrombosis or thromboembolic disease and history of such events; hypersensitivity to danazol.</td>
</tr>
<tr>
<td><strong>DOSAGE</strong></td>
<td>For intravenous use only. A dose of 1,000 Units can be administered every 3 or 4 days for routine prophylaxis against angioedema attacks. CINRYZE is administered at an injection rate of 1 mL per minute (10 min).</td>
<td>Recommended that patient be started on 200 mg, two or three times a day. After a favorable initial response is obtained in terms of prevention of episodes of edematous attacks, the proper continuing dosage should be determined by decreasing the dosage by 50% or less at intervals of one to three months or longer if frequency of attacks prior to treatment dictates. If an attack occurs, the daily dosage may be increased by up to 200 mg. During the dose-adjusting phase, close monitoring of the patient’s response is indicated, particularly if the patient has a history of airway involvement.</td>
</tr>
</tbody>
</table>

*More information can be found in the Danocrine Full Prescribing Information.

No adequate and well-controlled trials have been conducted comparing HAE therapies.

**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.
ADMINISTRATION OPTIONS PUT THE POWER OF 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.

SUPPORT COMPLIANCE WITH 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 patients about the benefits of staying compliant—even if they are experiencing fewer or no attacks, missing a dose of CINRYZE can result in breakthrough attacks.
  - CINRYZE is administered every 3 or 4 days for routine prophylaxis against attacks in HAE patients.

“I like being able to self-administer, because I can do my infusions at home and I don’t have to worry about the infusion center being closed. I like having more control of my schedule that way.”

Doug, a real HAE patient
PRODUCT SUPPORT SERVICES THROUGH ONEPATH®

Shire’s OnePath® provides one-on-one product support by:

- Helping to navigate insurance and facilitate access to therapy
- Offering access to a large community of support by, for example, providing you with information about Shire programs that may be available to patients and how to connect with patient advocacy organizations

ENROLLING IN ONEPATH

1. Sign Up
   All it takes is for you and your eligible patients to complete the downloadable OnePath Start Form from cinryze.com.

2. Case Managers
   A dedicated Case Manager completes benefits verification and helps provide information about the prior authorization process (if applicable) and financial support through a variety of patient assistance programs (if needed).

3. Product Access and Support
   The Case Manager sets up product shipment with a Specialty Pharmacy, serves as an ongoing resource for your patients throughout therapy, and coordinates self-administration training for appropriate patients through Path to Independence™, a complimentary patient program in which trained infusion nurses instruct patients on the specific techniques necessary for self-administration.

“Through the OnePath support service, I have my own Case Manager who has been a great help. He always keeps me informed.”

Dariela, 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).

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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.

Before prescribing CINRYZE, please read the Full Prescribing Information available at www.cinryze.com.
REFERENCES

ROUTINE PROPHYLAXIS CAN HELP PATIENTS TAKE CONTROL

- Patients face a constant threat of HAE attacks\(^1\)
- Decisions regarding routine prophylaxis should be based on overall disease burden in the context of individualized patient care\(^15-17\)

UNDERSCORE THE BENEFITS OF PREVENTION WITH CINRYZE\(^\circledR\)

- CINRYZE\(^\circledR\) (C1 esterase inhibitor [human]) is the only FDA-approved C1 esterase inhibitor for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE
- CINRYZE has been proven to reduce HAE attacks, including attack frequency, severity, duration, and days of swelling, in most patients
- Remind your patients about the benefits of staying compliant—even if they are experiencing fewer or no attacks, missing a dose of CINRYZE can result in breakthrough attacks
- Consider self-administration for all of your CINRYZE patients

SHIRE’S ONEPATH\(^\circledR\) PROVIDES PERSONALIZED PRODUCT SUPPORT BY:

- Helping to navigate insurance and facilitate access to therapy
- Offering access to a large community of support, including Shire programs that may be available to patients

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