Cinryze™ as the first approved C1 inhibitor in the USA for the treatment of hereditary angioedema: approval, efficacy and safety

Michael Lunn1
Carah Santos2
Timothy Craig1
1Penn State Hershey Section of Allergy, Asthma and Immunology, Hershey, PA USA; 2Stanford University Department of Pediatrics, Palo Alto, CA USA

Abstract: Hereditary angioedema (HAE) is a clinical disorder characterized by a deficiency of C1 esterase inhibitor (C1-INH). HAE has traditionally been divided into two subtypes. Unique among the inherited deficiencies of the complement system, HAE Types I and II are inherited as an autosomal dominant disorder. The generation of an HAE attack is caused by the depletion and/or consumption of C1-inhibitor manifested as subcutaneous or submucosal edema of the upper airway, face, extremities, or gastrointestinal tract. Attacks can be severe and potentially life-threatening, particularly with laryngeal involvement. Despite the availability of C1-INH for the treatment of HAE since the 1980s in Europe and other countries, HAE treatment in the United States was limited to androgen therapy. The human plasma-derived C1 esterase inhibitor (Cinryze™), distributed by Lev Pharmaceuticals, was approved in October 2008 for the prevention of HAE attacks based on the results of a phase III clinical trial. This review aims to describe the history of C1-INH replacement in HAE as well as the pharmacology, efficacy and safety of C1-INH, concentrating on Cinryze as the first approved chronic replacement treatment for the prophylaxis of HAE attacks.

Keywords: hereditary angioedema, C1 esterase inhibitor, Cinryze, prophylaxis, angioedema

Introduction
Hereditary angioedema (HAE) is a clinical disorder characterized by a deficiency of C1 esterase inhibitor (C1-INH). The disorder results from mutations of the C1-INH gene located on chromosome 11.1,2 Donaldson and Evans first recognized that C1-INH was deficient in the plasma of patients with HAE in 1963.3 Unique among the inherited deficiencies of the complement system, HAE Types I and II are inherited as an autosomal dominant disorder, with equal occurrence among men and women. Low levels of both C1-INH proteins distinguish Type I HAE, which accounts for approximately 80% to 85% of all HAE cases. Type II HAE, which occurs in 15% to 20% of patients, results from decreased functional activity of the C1-INH gene, but with normal C1-INH levels.4,5 Recently, a new subtype of HAE, Type III, has been described in the literature. Type III is characterized by an X-linked dominant inheritance and initially observed exclusively in women and is associated with normal levels and function of C1-INH.6 Most cases appeared to be estrogen induced;7 however, more recently males have been identified that appear to have type III HAE, but with normal levels of C4, C1-INH-A and C1-INH-F.

Generation of HAE attacks are caused by the depletion and/or consumption of C1 inhibitor. The role of C1-INH in regulation of the contact system activation, via inactivation of plasma kallikrein and factor XIIa, was discovered during the 1970s
and 1980s. C1-INH is the primary regulator of the classic complement pathway activation via inactivation of C1r and C1s. The low plasma concentration of functionally active C1-INH permits overactivation of the kallikrein-kinin system, the classical complement pathway, the fibrinolytic system and the coagulation system, with release of vasoactive peptides among which bradykinin is considered to be most important. Bradykinin is released by cleavage of kinogen by kallikrein and it is capable of inducing edema as a result of its effects on vasodilation and microvessel permeability.

The exact prevalence of HAE is not known, but it has been estimated to range from 1:10,000 to 1:150,000 in the general population. This suggests that there are 2000 to 30,000 affected patients in the United States (US). Patients with HAE typically begin to swell in childhood and often experience increase symptoms beginning about the time of puberty.

Clinically, HAE is characterized by episodic recurrent episodes of subcutaneous and sub-mucosal angioedema. Swelling affects the hands and feet but also involves the genitalia, trunk, face, upper airways, larynx, and gastrointestinal tract. The disease is characterized by swelling, which is not associated with urticaria, that does not respond to antihistamines, corticosteroids or epinephrine and usually subsides spontaneously in 72 hours. In one study, abdominal attacks were reported in more than 93% of patients and composed almost 50% of all angioedema attacks. However, skin swellings appear to be the most frequent symptoms of HAE.

