HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CORDCYTE safely and effectively. See full prescribing information for CORDCYTE.

CORDCYTE (HPC, Cord Blood)
Injectable Suspension for Intravenous Use
Initial U.S. Approval: 2013

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 the 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----------
CORDCYTE, HPC, 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 CORDCYTE should be done under the direction of a physician experienced in hematopoietic progenitor cell transplantation (2).
- The recommended minimum dose is 2.5 x 10^7 nucleated cells/kg at cryopreservation (2.1).
- Do not administer CORDCYTE through the same tubing with other products except for normal saline (2.3).

----------DOSAGE FORMS AND STRENGTHS----------
Each unit contains a minimum of 5 x 10^8 total nucleated cells with at least 1.25 x 10^6 viable CD34+ cells at the time of cryopreservation. The exact pre-cryopreservation nucleated cell content of each unit is provided on the accompanying records (3).

----------CONTRAINDICATIONS----------
None.

----------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% (5, 6.1).

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

To report SUSPECTED ADVERSE REACTIONS, contact the quality department for LifeSouth Community Blood Centers at 1-888-795-2707 and FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: No animal or human data. Use only if clearly needed (8.1).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

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

Graft-vs.-host disease (GVHD): GVHD is expected after administration of CORDCYTE, 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 CORDCYTE, consider testing for HLA antibodies to identify patients who are alloimmunized. *[See Warnings and Precautions (5.5)].*

1 INDICATIONS AND USAGE

CORDCYTE, HPC (Hematopoietic Progenitor Cell), Cord Blood is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor stem 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 on 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 CORDCYTE 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 x 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 CORDCYTE are documented in the accompanying records.

2.2 Preparation for Infusion

CORDCYTE should be prepared by a trained healthcare professional.

- Do not irradiate CORDCYTE.
- See the appended detailed instructions for preparation of CORDCYTE for infusion.
- Once prepared for infusion, CORDCYTE may be stored at room temperature (19-25ºC) or 4ºC for up to 2 hours when DMSO is removed in a washing procedure *[see Instructions for Preparation for Infusion]*. No data are available for the stability of CORDCYTE if DMSO is not removed.
- The recommended limit on DMSO administration is 1 gram per kg body weight per day *[see Warnings and Precautions (5.2) and Overdosage (10)]*.

2.3 Administration

CORDCYTE 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 CORDCYTE 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 CORDCYTE. Premedication can include any or all of the following: antipyretics, 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 CORDCYTE by intravenous infusion. Do not administer in the same tubing concurrently with products other than 0.9% Sodium Chloride, Injection (USP). CORDCYTE may be filtered through a 170 to 260 micron filter designed to remove clots. Do NOT use a filter designed to remove leukocytes.
7. For adults, begin infusion of CORDCYTE at 100 milliliters per hour and increase the rate as tolerated. For children, begin infusion of CORDCYTE at 1 milliliter per kg per hour and increase as tolerated. Reduce the infusion rate if the fluid load is not tolerated. Discontinue the infusion 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 CORDCYTE contains lysed red 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 unit of CORDCYTE contains a minimum of 5×10^8 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 in the accompanying records.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic reactions may occur with infusion of HPC, Cord Blood, including CORDCYTE. 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, hydroxyethylstarch, or a plasma component of CORDCYTE.

CORDCYTE 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 CORDCYTE 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 antipyretics, 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 CORDCYTE, 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 CORDCYTE. Classic acute GVHD is manifested as fever, rash, elevated bilirubin and liver

enzymes, and diarrhea. Patients transplanted with CORDCYTE also 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. PTLD is usually fatal if not treated.

The incidence of PTLD 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 CORDCYTE 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*. CORDCYTE is tested for sterility. There may be an effect on the reliability of the sterility test results if the cord blood donor was exposed to antibiotics in utero. These measures do not totally eliminate the risk of transmitting these or other transmissible infectious diseases and disease agents. Report the occurrence of a suspected transmitted infection to the quality department of LifeSouth Community Blood Centers at 1-888-795-2707.

Testing is also performed for evidence of donor infection due to cytomegalovirus (CMV). Test results may be found in the accompanying records.

