DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MD 20852

CLINICAL REVIEW MEMO

Re	**Revised PI: SECTION 14: CLINICAL STUDIES**
Product	**Voluven**
Indication	**Treatment and prophylaxis of hypovolemia**
IND/NDA	**9740/56; BN070012/144**
Sponsor	**Fresenius Kabi**
From	Laurence Landow MD, Medical Officer
To	File
Through	Nisha Jain MD, Chief, Clinical Review Branch

BACKGROUND

Two PMRs were required from the sponsor at the time of licensure (27-DEC-2007): a study in pediatric subjects undergoing open heart surgery in association with cardiopulmonary bypass and the CRYSTMAS study, a RCT in subjects with severe sepsis comparing Voluven (n=100) vs. normal saline (n=96) in the treatment of hypovolemia. The sponsor submitted a revised PI in early 2012.

In April 2012, FDA requested additional information to be used to determine whether (***a***) treatment emergent serious adverse experiences (TEAE; 53/100 vs. 44/96) and (***b***) TEAE leading to death (38 vs. 32) reported in the CRYSTMAS study should be characterized as SAEs (i.e., TEAE may or may not be causally related to product), suspected SARs (i.e., reasonable possibility that the TEAE was caused by the product), or SARs (i.e., TEAE was causally related to the product).[1] Both parties agreed at a telecon held on 18-APR-2012 to use a time interval of 7 days as a method to assess causality. NB: FDA previously had received *post hoc* data from the sponsor for (***c***) number of subjects undergoing RRT within the first 7 days (17 vs. 8).

SPONSOR RESPONSE

The sponsor provided the requested information in their response. TEAEs at 7 days were 39 vs. 34 and TEAEs leading to death by 7 days were 20 vs. 18.

The sponsor also requested that the following statement be added to the PI:

[1] Guidance for Industry and Investigators: Safety reporting requirements for INDs and BA/BE studies (2010)

"The frequency of intra-abdominal sepsis at baseline tended to be higher in the Voluven group (24.0%) than in the NaCl (18.8%) group, which might be important as treatment of intra-abdominal infections represents a particular challenge, primarily because of the polymicrobial nature of these infections and their association with high rates of morbidity and mortality."

FDA reviewer assessment/recommendation

1. TEAEs (53 vs. 44) and TEAEs leading to death (38 vs. 32) should be characterized as **SAEs** because the number of events occurring within 7 days of IP administration is similar between treatment arms, i.e., 39 vs. 34 and 20 vs. 18, suggesting insufficient data to rule in a causal relationship to IP.

2. Necessity for RRT should be classified as an **SAR** because the 7-day incidence in Voluven subjects was virtually twice that of control (17 vs. 8, p=0.07). Causality can be attributed to treatment with Voluven for two reasons: (a) the power of randomization to produce treatment arms with similar covariates at baseline and (b) strength of evidence (p=0.07) even though the trial was not powered for safety.

3. In addition to the abdomen (24 vs. 18) as a suspected site of sepsis, lung (53 vs. 58) and urogenital system (8 vs. 14) as suspected sites should be added to the PI (see sponsor's Table 4, below). The sponsor's claim that a 5.2% imbalance against the Voluven arm in the frequency of intra-abdominal sepsis at baseline accounted for differences in morbidity and mortality fails to account for baseline differences in subject characteristics going in the opposite direction for lung and urogenital system.

Table 4. Baseline characteristics with different distribution between treatment groups

	Voluven (N=100, ITT) n(%)	NaCl (N=96, ITT) n(%)
System organ class disorders		
Nervous system	19(19.0)	8(8.3)
Endocrine disorders	12(12.0)	5(5.2)
Reproductive system and breast disorders	9(9.0)	3(3.1)
Suspected site of sepsis		
Lung	53(53.0)	58(60.4)
Abdomen	24(24.0)	18(18.8)
Urogenital system	8(8.0)	14(14.6)
Anesthetics medications	60(60.0)	73(76.0)
Sufentanil	21(21.0)	27(28.1)
Etomidate	19(19.0)	23(24.0)
Fentanyl	16(16.0)	25(26.0)
Propofol	13(13.0)	19(19.8)
Concomitant medications		
Potassium chloride	47(47.0)	58(60.4)
Vasoactive Medications		
Propofol	32(32.0)	41(42.7)
Ca-antagonist	15(15.0)	23(24.0)

4. The PI should communicate this information as appropriate.