

HPC, CORD BLOOD- hpc, cord blood injection Bloodworks

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HPC, Cord Blood safely and effectively. See full prescribing information for HPC, Cord Blood.

HPC, Cord Blood

Injectable Suspension for Intravenous Use

Initial U.S. Approval: 2016

WARNING: FATAL INFUSION REACTIONS, GRAFT VERSUS HOST DISEASE, ENGRAFTMENT SYNDROME, AND GRAFT FAILURE.

See full prescribing information for complete boxed warning.

- **Fatal infusion reactions: Monitor patients during infusion and discontinue for severe reactions.** (5.1, 5.2)
- **Graft-vs-host disease (GVHD): GVHD may be fatal. Administration of immunosuppressive therapy may decrease risk of GVHD.** (5.3)
- **Engraftment Syndrome: Engraftment syndrome may be fatal. Treat engraftment syndrome promptly with corticosteroids.** (5.4)
- **Graft Failure: Graft failure may be fatal. Monitor patients for laboratory evidence of hematopoietic recovery.** (5.5)

INDICATIONS AND USAGE

HPC (Hematopoietic Progenitor Cell), Cord Blood is an allogeneic cord blood 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. (1)

The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells. (1)

DOSAGE AND ADMINISTRATION

- **For intravenous use only.**
- **Do not irradiate.**
- Unit selection and administration of HPC, Cord Blood should be done under the direction of a physician experienced in hematopoietic progenitor cell transplantation. (2)
- The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation. (2.1)
- Do not administer HPC, Cord Blood through the same tubing as other products except for normal saline. (2.3)

DOSAGE FORMS AND STRENGTHS

Each unit contains a minimum of 5×10^8 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. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions (5.1)
- Infusion Reactions (5.2)
- Graft-versus-Host Disease (5.3)
- Engraftment Syndrome (5.4)
- Graft Failure (5.5)
- Malignancies of Donor Origin (5.6)
- Transmission of Serious Infections (5.7)
- Transmission of Rare Genetic Diseases (5.8)

ADVERSE REACTIONS

Mortality, from all causes, at 100 days post-transplant was 25%. (6.1)

The most common infusion-related adverse reactions ($\geq 5\%$) are hypertension, vomiting, nausea, bradycardia, and fever. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bloodworks at 1-206-321-3108 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2016

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FULL PRESCRIBING INFORMATION

WARNING: FATAL INFUSION REACTIONS, GRAFT VERSUS HOST DISEASE, ENGRAFTMENT SYNDROME, AND GRAFT FAILURE

Fatal infusion reactions: HPC, Cord Blood administration can result in serious, including fatal, infusion reactions. Monitor patients and discontinue HPC, Cord Blood infusion for severe reactions. [See Warnings and Precautions (5.1, 5.2)]

Graft-versus-host disease (GVHD): GVHD is expected after administration of HPC, Cord Blood, and may be fatal. Administration of immunosuppressive therapy may decrease the risk of GVHD. [See Warnings and Precautions (5.3)]

Engraftment Syndrome: Engraftment syndrome may progress to multiorgan failure and death. Treat engraftment syndrome promptly with corticosteroids. [See Warnings and Precautions (5.4)]

Graft Failure: Graft failure may be fatal. Monitor patients for laboratory evidence of hematopoietic recovery. Prior to choosing a specific unit of HPC, Cord Blood unit, consider testing for HLA antibodies to identify patients who are alloimmunized. [See Warnings and Precautions (5.5)]

1 INDICATIONS AND USAGE

HPC (Hematopoietic Progenitor Cell), Cord Blood, is an allogeneic cord blood 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.

The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and other available treatments or types of hematopoietic progenitor cells.

2 DOSAGE AND ADMINISTRATION

- For intravenous use only.
- Do not irradiate.

Unit selection and administration of HPC, Cord Blood, should be done under the direction of a physician experienced in hematopoietic progenitor cell transplantation.

2.1 Dosing

The recommended minimum dose is 2.5×10^7 nucleated cells/kg at cryopreservation. Multiple units may be required in order to achieve the appropriate dose.

Matching for at least 4 of 6 HLA-A antigens, HLA-B antigens, and HLA-DRB1 alleles is recommended. The HLA typing and nucleated cell content for each individual unit of HPC, Cord Blood are documented on the container label and/or in accompanying records.

2.2 Preparation for Infusion

HPC, Cord Blood should be prepared by a trained healthcare professional.

- Do not irradiate HPC, Cord Blood.
- See the appended detailed instructions for preparation of HPC, Cord Blood for infusion.
- HPC, Cord Blood may be stored at 2 to 8°C for up to 4 hours from time of thaw. [See Instructions for Preparation for Infusion]
- The recommended limit on DMSO administration is 1 gram per kg body weight per day. [See

2.3 Administration

HPC, Cord Blood should be administered under the supervision of a qualified healthcare professional experienced in hematopoietic progenitor cell transplantation.

