

Summary Based Approval (Clinical Pharmacology) - Voluven

SUMMARY BASED APPROVAL (CLINICAL PHARMACOLOGY)

Division of Hematology

Office of Blood Review & Research

STN BN070012/0

Sponsor: Fresenius Kabi

Product: Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride)

Indication: A plasma substitute for the treatment of hypovolemia

Date Received: March 1, 2007

Reviewer: Iftekhar Mahmood, Ph. D.

RPM: Franklin Stephenson

Through: Basil Golding, M.D.

Date: October 31, 2007

Colloidal plasma volume substitutes containing hydroxyethyl starch (HES) have been in use for more than 25 years. HES is a derivative of thin boiling waxy corn starch which consists mainly of amylopectin, a highly branched glucose polymer. The pharmacological characteristics of the HES depend on the concentration of the component and the mean molecular weight and degree of hydroxyethyl substitution on the glucose units of the starch. Fresenius Kabi has developed a new HES product (Voluven) with the intent of improving the safety profile of HES with no reduction in efficacy. The HES component of Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is characterized by its medium molecular weight (130,000) and degree of molar substitution (0.4) on the glucose units of the starch.

In this submission, the sponsor has conducted 3 pharmacokinetic studies of voluven:

- A single dose study in healthy subjects.
- A multiple dose study in healthy subjects.
- A pharmacokinetic study in patients with different degrees of renal impairment.

Single Dose Study:

This was an open- label, randomized, parallel study with two groups of 12 healthy subjects in each group. There were 8 males and 4 females in each group (age: 20-39 years). The subjects received the following two products:

500 mL Hydroxyethyl starch (HES 130/0.5) 6% (Treatment A)

500 mL Hydroxyethyl starch (HES 130/0.5) 10% (Treatment B)

Subjects received a single IV dose of either treatment over 30 minutes. Blood and urine samples were collected till 72 hours. The C_{max} and AUC of HES increased with increasing dose, although, the increase was not proportional with dose. Half-life appears to be dose independent but the clearance of HES decreased in treatment B (higher dose group).

Approximately 62 % and 68% unchanged HES was excreted in the urine for treatment A and B, respectively. The renal clearance of HES was 19.5 mL/min for treatment A and 17.7 mL/min for treatment B. The pharmacokinetic parameters of voluven are summarized in the following Table.

Pharmacokinetics parameters of HES in healthy subjects following 500 mL IV dose

Parameters	Treatment A	Treatment B
C _{max} (mg/mL)	3.7 ± 0.6	6.5 ± 0.8
AUC _(0-infinity) h*mg/mL	14.5 ± 2.8	29.2 ± 5.6
Clearance (mL/min)	31.4 ± 6.9	26.0 ± 4.8
Half-life (hrs)	12.1 ± 2.5	12.8 ± 0.9
Amount in urine (g)	16.2 ± 2.4	30 ± 5.3

Multiple Dose Study:

This was an open-label study in 12 healthy males (age: 21-40 years) who received 500 mL HES (130/0.5) 10% as an IV infusion over 30 minutes for 10 consecutive days (every 24 hours). Blood and urine samples were drawn at regular intervals for 24 hours after the first dose and till 72 hours after the last dose.

The C_{max} and AUC of HES between single and multiple dosing were comparable. Although, there was a slight increase in the AUC after multiple dosing (accumulation ratio was approximately 1.2), there is no indication that HES accumulates in normal healthy person after multiple dosing. It took 2 to 3 days for HES to reach steady state. Clearance of HES between single and multiple dosing was comparable but half-life of HES after multiple dosing was at least 3-fold longer than the half-life following single dose. Based on the accumulation ratio the effective half-life of HES is about 8 hours and this should be considered as true half-life of HES.

Approximately 70% unchanged HES was excreted in the urine following single and multiple dosing. The renal clearance of HES was approximately 16.6 mL/min in healthy subjects.

Study in patients with different degrees of renal impairment:

This was an open-label, non-randomized, single-dose, single-center study in four groups of subjects (n = 19) with varying degrees of renal function. Male and female subjects (13 males and 6 females, ages 30-77 years) were enrolled in the study. Based on their creatinine clearance, the subjects were divided into 4 groups: CL_{cr} = 80-<120 mL/min, 50-<80 mL/min, 30-<50 mL/min, CL_{cr} = 15-<30 mL/min. The subjects received a single dose of 500 mL HES (130/0.4) 10% as an IV infusion over 30 minutes. Blood and urine samples were drawn till 72 and 96 hours, respectively.

The AUC increased and the systemic clearance decreased with decreasing creatinine clearance. There was a 73% increase in the AUC in subjects with creatinine clearance <50 mL/min as compared to subjects with creatinine clearance >50 mL/min. The amount of unchanged drug excreted in the urine was 15% lower in subjects with creatinine clearance 15-<30 mL/min as compared to subjects who had creatinine clearance >30 mL/min. The half-life of voluven in subjects with creatinine clearance <50 mL/min and with creatinine clearance >50 mL/min appears to be comparable.

Although the half-life of HES in patients with renal impairment does not appear to be different than the normal subjects, increased AUC and decreased clearance of HES are clear indications of the impact of renal impairment on the PK of HES. The patients with renal impairment (creatinine CL = < 50 mL/min) on HES therapy should be monitored regularly because dose adjustment may be needed in this patient population.

Iftekhar Mahmood, Ph. D.

Senior Clinical Pharmacology Reviewer

Division of Hematology

Office of Blood Review & Research
Date: October 31, 2007
Basil Golding, MD
Division Director
Division of Hematology
Office of Blood Review & Research