I concur with this review. M. Serabian 2/24/12; re-concurred on 6/23/12

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 #125407.000 and STN #125407.008
DATE RECEIVED (BY DCC): 09-September-2011
DATE REVIEW COMPLETED: 01-February-2012; amended 23-February-2012; amended 14-June-2012; amended 22-June-2012

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PRODUCT NAME: Hematopoietic Progenitor Cells, Cord Blood (HPC-C)
PRODUCT PROPRIETARY NAME: N/A

PROPOSED INDICATION: Allogeneic hematopoietic reconstitution in patients with hematological malignancies, certain lysosomal storage and peroxisomal enzyme deficiency disorders (such as 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.
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PROJECT MANAGER: Mark Davidson

Formulation and Chemistry:
The product, HPC-C, 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 (--(b)(4)--) contains 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40. This suspension is then cryopreserved at a controlled rate in liquid nitrogen (-(b)(4)-). The final product, HPC-C, contains a minimum of 5.0×10^8 total nucleated cells (TNCs), with a post-processing viability of at least (b)(4) and a minimum of 1.25×10^6 viable CD34+ cells.

Abbreviations:
BLA = Biologic License Application
CB = Cord Blood
CBU = Cord Blood Unit
DMSO = Dimethyl Sulfoxide
GVHD = Graft Versus Host Disease
HPCs = Hematopoietic Progenitor Cells
MNCs = Mononuclear Cells
NCBP = National Cord Blood Program
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 09-September-2011

Cross-Referenced Files:
----------(b)(4)----------

Table of Contents

Introduction:
The product, HPC-C, is manufactured by the Carolinas Cord Blood Bank (CCBB), at Duke University. The CB is collected into a collection bag containing anticoagulant, Citrate Phosphate Dextrose (CPD) (----------(b)(4)----------) by the gravity method, then processed by the ----------(b)(4)---------- to reduce the number of RBCs and the

plasma volume. ----------

----------(b)(4)----------

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The devices used by the sponsor to prepare HPC-C are provided below:

(b)(4)

Duke University **Module 2, Summaries**
Hematopoietic Progenitor Cells, Cord (HPC-C) **2.3S, Quality Overall Summary- Substance**

Container/Closure	Supplier	Product Code	Supplier Address	Documentation Present (Compatibility or NDA, 510K or DMF referenced)
Stainless Steel Storage Canister	ThermoGenesis	(b)(4)	ThermoGenesis Corp. 2711 Citrus Road Rancho Cordova, CA 95742	√ Product description- does not come into direct contact with the HPC-C product
Transfer Pack Unit (b)(4)	(b)(4)	(b)(4)	(b)(4)	√ International Product Certification √ (b)(4) Certificate ISO
Sampling Site Coupler	(b)(4)	(b)(4)	(b)(4)	√ Certificate of Manufacturing Compliance √ (b)(4) Certificate ISO

Comment:

- The original submission also specified the use of a validated ----------(b)(4)---------- processing method in addition to the ---(b)(4)--- method to prepare the HPC-C. However, based on amendment #008, submitted on June 1, 2012, the sponsor will no longer use the --(b)(4)-- method to prepare the HPC-C. The sponsor removed the SOP entitled, "CCBB-LAB-023 Red Blood Cell and Plasma Reduction via --(b)(4)-- Method" from the BLA submission. This reviewer confirmed this change with the lead CMC reviewer.

Proposed Mechanisms of Action:

Per the BLA, following intravenous administration the HPC-C migrate to the bone marrow, where they divide and mature, and are then released into the bloodstream, 'restoring blood counts and immunity'. The time from cell administration to recovery of adequate or normal blood counts usually ranges from 20-45 days. The transplantation of the allogeneic HPC-C sometimes induces a graft-vs.-tumor effect that can be beneficial in recipients who receive a transplant for treatment of malignancies. In subjects with inborn errors of metabolism the transplanted cells will produce the missing enzyme. The extent of disease correction depends on the disease and on the condition of the subject undergoing transplant.

Comment:

- The BLA submission did not include specific data in support of the purported mechanisms of action of the HPC-C in the proposed disease indications; however, published literature was provided in the Clinical Section of the BLA. This reviewer selected several articles from the BLA, 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.

Laughlin MJ et al., Hematopoietic engraftment and survival in adult recipients of umbilical cord-blood from unrelated donors. N Eng J Med, 344(24): 1815-1822, 2001
The authors studied the ability of transplanted UCB to restore hematopoiesis in 68 adults with life-threatening hematologic disorders. Following intensive chemotherapy or total-body irradiation, transplants consisting of HLA-mismatched UCB obtained from the Placental Blood Program of New York Blood Center (57 units) and other blood banks (11 units). Endpoints assessed included hematologic reconstitution, the occurrence of acute and chronic GVHD, relapse, and event-free survival. A total of 48/68 patients (71%) received units that were mismatched for two or more HLA antigens. Of the 60 patients who survived 28 days or more after transplantation, 55/60 had neutrophil engraftment at a median of 27 days (range of 13-59 days). The neutrophil recovery correlated with the number of nucleated cells in the UCB before it was frozen. Severe acute GVHD (grade III or IV) occurred in 11/55 patients evaluated within l00 days after transplantation. Chronic GVHD developed in 12/38 patients who survived more than 100 days after transplantation. The median follow-up time for survivors was 22 months (range of 1l-5l months). As of the writing of this article, 19/68 (28%) patients remained alive, with 18/19 (95%) disease-free at 40 months after transplantation. The presence of a high number of CD34+ cells in the graft was associated with improved event-free survival (P = 0.05).

