

Approval Memorandum - Voluven, December 20, 2007

APPROVAL MEMORANDUM

DATE: December 20, 2007

FROM: Elena Karnaukhova, Ph.D.; HFM-343; LBVB, DH, OBRR, CBER; (301) 402-4635, FAX (301) 402-2780

SUBJECT: Overview memo for original NDA 70012/0.0, including DMF2 IND#-----, and the related twenty two Amendments, for 6% hydroxyethyl starch (HES) 130/0.4 in 0.9% sodium chloride infusion (Voluven®), submitted by Carolina Research Group on behalf of Fresenius Kabi Deutschland GmbH

THROUGH: Abdu Alayash, Ph.D., Chief; HFM-343, LBVB, DH, OBRR, CBER; (301) 827-3813, FAX (301) 435-4034 Jonathan Goldsmith, M.D., Deputy Director CBER/OBRR

TO: File NDA BN70012/0.0

CC: Franklin Stephenson, Pauline Cottrell, Mahmood Farshid, Basil Golding, Larry Landow, Paul Buehler, Yiping Jia, Iftekhar Mahmood, Tie-Hua Ng, Nancy Chamberlin, Chiang Syin.

ACTION RECOMMENDED: Based on multidisciplinary review of NDA BN070012 and the individual conclusions of all members of the review committee, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion (Voluven®) can be approved with post marketing commitments.

SUMMARY

Submission date: 2-28-2007

CBER receipt date: 3-1-2007 (L#412822)

Sponsor: Fresenius Kabi Deutschland GmbH (FK)

US Agent: Carolina Research Group, Inc. (CRG)

Type of submission: Original NDA

Product licensed name: 6% HES 130/0.4 in 0.9% sodium chloride infusion

Proposed Proprietary Name: Voluven®

Proposed Indication: treatment and prophylaxis of hypovolemia

Route of Administration: Intravenous use

Dosage Form: Solution for intravenous infusion

Proposed Marketing Status: Prescription Product

Manufacturing facilities

Voluven® is manufactured by:

Fresenius Kabi Norge AS,

Svinesundveien 80,

NO-1753 Halden

Norway

HES for Voluven® is manufactured by:

Fresenius Kabi Austria GmbH,

Estermannstraße 17

A-4020 Linz

Austria

Sponsor:

Fresenius Kabi Deutschland GmbH

Else-Kröner-Straße 1
61352 Bad Homburg v.d.H.
Germany

This memo is an overview of the review process of a new drug application (including the original NDA BN070012, original Master Files DMF2 IND#-----, and the related twenty two Amendments) for 6% HES 130/0.4 in 0.9% sodium chloride infusion (Voluven®).

Review responsibilities for this NDA were as follows:

- Pre-Clinical Toxicology: Paul Buehler, Ph.D.
- Pre-Clinical Pharmacology: Iftekhar Mahmood, Ph.D.
- Clinical Pharmacology and Clinical Data: Laurence Landow, M.D.
- Statistical Analysis of Clinical Data: Tie-Hua Ng, Ph.D.
- Proprietary Name and Labeling: Nancy Chamberlin, Pharm.D.
- Chemistry, Manufacturing, and Controls (CMC): Yiping Jia, Ph.D., and Elena Karnaukhova, Ph.D. (chair)
- Establishment Inspection: Ms. Janie Russell.
- Regulatory Project Manager: Mr. Franklin Stephenson

Background

HES 130/0.4 is a white to yellowish white, odorless and tasteless, amorphous powder, soluble in water in every concentration, soluble in DMSO, and practically insoluble in most organic solvents.

Voluven® is a clear 6% hydroxyethyl starch (HES 130/0.4) solution in isotonic sodium chloride solution for intravenous infusion for the "Therapy and prophylaxis of hypovolaemia". The product is supplied in freeflex® bags made from co-extruded polyolefines of ----- and ship-shape ports. The nominal fill volume is 500 mL with filling limits of ----- mL. Voluven® contains HES 130/0.4 in a colloidal solution which expands plasma volume when administered intravenously. The effect of the HES contained in Voluven® on intravascular volume expansion and hemodilution is a function of the mean molecular weight (130,000 daltons; range 110,000 - 150,000 daltons), the molar substitution by hydroxyethyl groups (0.42; range 0.38 - 0.45) on glucose units of the starch, the pattern of hydroxyethyl substitution (C₂/C₆ ratio) of approximately 9:1, and the concentration (6%), as well as the dose and infusion rate.

The starting material for HES 130/0.4 is a thin boiling waxy corn starch, a polymeric glucose derivative (amilopectine) that mainly consists of α-1,4-connected glucose units with several α-1,6-branches, also containing a small amount of amylose. Hydroxyls at the 2, 3 and 6 positions of glucose are subject to partial derivatization to hydroxyethyl groups (see Attachments 1 and 2).

Stability

The post-approval stability protocol and stability study will be performed according to ----- primary packaging material (see Attachment 2). The monitoring parameters are Appearance: white to yellowish white powder; -----
----- Mw: 110,000 - 150,000 Dalton;
M at --- -----;
Molar substitution: 0.38 - 0.45; C₂/C₆ ratio: -----

Total -- batches of Voluven 6% drug product in the freeflex® container have been produced at Fresenius Kabi Norge AS (FK Norway). The ongoing stability studies will be continued up to a storage period of -----. The results of all stability studies demonstrate that Voluven 6% is stable during the tested period, independent of whether the product was manufactured at the facilities in Norway or in Germany. Stability data will be reported annually (21 CFR 314.81).

Adventitious agents safety evaluations

None of the raw materials used in the manufacturing of Voluven® is of ruminant origin as defined in section 2 of the CPMP-Guideline (CPMP/BWP/1230/98. No ruminant-derived materials from BSE countries as defined by the US Department of Agriculture (9CFR 94.11) are used.

Labeling

The proposed labeling was subject to multiple significant changes by the members of the review committee and by the sponsor. All reviewers agreed on the final version of the labeling.

Post-marketing commitments

There are two post-marketing commitments agreed to for clinical studies related to efficacy and safety of Voluven® as follows:

1. Completion of a multiple-dose, randomized, controlled trial (RCT) to be conducted in subjects with severe sepsis with or without renal dysfunction (see Attachment 6), and
2. According to the recommendation of the Pediatric Review Committee, the sponsor will conduct a clinical study of the efficacy and safety of 6% HES 130/0.4 vs. 5% HSA in volume substitution therapy during open heart surgery in 2 to 12 year old pediatric patients (see Attachment 10).

During the review process, there were several information requests and several telecons regarding CMC and clinical issues. The firm's responses were provided in twenty two Amendments to the referenced submission. The responses were found to be generally acceptable for the fore-mentioned post-marketing commitments.

Recommendation for approval of NDA BN07012 with the post-marketing commitments reflects the individual recommendations of all members of the review committee as evident from the following authorized review memos:

Attachment 1: Manufacturing Process and Controls (Yiping Jia)

Attachment 2: Analytical Procedures (Elena Karnaukhova)

Attachment 3: Establishment (Janie Russell)

Attachment 4: Pre-Clinical Toxicology (Paul Buehler)

Attachment 5: Pre-Clinical Pharmacology (Iftekhar Mahmood)

Attachment 6: Clinical Pharmacology/Data (Laurence Landow)

Attachment 7: Statistical Analysis (Tie-Hua Ng)

Attachments 8&9: Proprietary Name and Labeling (Nancy Chamberlin)

RECOMMENDATIONS

Based on a multidisciplinary review of NDA BN070012 and the individual conclusions of all members of the review committee, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion (Voluven®) can be approved with two post marketing commitments.

- Attachment 3: Establishment (Janie Russell) - Voluven [ARCHIVED]
- Attachment 5: Pre-Clinical Pharmacology (Iftexhar Mahmood) - Voluven [ARCHIVED]
- Attachment 7: Statistical Analysis (Tie-Hua Ng) - Voluven [ARCHIVED]
- Attachment 8: Proprietary Name - Voluven [ARCHIVED]
- Attachment 9: Labeling - Voluven [ARCHIVED]

Attachment 3: Establishment (Janie Russell) - Voluven

MEMORANDUM

DATE: August 31, 2007

FROM: Janie Russell, Review Biologist, CBER/OCBQ/DMPQ/MRB2, HFM-676

SUBJECT: Final Review Memo - Fresenius Kabi, NDA for 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion (Voluven), a plasma substitute for the treatment of hypovolemia

THROUGH: Chiang Syin, Ph.D., Chief, DMPQ, MRB II, HFM-676

TO: NDA File - STN: BN070012/0.0

DUE DATE: December 26, 2007

RECOMMENDED ACTION:

Recommend approval of Fresenius Kabi, NDA for 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion (Voluven), a plasma substitute for the treatment of hypovolemia pending outcome of inspection, successful completion of validation studies for the flush volume for redesigned solution delivery system, successful manufacture of three validation batches, and product office concurrence. The firm should be notified to perform microbiological (biological indicators) testing for their new autoclave --.

