

CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125317/0.1

Sponsor: CSL Behring

Product: Human Fibrinogen Concentrate, Pasteurized (Riastap)

Indication: For the treatment of congenital fibrinogen deficiency

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INTRODUCTION

Fibrinogen (factor I) is a soluble plasma glycoprotein with a molecular weight of approximately 340 kD and circulates in plasma as a precursor of fibrin. The native molecule is a homo-dimer, in which both subunits consist of three different polypeptide chains (A α , B β , and γ). All three polypeptide chains of the subunits as well as the dimer are linked with disulfide bonds. The three pairs of polypeptide chains named A α , B β , and γ are composed of 610, 461, and 411 amino acids, respectively.

Congenital fibrinogen deficiency comprises fibrinogen abnormalities that result in either reductions in the quantity (hypofibrinogenemia and afibrinogenemia) or functionality of fibrinogen (dysfibrinogenemia). Qualitative and quantitative abnormalities can also co-exist as hypodysfibrinogenemia.

Hypofibrinogenemia is the result of a reduced level of structurally normal fibrinogen (<150 mg/dL), whereas with dysfibrinogenemia, although there are normal plasma levels of fibrinogen, the function is abnormal. Congenital afibrinogenemia, a complete absence of fibrinogen in plasma, is a very rare coagulation disorder, usually with an autosomal recessive mode of inheritance. The prevalence is estimated at 0.5-1 cases per million people. Affected subjects are

homozygotes, and the disorder is characterized by moderate to severe bleeding after mild trauma or small surgical interventions. These bleeding events are observed soon after birth or in early childhood. In rare cases, thromboembolic complications occur. Typical laboratory findings in these patients include prolonged prothrombin time, partial thromboplastin time, thrombin, and reptilase time. The clinical symptoms are generally milder in patients with hypofibrinogenemia, specifically in those patients with fibrinogen plasma levels above 50 mg/dL.

The prevalence of hypofibrinogenemia and dysfibrinogenemia are unknown. There are estimated 150-300 patients who suffer from afibrinogenemia in the USA. Patients with any of these conditions are treated for bleeding either by substitution with a cryoprecipitate (Cohn I fraction) or substitution with fresh frozen plasma.

The proposed trade name for CSL Berhing's Human Fibrinogen Concentrate, Pasteurized (HFCP) product is Riastap™. The trade names outside the United States are Haemocomplertan® HS and Haemocomplettan®P.

HFCP is a sterile, preservative free, lyophilized fibrinogen concentrate in a single-use 100 ml vial. The labeled amount of HFCP is 1 g of fibrinogen with the actual potency for each lot indicated on the vial label and carton. HFCP is reconstituted with 50 mL Sterile Water for Injection (20 mg/mL) and is administered intravenously. Each vial contains 900 to 1300 mg fibrinogen, 400 to 700 mg human albumin, 375 to 660 mg L-arginine hydrochloride, 200 to 350 mg sodium chloride and 50 to 100 mg sodium citrate. Sodium hydroxide and hydrochloric acid may be added to adjust the pH.

HFCP is indicated for the treatment of congenital fibrinogen deficiency. The recommended initial dose is 70 mg per kg body weight with subsequent doses depending on target and measured fibrinogen levels. The infusion rate should not exceed 5 mL per minute (100 mg/minute).

The study described in this review is a multinational, multicenter, prospective, open-label, uncontrolled Phase II pharmacokinetic study.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.3 Pharmacokinetics

A pharmacokinetic (PK) study evaluated the single-dose PK and compared the maximum clot firmness (MCF) before and after administration of Riastap™ in subjects with afibrinogenemia (see [Clinical Studies \[14\]](#)).

A prospective, open label, uncontrolled, multicenter pharmacokinetic study was conducted in 5 females and 10 9 males with congenital fibrinogen deficiency, ranging in age from 8 to 61 years (2 children, 3 adolescents, 9 adults). Each subject received a single intravenous dose of 70mg/kg Riastap™. The median dose was 77.0 mg/kg body weight (range 76.6 – 77.4 mg/kg) with a mean average infusion rate of 4.35 mL per minute. Blood samples were drawn was sampled from 15 subjects (14 evaluable) from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. was complete. The pharmacokinetic parameters of Riastap in patients with congenital fibrinogen deficiency are summarized in Table 2.