5.8 Transmission of Rare Genetic Diseases

CORDCYTE 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. CORDCYTE 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 CORDCYTE 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 (≥ 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 CORDCYTE 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 ≥ 2.5 x 10^7/kg on a single-arm prospective trial or expanded access use (COBLT Study). The population was 60% male and the median age was 5 years (range 0.05-68 years), and included patients treated for hematologic malignancies, inherited metabolic disorders, primary immunodeficiencies, and bone marrow failure. Preparative regimens and graft-vs.-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 > 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 ≥ 1% of Infusions (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%

No information on the types and rates of infusion reactions were reported with CORDCYTE.

Other Adverse Reactions

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

Data from published literature and from observational registries, institutional databases, and cord blood bank reviews reported to the dockets 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 not sufficient 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

Pregnancy Category C. Animal reproduction studies have not been conducted with CORDCYTE. It is also not known whether CORDCYTE 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. CORDCYTE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. In general, administration of CORDCYTE to patients over age 65 years should be cautious, reflecting their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Disease

CORDCYTE contains Dextran 40 which is eliminated by the kidneys. The safety of CORDCYTE 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 LifeSouth CORDCYTE up to 71 x 10^7 TNC/kg have been administered. HPC, Cord Blood prepared for infusion may contain dimethyl sulfoxide (DMSO). The maximum tolerated 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 overdosage, general supportive care is indicated. The role of other interventions to treat DMSO overdosage has not been established.

11 DESCRIPTION

CORDCYTE 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 cord blood is determined by measuring the numbers of total nucleated cells (TNC) and CD34+ cells, and cell viability. Each unit of CORDCYTE contains a minimum of 5 x 10^8 total nucleated cells with at least 1.25 x 10^6 viable CD34+ cells at the time of cryopreservation. The cellular composition of CORDCYTE 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 in the accompanying records sent with each individual unit.

CORDCYTE has the following inactive ingredients: dimethyl sulfoxide (DMSO), Dextran 40, and hydroxyethylstarch. When prepared for infusion according to instructions, the infusate contains the following inactive ingredients: Dextran 40, human serum albumin, residual DMSO, and residual hydroxyethylstarch.

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 CORDCYTE, as defined by hematopoietic reconstitution, was demonstrated in one single-arm prospective study (COBLT Study), and in retrospective reviews of data from an observational database for CORDCYTE and 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 $\geq 2.5 \times 10^7$/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 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, Total Nucleated Cell (TNC) Dose ≥ 2.5 x 10^7/kg

Data Source	COBLT Study*	Docket* and Public Data*	CORDCYTE
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	22
Median age (years) (range)	4.6 (0.07 – 52.2)	7.0 (<1 – 65.7)	8 (0.6 – 61.8)
Gender	59% male 41% female	57% male 43% female	59% male 41% female
Median TNC Dose (x 10^7/kg) (range)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	5.1 (2.8 – 70.6)
Neutrophil Recovery at Day 42 (95% CI)	76% (71% – 81%)	77% (75% – 79%)	91% (71% - 98%)
Platelet Recovery at Day 100 of 20,000/microliter (95% CI)	57% (51% – 63%)	-	95% (79% - 99%)
Platelet Recovery at Day 100 of 50,000/microliter (95% CI)	46% (39% – 51%)	45% (42% – 48%)	95% (79% - 99%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58% – 71%)	-	-
Median time to Neutrophil Recovery	27 days	25 days	22 days
Median time to Platelet Recovery of 20,000/microliter	90 days	-	44 days
Median time to Platelet Recovery of 50,000/microliter	113 days	122 days	70 days
Median time to Erythrocyte Recovery	64 days	-	-

* HPC, Cord Blood (from multiple cord blood banks)

16 HOW SUPPLIED/STORAGE AND HANDLING

CORDCYTE is supplied as a cryopreserved cell suspension in a sealed bag containing a minimum of 5 x 10^8 total nucleated cells with a minimum of 1.25 x 10^6 viable CD34+ cells in a volume of 25 milliliters (ISBT 128 Product Code S1393, ISBT 128 Facility Identifier Number W2434). The exact pre-cryopreservation nucleated cell content is provided in the accompanying records.

