CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125267/0
Sponsor: Lev Pharmaceuticals, Inc
Product: Cinryze TM (C1 Esterase Inhibitor)
Indication: For the treatment of hereditary angioedema (HAE)
Date Received: July 31, 2007
Reviewer: Iftekhar Mahmood, Ph. D.
RPM: Nannette Cagungun
Through: Basil Golding, M.D.
Date: December 4, 2007

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INTRODUCTION

C1 esterase inhibitor (C1INH) is a naturally occurring single chain glycoprotein in human blood. C1INH is a serine protease inhibitor and a member of the serpin family. In its mature state, C1INH consists of 478 amino acids with an apparent molecular weight of 105 kDa. Its main function is to regulate the activity of serine proteinases.

C1INH is indicated for the treatment of hereditary angioedema (HAE). HAE is a syndrome resulting from the heterozygous deficiency of endogenous C1INH, and this deficiency results in attacks of non-itching swellings of the skin or mucosa. In general, these swellings do not hurt, but acute attacks of angioedema may be life threatening if sites such as the larynx are affected, and angioedema is often associated with significant morbidity if it occurs in the gastrointestinal system. Hence, HAE attacks require prompt treatment, often in an emergency room. Administration of an exogenously C1INH increases plasma levels of C1INH activity and temporarily restores the natural regulation of the contact, complement, and fibrolytic systems.

C1INH is obtained from US source plasma which is purified and concentrated. US commercial product will come solely from US plasma donors and will be collected in US licensed plasma collection centers.

Lev Pharmaceuticals, the sponsor for this product for the US market, has been granted orphan drug status, and has contract with Sanquin Plasma Products of Amsterdam, the Netherlands to manufacture this product for them. Sanquin is a producer of C1INH for Europe.

The name chosen by Lev Pharmaceuticals for this product for the US is Cinryze™. The final product is an aseptically filled, lyophilized product containing 500 U per vial. It is contained in an 8 mL Type I glass vial. The product is to be reconstituted with 5 ml of water for Injection to provide 100 U per ml as an injectable product. The route of administration of Cinryze is intravenous. The dosing regimen is as follows:

- Acute treatment: 1000 U per episode followed by a second dose of 1000 U if the patient has not responded within 60 minutes.
- Short term prophylaxis: 1000 U two 24 hours before ----(b)(4)------

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.3 Pharmacokinetics

A randomized, parallel group, open label pharmacokinetics (PK) study of Cinryze was performed in patients with non-symptomatic hereditary angioedema (HAE). The patients received either a single dose of 1000 U or 1,000 U followed by a second 1,000 U 60 minutes later. The PK results for functional C1 inhibitor are presented in the following Table.

Mean pharmacokinetic parameters of Functional C1INH

Parameters	Single Dose	Double Dose
$C_{baseline}$ (U/mL)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (U/mL)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
T_{max} (hrs)	3.9 ± 7.3 (n = 12)	2.7 ± 1.9 (n = 13)
$AUC_{(0-t)}$ (U*hr/mL)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
CL (mL/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Half-life (hours)	56 ± 36 (n = 7)	62 ± 38 (n = 9)

Numbers in parenthesis are number of subjects evaluated
Single dose = 1000 U
Double dose = 1,000 U followed by a second 1,000 U 60 minutes later

The maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) appeared to increase from the single to double dose, although the increase was not dose proportional. The mean half-lives of Cinryze were 56 hours (range: 11 to 108 hours) for a single dose and 62 hours (range: 16-152 hours) for the double dose.

In patients with an acute HAE attack, both the increase in C1 inhibitor plasma levels as well as half-life may be reduced (Sponsor: ----------(b)(5)----------).

Studies have not been conducted to evaluate the PK of Cinryze in special patient populations identified by gender, race, age (pediatric or geriatric), or in the presence of renal or hepatic impairment.

The sponsor has accepted the FDA's proposed clinical pharmacology labeling as suggested above (without change).

RECOMMENDATION

From pharmacokinetics perspective, this study is acceptable.

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Study #1

Study Title: Pharmacokinetics of C1 INH-nf (Cinryze) in hereditary angioedema subjects.

This was a randomized, parallel group, open label study to compare the PK of a single dose of Cinryze to that of 2 doses (1 dose followed by a second dose 60 minutes later). This study was performed in subjects with hereditary angioedema (HAE) who were not experiencing an HAE attack at the time the blood samples were obtained. Subjects were randomized to receive either 1 or 2 doses of Cinryze. Only subjects who had been enrolled or were currently enrolled in the safety and efficacy study (LEVP 2005-1) were eligible to participate in this study. Cinryze was administered at a dose of 1000 U by intravenous (IV) infusion.

