I concur with this review. M. Serabian 10/22/11

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Cellular, Tissue and Gene Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER: STN #125397.000
DATE RECEIVED (BY DCC): 07-January-2011
DATE REVIEW COMPLETED: 29-June-2011; amended 08-July-2011; amended 12-July-2011; amended 14-July-2011; amended 20-July-2011; amended 16-September-2011; amended 11-October-2011; amended 13-October-2011; amended 17-October-2011; amended 21-October-2011

SPONSOR: New York Blood Center
SPONSOR CONTACT: Pablo Rubinstein, MD
Vice-President, New York Blood Center
Director, National Cord Blood Program
Long Island City, NY 11101
Tel: 718-752-4792
Fax: 718-707-3747

PRODUCT NAME: Hematopoietic Stem/Progenitor Cells, Cord Blood (HPC-Cs)
PRODUCT PROPRIETARY NAME: HEMACORD

PROPOSED INDICATION: Allogeneic hematopoietic reconstitution in patients with hematological malignancies, Hurler Syndrome (MPS I), Krabbe Disease (Globoid Leukodystrophy), X-linked Adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure, and beta thalassemia

PHARM/TOX REVIEWER: ATM Shamsul Hoque, Sc.D.
PHARM/TOX SUPERVISOR: Mercedes Serabian, M.S., DABT
DIVISION DIRECTOR: Wilson Bryan, M.D.
OFFICE DIRECTOR: Celia Witten, Ph.D., M.D.
PROJECT MANAGER: Terrolyn Thomas, M.S., M.B.A.

Formulation and Chemistry:
HEMACORD is a cellular biologic product containing human umbilical cord blood (CB) cells generated after volume reduction and partial red blood cell (RBC) and plasma depletion. The final cell suspension (20 ml) contains 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40, prepared by addition of 5 mL of 50% DMSO in 5% Dextran 40. This suspension is then cryopreserved at a controlled rate in liquid nitrogen (-196°C).

The final HPC-C product contains a minimum of 5.0 $x10^8$ total nucleated cells (TNCs), with a post-processing viability of at least 85% and a minimum of 1.25 $x10^6$ viable CD34+ cells.

Abbreviations:
AXP = AutoXpress™ Platform
BLA = Biologic License Application
CB = Cord Blood
CBU = Cord Blood Unit
DMSO = Dimethyl Sulfoxide
GVHD = Graft Versus Host Disease
HPC-Cs = Hematopoietic Progenitor Cells, Cord
IND = Investigational New Drug application
MNCs = Mononuclear Cells
NCBP = National Cord Blood Program
NYBC = New York Blood Center
RBCs = Red Blood Cells
TNCs = Total Nucleated Cells
TRM = Treatment Related Mortality
UCB = Umbilical Cord Blood
WBCs = White Blood Cells

Application History:
- Complete BLA submitted on 07-January-2011

Cross-Reference:
- IND #6637 –ACTIVE. Stem cell concentrates from placental/umbilical cord blood. Storage for use in ----------(b)(4)----------. Sponsor: New York Blood Center, Inc. The IND was submitted to FDA on April 29, 1996.

Table of Contents

Introduction:
HemaCord is manufactured by the National Cord Blood Program (NCBP) of the New York Blood Center (NYBC). The CB is collected into a collection bag containing anticoagulant, then transferred to the automated AXP AutoXpress™ Platform (manufactured by Thermogenesis; cleared by FDA on Oct 5, 2007). This device consists of three bags: a processing bag, an RBC bag, and a freezing bag. This device