Store CORDCYTE at or below -150°C until ready for thawing and preparation.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients receiving CORDCYTE:

- 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-vs.-host disease, including rash, diarrhea, or yellowing of the eyes.

INSTRUCTIONS FOR PREPARATION FOR INFUSION

The cord blood unit (CBU) is stored continuously inside a steel canister in liquid nitrogen at temperatures ≤ -150°C. For shipment, the canister is placed inside a container specifically designed to keep the temperature at or below -150°C (dry shipper). It is recommended to keep the canister inside the dry shipper for short-term storage (up to 48 hours) or transfer it into a liquid nitrogen (LN_2)-cooled storage device at the Transplant Center for storage greater than 48 hours.

I MATERIALS

Equipment:

- Automated cell counter and/or microscope and cell count chamber for cell count and viability determination (optional)
- Biological safety cabinet (BSC)
- Canister-opening tool (supplied by LifeSouth Community Blood Centers)
- LN_2 storage freezer at -150°C or colder
- Plasma extractor/expressor
- Refrigerated centrifuge
- Scale
- Sterile docker
- Tube sealer compatible with polyvinyl chloride plastic
- Water bath

Personal Protective Equipment:

- Closed-toe shoes
- Cryo-protective gloves
- Lab coat
- Latex or non-latex gloves (sterile preferred)
- Safety glasses or face shield

Reagents:

- Dextran 40 (10% LMD) (stored at 2 to 6ºC)
- 5% Albumin (human) solution (stored at 2 to 6ºC)

Supplies:

- 30-mL sterile syringes
- 60-mL sterile syringes
- 300-mL or larger transfer packs
- Alcohol pads
- CBU
- Disinfectant solution
- Hemostats
- Needle-free luer locks
- Needles
- Paper towels
- Refrigerated gel packs
- Sampling site couplers
- Scissors
- Small sterile, resealable plastic bags
- Sterile sampling cups, pipettes, and syringes if necessary to perform emergency recovery procedure
- Sterile water for water bath
- Timer

Forms:

- *Umbilical Cord Blood Cryopreserved Unit Receipt Instructions*
- *Umbilical Cord Blood Cryopreserved Transfer Report*

II PROCEDURE NOTES

- Handle the frozen cord blood bag with extreme care at every step, including opening the metal containers, inspecting, thawing and/or washing.
- Use standard procedures and competent personnel to perform post-thaw sampling and/or bag recovery.
- Perform all steps on lab benches, under biological safety cabinet, or another surface to prevent inadvertent drop of the frozen unit.
- Put the frozen bag inside a resealable plastic prior to initiating the thaw to facilitate salvage of the product and to reduce the possibility of contamination.
- If the CBU is seen to be cracked when removed from the LN2 storage container, or if cracks or leaks occur during thawing, immediately notify LifeSouth at 1-888-795-2707. Notify the transplant physician/team and the laboratory director as soon as possible.

III PRODUCT IDENTITY VERIFICATION

1. Apply personal protective equipment.
2. Open the dry shipper lid upon receipt.
3. Verify that the National Marrow Donor Program (NMDP) number on the *Umbilical Cord Blood Cryopreserved Transfer Report* matches the NMDP number on the CBU. If the NMDP numbers do not match, contact LifeSouth Community Blood Centers at 1-888-795-2707.
4. Remove the canister from the dry shipper and the canister-opening tool from the shipment documentation packet (see Figure 1).

Figure 1:

5. Compare the product barcode label located on the side of the canister (see Figure 1) with the product identification (ID) information included in the package. Verify this information as soon as the shipment arrives and before administering the CBU. If the barcoded label is not found on the outside of the canister, the product barcode information can be found on the frozen CBU enclosed in the canister.
6. Using cryo-protective gloves and the canister-opening tool, open the canister at top and bottom using the following steps to avoid damaging the frozen cord blood bag:
    a. Align the canister-opening tool with the slot in the bottom of the canister (see Figure 2).
    b. Turn the canister-opening tool clockwise to open the bottom of the canister (see Figure 3).
    c. Align the canister-opening tool with the slot in the top of the canister (see Figure 4).
    d. Turn the canister-opening tool counterclockwise to open the top of the canister (see Figure 4).

