
Population pharmacokinetics of plasma-derived C1 esterase inhibitor concentrate used to treat acute hereditary angioedema attacks

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Background: C1 esterase inhibitor (C1-INH) replacement is recommended as a first-line therapy for acute edema attacks in hereditary angioedema (HAE). Only limited pharmacokinetic analyses of the administered C1-INH in plasma are available.

Objective: To investigate retrospectively the population pharmacokinetics of a plasma-derived C1-INH (pC1-INH) concentrate used to treat acute HAE attacks in a randomized, placebo-controlled phase 2/3 study in patients with HAE.

Methods: Acute abdominal and facial attacks were treated with either a pC1-INH concentrate (Berinert) at single intravenous doses of 10 or 20 U/kg body weight or placebo. Plasma sampling was conducted 0, 1, and 4 hours after dosing. A nonlinear retrospective population pharmacokinetic model was obtained using the assumption of a 1-compartment model.

Results: The final population pharmacokinetic model was based on data from 97 patients treated with 10 or 20 U/kg of pC1-INH concentrate. The estimated mean half-life was 32.7 hours (90% confidence interval, 16.6–48.8 hours), and the estimated mean clearance was 0.92 mL/kg/h (90% confidence interval, 0.50–1.33 mL/kg/h).

Conclusions: The half-life of the same pC1-INH concentrate reported in a previous study was confirmed by this retrospective population pharmacokinetic analysis in patients treated for acute HAE attacks. In contrast to other treatment options with shorter half-lives, the long half-life of pC1-INH concentrate may provide an extended period of protection, even after the symptoms of an attack have subsided.

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INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by decreased activity or decreased production of C1 esterase inhibitor (C1-INH).¹ The disease has a prevalence of approximately 1 in 50,000.² C1-INH belongs to the

serine protease inhibitor superfamily of enzymes. It is involved in the regulation of vascular permeability by inhibiting certain steps in the complement system (mainly C1 and C-kinins), the coagulation system (factor XIIa and kallikrein), and the fibrinolytic system (thrombin and tissue plasminogen

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activator).³ Three variants of HAE have been described: type 1, involving low C1-INH antigenic protein and functional activity (85% of cases; autosomal dominant); type 2, involving normal or elevated protein levels but low C1-INH function (15% of cases; autosomal dominant); and the more recently described and rare type 3 that occurs mainly in women, involving normal C1-INH protein levels together with functional mutations in coagulation factor XII and other defects yet to be identified.^{4–8}

Patients with HAE may experience recurrent edema of subcutaneous tissues (extremities, genitals, face, trunk, or elsewhere); intestinal swellings, with abdominal pain, nausea, vomiting, or diarrhea; and life-threatening swellings of the airway.⁴ Untreated attacks tend to be prolonged, typically increasing during the first 24 hours and then slowly and spontaneously subsiding after 48 to 72 hours. The frequency of attacks is variable and typically ranges from 1 to more than 26 attacks per year.^{9,10}

Androgens and antifibrinolytics are commonly used to prevent the occurrence of type 1 and 2 HAE attacks, but these drugs cannot stop an acute attack in progress.¹¹ Intravenous administration of plasma-derived C1-INH (pC1-INH) concentrate is the recommended first-line treatment for acute HAE attacks.² Berinert (CSL Behring, Marburg, Germany) is a highly purified, virus-inactivated pC1-INH that is approved in many countries for the treatment of acute HAE attacks.^{2,12} This product has been used for more than 20 years in more than 300,000 treatments, with a consistently excellent safety record.¹

Only limited data are available on the pharmacokinetics of pC1-INH concentrate after its administration for the treatment of acute HAE attacks. Recently, the placebo-controlled I.M.P.A.C.T.1 (International Multicenter Prospective Angioedema C1-INH Trial 1) study demonstrated that acute abdominal and facial attacks are safely and effectively treated with pC1-INH concentrate (Berinert) given at an intravenous dose of 20 U/kg body weight.¹³ Herein, we report a retrospective population pharmacokinetic analysis based on plasma concentrations of C1-INH measured during the I.M.P.A.C.T.1 study. The objective was to estimate pharmacokinetic variables for pC1-INH based on a relatively large number of patients, including an estimate of the half-life as an indicator that pC1-INH concentrate can provide an extended period of C1-INH activity after its administration for treating acute HAE attacks.