No statistically relevant difference was observed between males and females for fibrinogen activity. Subjects less than 16 years of age (n=4) had a lower median $t_{1/2}$, AUC, AUC for dose 70mg/kg and MRT and a higher median V_{ss} , and Cl had shorter half-life (69.9 ± 8.5) and faster clearance (0.73 ± 0.14) compared to subjects between >16 and 65 years of age. The number of subjects less than 16 years of age in this study limits statistical interpretations. Table 2 provides the PK results.

In addition, The incremental in vivo recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median mean incremental IVR was 1.8 mg/dL (range 1.30 – 2.73 mg/dL) increase per mg/kg body weight. with a mean of 1.8 mg/dL.

Table 2: Pharmacokinetic Parameters (n =14) for Fibrinogen Activity

Parameters	Mean ± SD
Half-life [hours]	78.7 ± 18.13 (55.73-117.26)
C _{max} [g/L]	1.4 ± 0.27 (1.00-2.10)
AUC for dose of 70 mg/kg [mg*hr/mL]	124.3 ± 24.16 (81.73-156.40)
Clearance [mL/h/kg]	0.59 ± 0.13 (0.45-0.86)
Mean residence time [hours]	92.8 ± 20.11 (66.14-126.44)
Volume of distribution at steady state [mL/kg]	52.7 ± 7.48 (36.22-67.67)

The values in the parenthesis are range

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12.4 Pharmacokinetics

A prospective, open label, uncontrolled, multicenter pharmacokinetic study was conducted in 5 females and 9 males with congenital fibrinogen deficiency, ranging in age from 8 to 61 years (2 children, 3 adolescents, 9 adults). Each subject received a single intravenous dose of 70mg/kg Riastap™. Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters of Riastap in patients with congenital fibrinogen deficiency are summarized in Table 2.

No statistically relevant difference was observed between males and females for fibrinogen activity. Subjects less than 16 years of age (n=4) had shorter half-life (69.9 ± 8.5) and faster clearance (0.73 ± 0.14) compared to subjects >16 years of age. The number of subjects less than 16 years of age in this study limits statistical interpretations.

The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The mean incremental IVR was 1.8 mg/dL (range 1.30 – 2.73 mg/dL) increase per mg/kg.

RECOMMENDATION

The pharmacokinetic study design and analysis of Haemocomplettan P is acceptable. The sponsor should incorporate the clinical pharmacology labeling of Haemocomplettan P as suggested by the FDA.

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Study Title: Pharmacokinetics of Haemocomplettan P in subjects with congenital fibrinogen deficiency

This was a Phase II multinational, multicenter (10 centers in the USA and Italy), prospective, open-label, and uncontrolled design study, conducted in subjects with congenital fibrinogen deficiency manifested as afibrinogenemia. Subjects were enrolled over a period of 6 months, and screened for afibrinogenemia before administration of Haemocomplettan P. Fifteen subjects were enrolled and treated in the study. There were 10 males and five females in the study. There were 11 subjects in the age group of 16 to <65 years and 4 subjects between 8 and 14 years with congenital fibrinogen deficiency (afibrinogenemia) and were in a non-bleeding state. Plasma fibrinogen activity and antigen at screening had to be undetectable (<20 mg/dL). Haemocomplettan P (human fibrinogen concentrate, pasteurized) was administered as a single intravenous infusion of 70 mg/kg body weight. Blood samples for pharmacokinetic study were drawn at pre-dose and at 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216, and 312 hours post-dosing. Fibrinogen concentrations (from frozen plasma samples) were determined by the Clauss assay (for activity) and by validated fibrinogen-specific ELISA (for antigen) using paired antibodies for fibrinogen antigen. Detection limits for fibrinogen levels were 0.2 g/L for Clauss assay and 0.004 g/L for ELISA. The pharmacokinetic parameters of Haemocomplettan P were estimated in individual subjects using a non-compartmental analysis. PK data were evaluated for 14 subjects because one subject's plasma samples thawed during the transport to the central laboratory. The PK parameters of Haemocomplettan P are summarized in the following Tables.

Pharmacokinetic parameters for fibrinogen activity:

The pharmacokinetics of Haemocomplettan P in terms of fibrinogen activity can be characterized as long half-life and slow clearance (Table 1). With the exception of half-life, the PK of Haemocomplettan P was not different between male and female patients. The difference in half-life may not be of any clinical significance.