automatically separates the CB components into these three bags. Plasma is collected in the processing bag, RBCs are collected in the RBC bag, and the buffy coat, which contains the HPC-Cs, is collected in the freezing bag. The freezing bag is divided into two compartments; the larger compartment contains 80% of the cell suspension (20 ml) and the smaller compartment contains 20% of the cell suspension (5 ml) (provided in Section 16 in BLA). Per the manufacturer of the bag, this storage modality enables the selective removal of the HPC-Cs from the smaller compartment without thawing any HPC-Cs in the larger compartment, for other uses (i.e., *in vitro* expansion, etc…). All connections between these two compartments are permanently separated by heat sealing. There is a small length of the inlet tubing that is integrally attached to the freezing bag that contains approximately -(b)(4)- of the HPC-Cs. This tubing, termed the 'third segment', can be used for cell or DNA extraction and testing by the ----(b)(4)------- (Section 16.1 in BLA). The freezing bag is overwrapped in a Teflon bag and the overwrap bag is sealed. This overwrapped bag is than placed into a stainless-steel canister, labeled, and cryopreserved.

Comment:

- During the Cellular, Tissue and Gene Therapies Advisory Committee meeting held on September 22, 2011 to discuss this application, the sponsor presentation stated that the inlet tubing is divided into 3 segments: Segment #1 is used for HLA phenotyping; Segment #2 is used to assess CD34+ cell counts, viability, ----------(b)(4)----------; and Segment #3 stays attached to the unit.

Proposed Mechanism of Action:

The sponsor states that hematopoietic reconstitution with allogeneic hematopoietic stem cell transplantation: a) allows for the treatment of hematological malignancies with high doses of radiation and chemotherapy that would have destroyed the recipient's bone marrow and the new graft can also exert an immunologic effect on the remaining malignant cells and b) helps replace the affected cells of patients with the indicated genetic diseases with cells that may produce the defective/missing enzyme or hematological component.

Comment:

- The BLA submission did not include specific data or cite published literature in support of the purported mechanisms of action of the HPC-Cs in the proposed disease indications. The draft package insert (PI) written by the sponsor listed various publications that are intended to support the proposed mechanisms of action. This reviewer selected a few representative articles from this list, which are summarized below.

Kurtzberg J et al., Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. New Eng J Med, 335(3): 157-166, 1996

In this article, the authors reported that partially HLA mismatched placental blood from unrelated donors was transplanted in 25 patients (primarily children) with an age range of 0.8 – 23.5 years, with a variety of malignant and nonmalignant conditions between 1993 and 1995. These patients with malignant and non-malignant received placental blood

from the unrelated donors (obtained from the Placental Blood Program, Duke University Medical Center), and were evaluated for hematologic and immunologic reconstitution and for GVHD. The patients received immunosuppressive agents post-transplant. Engraftment of the infused cells was documented in 23/25 transplant recipients. Hematopoietic reconstitution occurred by a median of 22 days (range of 14 - 37 days). Acute grade III GVHD occurred in 2/21 evaluable patients and another 2/21 patients had chronic GVHD. No patient developed acute grade IV GVHD. The *in vitro* proliferative T cell and B cell response to plant mitogens was detected at 53, 60, 95, 192, 380, and 820 days after transplantation. Natural killer cell function was normal in 6 patients tested at 2 - 3 months after transplantation. The overall 100-day survival rate among these patients was 64% and the overall event-free survival rate was 48%. The authors concluded that partially mismatched placental blood from unrelated donors is an alternative source of stem cells for hematopoietic reconstitution.

Wagner JE et al., Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. Blood, 100: 1611-1618, 2002

The authors used cryopreserved unrelated donor UCB (obtained from the New York Blood Center, St. Louis Cord Blood Bank, Netcord, Milano, Dusseldorf, and Firenze Blood Center) in an attempt to reduce the risk of GVHD and TRM, and improve survival in patients with malignant (n = 65) and non-malignant (n = 37) diseases (median age of 7.4 years [range of 0.2 – 56 years]), such as AML, ALL, CML, various bone marrow failure syndromes, immune deficiency, or various metabolic disorders received transplants between 1994 and 2001. The UCB grafts contained a median of 2.8×10^5 CD34 cells. The patients received immunosuppressive agents post-transplant. Results from these patients at a median follow-up time of 2.7 years (range of 0.3-7.2 years) showed: 1) incidence of neutrophil engraftment of 0.88; 2) incidence of platelet engraftment of 0.65; and 3) incidence of severe acute and chronic GVHD of 0.11 and 0.10, respectively. At one and two years post-transplant, the incidence of TRM was 0.3 and 0.35, respectively and the incidence of survival was 0.58 and 0.47, respectively. The rate of engraftment, TRM, and survival was associated with the CD34 cell dose (via Cox regression analyses).