A positive family history of angioedema is present in most patients, although up to 25% of patients have negative family histories with a de novo C1 inhibitor mutations. Thus, the absence of a family history in the presence of typical symptoms should not be a deterrent from making the diagnosis. Even within families with the same genetic aberration symptoms vary considerably and it is not unusual for one family member to have severe recurrent attacks and another to be relatively free of symptoms.

**History of C1-INH use for prophylaxis in HAE**

The first published manuscript on the treatment of HAE with C1-INH was published in 1980 by Gadek et al. During this study, the C1-INH protein was removed from pooled plasma via chromatography. They referred to 1 unit (U) of C1-INH as the amount of C1-INH found in 1 mL of plasma. C1-INH was given to 3 of the 8 patients during asymptomatic periods. The remaining patients were given the inhibitor during acute attacks. Administration of C1-INH during acute attacks was shown to reduce the severity and duration of symptoms and signs of the acute attack. No adverse reactions were noted in relation to the administration of C1-INH concentrate. However, because of the HIV crisis in the mid 1980s research into C1 esterase replacement in the US ceased. In Europe research continued and C1-INH inhibitor was approved for treatment of acute attacks of HAE.

In 1989, Bork described a patient treated with prophylactic C1-INH. The patient was treated with intravenous concentrate during a period of 1 year. The dose was determined empirically. The patient required C1-INH concentrate every fourth or fifth day and showed clinical improvement with almost complete cessation of attacks. In addition, there were no side effects noted during the treatment time course.

The first randomized double blind control trial of C1-INH used for prophylaxis was completed with purified and vapor heated plasma in 1996. A prophylactic group of 6 patients was evaluated in a cross-over study in which subjects were randomly assigned to receive C1-INH infusion every 3 days in two different 17-day treatment periods. Disease activity was reduced 60% during the C1-INH treatment period.

In a previous study by Zuraw et al, 22 patients were investigated over a 24-week period. Subjects received C1-INH 1000 U twice weekly or placebo for 12 weeks and then randomized to the other arm. Results demonstrated that subjects had fewer attacks during the C1-INH treatment period than the placebo period (P < 0.0001). While on chronic replacement, as compared to when subjects were on placebo, subjects not only had fewer attacks, but when they had attacks, the attacks were less severe and shorter in duration. Of the 22 patients, 2 worsened while on chronic replacement therapy and one had no change in attacks.

**Pharmacology and pharmacokinetics**

C1-INH is a naturally occurring single chain glycoprotein in human blood consisting of 478 amino acids and a molecular weight of 105 kDa. As a serine protease inhibitor, the main function of C1-INH is to regulate the activity of serine proteases. The biologic half-life of C1-INH in healthy subjects is 64 ± 1.4 hours suggesting that treatment every 3 days is necessary to restore C1-INH levels (Figure 1a).
Waytes et al\textsuperscript{22} demonstrated an increase in the level of C1 inhibitor after the initial infusions of concentrate, to a mean of 85\% of normal values. Twenty-four hours after the infusion, the mean levels of C1 inhibitor were approximately 70\% of normal. At 72 hours values fell to 48\% of normal value which is still significantly above the baseline level. Therefore, it was suggested that for prophylaxis, C-1-INH could be administered every 3 to 4 days given the level of C1-INH at the end of that timeframe. Unlike C-1-INH, C4 levels do not have a sharp rise and fall within a 72-hour period, suggesting that the biologic half life of C1-INH may exceed the serum half life. C4 levels increase more slowly and after administration of C1 inhibitor every 3 to 4 days levels of C4 persist within the normal range.\textsuperscript{22}

\textbf{Figure 1.} A) Infusion of C1 esterase every third day in subjects with HAE and associated serum levels of C1 esterase inhibitor (C-1-I) compared with serum levels from normal subjects and those with HAE receiving placebo infusions. B) C4 serum levels in normal patients, and those with HAE receiving placebo or during infusion of C1 esterase inhibitor (C-1-I).