Although the firm has some stability studies on -----, the container closure identified uses the ----- . Therefore licensing should clearly delineate the ----- for the container closure.

An inspection request was submitted to Janet Ishimoto, Branch Chief, Division of Inspections and Surveillance (DIS), on 4/6/07 for Field Assignment for prior approval inspection through DIS for the Halden, Norway facility. Specific items to be addressed during the inspection were requested in a memorandum dated 27 July 2007.

SUMMARY:

Fresenius Kabi has submitted a NDA for 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion (Voluven), a plasma substitute for the treatment of hypovolemia. This review encompassed sterility/sterilization, pyrogenicity, packaging integrity, equipment, facilities, validation, and environmental assessment in Module 3 (volumes 1 through 3), Module 1 (sections 1.38 and 1.39) and Methods Validation Package (volume 1 of 1). The review also included MF# -----, Master File Type III for "Freeflex® Packaging System (Polyolefine Bag)", volumes one through three; and BB-MF -----, Type II Master File for "Hydroxyethyl Starch 130/0.4 for Injection" for container closure, facilities and equipment and executed batch record for Linz Austria facility (2 volumes). The NDA packaged followed the CDER Guidance for the Format and Content of the CMC Section of an Application, February 1987. The firm has requested categorical exclusion.

Additional information was requested from firm on 9 April 2007, for BI certificates (section 3.2.P.3.5.2) for study N-1986 and N 1989, and on 30 July 2007. This was submitted by the firm on 26 July 2007 as STN BN070012/0.2 and on 16 August 2007 as STN BN70012/0.3.

REVIEW:

Facilities:

The following facilities perform segments of manufacturing:

- 1. Drug Substance HES 130/0.4 manufacturer:

Fresenius Kabi Austria GmbH
Estermannstrasse 17
A-4020 Linz
Austria

- 2. Container Closure:

Freeflex® bags-unprinted:
Fresenius Kabi Deutschland GmbH
D-61169 Friedberg
Germany

Overpouch foil -----:
Fresenius Medical Care
Plant St. Wendel
D-66606 St. Wendel
Germany

- 3. Formulation/Fill and Finish with Testing and Release:

Drug establishment registration no.: NO 980 250 008
Fresenius Kabi Norge AS
Svinesundveien 80
NO-1753 HALDEN
Norway

Batch Analyses:

Batch analyses are present for the following:

- Relevant batches manufactured at Linz Plant, Austria
- Nonclinical batches manufactured at Friedburg Plant, Germany
- Clinical batches manufactured at Friedburg Plant, Germany, most ----- with one batch filled in PE bags. Two batches were manufactured by Fresenius Kabi in Louviers, France for a clinical study conducted in France.
- Stability batches manufactured at Linz Plant, Austria and in Halden, Norway
Note the firm initially termed the product -----, however the actual degree of molar substitution is 0.4 therefore the product was named HES 130/0.4. The US product is to be produced in Halden, Norway (3.2.P.2.3.5). Stability batches were made in Norway however the batch sizes are different, ----- versus -----, and used ----- 500 mL containers which were ----- on-site with pre-made empty Freeflex bags on a ----- filling line.

Manufactured Conformance Lots:

The following lots were termed stability lots by the manufacturer and used for validation.

DS Lot No. of HES 130/0.4	DP Lot No. of Voluven	Date Voluven Manufactured	Voluven Volume Manufactured (L)	Fill Volume (mL)
-----	06C08J96	March 2006	----	---
-----	06C08J95	March 2006	----	---
-----	06C09J94	March 2006	----	---
-----	06C09J93	March 2006	----	---
-----	06C10J92	March 2006	----	---

----- non-clinical and -- clinical batches/Trials (NDA section 3.2.S.4) of the drug substance were manufactured at the Friedburg plant. Four batches of the HES 130/0.5 for the non-clinical product exceeded the specification of ----- at a maximum reported of -----, however were accepted. Two batches of the HES 130/0.5 for the clinical product exceeded the specification of ----- at a maximum reported of -----, however were accepted.

Lots of HES 130/0.4 drug substance manufactured at the Linz (Austria) facility (per NDA section 3.2.S.4.4.1) for commercial use with results for -----:

-----	-----	-----	-----	-----
----	-----	---	-----	-----
----	-----	---	-----	-----
----	-----	---	-----	-----

Manufacturing Process and Process Controls (NDA sections 3.2.S.2.2 and 3.2.P.3):

HES 130/0.4 (BB-MF ----- section 2.3):

HES 130/0.4 is manufactured in the Linz Austria facility. No materials of animal origin are used in the process. Total batch size is ----- . The manufacturing process is as follows:

**32
PAGE(S)
DETERMINED
TO BE
NOT RELEASABLE**

Attachment 5: Pre-Clinical Pharmacology (Iftekhar Mahmood) - Voluven

CLINICAL PHARMACOLOGY REVIEW

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

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Study # 2: Examination of pharmacokinetic and safety of hydroxyethyl starch (HES) 130/0.5 10% in healthy volunteers after multiple dosing.

Study # 3: Investigation of pharmacokinetics and tolerability of a single dose intravenous infusion of the new hydroxyethyl starch (HES) as 6% solution (130/0.4) in subjects with mild to severe renal impairment.

INTRODUCTION

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. Presently marketed HES-containing products are typically identified by the molecular weight and degree of hydroxyethyl substitution of the starch component. For example, a HES component designated as HES 650/0.75 (hetastarch) has a molecular weight of 650,000 and a degree of substitution of 0.75. 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

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

Study #1

Study Title: Examination of pharmacokinetic and safety of hydroxyethyl starch (HES) 130/0.5 6% and 10% in healthy volunteers after a single infusion of 500 mL solution. 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).

Test 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. In terms of mean HES dose, subjects in groups A and B received 26.3 and 44.1 grams, respectively. Blood samples were drawn at regular intervals till 72 hours (5, 10, 30, 60, 120, 240, 360, 420 minutes, and at 24, 48, and 72 hours). Urine samples were also collected till 72 hours. D-glucose was determined for HES concentrations.

Pharmacokinetic parameters for HES are summarized in Table 1

Table 1

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

Parameters	Treatment A	Treatment B
Amount in urine (g)	16.2 ± 2.4	30 ± 5.3

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. Mean HES concentrations versus time and HES excretion in the urine over time plots are shown in figures 1 and 2.