Figure 2:

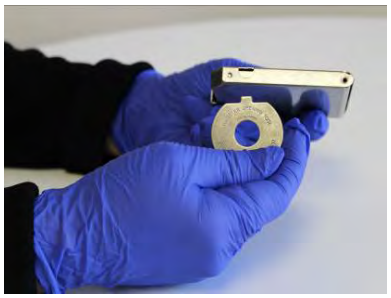


Figure 3:

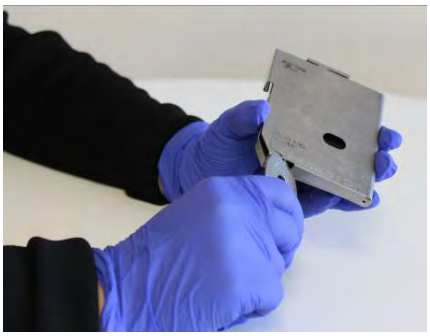


Figure 4:

e. Open the canister hinges (see Figure 5).

Figure 5:

7. When the canister is open, compare the product barcode information with your records.
8. Close canister after verification is complete.
9. Using cryo-protective gloves, return the canister to the dry shipper for short-term storage (up to 48 hours) or to an LN_2 cooled storage device for storage greater than 48 hours.
10. When all records are verified, indicate acceptance by recording initials and date in the indicated space on the *Umbilical Cord Blood Cryopreserved Unit Receipt Instructions* and *Umbilical Cord Blood Cryopreserved Transfer Report* forms.

For Incorrect Information:

1. If any information is incorrect or cannot be verified, close the canister and return the frozen CBU to the dry shipper for short-term storage (up to 48 hours) or to an LN_2-cooled storage device for storage greater than 48 hours.
2. Immediately report the discrepancy to LifeSouth at 1-888-795-2707 and to the transplant physician.
3. Perform a thorough investigation, while keeping the CBU frozen at or below -150°C until all discrepancies are resolved.
4. When all records are verified, indicate acceptance by recording initials and date in the indicated space on the *Umbilical Cord Blood Cryopreserved Unit Receipt Instructions* and *Umbilical Cord Blood Cryopreserved Transfer Report* forms.

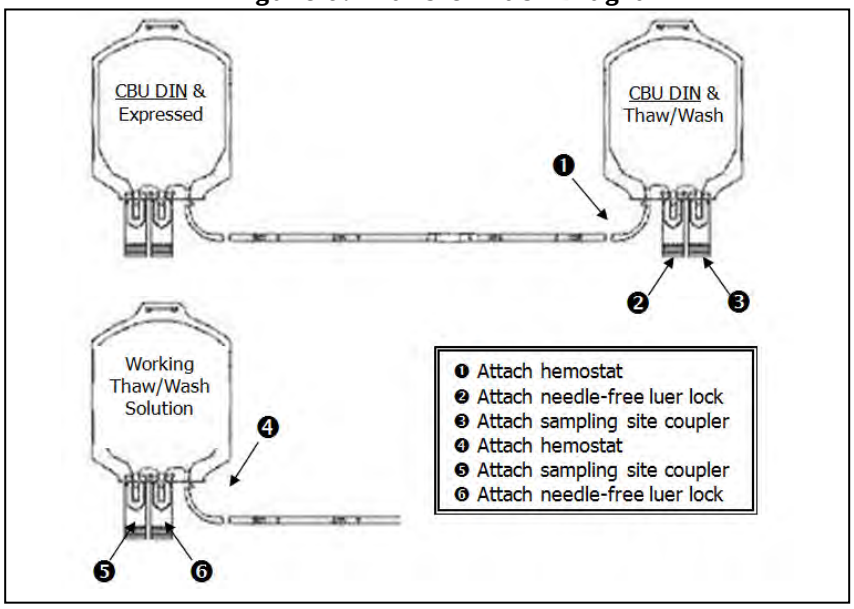
IV PREPARATION

A Prepare Thawing Solution

NOTE: Prepare thawing solution at least one hour and no more than 24 hours before thawing the CBU.