Modified from Waytes et al.\textsuperscript{22}
The pharmacokinetics of the human plasma-derived C1-INH Cinryze™ were analyzed in a randomized, parallel group, open label pharmacokinetics study. The study was performed in patients with documented HAE who were currently asymptomatic. The patients received either a single dose of 1000 U or 1000 U followed by a second 1000 U 60 minutes later. All doses were administered intravenously. There have been no additional studies to date evaluating pharmacokinetics particularly in special patient populations. There is a dearth of data on the pharmacokinetics of C1-INH. It is not known to what extent gender, race, age, disease severity or the presence of renal or hepatic impairment affects C1-INH levels when being replaced. In asymptomatic patients, the results showed that the drug has a long half life and slow clearance. The mean half-lives of Cinryze were 56 hours (range 11 to 108 hours) for a single dose and 62 hours (range 16 to 152 hours) for the double dose, as shown in Table 1. Administration of Cinryze led to an increase in the concentrations of C1-INH and complement C4 over baseline values. Both of these concentrations were higher following double dose than a single dose. However, administration of a second dose 60 minutes after the first did not follow linear kinetics.

As noted above, the safety and efficacy of Cinryze used as prophylaxis therapy showed a reduction in the incidence, severity, and duration of HAE attacks without any associated significant adverse events. These data from the single randomized, double blind, placebo controlled multi-center crossover study have not yet been published. The study consisted of 24 patients who were screened to confirm a diagnosis of HAE and a history of at least two HAE attacks per month. The patients with a mean age of 38.1 years (age range 9 to 73 years) were randomized to one of two treatment groups. The first group received Cinryze prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis. The other group was randomized to placebo prophylaxis for 12 weeks followed by 12 weeks of Cinryze prophylaxis. Patients were given blinded injections every 3 to 4 days. Patients subsequently recorded all angioedema symptoms daily. An attack was defined as the subject-reported indication of swelling at any location following a report of no swelling on the previous day. Efficacy was based on the number of attacks during the 12 week period while receiving Cinryze compared to the number of attacks during the placebo treatment period. Patients treated with Cinryze had a 66% reduction in days of swelling ($P < 0.0001$), and decreases in the average severity of attacks ($P = 0.0006$) and the average duration of attacks ($P = 0.0023$) as shown in Table 2. No studies to date have compared Cinryze to other agents used to treat HAE.

### Dosing strategy

Cinryze is available in single-use vials that contain 500 U per vial and is supplied as a single glass vial of powder to be reconstituted with 5 mL sterile water for injection. Two 500 U vials are needed to make a complete dose. The reconstituted solution must be used within 3 hours of reconstitution. The solution is drawn through the sterile filter needle into a sterile disposable syringe. The reconstituted solution should be colorless to slightly blue and free from visible particle. The full dose of 1000 U (reconstituted in 10 mL) of Cinryze is administered by intravenous injection at a rate of 1 mL per minute over 10 minutes.

### Use in special populations

Cinryze is classified as Pregnancy Category C. No animal data are available on use during pregnancy. No adequate and well-controlled studies were conducted in pregnant women during the initial trials. Therefore, it is unknown whether Cinryze can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

### Table 1 Mean pharmacokinetic parameters of functional C1 inhibitor (Cinryze)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Single dose</th>
<th>Double dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{Cmax}}$ (units/mL)</td>
<td>0.31 ± 0.20 (n = 12)</td>
<td>0.33 ± 0.20 (n = 12)</td>
</tr>
<tr>
<td>$C_{\text{Cmax}}$ (units/mL)</td>
<td>0.68 ± 0.08 (n = 12)</td>
<td>0.85 ± 0.12 (n = 13)</td>
</tr>
<tr>
<td>$T_{\text{Cmax}}$ (h)</td>
<td>3.9 ± 7.3 (n = 12)</td>
<td>2.7 ± 1.9 (n = 13)</td>
</tr>
<tr>
<td>AUC$_{\text{Cmax}}$ (units*h/mL)</td>
<td>74.5 ± 30.3 (n = 12)</td>
<td>95.9 ± 19.6 (n = 13)</td>
</tr>
<tr>
<td>$CL$ (mL/min)</td>
<td>0.85 ± 1.07 (n = 7)</td>
<td>1.17 ± 0.78 (n = 9)</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>56 ± 36 (n = 7)</td>
<td>62 ± 38 (n = 9)</td>
</tr>
</tbody>
</table>

Data from Cinryze package insert. Abbreviations: AUC, area-under-the-curve concentration; $C_{\text{Cmax}}$, peak concentration; $T_{\text{Cmax}}$, time to peak concentration.