Figure 1

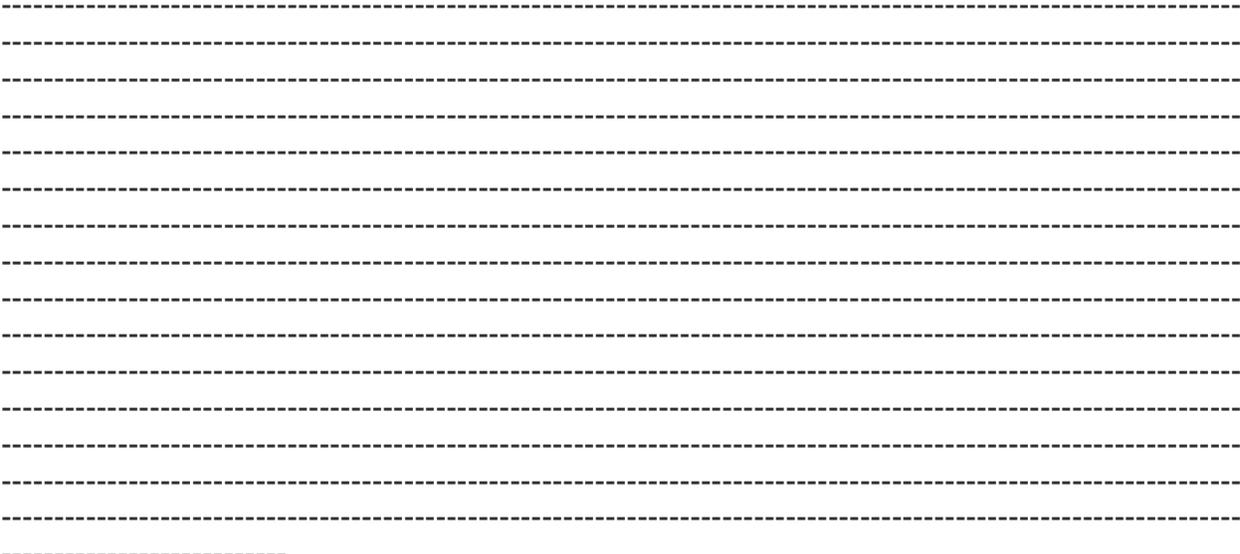
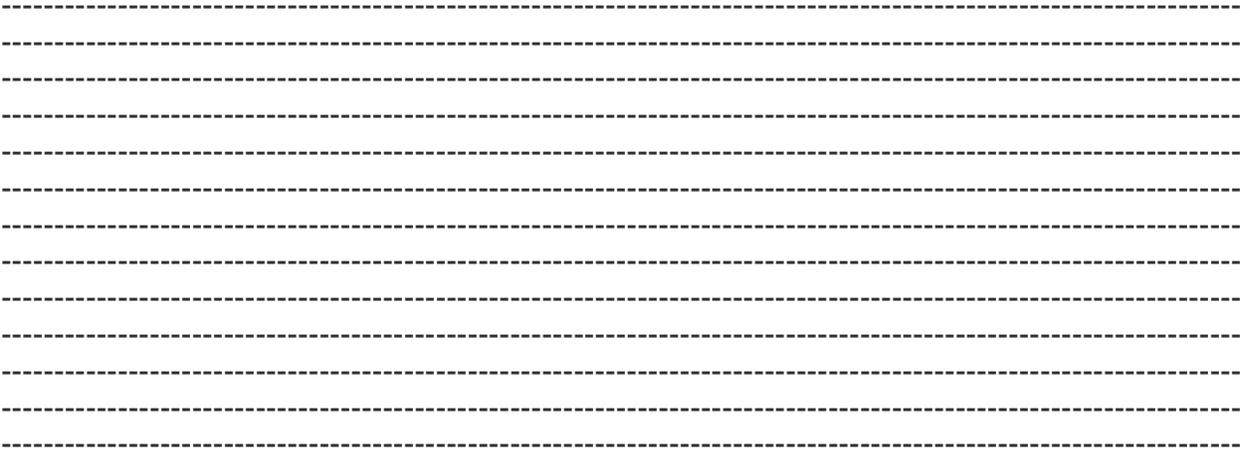


Figure 2



Study #2

Study Title: Examination of pharmacokinetic and safety of hydroxyethyl starch (HES) 130/0.5 10% in healthy volunteers after multiple dosing.

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 samples were drawn at regular intervals for 24 hours after the first dose and till 72 hours after the last dose. Blood samples were also taken before the administration of every dose (trough samples). Urine samples were also collected at regular intervals. D-glucose was determined for HES concentrations. Pharmacokinetic parameters for HES after single and multiple dosing are summarized in Table 2.

Table 1

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

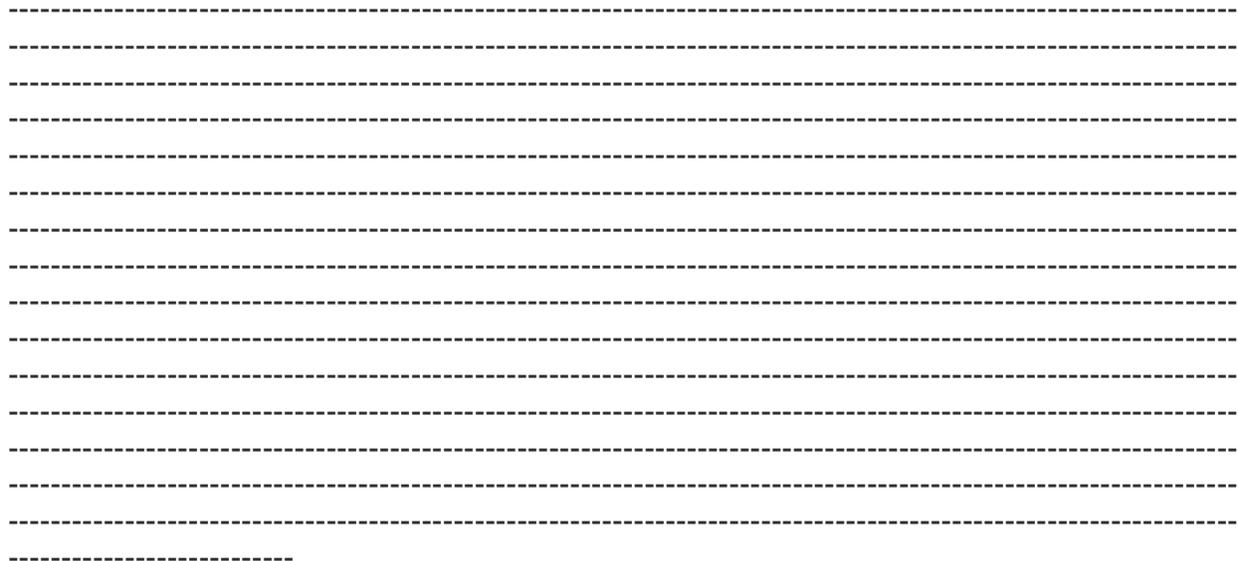
Parameters	Single dose	Multiple dose (day 10)
C _{max} (mg/mL)	7.78 ± 0.86	7.38 ± 0.66
AUC _(0-infinity) h*mg/mL	32.96 ± 3.54	35.95 ± 4.68
Clearance (mL/min)	23.87 ± 2.68	22.01 ± 2.99
Half-life (hrs)	7.10 ± 0.43	21.93 ± 1.26
Amount in urine (g)	32.25 ± 3.09	32.91 ± 2.37

The C_{max} and AUC of HES between single and multiple dosing are 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 (Figure 1). The maximum trough value was 0.367 mg/mL. 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.

Comments: Based on the accumulation ratio, the true half-life of HES in normal healthy subjects appears to be 8 hours. This should be considered as effective half-life of HES in this population.

Figure 1



Study #3

Study Title: Investigation of pharmacokinetics and tolerability of a single dose intravenous infusion of the new hydroxyethyl starch (HES) as 6% solution (130/0.4) in subjects with mild to severe 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. The subjects were divided based on their creatinine clearance as shown below:

CL_{cr} = 80-<120 mL/min (n = 4, 30-50 years)

CL_{cr} = 50-<80 mL/min (n = 5, 30-65 years)

CL_{cr} = 30-<50 mL/min (n = 4, 57-74 years)

CL_{cr} = 15-<30 mL/min (n = 6, 48-77 years)

The subjects received a single dose of 500 mL HES (130/0.4) 10% as an IV infusion over 30 minutes. Blood samples were drawn at regular intervals till 72 hours post-dose. Urine samples were also collected at regular intervals till 96 hours. D-glucose was determined for HES concentrations. Pharmacokinetic analysis was conducted using both compartmental and non-compartmental methods. Pharmacokinetic parameters for HES are summarized in Table 1. Plasma HES concentrations vs time plot in subjects with different degrees of renal function is shown in Figure 1.

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 (38.56 mg*hr/mL) as compared to subjects with creatinine clearance >50 mL/min (22.30 mg*hr/mL). There was a 42% decrease in the clearance of HES in

subjects with creatinine clearance <50 mL/min (0.793 liters/hr) as compared to subjects with creatinine clearance >50 mL/min (1.355 liters/hr).

