Consult Review Memo, October 7, 2011 - Hemacord

Date	7 October 2011
Product	Hemacord (HPC-C)
Sponsor	New York Blood Center
From	Laurence Landow MD, Medical Officer
To	Donna Przepiorka MD
Through	Nisha Jain MD, Chief, Clinical Review Branch

Introduction: CRB has received an Intercenter Request for Consultative Review regarding appropriate labeling instructions for administering the product diluted with 1% Dextran-40[1] with DMSO for cryopreservation. The Question posed is,

"What is the safe rate at which the infusion of this 5% Dextran-40-containing product should be initiated?"

Background: The cord blood unit is cryopreserved in 1% Dextran-40 with DMSO. Instructions for use provide (b)(4) methods for thaw and preparation. ----(b)(4)--------, the product is diluted to 170 mL in 5% Dextran-40. ----------(b)(4)----------. There is no rate of infusion specified in the proposed label, but common practice is "as quickly as possible" and usually within 30 minutes. Patients about to receive the product are prehydrated, and all are on a -----(b)(4)---------- (which causes renal insufficiency and hypertension). Most adults will receive two units back-to-back and most pediatric patients will receive a single unit.

CRB response: Licensed for over 40 years, 10% Dextran-40 is a colloid solution currently indicated for volume resuscitation, DVT prophylaxis, and as an additive to the

pump prime in the setting of surgical procedures involving cardiopulmonary pulmonary bypass.

Two types of adverse events have been reported postmarketing: anaphylaxis and volume overload.

- *Anaphylaxis*: A 2005 review of the Adverse Events Reporting System (AERS) database showed that 90 cases of severe anaphylaxis were reported for the period 1969-2003. Large (N=76,290), prospective, multicenter clinical trials conducted in Scandinavia in the late 1970's/early 1980s comparing the incidence of anaphylaxis in subjects receiving the hapten, dextran 1, immediate prior to Dextran administration *versus* the incidence in the pre-dextran 1 era among a historical control cohort from the same Swedish, Finnish, and Norwegian hospitals, reported that pre-injecting 20 mL dextran 1 immediately prior to infusion of Dextran 40/70 reduced the incidence of anaphylaxis from a control event rate of 25 cases/100,000 units Dextran 40/Dextran 70 to 3/100,000 units. Accordingly, it appears there is no "safe rate" at which Dextran-40 can be initiated without dextran 1 pretreatment.
- *Volume overload*: the market for 10% Dextran-40 is miniscule in the US but larger in Europe (especially Scandinavia) where it is used for volume resuscitation of traumatic hemorrhage, i.e., a setting quite different from the one under discussion. In the absence of clinical data from the target population, the rate at which ≤ 170 mL of this 5% colloid solution can be "safely administered" in the current setting is likely to be a function of the patient's baseline cardiopulmonary status. Following a "test dose" of 20 mL infused over 60 sec, a rate of 100 - 200 mL/hr is likely to be well-tolerated in otherwise healthy adults (ASA I classification) of normal weight; rates in ASA II-IV should be adjusted as clinically indicated. In children, a reasonable approach is to follow guidelines similar to those for 5% IVIG:

0-15 minutes	0.5 mL/kg/hour
15-45 minutes	1 mL/kg/hour
45-75 minutes	2 mL/kg/hour
Remainder of infusion	4 mL/kg/hour

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[1] Only 10% Dextran-40 formulations have been licensed. According to Dr. Przepiorka, the 1% and 5% Dextran-40 solutions are diluted with other components.

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