### Table 2 Clinical trial secondary efficacy outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cinryze N = 22</th>
<th>Placebo N = 22</th>
<th>Treatment effect P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean severity of HAE attacks (score from 1 to 3) (SD)</td>
<td>1.3 (0.85)</td>
<td>1.9 (0.36)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean duration of HAE attacks (days) (SD)</td>
<td>2.1 (1.13)</td>
<td>3.4 (1.4)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Days of swelling (SD)</td>
<td>10.1 (10.73)</td>
<td>29.6 (16.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data from Cinryze package insert. Abbreviation: HAE, hereditary angioedema.
Baker et al\textsuperscript{26} presented data on six pregnant women all of whom had normal healthy deliveries while on Cinryze being used as prophylaxis. Subjects received 1000 U of Cinryze replacement 1 to 2 times per week with benefit. Since then, another patient was reported who was in her second trimester and had no difficulties in regards to her pregnancy while on C1-INH replacement. The number of attacks and number of emergency medical visits were reduced by >85%. No adverse events secondary to Cinryze were reported and the therapy reportedly was tolerated well.\textsuperscript{26}

At the present time, no data are available to suggest that C1-INH replacement is beneficial or harmful for the newborn or mother during lactation. It is suggested that caution should be exercised when administering Cinryze to a nursing woman, but this is due to the lack of available data. It is unknown whether Cinryze is excreted in human milk. The lack of data suggests that therapy should only be used during lactation when benefit outweighs risk and only after informed consent has been given by the patient.

The safety and effectiveness of Cinryze have not been established in neonates, infants, or children. Previous data found that very high doses of C1-INH given to premature neonates without HAE can predispose to hypercoagulation and thrombotic events.\textsuperscript{27} The only information suggesting the safety of C1-INH replacement is from three of the 24 subjects that completed the prophylaxis efficacy study who were under the age of 18 years. The youngest in the study was 9 years of age. Benefit and adverse events seemed to be similar to those over the age of 18 years of age. In addition, the study did not include sufficient numbers of subject 65 years of age and older to determine whether they respond differently from younger subjects.

**Safety and tolerability**

As noted, Cinryze was well tolerated during the clinical trial. Most of the observed drug related adverse effects were mild. The most common drug related adverse reactions observed at a rate ≥5% were upper respiratory tract infections, sinusitis, rash, and headache.\textsuperscript{25} There were severe adverse reactions that were thought to be unrelated to the study drug. These included death due to non-catheter related foreign body embolus, pre-eclampsia resulting in emergency cesarean section, stroke, and exacerbation of HAE attacks.

Thrombotic events were reported in association with other C1-INH products when used off-label at high doses. The thrombotic adverse events occurred during clinical trials for another indication and at doses of 4000 Us given over approximately 5 hours (an average dose of 57 U/kg) and 9000 Units given over a 7-day period.\textsuperscript{27} At least one case of a thrombotic event has been reported to the Food and Drug Administration (FDA) during the Cinryze postmarketing period; however, it is not clear whether the thrombosis was secondary to an indwelling catheter, C1-INH or the combination of both.

In vitro and in vivo animal thrombogenicity studies with Cinryze showed a potential for clot formation when administered at doses 14 times the recommended clinical dose (greater than 200 U/kg). This is also supported by animal studies when given intravenous administration of other C1-INH products.\textsuperscript{28}