There was a discrepancy in the half-life calculated by compartmental and non-compartmental analysis. The compartmental analysis indicated that the half-life of HES is almost 1.7 times longer in subjects with creatinine clearance <50 mL/min than the half-life in subjects with creatinine clearance >50 mL/min. Two subjects (subject #11 in creatinine CL group of 15-<30 mL/min and subject #23 in creatinine CL group of 30-<50 mL/min) had approximately twice the half-life than other subjects irrespective of their creatinine clearance. After excluding these two subjects from the analysis, the half-life was comparable (1.2 times) between the aforementioned two groups. On the other hand, the half-life of HES calculated by non-compartmental analysis exhibited no outlier but the mean half-life across all creatinine clearance groups was twice than the mean half-life calculated by compartmental analysis. Theoretically, the pharmacokinetic parameters calculated from compartmental and non-compartmental analysis should be, to a great extent, similar but in this case the half-lives of HES are not similar. The reason for this discrepancy in the half-life of HES by the two methods is not known. The urine samples were collected till 96 hours. 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 \geq 30 mL/min. In subjects with creatinine clearance 15-<30 mL/min, the amount of unchanged drug excreted in the urine was 22.2% by the sixth hour which was substantially lower than other groups (30-<50 = 29.98%; 50-<80 = 41.96; 80-<120 = 47.13). The amount of unchanged drug excreted in the urine in subjects with varying degrees of renal function is summarized in Table 2. A plot of HES AUC and creatinine clearance is shown in Figure 2. Amylase activity increased with decreasing creatinine clearance (Figure 3). However, the clinical significance of increased amylase activity in renal impairment is not known.

TABLE 1

Pharmacokinetic parameters of HES in subjects with varying degrees of renal function

Parameters	Cr CL (mL/min)	Non-compartmental	Compartmental
C_{max} (mg/mL)			
	15 - <30	4.68 ± 1.19	4.63 ± 1.20
	30 - <50	4.37 ± 1.15	4.46 ± 1.16
	50 - <80	3.48 ± 1.13	3.49 ± 1.14
	80 - <120	5.11 ± 1.28	5.35 ± 1.24
AUC_(0-inf) (mg*hr/mL)			
	15 - <30	41.1 ± 1.22	37.0 ± 1.25
	30 - <50	35.1 ± 1.15	32.3 ± 1.08
	50 - <80	20.0 ± 1.07	17.5 ± 1.13
	80 - <120	25.5 ± 1.23	19.4 ± 1.42
Clearance (liters/hr)			

Parameters	Cr CL (mL/min)	Non-compartmental	Compartmental
	15 - <30	0.733 ± 1.22	0.813 ± 1.26
	30 - <50	0.853 ± 1.14	0.925 ± 1.07
	50 - <80	1.52 ± 1.07	1.73 ± 1.13
	80 - <120	1.19 ± 1.23	1.56 ± 1.42
Half-life (hrs)			
	15 - <30	15.9 ± 1.09	11.7 ± 1.48
	30 - <50	15.5 ± 1.10	13.4 ± 1.72
	50 - <80	15.9 ± 1.06	9.29 ± 1.20
	80 - <120	17.2 ± 1.07	5.64 ± 2.12

Table 2

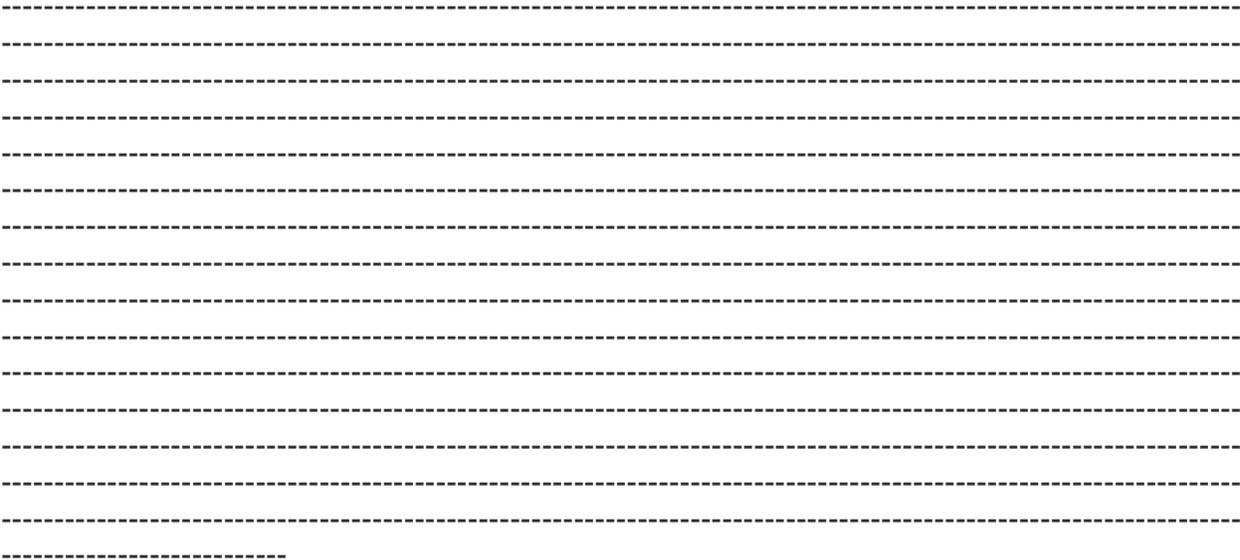


Figure 1

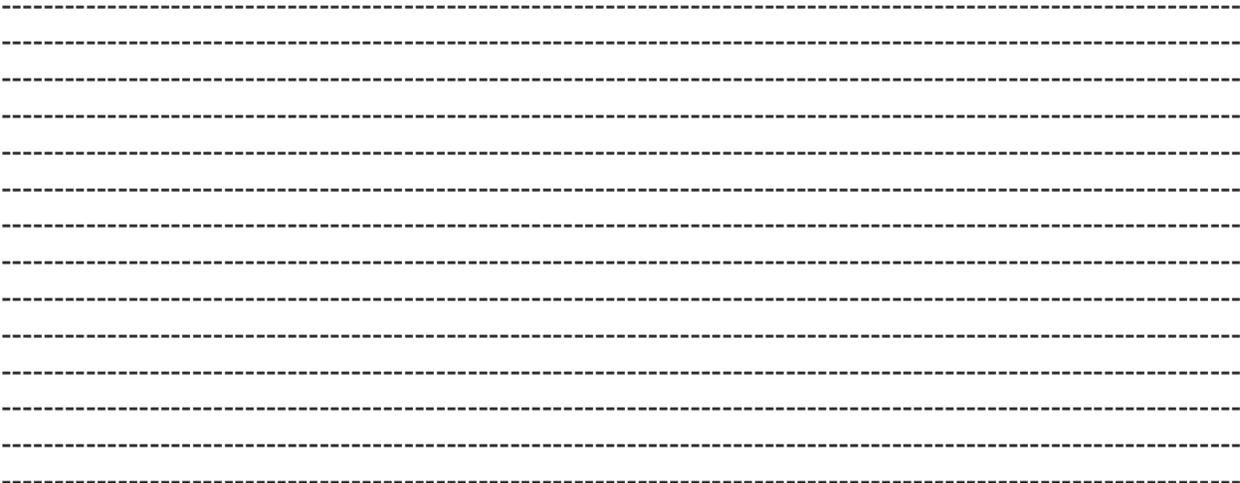


Figure 2

Figure 3

Conclusions

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. This is not surprising since HES is mainly excreted through the kidneys. 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.

Attachment 7: Statistical Analysis (Tie-Hua Ng) - Voluven

Statistical Review and Evaluation

Date: November 16, 2007

Type of Submission: NDA

STN: BN070012, BN070012/0.3

Applicant: Fresenius Kabi Deutschland GmbH

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

Indication: Treatment and prophylaxis of hypovolemia

Documents Reviewed: Modules 1, 2 and 5. Original NDA submission, submission date: February 28, 2007. Amendment 3, submission date: August 16, 2007

From: Tie-Hua Ng, Ph.D.

Mathematical Statistician, HFM-219

Concurrence: Ghanshyam Gupta, Ph.D., Chief
Therapeutics Evaluation Branch, HFM-219

To: HFM-380/Franklin Stephenson

HFM-392/Laurence Landow

cc: Original DCC

HFM-210/Steven Anderson

HFM-215/Henry Hsu

HFM-215/Chron.

I. Background

The only hydroxyethyl starch (HES) solution marketed for plasma volume expansion is hetastarch (**6% HES 450/0.7**). The investigational HES in this NDA, **6% HES 130/0.4**, has a lower molecular weight and *lower* degree of substitution. 6% HES 130/0.4 has been used widely in Europe - approximately 7,800,000 patients have been treated with the product - since it was approved in the late 1990s.

This NDA includes data from studies supporting licensure in Europe and data from the single US study in subjects undergoing orthopedic surgery.