1. Confirm the identity of the patient for the specified unit of HPC, Cord Blood prior to administration.
2. Confirm that emergency medications are available for use in the immediate area.
3. Ensure the patient is hydrated adequately.
4. Premedicate the patient 30 to 60 minutes before the administration of HPC, Cord Blood. Premedication should include any or all of the following: antipyretic, histamine antagonists, and corticosteroids.
5. Inspect the product for any abnormalities, such as unusual particulates, and for breaches of container integrity prior to administration. Prior to infusion, discuss all such product irregularities with the laboratory issuing the product for infusion.
6. Administer HPC, Cord Blood by intravenous infusion. Do not administer in the same tubing concurrently with products other than 0.9% Sodium Chloride, Injection (USP). HPC, Cord Blood may be infused through a 170 to 260 micron filter designed to remove clots. Do NOT use a filter designed to remove leukocytes.
7. HPC, Cord Blood should be infused over 15 to 60 minutes depending on the volume of the product and the weight of the patient. The rate of infusion should not exceed a maximum of 5 milliliters per kilogram per hour. The infusion rate should be reduced if the fluid load is not tolerated. The infusion should be discontinued in the event of an allergic reaction or if the patient develops a moderate to severe infusion reaction. [See Warnings and Precautions (5.2) and Adverse Reactions (6)]
8. Monitor the patient for adverse reactions during, and for at least six hours after, administration. Because HPC, Cord Blood contains lysed red blood cells that may cause renal failure, careful monitoring of urine output is also recommended.

NOTE: If product is being prepared for a multi-unit infusion, infuse units independently. Should a reaction occur, appropriately manage the reaction before the second unit is thawed for infusion.

3 DOSAGE FORMS AND STRENGTHS

Each HPC, Cord Blood unit contains a minimum of 5.0×10^8 total nucleated cells with a minimum of 1.25×10^6 viable CD34+ cells, suspended in 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40, at the time of cryopreservation.

The exact pre-cryopreservation nucleated cell content is provided on the container label and in accompanying records.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic reactions may occur with infusion of HPC, Cord Blood. Reactions include bronchospasm, wheezing, angioedema, pruritus, and hives. [See Adverse Reactions (6)]. Serious hypersensitivity reactions, including anaphylaxis, also have been reported. These reactions may be due to dimethyl sulfoxide (DMSO), Dextran 40, hydroxyethyl starch, or a plasma component of HPC, Cord Blood.

HPC, Cord Blood may contain residual antibiotics if the cord blood donor was exposed to antibiotics in

utero. Patients with a history of allergic reactions to antibiotics should be monitored for allergic reactions following HPC, Cord Blood administration.

5.2 Infusion Reactions

Infusion reactions are expected to occur and include nausea, vomiting, fever, rigors or chills, flushing, dyspnea, hypoxemia, chest tightness, hypertension, tachycardia, bradycardia, dysgeusia, hematuria, and mild headache. Premedication with antipyretic, histamine antagonists, and corticosteroids may reduce the incidence and intensity of infusion reactions.

Severe reactions, including respiratory distress, severe bronchospasm, severe bradycardia with heart block or other arrhythmias, cardiac arrest, hypotension, hemolysis, elevated liver enzymes, renal compromise, encephalopathy, loss of consciousness, and seizure also may occur. Many of these reactions are related to the amount of DMSO administered. Minimizing the amount of DMSO administered may reduce the risk of such reactions, although idiosyncratic responses may occur even at DMSO doses thought to be tolerated. The actual amount of DMSO depends on the method of preparation of the product for infusion. Limiting the amount of DMSO infused to no more than 1 gram per kilogram per day is recommended. *[See Overdosage (10)]*

Infusion reactions may begin within minutes of the start of infusion of HPC, Cord Blood, although symptoms may continue to intensify and not peak for several hours after completion of the infusion. Monitor the patient closely during this period. When a reaction occurs, discontinue the infusion and institute supportive care as needed.

If infusing more than one unit of HPC, Cord Blood on the same day, do not administer subsequent units until all signs and symptoms of infusion reactions from the prior unit have resolved.

5.3 Graft-versus-Host Disease

Acute and chronic graft-versus-host disease (GVHD) may occur in patients who have received HPC, Cord Blood. Classic acute GVHD is manifested by fever, rash, elevated bilirubin and liver enzymes, and diarrhea. Patients transplanted with HPC, Cord Blood should receive immunosuppressive drugs to decrease the risk of GVHD. *[See Adverse Reactions (6.1)]*

5.4 Engraftment Syndrome

Engraftment syndrome is manifested as unexplained fever and rash in the peri-engraftment period. Patients with engraftment syndrome also may have unexplained weight gain, hypoxemia, and pulmonary infiltrates in the absence of fluid overload or cardiac disease. If untreated, engraftment syndrome may progress to multiorgan failure and death. Once engraftment syndrome is recognized, begin treatment with corticosteroids to ameliorate the symptoms. *[See Adverse Reactions (6.1)]*

5.5 Graft Failure

Primary graft failure, which may be fatal, is defined as failure to achieve an absolute neutrophil count greater than 500 per microliter blood by Day 42 after transplantation. Immunologic rejection is the primary cause of graft failure. Patients should be monitored for laboratory evidence of hematopoietic recovery. Consider testing for HLA antibodies in order to identify patients who are alloimmunized prior to transplantation and to assist with choosing a unit with a suitable HLA type for the individual patient. *[See Adverse Reactions (6.1)]*

5.6 Malignancies of Donor Origin

Patients who have undergone HPC, Cord Blood transplantation may develop post-transplant lymphoproliferative disorder (PTLD), manifested as a lymphoma-like disease favoring non-nodal sites. PTLT is usually fatal if not treated.

