Office of Biostatistics and Epidemiology/Division of Epidemiology
Pharmacovigilance Review Memo

BLA/Supplement Number:	125397/0
Product Name:	HemaCord (Hematopoietic Progenitor Cells – Cord)
Sponsor:	New York Blood Center (NYBC)
Indication(s):	in conjunction with an appropriate preparative regimen for use in hematopoietic stem cell transplantation procedures for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
Applicant:	New York Blood Center
Date(s):	CBER receipt date: 01/10/2011; PDUFA date: 11/10/2011
Review Priority:	Standard (10-month)
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1. Introduction

OBE/DE/TBSB has completed a review of BLA STN 125397 for HemaCord (Hemato poietic Progenitor Cells – Cord) by New York Blood Center (NYBC). The purpose of this review is to evaluate the potential safety issue involving transfusion reactions and to assess the adequacy of the proposed pharmacovigilance plan (PVP) and post-market safety studies for safety monitoring should this product be licensed. Information on the clinical studies and safety data in this review is derived from the FDA Clinical Review Memorandum, and the Cellular, Tissue, and Gene Therapies (CTGT) Advisory Committee meeting Briefing Documents supplied separately by both the FDA and the NYBC (meeting held on September 22, 2011). Words in *Italics* are quoted from the CTGT Advisory Committee Briefing Documents.

2. Product Background

Transplantation of hematopoietic progenitor cells has been considered experimental, though lifesaving, therapy for rare genetic/ hematologic diseases. The National Cord Blood Program (NCBP), conducted by the New York Blood Center "*was the first public cord blood bank to collect, process and store cord blood grafts for transplantation to unrelated recipients*;" the first transplants occurring in 1993, and receiving FDA approved Investigational New Drug (IND) status in 1996 (BB IND 6637). From 1998 to 2000, the FDA solicited data (clinical, non-clinical, laboratory), comments, and proposals in an effort to establish standards that could ensure the safety and effectiveness of cord blood products used in transplantation therapy. This information now exists in a public docket (Docket No. FDA-2006-D-0157), and has since been used to complete the "Final Guidance for Industry: Minimally Manipulated Unrelated Allogeneic Placental/ Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications," published in 2009, and used as a guidance for cord blood licensure.

"Hematopoietic Progenitor Cells-Cord (HPC-C) manufactured and issued by the National Cord Blood Program of the New York Blood Center are minimally manipulated cellular biologic products that contain live human cord blood cells after volume reduction and partial Red Cell and Plasma depletion. The final cell suspension (20 mL) is cryopreserved by addition of 5 mL of 50% DMSO (Dimethyl Sulfoxide) in 5% Dextran 40, so that the final concentration of DMSO is 10% and that of Dextran is 1%, is frozen at controlled rate, and stored in liquid nitrogen (-196°C) to preserve the cell viability."

NYBC HPC-C products are indicated in conjunction with an appropriate preparative regimen for use in hematopoietic stem cell transplantation procedures for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment

"The hematopoietic stem and progenitor cells contained in an HPC-C product, after infusion to an appropriately prepared ("conditioned") recipient, regenerate and replace the recipient's blood and immune system. Overall, allogeneic hematopoietic stem cell

transplantation, a) allows treatment of malignancies, after high doses of radiation and chemotherapy, through reconstitution with new, healthy hematopoietic cells. The reconstituted system can also exert an immunologic effect on the remaining malignant cells and prevent relapse; or b) in cases of genetic diseases, transplantation replaces the patient's defective cells with healthy ones that provide normal proteins (e.g. hemoglobin or immunoglobulins) or normally functioning enzymes that can restore the recipient's defective systems."

3. Clinical Studies

Though NYBC provided cord blood units for national and foreign transplant procedures under its IND 6637, no treatment protocols were established, therefore no prospective clinical trials were conducted with HemaCord. The safety review for this product is based on voluntarily reported serious adverse events and an outcomes dataset submitted by the sponsor, with supporting literature as comparators.

4. Safety Database

4.1 Safety Outcomes Dataset

From 1993 to 2007 data was collected from voluntary questionnaires sent by the sponsor to transplant centers. From 2008 to 2011 data was collected electronically through the Stem Cell Therapeutic Outcomes Database (SCTOD), administered by the Center for International Blood and Marrow Transplant Research (CIBMTR) – a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program (NMDP). Data was collected from August 1993 through January 2011, for 3619 patients transplanted with 3946 cord blood units from NYBC. Of those, 409 patients received 432 NYBC units that were manufactured by the process proposed for licensure. And of the units manufactured by the intended licensed method, 244 had any infusion reaction data.