The sponsor has submitted data from **21 clinical studies** in volunteers and subjects ranging in age from newborns to the elderly (N=1315) in which the test agent was **6% HES 130/0.4**, but also where test arm subjects received **2% or 4% HES 130/0.4** (exclusively studied in one sudden hearing loss trial among otherwise healthy subjects) and **10% HES 130/0.4**. The comparator was **HES 200** for most of these studies, **HES 450** for the single US-conducted study (**HS-13-30-US**), and normal saline, albumin or gelatin in the small number of remaining studies. Both single and multiple dose studies were performed, the latter lasting up to 28 days.

Four Phase 3 trials were conducted, three of which were in Europe using 6% HES 200/0.5 as control and one in the U.S. using 6% HES 450/0.7 as control. See Table 7 below.

Table 7: Results of Efficacy Studies (Source: Sponsor)						
Study	Test Dosage	Control Dosage	Test: mL Infused	Control: mL Infused	Statistics	Secondary Endpoints
HS-13-13-DE 1 center	6% HES 130/0.4 ±2500 mL	6% HES 200/0.5 ±2500 mL	2019 ± 556	2188 ± 1050	Equivalence not shown (35 mL excess)	†FVIII and vWF in test group
HS-13-19-FR 4 centers	6% HES 130/0.4 ±3000 mL	6% HES 200/0.5 ±3000 mL	1960 ± 971	1928 ± 901	Equivalence shown	†FVIII in test group
HS-13-30-US 6 centers	6% HES 130/0.4 Unrestricted	6% HES 450/0.7 Unrestricted	1613 ± 778	1584 ± 958	Equivalence shown	No difference between groups
HS-13-14-NL 2 centers	6% HES 130/0.4 ±3000 mL	6% HES 200/0.5 ±3000 mL	2913 ± 779	2884 ± 1175	Equivalence not shown (35 mL excess)	†vWF in test group

Exclusion criteria for the European trials included a history of heart, **kidney, liver**, diabetes, or severe infectious diseases, history of coagulation disorders, known allergy to starch, BW >100 kg, pregnancy, and lactation. In the single US volume replacement study (**HS-13-30-US**), exclusion criteria included previous cardiac surgery, anemia, pancreatitis, known allergy to HES, **renal and hepatic disorders**, pregnancy, and lactation.

- **HS-13-13-DE** was a randomized control trial (**RCT**) for volume replacement therapy conducted in subjects (N=52) undergoing major **orthopedic surgery** that compared perioperative volume replacement using **6% HES 130/0.4** vs. **6% HES 200/0.5**.
- **HS-13-19-FR** was a confirmatory volume replacement RCT of HS-13-13-DE that compared **6% HES 130/0.4** vs. **6% HES 200/0.5** in 100 subjects undergoing **orthopedic surgery**.
- **HS-13-14-NL** was a double-blind, volume-replacement RCT in 2 centers designed to show equivalency in perioperative volume management in subjects undergoing **cardiac surgery**.
- **HS-13-30-US** was a multicenter, double-blind, pivotal volume replacement RCT in subjects undergoing orthopedic surgery designed to show equivalency of **6% HES 130/0.4** with **HES 450/0.7**.

Note: The background information above is abstracted from the medical review memo. This review (i) focuses on the single US volume replacement study (**HS-13-30-US**), and (ii) responds to a request made in July 2007 by the medical reviewer (Dr. Larry Landow) regarding the following statements in the draft labeling in the package insert.

II. Study Design (HS-13-30-US)

This was a controlled, randomized, double-blind, multicenter pivotal Phase 3 trial with parallel groups. Patients who were at least 18 years of age and were undergoing major elective orthopedic surgery with an expected blood loss ≥ 500 mL were randomly allocated to receive either study solution (6% HES 130/0.4, Voluven®) or control solution (HES 450/0.7, hetastarch) for intraoperative volume substitution.

The primary efficacy endpoint was the total volume of colloid solution (either Voluven® or hetastarch) required for intraoperative volume substitution. Primary safety endpoints were

(S1) the calculated total perioperative red blood cell loss (a higher loss is worse), (S2) minimum factor VIII activity between end of surgery and two hours later (lower values are worse), (S3) minimum von Willebrand factor (vWF) antigen between end of surgery and two hours later (lower values are worse), and (S4) the overall consumption of fresh frozen plasma (a higher consumption is worse).

The study was designed to show equivalency of the two treatment arms for efficacy based on the mean ratio. If the 95% confidence interval for the mean ratio of Voluven® over hetastarch using is within 0.55 and 1.82, the equivalency is claimed. The confidence intervals were calculated based on an analysis of variance (ANOVA) with treatment and center as effects according to the Fieller's method.

In addition, the study was designed to show the superiority of Voluven® with respect to the safety endpoints the mean ratio. The 95% confidence intervals for the safety endpoint S1 to S4 were based on ANOVA with treatment and center as effects. The 95% confidence intervals for the other two safety endpoint S2 to S3 were based on an analysis of covariance (ANCOVA) with treatment and center as effects and the baseline value as covariate. The null hypotheses for testing for superiority of Voluven® over hetastarch with respect to S1, S2, S3 and S4 were tested sequentially in the indicated order. The next null hypothesis would be tested only if the preceding null hypothesis was rejected. Each hypothesis was tested at significance level of 0.025. Since the procedure is sequential, the overall type I error is 0.025.

A total of 110 patients in 6 centers were randomized. However, 10 patients were withdrawn from the study prior to surgery. All other 100 patients were treated with study drug and completed the study. Forty-nine patients were randomized to Voluven® and 51 to hetastarch.

Only one patient population was considered: the intent-to-treat (ITT), defined as all randomized patients who were not withdrawn prior to surgery. In addition, the primary efficacy variable was analyzed for two subsets of ITT population: (i) Patients hemodynamically stable at end of surgery, and (ii) patients with no massive blood loss and no other colloids than study medication. The primary safety endpoints were analyzed for one subset of ITT population: Patients who received > 1000 mL study medication.

III. Reviewer's Comments (HS-13-30-US)

1. The equivalence range of 0.55 to 1/0.55 is fairly wide and should be reflected in labeling in the package insert. Note: Early draft of the package insert had been revised accordingly.
2. As reported by the sponsor, since there is no statistical significance difference in the first safety parameters tested (calculated total perioperative red blood cell loss), the superiority of Voluven® over hetastarch regarding the primary safety endpoints could not be concluded.
3. Although the 3 subsets of ITT population were defined *a priori*, the results of subgroup analyses should be viewed with caution because the treatments may affect the outcomes used to define the subsets.

IV. Analyses in response to the medical reviewer's request

The medical reviewer summarized the results of von Willebrand factor, Factor VIII, and Ristocetin cofactor in Tables 19, 20 and 22 of his review. This reviewer performed t-

tests to compare the two treatments based on change from baseline at each time point for each of the three variables. Results with p-value < 0.05 and p-value < 0.001 were indicated in the tables presented in the Appendix of this review.

In performing the above analyses, this reviewer raised the following question.

According to the dataset named "input" you provided in the NDA submission, patients 53, 54 and 60 in study HS-13-14-NL received both the test product (6% HES 130/0.4) and the control product (6% HES 200/0.5). Please describe how these patients were handled in your analyses.

In Amendment 3 (BN070012/0.3) submitted on August 16, 2007, the sponsor responded that these patients (53, 54, 60) were randomized to HES 130/0.4 and analyzed for this group. The sponsor further explained that they did not receive any HES 200/0.5 study medication, but open label marketed product HAES-steril 6% (HES 200/0.5) as concomitant medication.

V. Reviewer's Comments/Questions (Medical reviewer's request)

1. The results in Appendix of this review should be viewed with caution for the following reasons.
 - a. In the US study, as reported by the sponsor, the superiority of Voluven® over hetastarch regarding the primary safety endpoints could only be demonstrated in an exploratory way (see III.2 above).
 - b. Von Willebrand factor, Factor VIII, and Ristocetin cofactor are secondary endpoints among many other secondary endpoints that were specified in the protocols for the other three Non-US phase III studies. Consequently, the analyses are exploratory.
2. Does CBER allow a claim in the package insert supported by exploratory analyses as opposed to confirmatory analyses?
3. It is not clear from the sponsor's response if "HES 200/0.5 study medication" is different from "open label marketed product HAES-steril 6% (HES 200/0.5)".
4. The database provided by the sponsor in "Overall Safety Analysis" does not include "analyses datasets" for the primary efficacy and safety endpoints. If it is not too late, this reviewer would like to request these datasets from the sponsor including the ITT population and the three subsets used in their analyses.