Staba S et al., Cord blood transplants from unrelated donors in patients with Hurler's Syndrome. New Eng J Med, 350(19): 1960-1969, 2004

The authors report that between 1995 and 2002, following a myeloablative conditioning regimen, 20 children with Hurler's Syndrome received cryopreserved CB transplants from unrelated donors (source for CBU not specified, but most probably obtained from Placental Blood Program, Duke University Medical Center). The donors had normal α-L-iduronidase activity and were discordant for up to three of six HLA loci. The patients received immunosuppressive agents for up to nine months post-transplant. Neutrophil and platelet engraftment occurred at a median of 24 days (range of 10-39 days) after transplantation and the CD4+ cell counts progressively increased. A total of 25% (5/20) of the patients had grade II or grade III acute GVHD at a median of 21 days (range of 8-35 days) post-transplant; none had extensive chronic GVHD. Per the article, at

approximately one year post the last transplant, a total of 17/20 children were alive, (a median of 905 days [range of 333-2817 days]). These children displayed complete donor chimerism and normal α-L-iduronidase activity in peripheral blood samples. The authors conclude that CB transplantation improved the neurocognitive performance and decreased some somatic features of this disease.

Comment:

- Section 12.1 of the PI entitled, 'Mechanism of Action' will reflect the published data. Below is the proposed wording for this section as of the writing of this review:

  Hematopoietic stem/progenitor cell from HPC-C migrate to the bone marrow where they divide and mature. The mature cells are released into the blood stream, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function of blood-borne cells of marrow origin, including immune function [see Clinical Studies (14)].

  In patients with enzymatic abnormalities due to certain severe types of storage disorders, mature leucocytes resulting from HPC-C transplantation may synthesize enzymes that may be able to circulate and improve cellular functions of some native tissues. However, the precise mechanism of action is unknown [see Clinical Studies (14)].

Preclinical Studies:

Biocompatibility Studies:

No biocompatibility/leachable testing of the storage bags was conducted. The HPC-Cs are minimally manipulated cells, and the device components used to generate this biological product (i.e., the collection, processing, and cryopreservation of the cells), using the AXP AutoXpress™ Platform, are approved/cleared by FDA for CB collection. A list of devices used by the sponsor in the preparation of the HPC-Cs is provided in Table 1 below:

Comment:

- The AXP AutoXpress™ Platform includes the AXP bag set (processing bag, RBC bag, and freezing bag), the hardware, docking station, and the application software.

Table 1: FDA Container/Closure Approvals/Clearances

Container/Closure	Manufacturer	Approval/Clearance Type & Number	Approval/Clearance Date
Collection Bag – (b)(4)	(b)(4)	(b)(4)	(b)(4)
Collection Bag – (b)(4)	(b)(4)	(b)(4)	(b)(4)
Collection Bag – (b)(4)	(b)(4)	(b)(4)	(b)(4)
Sterile Tubing Welder	(b)(4)	(b)(4)	(b)(4)
AXP AutoXpress Platform with Processing Kit	ThermoGenesis Corp. Rancho Cordova, CA	BK070006 - CBER 510(k)	Cleared 10/5/2007

Proof-of-concept (POC) and Toxicology Studies:
No preclinical POC studies were conducted with the HEMACORD™ product. Toxicology studies as described in the International Conference on Harmonisation (ICH) Safety ('S') guidelines, consisting of pharmacokinetics, acute toxicology, chronic toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, safety pharmacology, and immunotoxicity, at: (http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html) were not conducted by the sponsor due to the minimal manipulation of the HEMACORD/HPC-Cs and the previous human experience with HPC-Cs.