Table 1
PK parameters for fibrinogen activity

Parameters	Mean \pm sd	Mean \pm sd	
		Male (n = 9)	Female (n = 5)
Half-life (hours)	78.7 \pm 18.1	84.2 \pm 19.9	68.9 \pm 9.1
C _{max} (g/L)	1.4 \pm 0.3	1.4 \pm 0.2	1.4 \pm 0.4
AUC (mg*h/mL)	124.3 \pm 24.2	127.9 \pm 27.2	117.8 \pm 18.4
CL (mL/hr/kg)	0.59 \pm 0.13	0.57 \pm 0.14	0.61 \pm 0.12
MRT (hr)	92.8 \pm 20.1	98.6 \pm 22.2	82.2 \pm 10.7
V _{ss} (mL/kg)	52.7 \pm 7.5	54.1 \pm 4.0	50.1 \pm 11.7

AUC adjusted for dose 70 mg/kg

In children 16 years or younger, the half-life and clearance of Haemocomplettan P were 15% shorter and 38% faster than the adults. Due to small sample size (n=4), it is difficult to make any outright conclusion. The PK parameters of Haemocomplettan P in children and adults are summarized in Table 2.

Table 2
PK parameters for fibrinogen activity by age

Parameters	<16 years (n =4)	≥16 to <65 years (n =10)
Half-life (hours)	69.9 ± 8.5	82.3 ± 20.0
C _{max} (g/L)	1.5 ± 0.5	1.4 ± 0.2
AUC (mg*h/mL)	98.7 ± 21.9	134.5 ± 16.6
CL (mL/hr/kg)	0.73 ± 0.14	0.53 ± 0.07
MRT (hr)	74.6 ± 9.1	100.0 ± 18.7
V _{ss} (mL/kg)	54.9 ± 13.3	51.8 ± 4.27

AUC adjusted for dose 70 mg/kg
<16 years = 8, 11, 12, and 14 years

Pharmacokinetic parameters for fibrinogen plasma antigen:

Like fibrinogen activity, the pharmacokinetics of Haemocomplettan P in terms of fibrinogen plasma antigen can be characterized as long half-life and slow clearance (Table 3). The PK of Haemocomplettan P was not different between male and female patients (Table 3).

Table 3
PK parameters for fibrinogen plasma antigen

Parameters	Mean ± sd	Mean ± sd	
		Male (n = 9)	Female (n = 5)
Half-life (hours)	85.9 ± 18.8	84.7 ± 21.4	88.1 ± 15.2
C _{max} (g/L)	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.4
AUC (mg*h/mL)	118.5 ± 22.6	118.2 ± 22.2	119.2 ± 25.9
CL (mL/hr/kg)	0.61 ± 0.13	0.61 ± 0.12	0.62 ± 0.16
MRT (hr)	120.2 ± 25.2	119.1 ± 27.7	122.2 ± 22.9
V _{ss} (mL/kg)	71.9 ± 13.4	70.3 ± 4.4	74.7 ± 22.1

AUC adjusted for dose 70 mg/kg

In children 16 years or younger, the half-life and clearance of Haemocomplettan P were 11% shorter and 32% faster than the adults. Due to small sample size (n=4), it is difficult to make any outright conclusion (if the difference in PK parameters between adults and children are real and are of clinical consequences). The PK parameters of Haemocomplettan P in children and adults are summarized in Table 4.

Table 4
PK parameters for fibrinogen plasma antigen by age

Parameters	<16 years (n =4)	≥16 to <65 years (n =10)
Half-life (hours)	78.7 ± 10.3	88.8 ± 21.1
C _{max} (g/L)	1.3 ± 0.4	1.3 ± 0.2
AUC (mg*h/mL)	97.9 ± 21.8	126.8 ± 17.7
CL (mL/hr/kg)	0.74 ± 0.15	0.56 ± 0.1
MRT (hr)	103.7 ± 14.7	126.8 ± 26.0
Vss (mL/kg)	77.1 ± 22.3	69.8 ± 8.9

AUC adjusted for dose 70 mg/kg
<16 years = 8, 11, 12, and 14 years

Conclusions

The pharmacokinetics of Haemocomplettan P in terms of fibrinogen activity and fibrinogen plasma antigen indicate that Haemocomplettan P is a long half-life and slow clearance drug. The PK of Haemocomplettan P was not different between male and female patients. In children 16 years or younger, the half-life and clearance of Haemocomplettan P were 11% shorter and 32% faster than the adults. However, due to small sample size (n =4), it is difficult to make any outright conclusion (if indeed the PK of Haemocomplettan P is different between children and adult and there are clinical consequences of these differences).