

I concur with this review. M. Serabian 2/26/18

FOOD AND DRUG ADMINISTRATION
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Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER:	STN #125657.000
DATE RECEIVED BY CBER:	June 06, 2017
DATE REVIEW COMPLETED:	December 19, 2017; amended January 08, 2018; amended January 17, 2017
PRODUCT:	Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood)
APPLICANT:	MD Anderson Cord Blood Bank
PROPOSED INDICATION:	Hematopoietic Progenitor Cell (HPC), Cord Blood, is an allogeneic hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.
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EXECUTIVE SUMMARY:

Hematopoietic Progenitor Cells, Cord Blood (HPC, Cord Blood), is a thawed cell suspension consisting of CD34+ and other cord blood cells. Published articles have demonstrated that HPC, Cord Blood, can restore blood counts and function (including immune function) of blood-borne cells of marrow origin after transplantation.

HPC, Cord Blood manufactured by the applicant has been used by the investigator for the treatment of various indications including blood cell malignancies, inherited metabolic diseases and severe combined immunodeficiency/immune disorders.

The sponsor did not conduct nonclinical pharmacology and toxicology studies to support the BLA application and the BLA submission did not contain nonclinical related module 2.4 and module 4.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There were no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of HPC, Cord Blood. The publicly available nonclinical information supports approval of the licensure application.

Formulation and Chemistry:

Twenty-five ml (25 ml) of HPC, Cord Blood is cryopreserved in a final concentration of 10% Dimethyl sulfoxide (DMSO), 1% Dextran 40, and 0.9% Sodium Chloride. This suspension is stored in liquid nitrogen at a maximum temperature of -150°C. Each HPC, Cord Blood unit contains a minimum of 9×10^8 total nucleated cells, with at least 1.25×10^6 viable CD34+ cells at the time of cryopreservation. The exact pre-cryopreservation nucleated cell content of each unit is provided on the container label and accompanying records.

Comment:

- Section 3.2.P.1 of the submission states that each unit contains a minimum of 9×10^8 total nucleated cells and 1.25×10^6 viable CD34+ cells. However, the proposed label states that each unit contains a minimum of 9×10^8 total nucleated cells with at least 1.25×10^6 viable CD34+ cells.

Abbreviations:

HPC	Hematopoietic progenitor cell
CB	Cord blood
DMSO	Dimethyl sulfoxide
HES	Hydroxyethyl starch
TNC	Total nucleated cells
UCB	Umbilical cord blood
GvHD	Graft versus host disease

Related File(s):

None

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INTRODUCTION

The product, HPC, Cord Blood, is manufactured by the MD Anderson Cord Blood Bank herein referred to as the 'Cord Blood Bank'). Cord blood (CB) is collected from consented, screened maternal donors. Per the submission, in-utero collections are performed during vaginal and C-section deliveries by trained and licensed health care professionals. Ex-utero collections are performed in a dedicated collection room by trained Cord Blood Bank collection staff. After the infant donor is delivered and detached from the cord, the physician/midwife cleans the selected venipuncture area of the cord. The needle is aseptically inserted into the cord and collection continues until blood flow ceases. The aseptically-collected units are transported under temperature-monitored conditions to the manufacturing facility, the Cord Blood Bank.

Once received by the Cord Blood Bank, the CB units that meet all pre-processing specifications are prepared for processing by aseptically adding (b) (4) by volume, supplied by (b) (4) as a sedimenting agent, to each unit. The bag containing the CB unit and (b) (4) Each CB unit bag is then connected to a sterile (b) (4) using a sterile connection device. Upon completion of the automated procedure, each unit is assessed for TNC, including nucleated red blood cell count, as well as bag appearance and integrity. Buffy coat enriched CB units meeting all manufacturing specifications are released for cryopreservation.

Note: Per the submission, all product manipulation is performed using a functionally closed system, an (b) (4) classified clean room processing facility.

Per the submission, a syringe containing 5 ml of premixed cryoprotectant solution (composed of (b) (4) DMSO, (b) (4) Dextran 40 in 0.9% saline to the fill line of the cryobag containing the buffy coat enriched CB unit using a sterile connect device. The cryobag is installed on an automated

mixing/cooling device (Biosafe CoolMix). While the buffy coat enriched CB unit is mixing on the device, a syringe pump is used to add the 5 ml of cryoprotectant over a period of 15 minutes. Immediately after completion of the addition of the cryoprotectant, three representative aliquots (designated as ‘segments’) are generated by sealing a small volume of the buffy coat containing cryoprotectant in the inlet fill line integrated into the bag. The bridge between the two compartments of the freeze bag is then heat-sealed to create independent fractions (80%/20%). The sealed bag and representative segments are sealed into a (b) (4) overwrap sleeve and placed inside the labeled storage canister. The prepared HPC, Cord Blood unit is cryopreserved using the controlled rate freezing functionality of the (b) (4) freezer. The final 25 ml of HPC, Cord Blood HPCs is in 10% DMSO, 1% Dextran 40, and 0.9% Sodium Chloride.

NONCLINICAL STUDIES

The submission did not contain the nonclinical Module 4. No nonclinical studies were conducted for HPC, Cord Blood. The following discussions are based on published literatures. Some of them are cited by the applicant in BLA submission.