1. Obtain two gel packs; place in refrigerator to cool.
2. Label a 300-mL or larger transfer pack with "Working Thaw/Wash Solution" and the date/time prepared (see Figure 6).
3. Perform the following steps under a biological safety cabinet to prepare the thaw/wash kit:
    a. Clean ports with alcohol, and attach a sampling site coupler to one port and a needle-free luer lock to the other port; attach hemostat to tubing (see Figure 6).
    b. Add at least 112.5-mL Dextran to the 300-mL transfer pack labeled Working Thaw/Wash Solution using 60-mL sterile syringes with needles (Albumin to Dextran ratio must be 1:1).
    c. Add at least 112.5-mL 5% albumin (human) solution to the same the 300-mL transfer pack labeled "Working Thaw/Wash Solution" using 60-mL sterile syringes with needles.
    d. Mix by inverting the pack at least 10 times.
    e. Label one transfer pack with CBU Donation Identification Number (DIN) and "Thaw/Wash." Clean ports with alcohol, and attach a sampling site coupler to one port and a needle-free luer lock to the other port (see Figure 6).
    f. Label the second transfer pack with CBU DIN and "Expressed."
    g. Attach a hemostat to the tubing approximately one inch above the sampling site coupler on the CBU DIN and Thaw/Wash transfer pack (see see Figure 6).
    h. Using a sterile docker, connect the two 300-mL transfer packs (see see Figure 6).
    i. Add 100 mL of thaw/wash solution to the CBU DIN and Thaw/Wash transfer pack.
    j. Label two 60-mL sterile syringes and two 30-mL sterile syringes as "Thaw/Wash Solution."
        i. Draw 20 mL of thaw/wash solution into each of the two 60-mL syringes; cap and set aside.
        ii. Draw 5 mL of thaw/wash solution into each of the two 30-mL syringes syringes; cap and set aside.
    k. Label a 60-mL sterile syringe "Resuspension Solution"; fill with 50 mL of pre-chilled thaw solution (1:1 ratio of Dextran/albumin (human) solution) for final end-product resuspension via needle-free luer lock. Cap and place in refrigerator to use after centrifugation.
    l. Place the transfer packs and syringes in the refrigerator for at least one hour and no longer than 24 hours.

Figure 6: Transfer Pack Diagram



B Thaw CBU

Schedule the transplant infusion time with the transplant team prior to performing the procedure. Reconfirm with the transplant team on the day of infusion so the start time for the thawing procedure can be adjusted as necessary in order to have the unit ready for infusion at a time the patient can receive the infusion.

Prepare a water bath using sterile water; allow water bath to equilibrate to a temperature of 37 °C ± 1 °C prior to retrieving CBU for thaw.

If canister is stored in liquid phase LN_2, wear cryo-protective gloves to lift the canister containing the CBU from the liquid phase of the LN_2 container, and rest canister in the vapor phase within the container for five to ten minutes before proceeding.

Note: Carefully check the identity of the unit to be thawed.

1. Open the canister with the canister-opening tool (refer to section **III PRODUCT IDENTITY VERIFICATION**). Avoid damage to the plastic bag containing the frozen CBU. Carefully examine the plastic bag for breaks or cracks.

   NOTE: Verify bag labels are intact, ports are unopened, and there is no visible damage throughout the remainder of thaw procedure.

2. Remove the CBU from the canister and remove the overwrap; place in a sterile, resealable plastic bag, remove excess air, and close tightly.
3. Place the resealable plastic bag containing the frozen cord blood into water bath (see Figure 7). Thaw CBU until slushy and not completely thawed; watch ports closely to ensure ports are thawed. Watch closely for any cracks or breaks, as shown by red cells leaking from the CBU into the resealable plastic bag; minimize loss of CBU by positioning or pinching the CBU to prevent leakage into the resealable plastic bag.

Figure 7:

4. If leakage occurs, keep the entire pack upright to prevent further leaking until product is slushy and not completely thawed. Perform section **VI EMERGENCY RECOVERY PROCEDURE IN THE EVENT OF A CONTAINER FAILURE**.
5. If no leakage occurs, remove the resealable plastic bag from water bath. Dry the outside of the bag, disinfect it with alcohol, and place it inside a biological safety cabinet.