The incidence of PTLT appears to be higher in patients who have received antithymocyte globulin. The etiology is thought to be donor lymphoid cells transformed by Epstein-Barr virus (EBV). Serial

monitoring of blood for EBV DNA may be warranted in high-risk groups.

Leukemia of donor origin also has been reported in HPC, Cord Blood recipients. The natural history is presumed to be the same as that for *de novo* leukemia.

5.7 Transmission of Serious Infections

Transmission of infectious disease may occur because HPC, Cord Blood is derived from human blood. Disease may be caused by known or unknown infectious agents. Donors are screened for increased risk of infection with human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), *T. Pallidum*, *T. cruzi*, West Nile Virus (WNV), transmissible spongiform encephalopathy (TSE) agents, and vaccinia. Donors are also screened for clinical evidence of sepsis, and communicable disease risks associated with xenotransplantation. Maternal blood samples are tested for HIV types 1 and 2, HTLV types I and II, HBV, HCV, *T. Pallidum*, WNV, and *T. cruzi*. HPC, Cord Blood is tested for sterility. There may be an effect on the reliability of the sterility test results if the cord blood donor mother was treated with antibiotics. These measures do not totally eliminate the risk of transmitting these or other transmissible infectious diseases and disease agents. Report the occurrence of transmitted infection to Bloodworks at 1-206-321-3108.

Testing is also performed for evidence of donor infection due to cytomegalovirus (CMV).

Test results may be found in accompanying records.

5.8 Transmission of Rare Genetic Diseases

HPC, Cord Blood may transmit rare genetic diseases involving the hematopoietic system for which donor screening and/or testing has not been performed [See *Adverse Reactions (6.1)*]. Cord blood donors have been screened by family history to exclude inherited disorders of the blood and marrow. HPC, Cord Blood has been tested to exclude donors with sickle cell anemia, and anemias due to abnormalities in hemoglobins C, D, and E. Because of the age of the donor at the time HPC, Cord Blood collection takes place, the ability to exclude rare genetic diseases is severely limited.

6 ADVERSE REACTIONS

Day-100 mortality from all causes was 25%.

The most common infusion-related adverse reactions ($\geq 5\%$) are hypertension, vomiting, nausea, bradycardia, and fever.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of HPC, Cord Blood is based primarily on review of the data submitted to the FDA dockets from various sources, the dataset for the COBLT Study, and published literature.

Infusion Reactions

The data described in Table 1 reflect exposure to 442 infusions of HPC, Cord Blood (from multiple cord blood banks) in patients treated using a total nucleated cell dose of $\geq 2.5 \times 10^7/\text{kg}$ on a single-arm trial or expanded access use (the COBLT Study). The population was 60% male and the medical age was 5 years (range 0.05 to 68 years), and included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-versus-host disease prophylaxis were not standardized. The most common infusion reactions were hypertension, vomiting, nausea, and sinus bradycardia. Hypertension and any grades 3-4 infusion-related reactions occurred more frequently in patients receiving HPC, Cord Blood in volumes greater than 150 milliliters and in pediatric patients. The rate of serious adverse cardiopulmonary

reactions was 0.8%.

Table 1: Incidence of Infusion-Related Adverse Reactions Occurring in $\geq 1\%$ of Infusions (The COBLT Study)

	Any Grade %	Grade 3-4 %
Any reaction	65.4	27.6
Hypertension	48.0	21.3
Vomiting	14.5	0.2
Nausea	12.7	5.7
Sinus bradycardia	10.4	0
Fever	5.2	0.2
Sinus Tachycardia	4.5	0.2
Allergy	3.4	0.2
Hypotension	2.5	0
Hemoglobinuria	2.1	0
Hypoxia	2.0	2.0

Information on infusion reactions was available from voluntary reports for patients who received HPC, Cord Blood, with a total nucleated cell dose of $\geq 2.5 \times 10^7/\text{kg}$. Of 212 infusions, there were 22 reports of grade 3 or higher reactions at time of infusion (10.3%). The population included 59% males and 41% females with median age of 35 years (range <1-72 years). The most common infusion reactions in these patients were hypertension (63.6%), nausea (27.3%), and chest pain (18.2%). Preparative regimens and graft-vs-host disease prophylaxis were not standardized.

Other Adverse Reactions

For other adverse reactions, the raw clinical data from the docket were pooled for 1299 (120 adult and 1179 pediatric) patients transplanted with HPC, Cord Blood (from multiple cord blood banks) with total nucleated cells $\geq 2.5 \times 10^7/\text{kg}$. Of these, 66% (n=862) underwent transplantation treatment for hematologic malignancy. The preparative regimen and graft-versus-host disease prophylaxis varied. The median total nucleated cell dose was $6.4 \times 10^7/\text{kg}$ (range, $2.5\text{-}73.8 \times 10^7/\text{kg}$). For these patients, Day-100 mortality from all causes was 25%. Primary graft failure occurred in 16%; 42% developed grades 2-4 graft-versus-host disease; and 19% developed grades 3-4 acute graft-versus-host disease.