Because Cinryze is derived from human plasma, there is an inherent risk of viral transmission with its use. Steps designed to reduce the risk of viral transmission include screening donors at U.S. licensed blood collection centers. Donors are screened for infection with human immunodeficiency virus (HIV-1/HIV-2), hepatitis B virus, hepatitis C virus, and parvovirus B19. In addition, to reduce the possibility of viral transmission the units of plasma are not released until the donor returns in 3 months and if at that time the serologies are negative the plasma is released for processing. This time interval helps assure that HIV is not missed since during the window phase of infection HIV may be present even though serologies are negative. The use of two independent viral reduction steps in the manufacturing of Cinryze further reduces the possibility of viral transmission and includes pasteurization (heat treatment at 60°C for 10 hours in solution with stabilizers) and nanofiltration through two sequential 15 nm Planova filters.\textsuperscript{25}

Cinryze is contraindicated in patients with any known hypersensitivity reactions to any constituents. An interesting concern arises when trying to distinguish between an acute angioedema attack versus a hypersensitivity reaction and as with other products used to treat HAE the occurrence of hypersensitivity may be over estimated secondary to HAE attacks mimicking hypersensitivity reaction.

No drug interaction studies have been conducted.

**FDA approval details**

The human plasma-derived C1-INH, Cinryze, distributed by Lev Pharmaceuticals, was approved in October 2008 for the prevention of HAE attacks based on the results of the phase III clinical trial. It is manufactured by Sanquin Blood Supply Foundation Amsterdam, The Netherlands. Sanquin is also a producer for C1-INH in Europe. The FDA has requested that postmarketing studies be performed to address the following issues to include the optimal dose.
Table 3 HAE prophylactic therapy consideration criteria (goal of therapy: enable each HAE patient to live as normal a life as possible)

<table>
<thead>
<tr>
<th>Consideration criteria</th>
<th>Prophylactic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of attacks</td>
<td>≥ 1/month</td>
</tr>
<tr>
<td>Rapid progression of attacks</td>
<td>Yes</td>
</tr>
<tr>
<td>Timely access to care</td>
<td>No</td>
</tr>
<tr>
<td>History of laryngeal attacks</td>
<td>Yes</td>
</tr>
<tr>
<td>Emergency visit to physician/hospital</td>
<td>&gt;3/year</td>
</tr>
<tr>
<td>Intubation due to HAE</td>
<td>Yes</td>
</tr>
<tr>
<td>Hospitalized due to HAE</td>
<td>&gt;1/year</td>
</tr>
<tr>
<td>ICU due to HAE</td>
<td>Yes</td>
</tr>
<tr>
<td>Missed days of school or work</td>
<td>≥ 10–15 days/year</td>
</tr>
<tr>
<td>Impacts lifestyle (vacation, family, sports)</td>
<td>Yes</td>
</tr>
<tr>
<td>Analgesic dependency</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes: These therapy consideration criteria are for guidance only. Therapy decisions are always based on close consultation between physician and patient on what the best course of therapy should be for a patient’s particular needs, problems and concerns.

Adapted from Craig et al.30

Abbreviation: HAE, hereditary angioedema.

for prophylaxis in males and females, immunogenicity and long-term safety. Currently, there are no submitted data on the safety profile of an intensified dose schedule of Cinryze for routine prophylaxis.

Table 4 A Comparison of approved and developing treatments for HAE in the USA

<table>
<thead>
<tr>
<th>Method of production</th>
<th>Mechanism of action</th>
<th>Half-life</th>
<th>Method of treatment</th>
<th>FDA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP (fresh frozen plasma)</td>
<td>Blood product</td>
<td>Replaces C1 esterase inhibitor</td>
<td>Long</td>
<td>IV</td>
</tr>
<tr>
<td>Androgens</td>
<td>Traditional therapeutics</td>
<td>Induces C1 esterase inhibitor production</td>
<td>long</td>
<td>Oral</td>
</tr>
<tr>
<td>Antifibrinolytics</td>
<td>Traditional therapeutics</td>
<td>Decreases activation of factor 12</td>
<td>Long</td>
<td>Oral</td>
</tr>
<tr>
<td>Berinert® P</td>
<td>Plasma concentrate</td>
<td>C1 inhibitor</td>
<td>24–46.5 h</td>
<td>IV</td>
</tr>
<tr>
<td>Cinryze™</td>
<td>Plasma concentrate</td>
<td>C1 inhibitor</td>
<td>24–46.5 h</td>
<td>IV</td>
</tr>
<tr>
<td>Rhucin®</td>
<td>Recombinant protein</td>
<td>C1 inhibitor</td>
<td>3 h</td>
<td>IV</td>
</tr>
<tr>
<td>Ecallantide</td>
<td>Recombinant protein</td>
<td>Kallikrein inhibitor</td>
<td>1–4 h</td>
<td>SC</td>
</tr>
<tr>
<td>Icatibant</td>
<td>Synthetic peptide</td>
<td>Bradykinin-2 receptor antagonist</td>
<td>1–4 h</td>
<td>SC</td>
</tr>
</tbody>
</table>

Abbreviations: HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous.