There were 27 subjects in the study (1 to 46 years of age). Of the 27 subjects, 13 received single dose and 14 received double dose. There were 5 subjects in each dosing group who were <15 years old (a total of 10 subjects). Subjects received either 1 dose (1000 U Cinryze) or 2 doses (1 dose followed by a second dose 60 minutes later). Blood samples were taken before dosing and at 5 minutes, 1, 3, 6, 24, 48, 96, and 168 hours post dosing. Plasma concentrations of antigenic C1 inhibitor, functional C1 inhibitor, and C4 antigen were measured for PK evaluation. The following assay methods were used to determine antigenic and functional C1 inhibitors and complement C4 concentrations:

Antigenic C1INH protein by immunoturbidimetry

Functional C1INH protein by ----(b)(4)---------- using kit manufactured by (b)(4)

Complement C4 in serum by -------(b)(4)----- on the -------(b)(4)-----

RESULTS

Antigenic C1I NH: The mean baseline value for antigenic C1INH was 0.86 ± 1.45 U/mL in single dose subjects and 0.76 ± 0.71 U/mL in double dose subjects. Following the administration of cinryze, the concentrations of antigenic C1INH increased. The baseline corrected C_{max} in single dose subjects was 0.62 ± 0.40 and 0.95 ± 0.30 U/mL in double-dose subjects. PK parameters were estimated by non-compartmental analysis. The clearance and half-life of antigenic C1INH in single-dose subjects were 0.65±0.60 mL/min and 45±12 hours, respectively. The clearance and half-life of antigenic C1INH in double-dose subjects were 0.70 ± 0.36 mL/min and 47±22 hours, respectively. The results of this study are summarized in Table 1 and Figure 1.