PHARMACOLOGY STUDIES

Proposed Mechanisms of Action:

The precise mechanisms of action are unknown. However, it is hypothesized that following intravenous administration of the HPC, Cord Blood may migrate to the bone marrow, where the cells divide and mature, and are then released into the bloodstream, to restore blood counts and function (including immune function) of blood-borne cells of marrow origin. In subjects with inborn errors of metabolism, mature leukocytes generated from HPC, Cord Blood transplantation may synthesize 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 nonclinical studies to support the purported mechanisms of action of HPC, Cord Blood in the proposed disease indications. In clinical Section 5.3.5.3 of the BLA submission, the applicant cited legacy clinical data from published reports, as well as their clinical data. Refer to the clinical BLA review memo for a comprehensive review of these data. This reviewer selected articles from the applicant’s list of published clinical data, as well as other representative articles, that relate to the purported mechanisms of action of this product.

Gluckman E et al., Hematopoietic reconstitution in a patient with Fanconi’s anemia by means of umbilical-cord blood from an HLA-identical sibling. *New Eng J Med*, 321 (17): 1174-1178, 1989

In this article, the authors reported that umbilical cord blood (UCB) from an HLA-identical sibling was transplanted into a boy with severe Fanconi’s anemia. The patient received a cyclophosphamide and irradiation conditioning regimen, followed by infusion of 0.4×10^8 TNCs/kg. Cyclosporine was administered for prevention of GVHD. Engraftment of donor cells

was demonstrated and the authors concluded that UCB can be an effective source of stem cells for hematopoietic reconstitution.

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 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 six 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) were administered. 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 100 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 11-51 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 ($P = 0.05$).

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 9 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 after 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 Eng J Med, 2069-2081, 2005

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 transplanted 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 rate of donor cell engraftment and survival was 100% and 43%, respectively. Restoration of normal blood galactocerebrosidase levels was 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 with thalassemia; n = 9 with 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 transplanted in patients with hemoglobinopathies.

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 (None)

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 treatment-related mortality (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).

BIOCOMPATIBILITY STUDIES

No biocompatibility or extractables and leachables testing of the storage bags were conducted by the sponsor. HPC, Cord Blood is composed of cells, and the device components used to generate this biological product (i.e., the collection, processing, and cryopreservation of the cells) are approved/cleared by the FDA.

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies were conducted.

PHARMACOKINETIC STUDIES (Cell Distribution)

No pharmacokinetic studies were conducted.

TOXICOLOGY STUDIES

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 (as described at <http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html>) were not conducted by the sponsor due to the previous human experience with HPC, Cord Blood.

HPC, Cord Blood contains DMSO (C₂H₆OS; 10%). Per Regan et al., the maximum recommended dose of DMSO is 1 g/kg. 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, Cord Blood is 10% (unwashed). The residual amount of DMSO in a single washed HPC, Cord Blood unit was not provided. Please refer to the clinical review memo for a discussion of the potential toxicities following exposure to DMSO.

Developmental and Reproductive Toxicology Studies:

Following intraperitoneal injections of 5-12 g/kg of 50% DMSO on gestation days 6-12, a total of 7/100 (7%) mouse fetuses obtained near, or at term were deformed and 11/729 (1.5%) rat fetuses were deformed. Malformations noted consisted of 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% embryo lethality was observed for dams administered 15 g/kg, with exencephaly and anencephaly in 100% of the surviving fetuses.^{3,4}

As previously noted, HPC, Cord Blood also contains 1% Dextran 40. Please refer to the clinical review memo for the potential toxicities following exposure to this agent.

Genotoxicity Studies:

Studies were not conducted to evaluate this safety endpoint. This test is not applicable to HPC, Cord Blood.

Carcinogenicity/Tumorigenicity Studies:

Studies were not conducted to evaluate this safety endpoint. This test is not applicable to HPC, Cord Blood, which is minimally manipulated.

¹ Regan DM et al., Comparison of cord blood thawing methods on cell recovery, potency, and infusion. Transfusion, 50:2670-2675, 2010.

² Fung S-Y, et al., The potential of nanoscale combinations of self-assembling peptides and amino acids of the Src tyrosine kinase inhibitor in acute lung therapy. Biomaterials 32: 4000-4008, 2011.

³ Package Insert (Prescribing Information) – RIMSO-50 Dimethyl Sulfoxide, Bioniche Pharma USA LLC.

⁴ David NA. The pharmacology of dimethyl sulfoxide 6544. Ann. Rev. Pharmacol. 12:353-374, 1972

Other Safety/Toxicology Studies

No additional safety/toxicology studies were conducted.

APPLICANT'S PROPOSED LABEL

Subsection 8.1 ('Pregnancy') of Section 8 ('Use in Specific Populations') should be revised to comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14).⁵ Subsection 8.2 ('Lactation') should also be added per these citations.

CONCLUSION OF NONCLINICAL STUDIES

All device components used to prepare this product, HPC, Cord Blood, have been previously cleared or exempted by FDA. No additional nonclinical testing with HPC, Cord Blood was conducted by the sponsor. This reviewer did not identify any safety concerns that could not be addressed in the product label. The approval of the license application is supported.

KEY WORDS/TERMS

(b) (4) device; HPC, Cord Blood; CB; UCB; DMSO; Dextran 40; transplantation; toxicology; biocompatibility; reproductive/developmental toxicity

⁵ Sections 8.1-8.3 of the PI are required according to 21 CFR Part 201 titled, 'Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling' that was released on December 4, 2014 in Federal Register Notice No. 233 (<https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for>). Also refer to the FDA draft guidance titled, *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format* (June 2015) at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm450636.pdf>