METHODS

Study Design

I.M.P.A.C.T.1 was a multinational, parallel-group, randomized, placebo-controlled, 3-arm, double-blind, phase 2/3 study conducted between August 2005 and December 2007 to investigate the efficacy and safety of pC1-INH concentrate in the treatment of acute HAE attacks. An independent ethics committee or institutional review board at each participating center approved the protocol. Each patient gave written in-

formed consent, or, in the case of a minor, consent was given by a legally acceptable representative. Assents were also obtained when appropriate. An independent data and safety monitoring board constituted specifically for the I.M.P.A.C.T.1 study oversaw the safety of the study.

Patients were included in the study if they had laboratory-confirmed C1-INH deficiency (type 1 or 2 HAE), were 6 years or older, and had been treated with pC1-INH concentrate (Berinert) at a single intravenous dose of 10 or 20 U/kg on presentation of an acute moderate to severe abdominal or facial attack within 5 hours of the attack attaining moderate intensity (as assessed by the patient and confirmed by the investigator). In addition, patients were included if pC1-INH concentrate was given as rescue study medication (see the next paragraph). The main exclusion criteria were a history of hypersensitivity to C1-INH concentrate, acquired and all other types of angioedema, abdominal or facial pain not associated with C1-INH deficiency, use of pain medication during a current attack, and treatment with any C1-INH concentrate or other drug appropriate for acute angioedema or with fresh frozen or native plasma within 7 days before the start of treatment in the present study.

Patients were observed for onset of symptom relief for at least 4 hours after treatment, after which they could receive a second dose of study treatment (called “rescue study medication”) if they reported insufficient or no symptom relief: pC1-INH, 20 U/kg, for patients taking placebo; pC1-INH, 10 U/kg, for patients taking pC1-INH, 10 U/kg; and placebo for patients taking pC1-INH, 20 U/kg.

The design of the I.M.P.A.C.T.1 study, together with the efficacy and safety data obtained, have been reported by Craig et al.¹³ Herein we report a retrospective population pharmacokinetic analysis that was based on plasma concentrations of C1-INH measured during the study.

Pharmacokinetic Analysis

Blood sampling for the determination of plasma C1-INH concentrations was performed 0, 1, and 4 hours after each treatment with pC1-INH concentrate (10 or 20 U/kg), which was given either during initial dosing for an acute abdominal or facial HAE attack or as rescue study medication after 4 hours. Sampling extended up to 24 hours after dosing in some patients until their discharge from the clinic. C1-INH activity was measured using a nephelometric assay at the study’s central laboratory (Laboratory Prof. Seelig und Kollegen, Karlsruhe, Germany).

The following retrospective population pharmacokinetic model was used, assuming that C1-INH elimination in plasma follows a 1-compartment model:

$$C(t) = \text{Dose}/V \times \exp(-\lambda t),$$

where V represents the volume of distribution; λ , the elimination rate constant; and $C(t)$, the change in C1-INH concentration from baseline to time t .

In cases where a patient received rescue study medication, the second dose was included in the model as a single dose

that was equivalent to the sum of the initial dose of study treatment and the dose of rescue study medication.

The previous model was transformed into a preliminary linear model as follows:

$$\text{Log}[C(t)/\text{Dose}] = -\text{Log}(V) - \lambda t.$$

The linear data were analyzed in a random coefficient regression model using the SAS procedure MIXED, with patients (intercepts and slopes) as a random effect and treatment phase (initial, rescue, or emergency) as a fixed effect. Using all available data, preliminary estimates were obtained (after back transformation to original scale units) for population means of volume of distribution and half-life. Half-life was estimated from λ as $0.693/\lambda$.