Data from the published literature and from observational registries, institutional databases, and cord blood bank reviews reported to the docket for HPC, Cord Blood (from multiple cord blood banks) revealed nine cases of donor cell leukemia, one case of transmission of infection, and one report of transplantation from a donor with an inheritable genetic disorder. The data are insufficient to support reliable estimates of the incidences of these events.

In the COBLT Study, 15% of the patients developed engraftment syndrome.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with HPC, Cord Blood use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with HPC, Cord Blood. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of HPC, Cord Blood in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HPC, Cord Blood and any potential adverse effects on the breastfed infant from HPC, Cord Blood or from the underlying maternal condition.

8.4 Pediatric Use

HPC, Cord Blood has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment. [See *Dosage and Administration (2)*, *Adverse Reactions (6)*, and *Clinical Studies (14)*].

8.5 Geriatric Use

Clinical studies of HPC, Cord Blood (from multiple cord blood banks) did not provide sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. In general, administration of Bloodworks HPC, Cord Blood to patients over age 65 should be cautious, reflecting their greater frequency of decreased hepatic, renal or cardiac function, and concomitant disease or other drug therapy.

8.6 Renal Disease

HPC, Cord Blood contains Dextran 40 which is eliminated by the kidneys. The safety of HPC, Cord Blood has not been established in patients with renal insufficiency or renal failure.

10 OVERDOSAGE

10.1 Human Overdosage Experience

There has been no experience with overdosage of HPC, Cord Blood, in human clinical trials. Single doses of HPC, Cord Blood from Bloodworks of $29.6 \times 10^7/\text{kg}$ have been administered. HPC, Cord Blood prepared for infusion may contain dimethyl sulfoxide (DMSO). The maximum dose of DMSO has not been established, but it is customary not to exceed a DMSO dose of 1 gm/kg/day when given intravenously. Several cases of altered mental status and coma have been reported with higher doses of DMSO.

10.2 Management of Overdose

For DMSO overdose, general supportive care is indicated. The role of other interventions to treat DMSO overdosage has not been established.

11 DESCRIPTION

HPC, Cord Blood consists of hematopoietic progenitor cells, monocytes, lymphocytes, and granulocytes from human cord blood for intravenous infusion. Blood recovered from umbilical cord and placenta is volume reduced and partially depleted of red blood cells and plasma.

The active ingredient is hematopoietic progenitor cells which express the cell surface marker CD34. The potency of the cord blood is determined by measuring the numbers of total nucleated cells (TNC) and CD34+ cells, and cell viability. Each unit of HPC, Cord Blood contains a minimum of 5×10^8 total nucleated cells with at least 1.25×10^6 viable CD34+ cells at the time of cryopreservation. The cellular composition of HPC, Cord Blood depends on the composition of cells in the blood recovered from the umbilical cord and placenta of the donor. The actual nucleated cell count, the CD34+ cell count, the ABO group, and the HLA typing are listed on the container label and/or accompanying records sent with each individual unit.

HPC, Cord Blood has the following inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethyl starch, and Dextran 40. When prepared for infusion according to instructions, the infusate contains the following inactive ingredients: Dextran 40, human serum albumin, DMSO, and CPD.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

In patients with enzymatic abnormalities due to certain severe types of storage disorders, mature leukocytes resulting from HPC, Cord Blood 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.

14 CLINICAL STUDIES

The effectiveness of Bloodworks HPC, Cord Blood, as defined by hematopoietic reconstitution, was demonstrated in one single-arm prospective study and in retrospective reviews of data from an observational database for Bloodworks, and in data in the dockets and public information. Of the 1299 patients in the dockets and public data, 66% (n=862) underwent transplantation as treatment for hematologic malignancy. Results for patients who received a total nucleated cell dose $\geq 2.5 \times 10^7/\text{kg}$ are shown in Table 2. Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil count more than 500 per microliter. Platelet count recovery is the time to a platelet count more than 20,000 per microliter. Erythrocyte recovery is the time to a reticulocyte count greater than 30,000 per microliter. The total nucleated cell dose and degree of HLA match were inversely associated with the time to neutrophil recovery in the docket data.