4.2 Adverse Event: Infusion reactions

Of the 244 units manufactured by the intended licensed method and having infusion reaction data, there were 41 (17%) reporting any transfusion reaction (at least 1% of patients reported hypertension, nausea, vomiting, hypoxemia, dyspnea, tachycardia, cough, chest tightness/ pain). Serious adverse events (SAEs) include any adverse drug experience that results in death, life-threatening adverse drug experience, inpatient hospitalization, or persistent or significant disability. There were no SAEs reported in this group.

Of the 3946 total units transplanted, 4 (0.1%) SAEs were reported having fatal or life-threatening cardiopulmonary or renal symptoms. To note, none of these cases involved units that were manufactured by the process intended for licensure; three cases were attributed to chemotherapy or immunosuppressant drugs, and one case considered an allergic reaction; no manufacturing deviations were found during NYBC's investigation of events.

4.3 Supporting Information

The Cord Blood Transplantation Study (COBLT) – the only dataset with prospective clinical monitoring for infusion reactions, comprised data for 511 patients receiving 523 cord blood units, resulting in 65% of infusions associated with any reaction, and 4 (0.8%) cases reported as an SAE with cardiopulmonary symptoms.

Ruiz-Delgado, et al. Dimethyl sulfoxide-induced toxicity in cord blood stem cell transplantation: report of three cases and review of the literature, Acta Haematol., 2009, reported the incidence of any cord blood infusion reaction ranging from 4% to 65%, with life-threatening infusion reactions occurring in up to 4.6% of patients.

5. Pharmacovigilance Planning

5.1 Potential risks

Infusion reactions are known, common events, and usually mild; the issue in this review is not their occurrence, but rather their severity. NMDP reported 13 cases with cardiopulmonary SAEs in 2009, one of which involved one NYBC unit (this case was also one of the 4 SAE cases reported in NYBC's safety database). However, this case was not one of the 432 manufactured using the process intended for licensure.

Severe infusion reactions are thought to be attributed to the cryopreservative and/or dilutional agents DMSO or Dextran-40 which are necessary in preparation of cord blood units. Known side effects of Dextran are renal failure, pulmonary edema, congestive heart failure, coagulopathy, and anaphylactoid reactions. Side effects of DMSO include hypernatremia, fluid overload, dysgeusia, nausea, vomiting, elevated liver enzymes, hemolysis, renal failure, and allergic reaction.

Data submitted by NYBC overall is passively reported (voluntary), with only 244 out of 432 units manufactured with the process intended for licensure having infusion data. Given this, under-reporting or under-estimation of the risk must be considered. In addition, severe infusion reactions cases observed with other units from NYBC may still suggest a potential risk with the process intended for licensure.

5.2 Proposed Pharmacovigilance Plan (PVP)

NYBC intends to conduct routine monitoring and adverse event reporting according to 21 CFR 600.80, as outlined in the Guidance for Industry (see product background).

"NCBP has developed and implemented a web-based system of communication with the transplant centers (TCs). WebSearch is currently used by transplant centers to perform searches and to request tests and CB unit information, as well as request and arrange shipment of CB units. In addition, the program provides an Alert system for direct

communication between NCBP and TCs…Our aim is…to obtain timely, accurate and direct information from the TCs regarding any infusion reactions of the CBUs manufactured by the NCBP."