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 the 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.

Escolar ML et al., Transplantation of Umbilical-Cord Blood in Babies with Infantile Krabbe's Disease. N Engl J Med, 2069-2081, 2005

In this article the authors transplanted UCB from unrelated donors (source: National Marrow Donor Program and New York Blood Center) in 11 newborn patients before the development of infantile Krabbe's disease symptoms occurred (4 boys and 7 girls; 12-44 days old) and in 14 newborn patients after the development of disease symptoms (8 boys and 6 girls; 142-352 days old). Both the asymptomatic and the symptomatic infants were transplantated after myeloablative chemotherapy. Outcomes among these newborns were

compared to each other and to the outcomes in a cohort of affected children that were not transplanted. Engraftment (neutrophil and platelet), survival, and neurodevelopmental function were evaluated longitudinally for four months to six years.

The results showed that among the asymptomatic infants (median follow-up of 3.0 years), the rates of donor cell engraftment and survival were 100%. Among the symptomatic infants (median follow-up of 3.4 years) the rates of donor cell engraftment and survival were 100% and 43%, respectively. Restoration of normal blood galactocerebrosidase levels were observed in all surviving infants. Infants who received UCB before the development of symptoms showed progressive central myelination and continued gains in developmental skills, and while most had age-appropriate cognitive function and receptive language skills, a few had mild-to-moderate delays in expressive language and mild-to-severe delays in gross motor function. Infants who received UCB after the onset of symptoms had minimal neurologic improvement.

Ruggeri A et al. Umbilical cord blood transplantation for children with Thalassemia and sickle cell disease. Biol Blood Marrow Transplant, 1-9, 2011
In this article the authors reported the efficacy of unrelated CB transplantation in children with thalassemia (n = 35) and sickle cell disease (SCD; n = 16), using data reported to three registries (National Cord Blood Program [NCBP], New York Blood Center, and Center for International Blood and Marrow Transplantation Registry). All children received a single unmanipulated CB unit. Transplant conditioning was myeloablative (n = 39) or reduced intensity (n = 12). Neutrophil recovery was measured for three consecutive days, with donor engraftment determined by a chimerism assay. The results showed neutrophil recovery with complete donor chimerism in 24/51 (47%; n = 15 thalassemia, n = 9 SCD) patients and the median time of neutrophil recovery was 22 days (range of 10-62 days). None of the patients developed secondary graft failure. The median time to platelet recovery was 40 days (range of 15-127 days). Eleven patients developed grade II-IV acute GVHD and 10 patients developed chronic GVHD. Overall survival and disease-free survival were 62% and 21% respectively, for thalassemia patients and 94% and 50% respectively, for SCD patients. The engraftment rate (P = 0.05) and disease-free survival (P =0.01) were higher with administration of $>5 \times 10^7$ TNCs/kg. Primary graft failure occurred in 20 [out of 35] (fatal in 5/7 cases) patients with thalassemia and 7 [out of 16] patients with SCD. The authors conclude that only CB units containing an expected infused dose of $>5 \times 10^7$ TNCs/kg should be transplantated in patients with hemoglobinopathies.

Comment:

- Section 12 of the PI entitled, 'Clinical Pharmacology' reflects the published data. Below is the proposed wording for this section as of the writing of this review:

  HPC Cord blood products are administered intravenously. After entering the bloodstream, cells migrate to the bone marrow where they divide and mature. The mature cells are released into the blood stream, restoring blood counts and immunity. The time from administration of HPCs to recovery of adequate or normal blood counts is variable but typically ranges from 20 to 45 days. [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.

Preclinical Studies:

Biocompatibility Studies:

No biocompatibility/leachable testing of the storage bags was conducted by the sponsor. The HPC-C are minimally manipulated cells, and the device components used to generate this biological product (e.g., the collection, processing, and cryopreservation of the cells are approved/cleared by FDA. Refer to Table S.6-1, at the beginning of this review, for a detailed listing of each component.

Proof-of-Concept (POC) and Toxicology Studies:

No preclinical POC studies were conducted with the HPC-C 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 HPC-C and the previous human experience with HPC-C.

HPC-C 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 HPC-C is 10% (unwashed). Note that the residual amount of DMSO in a single washed HPC-Cord was not provided. Refer to the clinical reviews for a discussion of the potential toxicities following exposure to DMSO.

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[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.

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' states "There are no studies in pregnant women. Potential risks are unknown." Below is the proposed wording for this section as of the writing of this review:

  Pregnancy Category C. Animal reproduction studies have not been conducted with HPC-Cord. It is also not known whether HPC- C can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. There are no adequate and well controlled studies in pregnant women. HPC-C should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

As previously noted, HPC-C 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, HPC-C, have been previously cleared or exempted by FDA. The anticoagulant used to prepare HPC-C is approved by FDA. No additional preclinical testing with HPC-C was conducted by the sponsor.

Key Words/Terms: ----------(b)(4)----------, HPC-C, CB, UCB, cell transplantation, preclinical, toxicology, biocompatibility, teratogenic, DMSO, Dextran 40