Table 2: Hematopoietic Recovery for Patients Transplanted with HPC, Cord Blood, COBLT and Docket Data Total Nucleated Cell (TNC) Dose $\geq 2.5 \times 10^7/\text{kg}$

Data Source	The COBLT Study*	Docket* and Public Data*	Bloodworks Cord Blood Program**
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	Variable*
Median age (range)	4.6 (0.07 – 52.2) yrs	7.0 (<1 – 65.7) yrs	35 (0 – 72) yrs
Gender	59% male 41% female	57% male 43% female	59% male 41% female
Median TNC Dose (range) ($\times 10^7/\text{kg}$)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	3.9 (2.5 – 42.3) ^β
Neutrophil Recovery at Day 42 (95% CI)	76% (71% – 81%)	77% (75% – 79%)	82% (77% – 87%)
Platelet Recovery at Day 100 of 20,000/ μL (95% CI)	57% (51% – 63%)	-	66% (60% – 72%)
Platelet Recovery at Day 100 of 50,000/ μL	46% (39% – 51%)	45% (42% – 49%)	50% (42% – 58%)

(95% CI)	(59% – 71%)	(42% – 48%)	(42% – 59%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58% – 71%)	-	-
Median time to Neutrophil Recovery	27 days	25 days	21.5 days
Median time to Platelet Recovery (20,000/ μ L)	90 days	-	46 days
Median time to Platelet Recovery (50,000/ μ L)	113 days	122 days	53 days
Median time to Erythrocyte Recovery	64 days	-	-

*FDA-1997-N-0010

**Sample size for median age = 468. N for gender = 468. Median TNC dose n = 194 (from units $\geq 2.5 \times 10^7$)
Neutrophil data n = 339. For $\geq 20k$ Platelet n=328. N for 50k platelet = 267.

^{β} Median TNC dose (all doses) = 3.2×10^7

16 HOW SUPPLIED/STORAGE AND HANDLING

HPC, Cord Blood is supplied as a cryopreserved cell suspension in a sealed bag containing a minimum of 5×10^8 total nucleated cells with a minimum of 1.25×10^6 viable CD34+ cells in a volume of 25 milliliters (ISBT 128 Product Code S1393, ISBT 128 Facility Identifier Number W1640). The exact pre-cryopreservation nucleated cell content is provided on the container label and accompanying records.

Store HPC, Cord Blood at or below -150°C until ready for thawing and preparation.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients receiving HPC, Cord Blood.

- Report immediately any signs and symptoms of acute infusion reactions, such as fever, chills, fatigue, breathing problems, dizziness, nausea, vomiting, headache, or muscle aches.
- Report immediately any signs or symptoms suggestive of graft-versus-host disease, including rash, diarrhea, or yellowing of the eyes.

INSTRUCTIONS FOR PREPARATION FOR INFUSION

I. MATERIALS, REAGENTS, AND EQUIPMENT

Materials:

- Large zip-lock plastic bag (sterile interior is recommended)
- Sampling site couplers
- Tubing Clamps
- Sterile 300 mL Transfer Bag (labeled "LMD/25% HSA Solution #1")
- Sterile 300 mL Transfer Bag (labeled "LMD/5% HSA Solution #2")
- Sterile 300 mL Transfer Bag (labeled "Thawed Final Product")
- 14 gauge needles
- 3-5 inch blunt needle (a sterile spinal needle with trochar removed, if available) for emergency product recovery
- Sterile Syringes: 1, 10, 30 and 60 mL
- Sample tubes
- Isopropyl alcohol prep pads, 70% v/v
- Refrigerated gel packs
- Scissors

Reagents:

- 10% Low Molecular Weight Dextran-40 (LMD)
- Human Serum Albumin, USP (HSA), 25% and 5% Solution

Equipment:

- Refrigerator
- Biological Safety Cabinet
- Large water bath, 37°C ± 2°C
- Thermometer
- Di-electric sealer

NOTE: If performing wash step after dilution, then you will also need:

- Sterile Connecting Device
- Centrifuge blood bag adapter and insert (to support low volume bag)
- Centrifuge
- Manual Plasma Extractor
- Scale

Forms:

- *Shipping Information*
- *CBU Summary sheet*
- *HPC, Cord Blood Release Specifications for Distribution*
- *HPC, Cord Blood Final Eligibility Determination*
- *NMDP Receipt of Cord Blood Unit*

II. PRODUCT RECEIPT

The HPC, Cord Blood unit is shipped frozen in a dry-shipper that maintains the temperature at $\leq -150^{\circ}\text{C}$. The dry shipper is capable of maintaining the temperature of $\leq -150^{\circ}\text{C}$ for 5 days from the shipping date. If the unit will not be used within that timeframe, transfer the unit into a storage device capable of maintaining the unit at $\leq -150^{\circ}\text{C}$.

Temperature during shipment is continuously monitored and a printout can be obtained upon request.

Handle the cryobag with extreme caution when removing it from the liquid nitrogen, metal cassette, and protective overwrap, and during the thaw procedure. Cryobags can be very fragile. This is applicable both during inspection of the product upon arrival and during the thawing process.

1. Upon receiving the shipper, perform the following steps:
 - a. Inspect the shipper for tampering or damage prior to opening.
 - b. Inspect the temperature monitor on the shipper; mark on the *Shipping Information* form which light is flashing: Normal, Warning, or Alarm.
NOTE: If the Warning or Alarm light is flashing, immediately contact Bloodworks. See section VI, Contact Information.
 - c. Open the shipper and remove the Tyvek envelope containing a cardboard box.
 - d. Open the cardboard box and remove the metal cassette that contains the unit.
 - e. Carefully open the cassette. The cassette will contain the unit (cryobag) sealed in an overwrap and padded in an absorbent sheet. Cracks or breakages in the overwrap do not indicate damage to the unit.
 - f. Inspect the integrity of the cryobag.
NOTE: If there is damage to cryobag, replace the cryobag into storage at $\leq -150^{\circ}\text{C}$ (contain the cryobag in additional overwrap if necessary). Consult with the transplant physician and contact Bloodworks.
 - g. Document location of inspection, identity of inspector, and date and time of inspection on the *Shipping Information* form.