C Add Thawed CBU to Transfer Pack

Complete the following steps inside a biological safety cabinet:

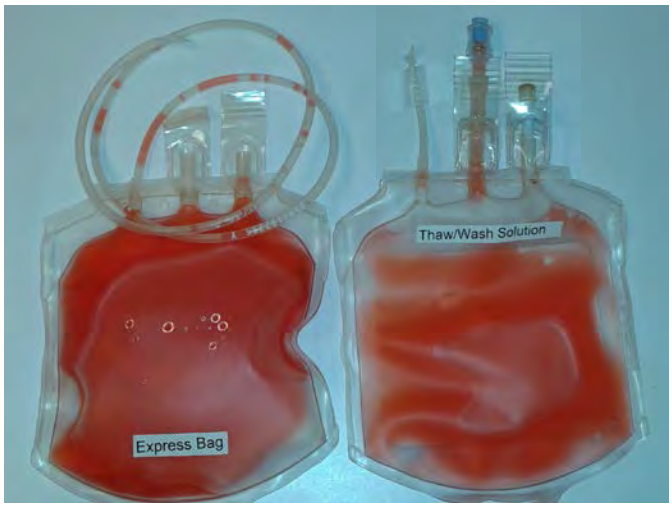
1. Obtain and disinfect materials before placing under BSC.
2. Remove two gel packs, two 30-mL syringes, and two 60-mL syringes from refrigerator; disinfect and place under BSC. Place absorbent material, such as a paper towel, on top of one of the gel packs.
3. Obtain CBU; disinfect, place under BSC, and remove from resealable plastic bag.
4. Obtain scissors; disinfect scissors and port covers, then cut off port covers.
5. Disinfect cut port-cover surfaces with alcohol and attach one needle-free luer lock to each port.
6. Obtain 30-mL syringe containing 5 mL of thaw/wash solution and insert into small compartment port; slowly inject thaw/wash solution into small compartment. Do not remove syringe.
7. Obtain 60-mL syringe containing 20 mL of thaw/wash solution and insert syringe into large compartment port; slowly inject thaw/wash solution into large compartment. Do not remove syringe.
8. Place CBU on refrigerated gel pack. Set timer for 5 minutes, and place second gel pack on top of CBU When alarm sounds, remove CBU from gel packs.
9. Slowly pull back and push in the syringe plunger to mix the cord blood and thaw/wash solution; repeat until thoroughly mixed.
10. Draw all fluid from the compartments; inject into the CBU DIN and Thaw/Wash Solution transfer pack via sampling site coupler while slowly mixing Thaw/Wash Solution transfer pack.
11. Obtain second set of syringes, including a 30-mL syringe containing 5 mL of thaw/wash solution and up to 5 mL of air and a 60-mL syringe containing 20 mL of thaw/wash solution and up to 20 mL of air. Repeat steps 7, 9 and 10.

12. Mix the CBU DIN and Thaw/Wash Solution transfer pack well by inverting the transfer pack 180° about 10 to 15 times.
13. Discard remaining Working Thaw/Wash Solution.

D Wash the Thawed CBU

1. Obtain thawed CBU in Thaw/Wash Solution transfer pack containing the hemostat, sampling site coupler, luer lock, and additional transfer pack; mix by inverting at least ten times. Place into a resealable plastic bag, and place in the refrigerated centrifuge in an upright position. Do not allow pack to crease.
2. Ensure the centrifuge is balanced before beginning centrifugation cycle.
3. Centrifuge at 400 g or 1200 rpms (rpms will be centrifuge specific) for 20 minutes at 10°C with no brake and slow stop.
4. After centrifugation, carefully remove the Thaw/Wash Solution transfer pack from the centrifuge and look for clear separation of supernatant from cell pellet.
5. Place transfer pack containing CBU and thaw/wash solution into a plasma extractor and allow supernatant to flow into second transfer pack labeled Expressed Solution by removing the hemostat from the tubing. Express as much supernatant as possible without sacrificing cells; the volume should be as low as possible to remove the DMSO and thaw waste without allowing the cell pellet to escape.
6. Hemostat tubing after expressing to close the tubing.
7. Place Thaw/Wash Solution transfer pack on a flat surface and gently massage the pellet to release the cells into suspension.
8. Heat seal tubing with spike on CBU DIN and thaw/wash solution closest to primary pack three times; ensure the first seal is approximately three inches away from the primary pack (see Figure 8). Cut the middle seal.