Using the truncated mean approach of removing 3 patients each with the smallest and largest elimination rates, the final pharmacokinetic estimates were then obtained using the untransformed (nonlinear) model (using the SAS procedure NLMIXED). All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Study Population

As reported by Craig et al,¹³ 125 patients were randomized for treatment in the I.M.P.A.C.T.1 study. The treatment groups were similar in terms of sex, age, and race or ethnic group, and 108 patients had type 1 HAE. Overall, 98 patients experienced abdominal attacks, 25 experienced facial attacks, and 1 experienced a laryngeal attack. Another patient needed emergency rescue study medication (pC1-INH, 20 U/kg) for a laryngeal attack before randomization for the intended (initial) treatment. Patients were initially treated as follows: placebo: 41 patients; pC1-INH, 10 U/kg: 39 patients; and pC1-INH, 20 U/kg: 45 patients. The number of patients who received rescue study medication was considerably higher with placebo ($n = 24$) than with pC1-INH, 10 U/kg ($n = 13$) or 20 U/kg ($n = 8$).

Outcomes

Of the 108 patients treated with pC1-INH concentrate (10 or 20 U/kg), either initially or as rescue study medication, 4 had no available C1-INH data after baseline and 1 had unreliable C1-INH data (no increase after baseline). Therefore, 103 patients were evaluated in the pharmacokinetic analysis according to the preliminary linear model. After removal of 3 additional patients each with the smallest and largest elimination rates, 97 patients were included in the pharmacokinetic analysis according to the final nonlinear model. For this analysis, samples were available from 97 patients 0 and 1 hour after treatment, from 87 patients 4 hours after treatment, and from 11 patients 4 to 24 hours after treatment.

Using all available data from 103 patients, and after back transformation to original scale units, the mean population estimates from the preliminary (linear) model were 28.7 hours for the half-life of pC1-INH concentrate and 0.48 dL/kg for volume of distribution (Table 1). Based on data

Table 1. Retrospective Population Pharmacokinetic Analysis of pC1-INH Concentrate After Single-Dose Administration for the Treatment of Acute HAE Attacks

Pharmacokinetic variable	Estimate of expected mean	90% CI
Preliminary (linear) model ($n = 103$)		
Half-life, h	28.7	15.3–237.4
Volume of distribution, dL/kg	0.48	0.42–0.55
Final (nonlinear) model ($n = 97$)		
Half-life, h	32.7	16.6–48.8
Volume of distribution, dL/kg	0.43	0.40–0.47
Clearance, mL/kg/h	0.92	0.50–1.33

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; n , number of subjects; pC1-INH, plasma-derived C1 esterase inhibitor.

from the 97 patients included in the final (nonlinear) model, the estimated values for the pharmacokinetics of pC1-INH concentrate were 32.7 hours for half-life, 0.43 dL/kg for volume of distribution, and 0.92 mL/kg/h for clearance (Table 1).

DISCUSSION

In this study, the population pharmacokinetics of pC1-INH were analyzed retrospectively using plasma samples obtained mostly during the first 4 hours after treatment of acute abdominal and facial attacks with C1-INH concentrate in the I.M.P.A.C.T.1 study.¹³ The main focus of this pharmacokinetic analysis was to evaluate the half-life of C1-INH when given in response to an acute attack, ie, in patients with symptomatic HAE, in a relatively large number of patients. The half-life gives insight into the potential for pC1-INH concentrate to provide an extended period of C1-INH activity and, thereby, minimize the risk of rebound edema. Other potential therapeutic options for treating acute HAE attacks, most of which have yet to be marketed, include ecallantide (a protein kallikrein inhibitor), icatibant (a bradykinin B_2 receptor antagonist), and transgenic human C1-INH. These therapies all have a short half-life and, therefore, a limited prophylactic effect,¹⁴ so their use for treating acute HAE attacks could be associated with an increased risk of rebound edema. The population estimate for the half-life of pC1-INH was 32.7 hours, which is considerably longer than the half-life of ecallantide (1.2 hours),¹⁵ icatibant (1.2–1.5 hours),¹⁶ or transgenic human C1-INH concentrate (approximately 3 hours).¹⁷ The remarkable difference in half-life between transgenic C1-INH and pC1-INH concentrates is believed to be due to alterations in the N-linked glycosylation pattern of the transgenic molecule, which is expressed in the milk of transgenic rabbits compared with the human plasma-derived molecule.¹⁷