- h. Verify that the unit ID number on the cryobag matches the unit ID number on all applicable paperwork, the unit ID number matches the expected unit for the intended recipient. Document verification on the *Shipping Information* form.
NOTE: If there are any discrepancies in unit ID, consult with the transplant physician and contact Bloodworks.
Store the product in an LN2 Storage vessel that maintains a temperature at or below -150°C.

III. PREPARATION

1. Initial preparation
 - a. Coordinate with the clinical team
 - i. Confirm the infusion time in advance. Adjust the start time for the thaw so that the unit is available for infusion when the recipient is ready.
 - ii. Consult with the clinicians about final product volume based on the recipient's weight and possible fluid restrictions, to determine if the Alternate Procedure (see Section IV.4) for DMSO removal and volume reduction should be followed.
 - b. Perform clearance of workspace, including disinfection of lab bench and equipment.
 - c. Prepare the water bath and verify the temperature is 37°C ± 2°C.
 - d. Inspect LMD visually for particulate matter. If crystallization is observed, do not use and discard appropriately.
 - e. Pre-cool the LMD, 25% and 5% HSA Solutions in the refrigerator.
 - f. Prepare three sterile 300 mL transfer bags.
 - i. Using a di-electric sealer, make three seals along the tubing close to the transfer bag, inspect seals for integrity and separate the tubing at the center seal.
NOTE: If DMSO removal and volume reduction is required, for the 300mL transfer labeled "Thawed Final Product", seal tubing approximately 4-5 inches above the bag to allow for sterile connection in step IV.4.a.
 - ii. Place the transfer bags into the Biological Safety Cabinet. Insert a sampling coupler in each bag.
2. Prepare Solution #1 with 25% HSA/LMD in the Biological Safety Cabinet.
 - a. With a syringe and needle, add 25 mL of cold LMD and 5 mL of cold 25% HSA (per each product being thawed) into a sterile, labeled 300 mL transfer bag.
 - b. Mix Solution #1 by inverting and swirling the bag several times thoroughly without creating excessive bubbles.
 - c. Store Solution #1 in refrigerator to cool.
NOTE: The LMD/HSA Solution #1 must be used within 4 hours.
3. Prepare Solution #2 with 5% HSA/LMD in the Biological Safety Cabinet.
 - a. With a syringe and needle, add 25 mL of the cold LMD and 25 mL of cold 5% HSA (per each product being thawed) into a sterile, labeled 300 mL transfer bag.
 - b. Mix Solution #2 by inverting and swirling the bag several times thoroughly without creating excessive bubbles.
 - c. Store Solution #2 in refrigerator to cool.
NOTE: The LMD/HSA Solution #2 must be used within 4 hours.

IV. PROCEDURE

Reconstitution or simple dilution of HPC, Cord Blood with LMD/HSA solution, using the Thaw and Diluting procedures described below (steps IV.1-IV.3), is recommended. The Alternate Procedure: Washing in Section IV.4 should be followed if the infusion volume and/or DMSO dose (>1 g/kg body weight) are contraindicated for the patient.

1. Thaw HPC, Cord Blood
 - a. Verify the identity of the HPC, Cord Blood being thawed.
 - b. Using scissors that have been wiped down with alcohol, remove overwrap, detach any segments

and store the segments at $\leq -150^{\circ}\text{C}$ until needed.

- c. Wipe the external surface of the cryobag with isopropyl alcohol. Place the HPC, Cord Blood cryobag inside the large zip-lock plastic bag. Seal the bag closed.

NOTE: Wiping the external surface of the cryobag with isopropyl alcohol before placing inside the sterile zip-lock bag allows the thawing laboratory to potentially recover the product in the case of an unexpected leak or container failure during thawing.

- d. Completely immerse the bag in the $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ water bath.
- e. Gently agitate and knead the cryobag until the product reaches a slushy liquid consistency.
- f. Remove bag from the water bath and quickly inspect for tears or leaks.

NOTE: If container integrity is observed to be compromised, position the cryobag and/or clamp with hemostats to prevent further escape of product. If visible cracks or breaks are observed, consult the transplant physician before proceeding. See Section V for Emergency Product Recovery procedures.

- g. Remove the thawed cryobag from zip-lock bag, wipe with alcohol, and place the cryobag into the Biological Safety Cabinet.

2. Transfer the thawed HPC, Cord Blood into a 300 mL Transfer Bag

NOTE: Perform the transfer procedure in a Biological Safety Cabinet.