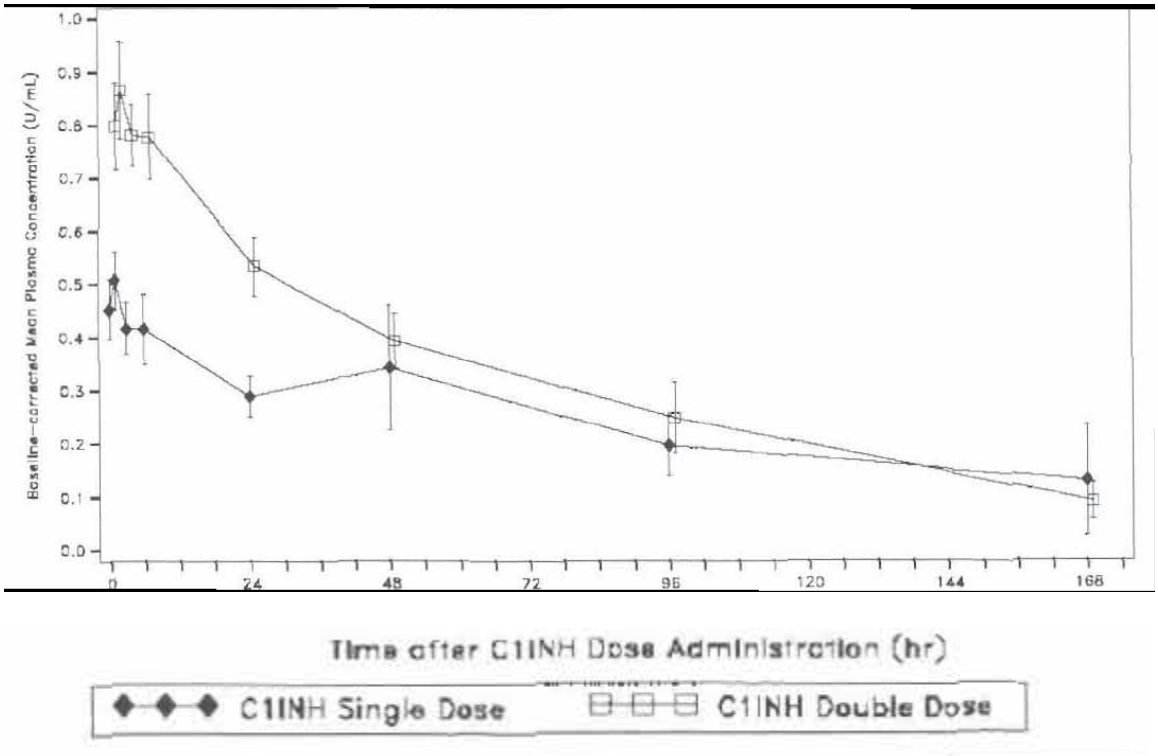
TABLE 1

Mean pharmacokinetic parameters of Antigenic C1INH

Parameters	Single Dose	Double Dose
$C_{baseline}$ (U/mL)	0.86 ± 1.45 (n = 13)	0.76 ± 0.71 (n = 14)
Baseline corrected C_{max} (U/mL)	0.62 ± 0. 40 (n = 13)	0.95 ± 0.30 (n = 14)
Baseline corrected $AUC_{(0-\infty)}$ (U*hr/mL)	36.8 ± 15.7 (n = 8)	61.8 ± 37.7 (n = 11)
CL (mL/min)	0.65 ± 0.60 (n = 8)	0.70 ± 0.36 (n = 11)
Half-life (hours)	45 ± 12 (n = 8)	47 ± 22 (n = 11)
Mean residence time (MRT) hrs	66 ± 19 (n = 8)	66 ± 28 (n = 8)

Both C_{max} and $AUC_{(0-\infty)}$ values were higher with the double dose than the single dose. Baseline corrected C_{max} and $AUC_{(0-\infty)}$ values increased by 1.53- and 1.68-fold for double dose.

Figure 1: Baseline corrected plasma concentration vs time plot of Antigenic C1I NH



Functional C1INH: The mean baseline value for functional C1INH was 0.31 ± 0.20 U/mL in single dose subjects and 0.33 ± 0.20 U/mL in double dose subjects. Following the administration of cinryze, the concentrations of functional C1INH increased. The baseline corrected C_{max} in single dose subjects was to 0.37 ± 0.15 and 0.51 ± 0.19 U/mL in double-dose subjects. The clearance and half-life of functional C1INH in single-dose subjects were 0.85 ± 1.07 mL/min and 56 ± 36 hours, respectively. The clearance and half-life of functional C1INH in double-dose subjects were 1.17 ± 0.78 mL/min and 62 ± 38 hours, respectively. The results of this study are summarized in Table 2.

TABLE 2

Mean pharmacokinetic parameters of Functional C1INH

Parameters	Single Dose	Double Dose
$C_{baseline}$ (U/mL)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
Baseline corrected C_{max} (U/mL)	0.37 ± 0.15 (n = 12)	0.51 ± 0.19 (n = 12)
Baseline corrected $AUC_{(0-\infty)}$ (U*hr/mL)	24.5 ± 19.1 (n = 7)	39.1 ± 19.9 (n = 9)
CL (mL/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Half-life (hours)	56 ± 36 (n = 7)	62 ± 38 (n = 9)
Mean residence time (MRT) hrs	84 ± 50 (n = 7)	91 ± 52 (n = 9)

Both C_{max} and $AUC_{(0-\infty)}$ values were higher with the double dose than the single dose. Baseline corrected C_{max} and $AUC_{(0-\infty)}$ values increased by 1.37- and 1.60-fold for double dose.

Complement C4 Concentrations: At baseline, C4 levels were 6.5 ± 5.4 and 8.5 ± 6.3 mg/dL in the single-dose and double-dose groups, respectively. Following a single dose administration of Cinryze, the C_{max}, C_{min}, and T_{max} values of C4 were 11.2 ± 6.2 mg/dL, 4.1 ± 3.5 mg/dL, and 48 ± 32 hrs, respectively. Following the double dose of Cinryze, the C_{max}, C_{min}, and T_{max} values of C4 were 16.5 ± 5.8 mg/dL, 6.6 ± 5.4 mg/dL, and 57 ± 29 hrs, respectively.

Conclusions

The PK of Cinryze in subjects with hereditary angioedema (HAE) indicates that in terms of antigenic C1INH and functional C1INH, the drug has a long half-life and slow clearance. Administration of Cinryze led to the increase in the concentrations of C1INH and complement C4 over the baseline. The concentrations of C1INH and complement C4 were higher following double dose than a single dose. However, administration of the second dose of Cinryze 60 minutes after the first dose did not follow the linear kinetics (C_{max} and AUC were not dose proportional).

Study #2

Study Title: Open-label cross-over study in hereditary angioedema (HAE) patients to compare PK of C1-esteraseremmer-N with Cetor.