As summarized in Table 2, limited data are available in the literature on the pharmacokinetics of pC1-INH concentrate. The comparison of the present data with these studies based on single dosing is valid because the present study was

Table 2. Summary of the Single-Dose Pharmacokinetic Variables for pC1-INH Concentrate Reported in the Literature

pC1-INH product (dose)	Population	Mean (SD)	
		Half-life, h	Clearance, mL/kg/h
Beriner ¹⁸ (500 or 1000 U)	Adults with asymptomatic HAE (individual replacement therapy, n = 15)	33.3 (23.2)	1.1 (1.8)
Noncommercial product ¹⁹ (25 plasma U/kg body weight)	Adults with asymptomatic HAE (on-demand therapy, n = 19)	47.8 (21.2)	0.9 (0.4)
	Adults and children with symptomatic HAE (n = 11)	37.9 (19.8)	1.2 (0.4)
Cinryze ²⁴ (1000 U)	Adults with asymptomatic HAE (n = 7)	56 (36)	0.85 (1.07)
C1-esterase inhibitor-N ²⁸ (1000, 1500, or 2000 U)	Adults with asymptomatic HAE (n = 36)	40.2 (NA)	0.70 (NA) ^a
Noncommercial product ²⁵ (1 mg of ¹²⁵ I-C1-INH in 2 mL)	Healthy adults (n = 3)	64.0 (1.4)	NA
	Adults with asymptomatic HAE (n = 3)	67.7 (4.9)	NA

Abbreviations: HAE, hereditary angioedema; n, number of subjects; NA, not available; pC1-INH, plasma-derived C1 esterase inhibitor; SD, standard deviation.

^a Calculated assuming 75 kg of body weight, the reported value was 0.0527 L/h.

essentially a single-dose study despite administration of rescue medication in some cases. Where it occurred due to administration of rescue study medication, the second dose was included in the model as being equivalent to the sum of the initial dose of study treatment and the dose of rescue study medication. Although this approach to handling patients who received rescue medication could be considered a limitation of this analysis, it also reflects the regimen that is used in practice for treating acute attacks.

The most relevant data for comparison of these findings were reported by Martinez-Saguer et al,¹⁸ who treated patients with a single 500- or 1000-U dose of the same pC1-INH concentrate (ie, Beriner) during an attack-free and substitution-free interval of at least 3 days. The mean half-life of pC1-INH in adults with a high frequency of severe attacks (≥ 1 attack per week, treated with individual replacement therapy) was 33.3 hours, and the mean half-life in adults with a lower frequency of severe attacks (maximum of 1–2 attacks per month, treated with on-demand therapy) was 47.8 hours. The population estimate of 32.7 hours for the half-life of pC1-INH, obtained in patients with symptomatic HAE, was comparable with these values, especially for adults with a high frequency of severe attacks. This estimate was also comparable with the mean half-life of 37.9 hours reported for patients with symptomatic HAE treated with a different pC1-INH concentrate.¹⁹ Our own data, as well as these published data for the half-life of pC1-INH concentrate, are also consistent with the half-life of 35.5 hours that was reported when pC1-INH concentrate was administered for the treatment of myocardial injury.^{20,21}