Data for using Cinryze to treat active HAE attacks has been submitted to FDA, but Viropharma did not receive an approval for Cinryze for acute attacks of HAE. Open label data were presented at the American College of Allergy, Asthma and Immunology (ACAAI) annual meeting in 2008 for the treatment of acute attacks with Cinryze. Dr. Bruce Zuraw presented data titled: “Results of open-label administration of nanofiltered C1-inhibitor for the treatment of acute HAE attacks”.29 The study enrolled 88 subjects with documented HAE. Patients were screened and enrolled in an acute treatment open-label protocol. Eligible subjects received open-label injections of Cinryze for acute attacks of angioedema occurring at any anatomical site and could receive a second open-label injection of Cinryze 60 minutes later if they had not improved. Twenty-four subjects were followed for greater than one year. Throughout the study, 447 acute attacks were treated in 82 subjects who had at least 1 attack. The primary locations of treated attacks were extremities, facial, gastrointestinal, genitourinary, and laryngeal. The median time to improvement was 30 minutes in the 447 attacks that occurred, and 93.4% of patients reported improvement in symptoms within 4 hours. This was noted regardless of how many times they had previously received Cinryze. None of the subjects in this study treated...
for laryngeal attacks required hospitalization or intubation. Despite this positive data, the P value for the primary outcome did not reach significance and the drug was not approved in the US for use in acute attacks. There were no serious adverse reactions thought to be related to Cinryze administration.

Conclusions

The recommended dose for HAE prophylaxis is 1000 units (two 5 mL vials) every 3 or 4 days. Thus, a maximum of 10,000 U are considered medically necessary per 30 days for HAE prophylaxis. The current wholesale price for Cinryze is $2,437.50 per vial. With a therapeutic dosing regimen, the monthly cost of therapy would range from $36,562 to $48,750 per patient. This cost is a major burden on the patient even if the patient needs to pay a small co-pay.

Controversy exists on when to treat people with chronic replacement therapy, especially since medications such as androgens are effective, inexpensive and often tolerated well at low doses as shown in Table 3. It appears that patients with severe disease, those who fail to be controlled with androgens, or those with adverse events to androgens are good candidates for Cinryze chronic replacement therapy.

Further studies need to be conducted for special populations including pediatric patients, geriatric patients, and women during pregnancy. Also, dose escalation studies in those that are not controlled on approved doses of Cinryze are needed and according to the Clinical Trials Website are being conducted at the present time. Safety when using higher doses is important because of the prior evidence of thrombotic events in neonates treated with high doses of C-1-INH.

Postmarketing surveillance will also be important especially since Cinryze was approved for chronic replacement therapy based upon safety from a limited number of subjects. It appears that phase III studies will need to be repeated before approval of Cinryze for acute attacks. The use of Cinryze on demand at the time of prodromal symptoms should be effective in preventing an acute attack, but this study still needs to be performed. In addition, short-term prophylaxis, such as treatment before dental work and surgery, need to be performed to confirm the efficacy and safety when using Cinryze for short-term prophylaxis.

In summary, Cinryze provides replacement therapy in those that have deficiency of the protein and thus is a physiologic approach to therapy and hopefully will add significantly to the quality of life in patients that have HAE. It is anticipated that the safety and tolerance will continue to be benign and acceptable. As other medications become available (Kalbitor® Berinert®) and still others are approved (Icatibant®) for use in the US it will be interesting to see how the use of Cinryze evolves over the next 5 to 10 years (Table 4).

Disclosure

The authors declare no conflicts of interest.

References