Figure 8:



9. Remove hemostat from tubing.
10. Weigh and calculate the volume of the Thaw/Wash Solution transfer pack.
11. Weigh and calculate the volume of the Expressed Solution transfer pack.

E Resuspend and Sample the Thawed CBU

1. Obtain the prepared 60-mL syringe labeled "Resuspension Solution" from the refrigerator.

2. Clean the port with alcohol, and slowly add 50 mL of thaw solution to the Thaw/Wash transfer pack from the 60-mL syringe.
3. Mix Thaw/Wash transfer pack well by inverting the transfer pack 180° about 10 to 15 times.
4. Complete sampling for any necessary testing.
5. Label DIN and Thaw/Wash Solution transfer bag with the expiration time and time of wash completion. The recommended expiration time is 2 hours after the completion of wash until infusion, if stored at room temperature (19 to 25ºC) or 4ºC.
6. Notify the Transplant Center that the CBU is thawed, washed, and available for infusion.

V ADMINISTRATIVE REQUIREMENTS

1. Prepare a written summary of the procedure, including:
   a. CBU ID number
   b. Date of receipt of CBU
   c. Liquid nitrogen storage temperature
   d. Date of thaw, including whether and at what stage leaks or cracks occurred
   e. Date and time CBU removed from liquid nitrogen storage
   f. Volume of final product
   g. TNC (Total nucleated cell) count, CD34+ count
   h. Viability of recovered cells (TNC or CD34+) plus name of method used
   i. Results of bacterial and fungal cultures
2. Make a copy of the report for your records.
3. Fax a copy of the report to LifeSouth at (352) 334-7758.
4. Return the dry shipper to LifeSouth. The return address is:

   LifeSouth Community Blood Centers, Inc.
   LifeCord Cord Blood Bank
   4039 Newberry Road
   Gainesville, FL 32607

   Phone: (888) 795-2707
   Fax: (352) 334-7758

VI EMERGENCY RECOVERY PROCEDURE IN THE EVENT OF A CONTAINER FAILURE

The transplant physician or team will determine whether to use or discard the CBU product and whether any additional units should be requested. If the transplant phsician or team decides the leaking CBU can be used, recover the CBU as follows:

1. Obtain sterile sampling cups, pipettes, and syringes.
2. Open sterile sampling cups and arrange in workspace to receive contents of the resealable plastic bag and the cracked/leaking CBU.
3. If any contents remain in the CBU, remove using the syringes prepared in Section **A Prepare Thawing Solution.** Wash all of the CBU contents and add to the CBU Thaw/Wash Solution transfer pack contained in the transfer set.
4. Using a sterile syringe, transfer 20 mL from the CBU Thaw/Wash Solution transfer pack into a sterile sample cup.

5. Using a sterile pipette, obtain 3 mL of thaw/wash solution from the sterile sample cup; add to the resealable plastic bag containing the CBU contents that leaked when thawing.
6. Using a sterile pipette, remove the CBU and thaw/wash solution from the resealable plastic bag and place in a sterile sample cup.
7. Repeat steps 5 through 6 until all remaining CBU is transferred into a sample cup.
8. Using a sterile 20-mL syringe, draw the CBU and thaw/wash solution from the sterile sampling cups into the syringe; add to the Thaw/Wash Solution transfer pack. Repeat until all of the CBU and thaw/wash solution is transferred.
9. Using a sterile 20-mL syringe, remove the remaining thaw/wash solution from the Thaw/Wash Solution transfer pack; add to the CBU and Thaw/Wash Solution transfer pack.
10. When all of the thaw/wash solution in the Thaw/Wash Solution transfer pack has been transferred into the CBU and Thaw/Wash Solution transfer pack, mix the CBU and Thaw/Wash Solution transfer pack well by inverting 180° about 10 to 15 times.
11. Proceed to Section **D Wash the Thawed CBU**.

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