In general, the variability (% coefficient of variation) in the half-lives reported for pC1-INH was relatively high, ranging from 44% to 74% in the study by Martinez-Saguer et al,¹⁸ and with a mean of 52% in the study by Kunschak et al (Table 2).¹⁹ A direct comparison with the variability around the population estimate in the present study is not possible due to

the methodological difference, but despite use of the truncated mean method to reduce variability, the relatively wide 90% confidence interval (16.6–48.8 hours) around the estimated mean of 32.7 hours indicates a relatively high degree of variability (Table 1). This variability was probably affected by having had more samples obtained at earlier rather than later times after treatment, ie, by the concentration of samples obtained up to 4 hours after treatment. Given the variability seen in other studies involving sampling periods of 24 hours or more, it is improbable that the variability seen in this study was driven only by the fact that the estimate for half-life was based mostly on samples taken for up to only 4 hours after treatment. The variability in the elimination of C1-INH may be inherently high owing to different degrees of complement activation during an attack, leading to variability in the rates of metabolic clearance.^{22,23}

A pC1-INH concentrate recently approved in the United States for prophylactic treatment of HAE attacks (Cinryze; ViroPharma, Exton, Pennsylvania) was reported to have a half-life of 56 hours in adults with asymptomatic HAE (n = 7),²⁴ and a noncommercial product had a half-life that exceeded 60 hours in adults with asymptomatic HAE (n = 3) and in healthy adults (n = 3)²⁵ (Table 2). There is no obvious explanation as to why these half-lives were so much longer than those observed in the present study and in the studies by Martinez-Saguer et al¹⁸ and Kunschak et al.¹⁹ However, of note is that in the study by Brackertz et al,²⁵ the patients had been symptom free for at least 2 months before treatment, and in the Cinryze study they had been symptom free for at least 7 days.²⁶ One potential effect on the half-life of C1-INH in plasma is the temporal relationship between an HAE attack and the administration of pC1-INH concentrate on which the pharmacokinetic analysis is based. C1-INH is degraded only in plasma when it complexes with its target proteinases.²⁷ Hence, the half-life of pC1-INH could tend to be

longer in patients who had been asymptomatic for a relatively long period.

A further consideration is the small number of participants in these studies and the relatively high degree of variability in the pharmacokinetics of C1-INH, as described previously herein. For example, for C1-esteraseremmer-N, a C1-INH concentrate identical to Cinryze but made from plasma sourced from outside the United States, a study²⁸ in 36 patients with asymptomatic HAE reported a half-life of only 40.2 hours compared with the 56 hours reported for Cinryze in 7 patients.²⁴ Although retrospective in nature, a strength of this analysis is that the data were obtained in 97 patients, which is a relatively large population in this indication. Further confidence in these data is provided by the general agreement with the pharmacokinetic data reported by Martinez-Saguer et al¹⁸ for the same C1-INH concentrate.

The estimated clearance of 0.92 mL/kg/h in this study fell within the range of values reported in other studies for the same pC1-INH concentrate (mean values of 0.9–1.1 mL/kg/h)¹⁸ and for other pC1-INH concentrates (mean values of 0.7–1.2 mL/kg/h)^{19,24,28} (Table 2).

In conclusion, this retrospective population pharmacokinetic estimate of 32.7 hours for the half-life of pC1-INH concentrate based on samples collected during the I.M.P.A.C.T.1 study confirms the values obtained using intensive pharmacokinetic analyses in the study by Martinez-Saguer et al¹⁸ using the same pC1-INH concentrate. Thus, in the I.M.P.A.C.T.1 study, in addition to the rapid onset of relief (median, 30 minutes), none of the patients treated with pC1-INH concentrate at the recommended dose of 20 U/kg experienced rebound edema, which was defined as the lack of a new attack before complete resolution of the previous attack.¹³ These results indicate that when pC1-INH concentrate is dosed as recommended, and in contrast to other treatment options with shorter half-lives, its long half-life provides an extended period of C1-INH activity, even after the symptoms of an attack have subsided. This information on the half-life of C1-INH is essential for practitioners to be able to proactively address the clinical needs of their patients with HAE.