VI. Appendix

Table 19: FVIII in Studies Where Captured(Source: FDA analysis of line listings)		
Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-13-DE: 6% HES 130 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=24 vs. 25)	43	46
End of surgery (N=19 vs. 18)	26 (60)	26 (57)
4-6 h (N=23 vs. 24)	36 (84)	35 (76)
1 day after surgery (N=4 vs. 1).	57 (133)	46 (100)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (N=49 vs. 44)	115	127

Table 19: FVIII in Studies Where Captured (Source: FDA analysis of line listings)

Study	Test Mean (% of baseline)	Control Mean (% of baseline)
End of surgery (N=48 vs.43)	95 (83)	98 (77)
4-6 h (N=48 vs. 45)	148 (129)	139 (109)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs. 29)	136	133
After 45 mL/kg of solution (N=30 vs. 28)	109 (80)	116 (87)
24 h (N=30 vs. 28)	130 (96)	134 (100)
48 h (N=30 vs.28)	164 (121)	169 (127)
HS-13-25-CH: 6% HES 130/0.4 vs. 6% HES 200 (N= 16 vs. 15)		
Baseline (N=16 vs.16)	83	89
Day 2 (N=16 vs.14)	81 (98)	85 (96)
Day 4 (N=13 vs.15)	135 (163)*	107 (120)
Day 6 (N=9 vs.14)	153 (184)	142 (160)
Day 8 (N=6 vs. 12)	141 (170)	144 (162)
3 days after last infusion (N=13 vs.10)	170 (205)	156 (175)
HS-13-30-US: 6% HES 130/0.4 vs. HES 450 (N=49 vs. 51)		
Baseline (N=49 vs. 50)	146	143
2 h post-surgery (N=49 vs.48)	158 (108)	130 (91)
24 h (N=49 vs.46)	239 (164)***	146 (102)
48 h (N=49 vs.44)	315 (216)***	228 (159)

p-value of t-test comparing test versus control based on change from baseline: * p < 0.05; *** p <0.001

Table 20: vWF in Studies Where Captured (Source: FDA analysis of line listings)

Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-13-DE: 6% HES 130 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=25 vs. 25)	60	56
End of surgery (N=19 vs. 17)	47 (78)	32 (57)
4-6 h (N=23 vs. 23)	60 (100)*	38 (68)
24 h (N=4 vs.1)	61 (100)	76 (136)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (N=51 vs.44)	107	112
End of surgery (N=49 vs. 43)	83 (78)	84 (75)
4-6 h (N=49 vs. 46)	144 (135)	132 (118)

Table 20: vWF in Studies Where Captured (Source: FDA analysis of line listings)

Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs. 29)	133	134
After 45 mL/kg of solution (N=31 vs. 29)	137 (103)	157 (117)
24 h (N=31 vs. 29)	188 (141)	175 (131)
48 h (N=31 vs. 28)	219 (165)	211 (158)
HS-13-30-US: 6% HES 130/0.4 vs. HES 450 (N=49 vs. 51)		
Baseline (N=49 vs. 50)	133	135
2 h post-surgery (N=49 vs. 48)	135 (102)*	113 (84)
24 h (N=49 vs. 46)	220 (165)***	147 (109)
48 h (N=49 vs. 44)	259 (195)***	211 (156)

p-value of t-test comparing test versus control based on change from baseline: * p < 0.05; *** p < 0.001

Table 22: Ristocetin Values Where Captured (Source: FDA analysis of line listings)

Study	Test Mean (% of baseline)	Control Mean (% of baseline)
HS-13-13-DE: 6% HES 130 vs. 6% HES 200 (N=26 vs. 26)		
Baseline (N=24 vs. 26)	98	110
End of surgery (N=19 vs. 18)	79 (81)	70 (64)
4-6 h after end of surgery (N=23 vs. 23)	102 (104)*	79 (72)
HS-13-14-NL: 6% HES 130/0.4 vs. 6% HES 200 (N=30 vs. 32)		
Baseline (N=28 vs. 29)	151	166
After ECC (after protamine infusion) (N=28 vs. 30)	129 (85)	142 (86)
1st post-operative morning (N=27 vs. 29)	223 (148)***	184 (111)
HS-13-19-FR: 6% HES 130 vs. 6% HES 200 (N= 52 vs. 48)		
Baseline (=49 vs.47)	94	116
End of surgery (N=50 vs. 43)	87 (93)	81 (70)
4-6 h after end of surgery (N=48 vs. 46)	142 (151)	134 (116)
HS-13-24-DE: 6% HES 130/0.4 vs. 6% HES 200 (N=31 vs. 30)		
Baseline (N=30 vs.29)	158	152
After 45 mL/kg of solution (N=30 vs.28)	237 (150)	220 (145)
24 h (N=30 vs.28)	259 (164)	234 (154)
48 h (N=30 vs. 28)	328 (208)	311 (205)
HS-13-25-CH : 6% HES 130/0.4 vs. 6% HES 200(N=16 vs. 15)		
Baseline (N=16 vs.15)	107	120

Table 22: Ristocetin Values Where Captured (Source: FDA analysis of line listings)

Study	Test Mean (% of baseline)	Control Mean (% of baseline)
Day 2 (N=16 vs. 14)	143 (134)*	114 (95)
Day 4 (N=13 vs. 15)	164 (153)	141 (118)
Day 6 (N=9 vs. 14)	167 (156)*	139 (116)
3 days after last infusion (N=13 vs. 10)	172 (161)	169 (141)

p-value of t-test comparing test versus control based on change from baseline: * $p < 0.05$; *** $p < 0.001$

Attachment 8: Proprietary Name - Voluven

MEMORANDUM

Date: November 6, 2007

TO: Franklin T. Stephenson, CSO, OBRR/DBA/RPMB, HFM-380
Elena Karnaukhova, Committee Chair, OBRR/DH/LBVB, HFM-343
Laurence Landow, MD, OBRR/DH/CRB, HFM-392

From: Nancy Chamberlin, Pharm.D, Regulatory Review Officer, Advertising and Promotional Labeling Branch (APLB), Division of Case Management (DCM), HFM-602

Through: Ele Ibarra-Pratt, RN, MPH, Branch Chief, APLB, DCM, HFM-602

Through: Robert A. Sausville, Director, DCM, HFM-610

Subject: Review of proposed proprietary name Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion) (BN070012)

Executive Summary:

APLB recommends that the proposed proprietary names, **Voluven®** be found Acceptable with Concerns at this time.

Background:

On February 28, 2007, Fresenius Kabi Deutschland GmbH submitted NDA for **Voluven** (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion). The sponsor submitted a request for review of their proposed proprietary name on which was received in the CBER Document Control Room on October 5, 2007, and in APLB on October 5, 2007.

"**Voluven®**" has been registered as a trademark with the U.S. Patent and Trademark Office since April 9, 2002.

In the submission the sponsor states, "Based on the accumulated experience with this proprietary name in more than seven years of international marketing, it is not thought that the name misrepresents the efficacy or safety of the product or presents a potential to contribute to medication errors or to confusion in the marketplace". The sponsor's rationale for choosing the name is that the terms "Volu" is derived from "volume" as in plasma volume substitute and "ven" is derived from "vein" as in intravenous infusion.

Overview of the Proposed Indication, Dose, Dosage Form, Administration, and Storage Information:

The proposed indication for **Voluven** is for treatment and prophylaxis of hypovolemia. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion. It will be supplied as 500 mL flexible plastic intravenous solution container.

The initial **Voluven** dose of 10 to 20 mL will be infused slowly to observe for possible anaphylactoid reactions. The proposed **Voluven** daily dose and rate of infusion will depend on the patient's blood loss, on the maintenance or restoration of hemodynamics and on the hemodilution (dilution effect). The adult dose may be up to 50 mL /kg/day. Administration of the product requires close and continued observations by the healthcare provider.

Proposed Proprietary Name Evaluation:

1. False or Misleading [21 CFR 201.6 (a)]:

The proposed proprietary name **Voluven** is not regarded to be false or misleading.

2. Fanciful [21CFR 201.10 (c)(3)]:

The proposed proprietary name **Voluven** is not regarded to be fanciful. It does not appear to imply that the drug or ingredient has some unique effectiveness or composition beyond that supported by the data.