HEMACORD contains DMSO (C_2H_6OS; 10 %). Per Regan et al, the maximum recommended dose of DMSO is 1 g /kg. Note that this author also stated that the transplantation experience has shown that the toxicity of DMSO in the doses delivered by HPC products is generally minimal and transient.[1] When 20% DMSO-saline was administered via the tail vein in healthy Sprague Dawley rats (250-300 gm) hemolysis, leading to blood in the urine, occurred at 1 hour post-injection. No hemolysis was observed when 20% DMSO-saline was injected into the jugular vein of the rats. This difference was attributed to the rapid dilution of DMSO by the relatively higher blood flow in the jugular vein compared to that in the tail vein.[2]

Comment:

- The worst-case amount of DMSO that can be administered with one unit of HEMACORD 10% (unwashed). Note that the residual amount of DMSO in a

[1] Regan DM et al., Comparison of cord blood thawing methods on cell recovery, potency, and infusion. ransfusion, 50:2670-2675, 2010.
[2] Fung S-Y, Oyaizu T, Yang H, Yuan Y, Han B, Keshavjee S and Liu M. The potential of nanoscale combinations of self-assembling peptides and amino acides of the Src tyrosine kinase inhibitor in acute lung therapy. Biomaterials 32: 4000-4008, 2011.

washed HPC-C unit was not provided. Refer to the clinical reviews for the potential toxicities following exposure to DMSO.

Reproductive/Developmental Toxicity:
Following intraperitoneal injections of 5 to 12 g/kg of 50% DMSO on gestation days 6-12, 7/100 (7%) mice fetuses obtained near or at term were deformed and 11/729 (1.5%) rat fetuses were deformed. Malformations noted were anencephalia, microphalia, celosomia, edema, and limb, jaw, and/or tailbud deformities. Following intraperitoneal injection of 2.5-15 g/kg of 100% DMSO in hamsters on gestation days 6-14, 25% embryolethality was observed for dams given 15 g/kg, exencephaly and anencephaly in 100% of the surviving fetuses.

Comment:

- Section 8.1 of the PI entitled, 'Pregnancy' reflects the potential adverse effects of DMSO on the developing fetus. Below is the proposed wording for this section as of the writing of this review. Note that the underlined is optional given the absence of data in pregnant animals or humans following administration of HEMACORD itself and the significant level of DMSO alone that the pregnant animals were exposed to:

Pregnancy Category C. Animal reproduction studies have not been conducted with HEMACORD. It is also not known whether HEMACORD can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

HEMACORD contains dimethyl sulfoxide (DMSO). DMSO caused embryolethality and teratogenic responses following intrperitoneal administration in pregnant hamsters (100% DMSO; 15 gm/kg) and teratogenic responses following administration in pregnant rats and mice (50% DMSO; 5-12 gm/kg).[1] *There are no adequate and well controlled studies in pregnant women. HEMACORD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.*

[1]*David N. The Pharmacology of Dimethyl Sulfoxide 6544. Annu. Rev. Pharmacol. 1972.12:353-374.*

As previously noted, HEMACORD also contains 1% Dextran 40. Refer to the clinical reviews for the potential toxicities following exposure to this agent.

CONCLUSION

All device components used to prepare this product, HEMACORD, have been previously cleared by FDA for cord blood processing. The anticoagulant used to prepare HEMACORD is approved by FDA. No additional preclinical testing with HEMACORD was conducted by the sponsor.

Key Words/Terms: AXP AutoXpress™ Platform, HPC-C, CB, UCB, HEMACORD, cord blood, cell transplantation, preclinical, toxicology, biocompatibility, teratogenic, DMSO, Dextran 40