In addition, *"The Stem Cell Therapeutic and Research Act of 2005 established the CW Bill Young Transplantation Program. Under this Program, the Stem Cell Therapeutic Outcomes Database (SCTOD) administered by the CIBMTR, was charged with collecting, analyzing and reporting on outcomes of all allogeneic transplants in the US, including CB* (cord blood) *transplants. CIBMTR must also provide accrued data to the CB Banks in electronic format monthly."* This collection from and reporting of outcomes data to the cord blood banks is required and under the direction of the Health Resources and Services Administration (HRSA). The focus of the CIBMTR data collection is clinical outcomes; however, some information on infusion reactions may be reported by transplant centers. According to the "Overview of CIBMTR Cord Blood Data Collection Program" submitted by the sponsor as briefing materials for the FDA Advisory Committee meeting 9/22/2011: *"Although real-time data collection of adverse events related to cord blood transplantation is not the purpose of the observational data systems of the CIBMTR, summary information about infusion-related adverse events is collected by the CIBMTR and is provided to banks as a tool for verification of adverse event reporting associated with cord blood units. Data regarding infusion-related adverse events is collected in summary fashion on the infusion form for validation and research purposes, and is not meant to replace real-time AE reporting by HCT centers to the CBCC or the originating bank or registry."* Use of SCTOD helps avoid duplicate efforts as "*Using the centralized platform of the CIBMTR brings value to cord banks by streamlining data collection to a single, cooperatively developed mechanism which collects standardized data elements with quality monitoring in the setting of required reporting. Banks receiving outcome reports can focus on analysis of the data for the benefit of their manufacturing processes, without being burdened by development of their own data collection processes. Transplant centers who use cord blood products for hematopoietic transplantation benefit from a universal data collection system and processes that avoid redundant data submission that is burdensome and error-prone, provide validation closer to the source of the data, and are accompanied by education efforts targeted to improving data quality*."

Thus, NYBC must report basic cord blood unit information to SCTOD (CIBMTR), who then is required to report accrued outcomes data back to NYBC monthly. Such reporting mechanisms may facilitate more complete and accurate outcome and exposure data than is currently available.

6. Assessment and Recommendations

1. No clinical studies evaluating the risk of infusion reactions (serious or non-serious) specific to NYBC cord blood units were submitted, and the infusion safety data presents a concern for under-reporting and under-estimation due to passive reporting and 44%

missing data. Lack of true denominator data and missing information inhibit the calculation of true incidence rates and the reliability of the dataset.

The severe infusion reactions observed in a small number of cord blood units from NYBC represent a potential safety concern with HemaCord. Given that no cases were observed in the 244 units with reaction information that were manufactured with the process intended for licensure, and only 4 cases were reported from the over 3000 NYBC cord blood units infused, severe infusion reactions are likely rare and the strength of association with the product is likely low. However, only slightly more than half of the units manufactured with the intended process had any reaction information. The relatively small size of the treated population limits our ability to conclude that these cases do not represent an excess over the expected background rate in this kind of clinical population.

2. Because each cord blood unit released for infusion is linked to a specific, matched patient, communication between the Cord Blood Center and the infusing center is enhanced over routine passive surveillance. Given this aspect of the product as well as the already established statutory requirements for adverse event reporting by Transplant Centers under the *CW Bill Young Transplantation Program* (SCTOD), adverse event reporting as required by 21 CFR 600.80 will be sufficient for addressing the concern of serious infusion reactions. Each cord blood unit released from the blood bank is linked to a specific patient. NYBC's Websearch communication system utilizes the link between released units and specific recipients for instances of adverse event reporting, to enhance the transfer of *timely, accurate and direct information from the Transplant Centers regarding any infusion reactions*. Additional follow-up information to elucidate possible association between HemaCord and infusion reactions can be requested from the sponsor as part of root cause analysis of any serious infusion reactions reported to FDA.

3. Section 505(o) of FDA Amendments Act (FDAAA) authorizes the FDA to require post-marketing studies or clinical trials after approval, if the FDA becomes aware of new safety information that suggests a higher or more severe risk of serious infusion reactions with HemaCord than was known at the time of approval.

4. Although they are labeled events, the FDA should require expedited reporting of all serious infusion reactions with HemaCord.

5. FDA regulations required quarterly Periodic Adverse Experience Reports (PAERS) to contain a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (21 CFR 600.80(c)2). The narrative summary in PAERs for HemaCord should include a detailed summary and assessment of all serious infusion reactions observed during the reporting period, as well as the sponsor's assessment of each case and the overall frequency of serious infusion reactions since approval and during the reporting period. The sponsor should also include any adverse event information forwarded from SCTOD to the sponsor during the reporting period (e.g., infusion reaction or other adverse event information). PAERs

should also include the number of units released for infusion and the number of patients receiving infusions with HemaCord during the reporting period.

6**.** Exposure to DMSO and Dextran-40, though not completely avoidable, can be limited by proper preparation before infusion of cord blood. Warnings and instructions for preparation (e.g. thawing, washing, dilution) should be included in the label.

Letter comments for communication to the sponsor:

None at this time.