- a. Wipe down the cryobag port covers with alcohol to disinfect.
- b. Cut off port covers with scissors that have been wiped down with alcohol. Only cut through the outer layer of plastic. Do not cut the inner port column.
- c. Insert a sampling site coupler into each port using aseptic technique.
- d. Using a 30 mL syringe with a 14 gauge needle, aseptically withdraw the contents from both compartments into the syringe.
- e. Record the product volume removed (approximately 25 mL).
- f. Using an inserted sampling site coupler, slowly and aseptically transfer the product to a sterile 300 mL transfer bag (labeled as "Thawed Final Product").
- g. Place the product on refrigerated gel packs in the Biological Safety Cabinet.

3. Dilute HPC, Cord Blood

NOTE: Perform the following dilution procedure in a Biological Safety Cabinet.

- a. Remove the 300 mL Transfer Bag containing Solution #1 from the refrigerator.
- b. Using a 60 mL syringe with a 14 gauge needle, aseptically fill the syringe with Solution #1 of a volume equal to the product volume noted in step 2.e (approximately 25 mL).
- c. Aseptically attach the 60 mL syringe containing Solution #1 to the 300 mL transfer bag containing the thawed product.
- d. Slowly add Solution #1 to the transfer bag while gently agitating the contents of the bag.
- e. Allow product to rest for 5 minutes. Maintain the bag chilled on refrigerated gel packs.
- f. Remove the 300 mL Transfer Bag containing Solution #2 from the refrigerator.
- g. Use a 60 mL syringe with a 14 gauge needle to aseptically fill the syringe with Solution #2, using two times the original product volume noted in step 2.e (approximately 50 mL).
- h. Aseptically attach the 60 mL syringe containing Solution #2 to the 300 mL transfer bag containing the product.
- i. Slowly add Solution #2 to the product while gently agitating the bag. Maintain the syringe and transfer bag chilled on refrigerated gel packs.
- j. Calculate the product volume from the volume noted in steps 2.e, the volume of Solution #1 from step 3.b, and the volume of Solution #2 in step 3.g.
- k. Aseptically remove samples for quality control tests (such as nucleated cell counts, viability testing, CD34 analysis, Colony Forming Units (CFU), and sterility testing) and transfer the samples into appropriately labeled tubes. Document the volume removed.
- l. Subtract the volume removed from the volume noted in step 3.j, thus determining the infusion volume. Document the infusion volume, which will be used for calculating cell numbers.
- m. Immediately transport the product to the clinical infusion site per the facility's SOP.

NOTE: The recommended expiration time of thawed HPC, Cord Blood product is 4 hours from the time of thaw, if stored at 2-8°C.

4. Alternate Procedure: Washing (DMSO removal and volume reduction)

Perform all steps of the Thaw and Transfer procedures, and steps 3.a through 3.i of the Dilute procedure as outlined above, and then complete the following steps:

- a. Sterile connect an empty sterile 300 mL transfer bag to the product bag from step 3.i. Place a tubing clip on the tubing close to the product bag.
- b. Place the thawed, diluted product bag and attached 300 mL transfer bag in a blood bag adapter with insert to support the low volume bag and centrifuge at 400 x g for 20 minutes at 4°C.
- c. Place the concentrated HPC, Cord Blood product bag in a manual plasma extractor.
- d. Place the attached empty 300 mL transfer bag on a scale and tare the scale.
- e. Remove the tubing clip. Use the plasma extractor to press off the supernatant into the attached transfer bag until approximately 20 mL cell pellet remains, and clamp the HPC, Cord Blood bag tubing.
- f. Resuspend the cell pellet by gentle agitation. In a Biological Safety Cabinet, use a 30 mL syringe to volumetrically measure the concentrated product. If necessary, add back supernatant to reach a final total volume of 20 mL.
- g. In a Biological Safety Cabinet, aseptically remove samples for quality control tests (such as nucleated cell counts, viability test, CD34 analysis, Colony Forming Units (CFU)) and transfer the samples into appropriately labeled tubes. Do not remove more than 500 microliters. Document the volume removed.
- h. Subtract the sample volume removed in step 4.g from the volume noted in step 4.f, thus determining the infusion volume. Document the infusion volume, which will be used for calculating cell numbers.
- i. In a Biological Safety Cabinet, aseptically add a sampling site coupler to the supernatant transfer bag and remove samples for sterility testing.
- j. Immediately transport the product to the clinical transport site per the facility's SOP.

NOTE: The recommended expiration time of thawed HPC, Cord Blood product is 4 hours from the time of thaw, if stored at 2-8°C.