3. Similarity in Spelling or Pronunciation [21 CFR 201.10 (c) (5)]:

Voluven may be confused with the proprietary name or the established name of a different drug because of similarity in spelling or pronunciation. Since, drug products are prescribed through written, verbal, and /or electronic orders, such forms of communication may lead to medication errors, particularly if proprietary and /or established names sound or look alike. Even when proprietary names are only slightly similar, overlapping product characteristics may create a greater potential for confusion. Products are listed in the table below from the highest to lowest potential for causing a medication error.

APLB also has concerns with similar letters in the first part of a proprietary or established name because the prescriber's handwriting may become less legible at the end of the name making these names undistinguishable with sound-alike, look-alike names for products that already exist in the U.S. marketplace.

There is a similarity in spelling and pronunciation with proprietary names for other marketed products:

- Marketed products like **Voluven** that contain the "Vol" prefix in their proprietary name could appear similar: **VoLumen** (oral contrast media) and **Voltaren** (oral, ophthalmic, and topical). There is an increased potential for medication error due to similarity in spelling and pronunciation and handwriting of these products with **Voluven**. Potential for medication errors increases with similarity in placement of letters in the names. **VoLumen** (oral) has 6 letters similar with the L capitalized, **Voltaren** has 5 similar letters and could potentially be confused with written and verbal orders for **Voluven**.
- **Valtropin** and **Valium** had a similar beginning and ending with **Voluven** and could potentially be confused with poor handwriting and verbal orders.
- There are marketed product with the "Flo" prefix included in its proprietary name: **Flovent** (inhaler), **Flovent HFA** (inhaler), and **Flonase** (intranasal) which could be confused with the "Vol" prefix of **Voluven** due to similarity in spelling and pronunciation with verbal order.
- Other marketed products whose names may be confused due to similarity in verbal and poor handwritten orders for **Voluven** are: **Ventolin** (4 similar letters), **Fulvicin** (3 similar letters) and **Flolan** (3 similar letters).
- Marketed influenza products: **Afluria**, **Fluarix**, **Flulaval**, **Fluzone**, **FluMist** and **Fluvirin** are often ordered as "Flu" which is only one syllable and would have a minimal risk for confusion with **Voluven**.
- Also because orders often are written with the established name there is potential for confusion with **fluticasone** (inhaler), and **fluvoxamine** (oral) because they contain the "Flu" prefix which could be confused with "Vol" prefix.

Name	Dosage Form	Rx or OTC	Dose & Administration	Indication	Storage	Potential
Voluven 6% hydroxyl-ethyl starch 130/0.4 in 0.9% sodium chloride infusion	Suspension for Injection: 500 mL IV bag	RX	Initial dose of 10 to 20 mL slow IV infusion. The proposed daily dose and rate of infusion will depend on the patient. The adult dose may be up to 50 mL /kg/day.	Treatment and prophylaxis of hypovolemia	Room temperature	N/A
VoLumen ® Low Hounsfield Value (LHV) Barium Sulfate Suspension	Suspension, for Oral Contrast as 0.1 w/v, 0.1%w/w in a 450 ml bottle	RX	7 to 11 capsules daily, or as directed by physician	To be used in oral contrast for MDCT and PET/CT studies	Room temperature	High
Voltaren (diclofenac)	Delayed Release tablets: 75 mg	RX	Osteoarthritis dose:100 to 150mg/day in divided doses; RA dose: 150 to 200 mg/day in divided doses Ankylosing Spondylitis: 100 to 125mg/ day	Relief of sign and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis	Room temperature	High
Voltaren XR (diclofenac)	Extended Release tablets: 100 mg	RX	Osteoarthritis dose:100 mg/day; RA dose: 100 mg/day	Relief of sign and symptoms of osteoarthritis and rheumatoid arthritis.	Room temperature	High
Voltaren (diclofenac)	Ophthalmic Solution: 0.1% in 2.5 and 5 ml dropper bottles	RX	Instill 1 to 2 drops into affected eye 4 times a day for up to 14 days.	Postoperative ocular inflammation and ocular pain/photophobia	Room temperature	High
Voltaren	Topical gel:	RX	Apply gel (2-4	Osteoarthritis of		High

Name	Dosage Form	Rx or OTC	Dose & Administration	Indication	Storage	Potential
(diclofenac)	1%		gm) to the affected area 4 times a day.	joints amenable to topical treatment such as knees and hands.		
Ventolin HFA (albuterol)	Metered Inhaler: Eq 0.09 mg base/inh	RX	For Asthma: 2 puffs every 4 to 6 hours; Exercise Induced B.: 2 puffs 15 to 30 minutes before exercise	Treatment or prevention of bronchospasm in adults & children 4 years of age with reversible obstructive airway disease and prevention of exercise induced bronchospasm in patients 4 years and older	Room temperature	Moderate
Flovent Rotadisk (fluticasone)	Powder for inhalation: 0.05mg/inh, 1mg/inh, and 0.25mg/inh	RX	Orally inhaled dose: Peds 4-11 years: 50-100 mcg twice a day; ≥12 years: 100-500 mcg twice a day	Prophylactic therapy in chronic asthma in patients over 4 years of age	Room temperature	Moderate
Flovent Diskus (fluticasone)	Powder for inhalation: 0.05mg/inh, 1mg/inh, and 0.25mg/inh	RX	Orally inhaled dose: Peds 4-11 years: 88 mcg twice a day; ≥12 years: 88-880 mcg twice a day	Prophylactic therapy in chronic asthma in patients over 4 years of age	Room temperature	Moderate
FloventHFA (fluticasone propionate)	Aerosol: 44 mcg/actuation, 110 mcg/actuation, 220 mcg/actuation in canister.	RX	Orally inhaled dose: Peds 4-11 years: 88 mcg twice a day; ≥12 years: 88-880 mcg twice a day	Prophylactic therapy in chronic asthma in patients over 4 years of age	Room temperature	Moderate

Name	Dosage Form	Rx or OTC	Dose & Administration	Indication	Storage	Potential
Valtropin (somatropin recombinant DNA origin)	Lyophilized Powder for Injection: 5 mg/vial	RX	Subcutaneous injection Preferably in the thighs. Peds with GHD: 0.17-0.03 mg/kg/day; Peds with Turner syndrome: 0.053 mg/kg/day; Adults: 0.005 to 0.010 mg/kg/day (maximum 0.66 mg/day)	Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone; or growth failure associated with Turner syndrome in patients with open epiphyses. In adults with growth hormone deficiency as a result of hypothalamic disease, surgery, radiation therapy or trauma or deficiency of growth hormone during childhood.	Refrigerate	Moderate
Fulvicin U/F (griseofulvin, microcrystalline)	Oral tablet: 250 mg, and 500 mg	RX	Adults & teenagers: fungus infections of feet and nails: 250 to 375 mg every 12 hours; infections of scalp, skin and groin: 250 to 375 mg once a day; Infants up to 2 yrs: MD determines dose Children over 2 yrs: 2.75 to 3.65 mg/kg every 12 hrs,	Antifungal	Room temperature	Moderate

Name	Dosage Form	Rx or OTC	Dose & Administration	Indication	Storage	Potential
Flolan (epoprostenol)	Powder for Injection: 0.5 mg base/vial, and 1.5 mg base/vial	RX	2ng/kg/min IV infusion and increase as tolerated (mean dose 11.2 ng/kg/min)	Long-term IV treatment of primary pulmonary hypertension and primary pulmonary hypertension associated with scleroderma	Unopened vials are stored at room temperature, Reconstituted must store in refrigerator	Moderate
Flonase (fluticasone)	Intranasal spray: 50 mcg/ Actuation in 16 g amber bottles with nasal adapter	RX	4-11 years: 1 spray in each nostril once a day; ≥12 years: 2 sprays in each nostril once daily	Management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older	Room temperature	Moderate
<i>Established name of</i> fluvoxamine	Oral tablets: 25mg, 50 mg, and 100 mg	RX	Children 8-17 years of age: Initiate dose as 25 mg at bedtime and increase if needed up to 100 mg twice a day; Adults: initiate with 50 mg at bedtime and increase up to 150 mg twice a day	Obsessive compulsive disorder (OCD)	Room temperature	Moderate
Valium (diazepam)	Oral tablets: 2 mg, 5 mg, and 10 mg	RX	Child doses: 1 to 2.5 mg 3 or 4 times a day Adult doses: Anxiety: 2 to 10 mg 2 to 4 times a day	Anxiety disorders, acute alcohol withdrawal, skeletal muscle relaxant, anticonvulsant	Room temperature	Moderate

Name	Dosage Form	Rx or OTC	Dose & Administration	Indication	Storage	Potential
			Acute alcohol withdrawal: 5-10 mg 3 or 4 times a day Muscle relaxant: 2 to 10 mg 3 to 4 times a day Anticonvulsant: 2 to 10 mg 2 to 4 times a day Geriatrics 2 to 2.5 mg 1 to 2 times a day.			