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REFERENCES

1. Bork K. Pasteurized C1 inhibitor concentrate in hereditary angioedema: pharmacology, safety, efficacy and future directions. *Expert Rev Clin Immunol*. 2008;4:13–20.
2. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol*. 2008;100(suppl 2):S30–S40.
3. Davis AE. The pathophysiology of hereditary angioedema. *Clin Immunol*. 2005;114:3–9.
4. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(suppl):S51–S131.
5. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356:213–217.
6. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol*. 2004;114:629–637.
7. Cugno M, Zanichelli A, Foeni F, Caccia S, Cicardi M. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends Mol Med*. 2009;15:69–78.
8. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006;343:1286–1289.
9. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol*. 2006;101:619–627.
10. Levy JH, O'Donnell PS. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Investig Drugs*. 2006;15:1077–1090.
11. Epstein TG, Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs*. 2008;68:2561–2573.
12. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol*. 2005;139:379–394.
13. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124:801–808.
14. Craig T, Riedl M, Dykewicz MS, et al. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol*. 2009b;102:366–372.
15. Zuraw BL. Novel therapies for hereditary angioedema. *Immunol Allergy Clin North Am*. 2006;26:691–708.
16. Wagner F, Rosenkranz B, Knolle J. Absolute bioavailability of subcutaneously administered icatibant, a selective and potent bradykinin B₂ receptor antagonist. *J Allergy Clin Immunol*. 2007;119:S274.
17. van Doorn MB, Burggraaf J, van Dam T, Eerenberg A, Levi M, Hack CE. A phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. *J Allergy Clin Immunol*. 2005;116:876–883.
18. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, von Hentig N, Klingebiel T, Kreuz W. Pharmacokinetic analysis of human plasma-derived pasteurized C1-inhibitor concentrate in adults and children with hereditary angioedema: a prospective study. *Transfusion*. 2010;50:354–360.
19. Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion*. 1998;38:540–549.
20. de Zwaan C, Kleine AH, Diris JH, Glatz JF, Wellens HJ, Strengers PF. Continuous 48-h C1-inhibitor treatment, following reperfusion therapy,

-
- in patients with acute myocardial infarction. *Eur Heart J*. 2002;23:1670–1677.
21. Diris JH, Hermens WT, Hemker PW, Lagrand WK, Hack CE, van Diejen-Visser MP. Pharmacokinetics of C1-inhibitor protein in patients with acute myocardial infarction. *Clin Pharmacol Ther*. 2002;72:498–504.
22. Blaskó B, Széplaki G, Varga L, et al. Relationship between copy number of genes (C4A, C4B) encoding the fourth component of complement and the clinical course of hereditary angioedema (HAE). *Mol Immunol*. 2007;44:2667–2674.
23. Varga L, Széplaki G, Visy B, et al. C1-inhibitor (C1-INH) autoantibodies in hereditary angioedema: strong correlation with the severity of disease in C1-INH concentrate naïve patients. *Mol Immunol*. 2007;44:1454–1460.
24. Cinryze [US package insert]. Exton, PA: ViroPharma; 2008.
25. Brackertz D, Isler E, Kueppers F. Half-life of C1INH in hereditary angioneurotic oedema (HAE). *Clin Allergy*. 1975;5:89–94.
26. Lev Pharmaceuticals Inc. Pharmacokinetics of C1 esterase inhibitor in hereditary angioedema subjects. <http://clinicaltrials.gov/ct2/show/NCT00432510?term=angioedema&rank=14>. Accessed November 10, 2009.
27. Caliezi C, Wuillemin WA, Zeerleder S, Redondo M, Eisele B, Hack CE. C1-esterase inhibitor: an anti-inflammatory agent and its potential use in the treatment of diseases other than hereditary angioedema. *Pharmacol Rev*. 2000;52:91–112.
28. Cinryze FDA clinical pharmacology review. <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm094084.pdf>. Accessed November 10, 2009.
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