V. EMERGENCY PRODUCT RECOVERY IN THE EVENT OF A CONTAINER FAILURE

1. Handle the cryobag with extreme caution when removing it from the liquid nitrogen, metal cassette, and protective overwrap and during the thaw procedure. Cryobags can be very fragile. This is applicable both during inspection of the product upon arrival and during the thawing process.
2. Wipe the external surface of the cryobag with isopropyl alcohol before the cryobag is placed inside a sterile zip-lock bag. This process allows the thawing laboratory to potentially recover the product in the case of an unexpected leak or container failure during thawing or centrifugation.
3. Notify Bloodworks, the transplant physician/team, and local laboratory director immediately if any portion of the product or container seems to be damaged or compromised.
4. If the cryobag is compromised, move further handling into a Biological Safety Cabinet.
5. It is the physician's responsibility to determine whether the product will be used or discarded if the container is compromised at any step of the procedure. If the product is accepted for use, recovery of the product may be attempted as described below.
 - a. Prepare an empty transfer bag with a sampling site coupler.
 - b. Use a long (3-5 inch) blunt needle (a sterile spinal needle with trochar removed, if available).
 - c. Attach the blunt needle to a sterile 60 mL syringe.
 - d. Aspirate the product, replace the blunt needle with a standard needle and inject it into a sterile transfer bag via a sampling site coupler.
 - e. Continue processing of the transferred product from the point container failure was identified.
 - f. Perform sterility testing on the product sample after final preparation step.

VI. CONTACT INFORMATION

Bloodworks
Cord Blood Services
921 Terry Ave.
Seattle, WA 98104

Hours: 7:30 AM - 6:00 PM, Pacific Standard Time
Phone Number: 206-689-6696
Alternate Phone Number: 1-800-366-2831, ext. 1896

After Hours

Cell Phone Number: 206-231-3108

Distributed by:
Bloodworks
Cord Blood Services
921 Terry Ave.
Seattle, WA 98104
License Number 2042

Principal Display Panel - Carton Label

"W1640 16 999999"

Product: S1393V00

HPC, CORD BLOOD

10% DMSO, Other additives present,
Cryopreserved, Buffy Coat Enriched

See Accompanying Documentation

Total Volume 25.13 mL

Store at -150 C or colder

Expires:

Bloodworks
921 Terry Ave
Seattle, WA 98104



W1640 16 999999 8 8

Product: S1393V00

HPC, CORD BLOOD

10% DMSO, Other additives present,
Cryopreserved, Buffy Coat Enriched

See Accompanying Documentation

Total Volume 25.13 mL

Store at -150 C or colder

Expires:

Bloodworks
921 Terry Ave
Seattle, WA 98104

32

Principal Display Panel - Bag Label

"W1640 16 999999"

Bloodworks
921 Terry Avenue
Seattle, WA 98104

Collection
Date/Time "0160281000"

28 Jan 2016 10:00 PST
(28 Jan, 2016 18:00 UTC)

Do Not Irradiate
Do Not Use Leukoreduction Filters
RX Only

"S1393V00"

HPC, CORD BLOOD

10% DMSO, Other additives present,
Cryopreserved, Buffy Coat Enriched

See Accompanying Documentation

Total Volume 25.13 mL

Store at -150 C or colder

US License #: 2042

"6200"

A

Rh Positive

For Intravenous Administration

See package insert for full prescribing information and instructions for preparation.

Expiration

Date/Time

"0180281000"

28 Jan 2018 10:00 PST

(28 Jan, 2018 18:00 UTC)

Intended Recipient

Smith, Bob

Recipient ID: 9987-1234-5

Date of Birth: 04 Jul 1970



W1640 16 999999 8



6200

Bloodworks
921 Terry Avenue
Seattle, WA 98104

A

Rh POSITIVE

Collection
Date/Time

0160281000

28 Jan 2016 10:00 PST

(28 Jan, 2016 18:00 UTC)

For Intravenous Administration

See package insert for full prescribing information and instructions for preparation.

Do Not Irradiate
Do Not Use Leukoreduction Filters
RX Only



S1393V00

HPC, CORD BLOOD

10% DMSO, Other additives present,
Cryopreserved, Buffy Coat Enriched



0180281000

Expiration
Date/Time

28 Jan 2018 10:00 PST

(28 Jan, 2018 18:00 UTC)

See Accompanying Documentation
Total Volume 25.13 mL
Store at -150 C or colder

Intended Recipient
Smith, Bob
Recipient ID: 9987-1234-5
Date of Birth: 04 Jul 1970

US License #: 2042

3 3 0c

HPC, CORD BLOOD

hpc, cord blood injection

Product Information

Product Type

LICENSED MINIMALLY MANIPULATED
CELLS

Item Code
(Source)

ISBT:W1640-S1393

Route of Administration

INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name

Basis of Strength

Strength

HUMAN CORD BLOOD HEMATOPOIETIC PROGENITOR CELL (UNII: XU53VK93MC) (HUMAN CORD BLOOD HEMATOPOIETIC PROGENITOR CELL - UNII:XU53VK93MC)	HUMAN CORD BLOOD HEMATOPOIETIC PROGENITOR CELL	500000000 in 25 mL
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Inactive Ingredients

Ingredient Name	Strength
DIMETHYL SULFOXIDE (UNII: YOW8V9698H)	
DEXTRAN 40 (UNII: K3R6ZDH4DU)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	ISBT:W1640-S1393-02	1 in 1 CARTON		
1	ISBT:W1640-S1393-01	25 mL in 1 BAG; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125585	01/28/2016	

Labeler - Bloodworks (092881085)

Establishment

Name	Address	ID/FEI	Business Operations
Bloodworks		092881085	manufacture(W1640-S1393) , label(W1640-S1393) , pack(W1640-S1393)

Revised: 1/2016

Bloodworks