



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics
Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

MEMORANDUM

Date: October 30, 2007

From: Yiping Jia, Ph.D.; HFM-343; LBVB, DH, OBRR, CBER;
(301) 451-3952, FAX (301) 402-2780

Subject: NDA BN070012/0; CMC sections of the original NDA submitted by Carolina Research Group on behalf of Fresenius Kabi Deutschland GmbH for Voluven® 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion

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

To: Franklin Stephenson, RPM; HFM-380; RPMB, DBA, OBRR, CBER; (301)827-6165

The File (NDA BN070012)

Recommended Action: Approval

SUMMARY

This submission is an original NDA with document date of 28-Feb-2007, and was received in CBER/DCC on 01-Mar-2007 (L412822). I have received a copy of Module 3 and reviewed the CMC information related to the process validation, as well the DMF2 IND [REDACTED] that was dated on 12-Jan-2007 and received by CBER/DCC on 16-Jan-2007.

Hydroxyethyl starch 130/0.4 is a derivative of a thin boiling waxy maize starch, which mainly consists of a glucose polymer (amylopectine) consisting of α -1,4-connected glucose units with several α -1,6-branches. In addition to amylopectine small amount of amylose are present depending on the source of the starch. Thin boiling waxy maize starch has a particularly high content of amylopectine.

10 PAGES

DETERMINED NOT

TO BE

RELEASABLE

NDA BN070012/0; Fresenius Kabi; Voluven® (6% Hydroxyethyl starch³ 130/0.4 in 0.9% NaCl infusion)

Response from the sponsor:

Section 3.2.S.4.1 Specification and section 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment of the Type II Master File for "Hydroxyethyl Starch 130/0.4 for Injection" (Code no.: BB-MF [REDACTED]) have been revised accordingly. (Copies of these revisions are being submitted separately to BB-MF [REDACTED])

In addition, section 3.2.S.4.1 Specification for Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride infusion) of STN: BN070012 has been revised accordingly.

Reviewer's comment: the response is adequate.

Recommended Action: Approval

NDA BN070012/0; Fresenius Kabi; Voluven® (6% Hydroxyethyl starch² 130/0.4 in 0.9% NaCl infusion)

Amylopectine contains free hydroxyl groups at the 2,3 and 6 positions of the glucose moieties. These functional groups are partially subjected to derivatization by hydroxyethyl groups.

Hydroxyethyl starch is a mixture of molecules of different molecular weights. This is caused by the already existing molecular weight distribution of the starting material (starch) and the cleavage of glycosidic bonds during the hydrolysis process. This distribution is commonly described by the weight average (Mw), by the number average molecular weight (Mn) and by other parameters, e.g. the Mw at the upper and lower 10% mass fraction of the molecular weight distribution curve determined by size exclusion chromatography.

On an average there are 0.42 hydroxyethyl ether groups per glucose unit (0.38 - 0.45) in this type of hydroxyethyl starch. This parameter is called the molar substitution (MS). The weight average molecular weight of HES 130/0.4 lies between 110,000 and 150,000 which corresponds approximately to 610 to 830 partially hydroxyethylated glucose units. Molecular weights 10% upper fraction and lower fraction are [REDACTED] respectively.

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 is practically insoluble in most organic solvents.

Hydroxyethyl starch is manufactured at the site in Linz/ Austria:

Fresenius Kabi Austria GmbH
Estermannstraße 17
A-4020 Linz
Austria, Europe

Manufacturing process can be summarized as follows.