The following risk factors should also be considered when evaluating the degree to which **Voluven** may be of concern for medication errors.

Strength/ Dose/Dosage Form/Route of Administration:

Two different products with similar or identical strengths and with proprietary names that sound or look alike could be more easily confused than two products with very different strengths. The risk of confusion increases substantially if two products with similar proprietary names have identical strengths and dosing intervals.

The risk of a medication error is increased when products with similar proprietary names are dosed or prescribed in an identical manner (i.e., once a day). In addition, there is evidence that medication errors can occur even between different dosage forms and routes of administration (capsule vs. injection) and between products with similar proprietary names.

Voluven is supplied as a suspension in 500 mL plastic IV bags. The dose will be individualized and *given intravenously* by a trained healthcare provider. It will be given over as many days as medically needed.

VoLumen® Low Hounsfield Value (LHV) Barium Sulfate Suspension, 0.1 w/v, 0.1%w/w, is supplied in a 450 ml bottle and *administered orally* within 6 hours of the diagnostic procedure. Handwritten or verbal orders for **Voluven** and VoLumen could lead to some confusion with only one letter difference in the name. However, most orders are written using the generic name "barium sulfate", the patient needs dietary restrictions prior to giving the oral barium, and is used for MDCT and PET/CT procedures. Therefore, the likelihood of confusion with the IV **Voluven** would be lessened.

Unlike **Voluven**, **Valtropin** and **Flolan**, are *injectable* products that are supplied as powders in small volumes. **Voltaren** is supplied as oral tablets, ophthalmic solution, and topical gel. **Ventolin** and **Flovent** are inhalational products. **Flonase** is an intranasal spray. While **Fulvicin**, **Fluvoxamine** and **Valium** are oral tablets. None of the listed

products are dosed similar to **Voluven**. However, the potential for confusion due to dosage form and route of administration dosing interval could occur.

Indications and/or Pharmacological-Therapeutic Categories:

The proposed indication for **Voluven** is for treatment and prophylaxis of hypovolemia. Other products in the table will be not used for hypovolemia.

VoLumen is a neutral oral contrast for MDCT and PET/CT studies. It works with IV contrast to help achieve bowel distension and lumen-to-wall differentiation for visualization. It is administered within 6 hours of the diagnostic procedure which may limit its potential for confusion with **Voluven**.

Voltaren is a nonsteroidal anti-inflammatory agent used in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and ocular pain or photophobia. It could be used in the same hospital patient setting as **Voluven**, however because of the difference in dosage forms and a patient needing IV volume replacement the likelihood for a confusion between these products would be lessened.

Different indications will not decrease the risk of confusion since the intended use or indication is not routinely written on a prescription for medication order. Therefore, the possibility of a medication error still exists between the products listed in the table and **Voluven** if a verbal or written order is received.

Storage Location:

The use of a different storage location (i.e., refrigerator vs. room temperature, oral dosage form location vs. intravenous dosage form location) for two different products with similar names does not significantly decrease the risk of wrong product selection by the health care professional. Therefore, the use of different storage locations for drugs with names that look or sound alike may not mitigate the potential risk of medication errors.

Voluven, Voltaren, Ventolin, Flovent, Fulvicin, Flolan, Flonase, Fluvoxamine, and Valium will be stored at room temperature. **VoLumen** is also stored at room temperature in pharmacies and areas that supply contrast media. **Valtropin** will be stored in the refrigerator.

Marketing Status:

Two products with similar proprietary names that are in the same marketing arena (e.g., prescription drug products) could more easily be confused than two products with similar names in different markets (one Rx and the other OTC). Therefore the potential for confusion of these products with **Voluven** due to marketing status exists.

Packaging and Labeling:

When the container labels, carton labeling, and/ or packaging is similar for two different drug products with similar proprietary names, the risk for confusion with similar proprietary names is increased. The packaging/labeling of the some of marketed products was not available; therefore, the risk of confusion with **Voluven** due to packaging/labeling could not be evaluated.

Recommendations for proposed names:

APLB recommends that the proposed proprietary name **Voluven** be found acceptable with concerns. There appears to be a minimal risk for medications errors with the proprietary names for other marketed products, such as, **VoLumen** and **Voltaren**, taking into account similarity in spelling, therapeutic class, indication, pronunciation, handwriting, storage, dosage form, route of administration, and marketing status.

If OBRR accepts our recommendation that the proposed proprietary name **Voluven** be found acceptable with concerns, please include the following text in your letter to the manufacturer:

We have considered your proposed proprietary name **Voluven** in consultation with CBER's Advertising and Promotional Labeling Branch (APLB) and conclude that under 21 CFR Part 201 the proposed proprietary name is acceptable with concerns at this time. You should request another proprietary name review of **Voluven** closer to the time of approval since a significant amount of time may pass between now and licensure of the product and to ensure that FDA has not approved a product with a conflicting proprietary name in the interim.

If you have any questions regarding this review please contact Nancy Chamberlin, at 301-827-3028.

*The following references were used:

1. <http://www.thomsonhc.com/pdrel/librarian> (Electronic Physicians' Desk Reference 2007)
2. <http://www.factsandcomparisons.com> (Drug Facts and Comparisons)
3. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (CDER approved drug products through October 31, 2007)
4. <http://www.fda.gov/cder/ob> (Electronic Orange Book through October 17, 2007)
5. <http://www.rxlist.com> (RxList)
6. <http://www.fda.gov/cber/products/htm> (CBER New BLA, 510 (k) Devices, NDA and PMA approvals lists through October 31, 2007)
7. <http://www.ama-assn.org/ama/pub> (American Medical Association Website-Newly Approved USAN stems through October 5, 2007)
8. <http://www.acronymfinder.com>
9. APhA Handbook of Nonprescription Drugs, 13th Edition, ©2002
10. 2007 American Drug Index

Attachment 9: Labeling - Voluven

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch

REVIEW MEMORANDUM

DATE: November 7, 2007

FROM: Nancy Chamberlin, Pharm.D, CSO, APLB/DCM/OCBQ, HFM-602

THROUGH: Ele Ibarra-Pratt, RN, MPH, Branch Chief, APLB, HFM-602

TO: Abdu Alayash, Ph.D.; HFM-343; LBVB, DH, OBRR, CBER; (301)827-3813

TO: Franklin T. Stephenson, CSO, OBRR/DBA/RPMB, HFM-380

Elena Karnaukhova, Committee Chair, OBRR/DH/LBVB, HFM-343

Laurence Landow, MD, OBRR/DH/CRB, HFM-392

RE: Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion)
(BN070012)

Submission Date: February 28, 2007 and October 2, 2007

Background:

Proposed Voluven professional labeling was submitted with the application on February 28, 2007 and on October 2, 2007, the application was amended to include revised Voluven labeling in the new PLR format. Proposed carton and container labels were also included.

Highlights and Prescribing Information:

We have reviewed the proposed labeling for Voluven and provide our comments below on the draft version dated October 2, 2007:

Highlights Section:

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Prescribing Information:

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Carton and Container Labels

The sponsor did not submit actual mock-ups of proposed carton labels and containers. The sponsor submitted a narrative version of what items would be expected on the container and carton labels. However, without mock-ups it is difficult to determine the size and prominence of the brand and established names, and assess whether the proposal is in compliance with the regulations, 21 CFR 610.62. Based on the narrative listing, we note that the container and package labels would be missing license number, bar code and NDC numbers. The carton and container labels should comply with applicable regulations for container labels and carton package labels, 21 CFR 610.60, 610.61, 610.62, and 610.67.

Conclusion:

We recommend that the proposed prescribing information and carton and container labels be revised in accordance with our comments above to ensure compliance with applicable regulations.

Our comments are provided from an advertising and promotional labeling perspective. If you have any questions with regards to the above comments please call Nancy Chamberlin at 301-827-3028.