This was a randomized, double-blind, cross over study designed to evaluate and compare the PK of Cl-esteraseremmer-N and Cetor in subjects with HAE. CI-esteraseremmer-N is identical to Cinryze with the exception of the use of U. S. source plasma for Cinryze. The objective was to demonstrate that introduction of nanofiltration and deletion of hepatitis B immunoglobulin in the manufacturing process did not affect the PK of the product. Both products (Cl-esteraseremmer-N and Cetor) were administered intravenously. Subjects were randomized to receive 1 of 3 dose levels: 1000, 1500, or 2000 U. There were 12 subjects in each arm of the study. The same dose of Cetor and C1-esteraseremmer-N were used for each patient. Blood samples were taken at pre-dose and at 5 minutes, 1, 3, and 6 hours, and at 1, 3, and 7 days following the administration of study drug.

Population PK approach (----------(b)(4)----------) was used to assess the PK of C1INH. A previously developed 2-compartment model was used as the basic model. In this model, the data from the functional assay and the antigen assay were assessed simultaneously. The following primary PK parameters were modeled: Clearance (CL), volume of distribution (V), and the fraction of C1INH detected by the antigen assay relative to the functional assay (F_{func}). Using the basic model, the influence of covariates sex, age, and weight on CL was assessed. Significance of these covariates was tested using the likelihood ratio test. Using the full model, the influence of the manufacturing process on the PK parameters was assessed by introducing the product as covariate on the primary PK parameters. The precision of the relative difference between the 2 formulations (i.e., the 95% confidence interval of Theta 2) was assessed by log likelihood. From the primary PK parameters, the following secondary parameters were calculated: MRT, half-life and AUC. The incremental recovery (IR) was calculated from the observed concentration versus time curve as (C_{max} - C_{min})/(Dose/Body Weight).

Pharmacokinetic parameters (Table 1) such as MRT, elimination half-life, and AUC values were not significantly different between the two products. Table 2 shows that the population estimates of the primary PK parameters were equivalent. Inter-individual variability for CL, V, and F_{func} were 20.1%, 19.6% and 33.5%, respectively.

The results of this population PK study indicate that the two products are pharmacokinetically equivalent.

Comment: The sponsor has provided only summary of the study and is a poorly written submission. However, this study is of little practical value for the clinical pharmacology labeling. PK parameters generated in this study are comparable with the parameters generated from study 1 (non-compartmental analysis).

Table 1

Functional C1INH PK parameters

PK parameter	Cetor			C1-esteraseremmer-N		
	Value	RSE[a] (%)	95 % range	Value	RSE (%)	95 % range
CL ($L \cdot hr^{-1}$)	0.0511	2.11	0.0489 - 0.0531	0.0527	2.11	0.0523 – 0.0569
V (L)	3.13	1.87	3.01 -3.25	3.06	1.87	2.90 – 3.12
F_{func}	0.821	3.20	0.77 – 0.87	0.819	3.20	0.78 – 0.88
IR ($kg \cdot mL^{-1}$)	0.029			0.025		
MRT (hr)[c]	61.3			58.06		
$t_{½}$ (hr)[c]	42.2			40.2	b	
AUC_{1000} ($U \cdot hr \cdot L^{-1}$)[c]	$21.2 \cdot 10^3$			$21.2 \cdot 10^3$		
AUC_{1500} ($U \cdot hr \cdot L^{-1}$)[c]	$36.3 \cdot 10^3$			$34.3 \cdot 10^3$		
AUC_{2000} ($U \cdot hr \cdot L^{-1}$)[c]	$50.9 \cdot 10^3$			$48.4 \cdot 10^3$		

a Relative Standard Error.

b IR calculated from the data of the level of functional C1-inhibitor. MRT, $t_{½}$ and AUCs calculated from the primary PK parameters. Parameters shown as point estimates since no reliable estimates of the confidence interval of these secondary parameters can be obtained using non-linear mixed models coded in the indicated.

Table 2

Relative differences on Functional C1INH PK parameters between C1-esteraseremmer-N and cetor

Parameter	Mean ratio	95% Confidence interval	
		Lower bound	Upper bound
CL	107%	93%	123%
V	96%	88%	107%
F_{func}	101%	92%	110%

NB. Confidence intervals were determined by log likelihood profiling. Percentages are shown as the ratio of the parameter estimate for Cetor divided by the parameter estimate for C1-esteraseremmer-N, which is estimated in the model as θ_2 (in equation 1). E.g. a ratio 107% for clearance means that the estimate of clearance of C1-esteraseremmer-1 was 7% higher than that of Cetor, although this difference was not significant since the 95% interval contained 1 (0.93-1.23).