HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLEVECORD safely and effectively. See full prescribing information for CLEVECORD.

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

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-versus-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----------
CLEVECORD, 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 CLEVECORD 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 CLEVECORD 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 in the 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%. (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 Cleveland Cord Blood Center at 1-216-378-3032 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: XX/XXXX

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

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

1 INDICATIONS AND USAGE

CLEVECORD, 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 CLEVECORD 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

CLEVECORD are documented in the accompanying records.

2.2 Preparation for Infusion

CLEVECORD should be prepared by a trained healthcare professional.

- Do not irradiate CLEVECORD.
- See the appended detailed instructions for preparation of CLEVECORD for infusion.
- CLEVECORD may be stored at 15-25°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 Warnings and Precautions (5.2) and Overdosage (10)]*

2.3 Administration

CLEVECORD 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 CLEVECORD prior to administration.
2. Confirm that emergency medications are available for use in the immediate area.
3. Ensure the patient is hydrated adequately.
4. Pre-medicate the patient 30 to 60 minutes before the administration of CLEVECORD. Premedication should 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 CLEVECORD by intravenous infusion. Do not administer in the same tubing concurrently with products other than 0.9% Sodium Chloride, Injection (USP). CLEVECORD may be infused through a 170 to 260 micron filter designed to remove clots. Do NOT use a filter designed to remove leukocytes.
7. Infuse CLEVECORD 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. Reduce the infusion rate if the patient cannot tolerate the fluid load. 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 (6.1)]*
8. Monitor the patient for adverse reactions during, and for at least six hours after, administration. Because CLEVECORD 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, prepare and infuse each unit independently. Should a reaction occur, appropriately manage the reaction before another unit is thawed for infusion

3 DOSAGE FORMS AND STRENGTHS

Each CLEVECORD unit 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 CLEVECORD. Reactions include bronchospasm, wheezing, angioedema, pruritus, and hives *[see Adverse Reactions (6.1)]*. 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 CLEVECORD.

CLEVECORD 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 CLEVECORD administration.

5.2 Infusion Reactions

Infusion reactions are expected to occur and may 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 CLEVECORD, 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 CLEVECORD. Classic acute GVHD is manifested as fever, rash, elevated bilirubin and liver enzymes, and diarrhea. Patients transplanted with CLEVECORD 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 in order 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 CLEVECORD 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, vaccinia, and Zika virus. 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*. CLEVECORD is tested for sterility. There may be an effect on the reliability of the sterility test results if the cord blood donor's 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 a transmitted infection to the Cleveland Cord Blood Center at 1-216-378-3032.

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

CLEVECORD 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. CLEVECORD 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 CLEVECORD 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 CLEVECORD is based primarily on review of the data submitted to the FDA dockets from various sources, the dataset from 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 trial or expanded access use (the COBLT Study). The population was 60% male and the median 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 ≥ 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 %	0.0 %
Fever	5.2 %	0.2 %
Sinus tachycardia	4.5 %	0.2 %
Allergy	3.4 %	0.2 %
Hypotension	2.5 %	0.0 %
Hemogloburia	2.1 %	0.0 %

Hypoxia	2.0 %	2.0 %

Information on infusion reactions was available from voluntary reports for 91 patients who received a total nucleated cell dose of $\geq 2.5 \times 10^7$/kg from at least a single unit of CLEVECORD, alone or in combination with another unit of HPC, Cord Blood and who had an HLA match > 3/6. The population included 55% males and 45% females with median age of 38 years (range <1-68 years). Preparative regimens and graft-versus-host disease prophylaxis were not standardized. The reactions were not graded. An infusion reaction occurred in 20% of patients. The most common infusion reactions, occurring in ≥ 1% of infusions, were hypertension (17%), nausea or vomiting (3%), and hypoxia (3%).

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 cell dose of $\geq 2.5 \times 10^7$/kg. Of these, 66% (n=862) underwent transplantation as treatment for hematologic malignancy. The preparative regimens and graft-versus-host disease prophylaxis varied. The median total nucleated cell dose was 6.4×10^7/kg (range, 2.5-73.8 $\times 10^7$/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-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 CLEVECORD use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with CLEVECORD. 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 CLEVECORD 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 CLEVECORD and any potential adverse effects on the breastfed infant from CLEVECORD 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 and over to determine whether they respond differently than younger subjects. In general, administration of CLEVECORD to patients over age 65 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

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

10 OVERDOSAGE

10.1 Human Overdose Experience

There has been no experience with overdose of HPC, Cord Blood in human clinical trials. Single doses of CLEVECORD up to 45 x 10^7 TNC/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 overdose has not been established.

11 DESCRIPTION

CLEVECORD 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 CLEVECORD 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 CLEVECORD 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.

CLEVECORD 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, residual hydroxyethyl starch 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 CLEVECORD as defined by hematopoietic reconstitution, was demonstrated in one single-arm prospective study and in retrospective reviews of data from an observational database for CLEVECORD and in data in the dockets and public information. Of the 1299 patients in the docket 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 $\geq 2.5 \times 10^7$/kg

Data Source	COBLT Study*	Docket* and Public Data*	CLEVECORD**
Design	Single-arm prospective	Retrospective	Retrospective
Number of patients	324	1299	91***
Median age (range)	4.6 (0.07 – 52.2) yrs	7.0 (<1 – 65.7) yrs	38 (<1 – 68) yrs
Gender	59 % male 41 % female	57 % male 43 % female	55 % male 45 % female
Median TNC Dose (range) ($\times 10^7$kg)	6.7 (2.6 – 38.8)	6.4 (2.5 – 73.8)	4.6 (2.9 – 45.0)
Neutrophil Recovery at Day 42 (95% CI)	76% (71% –	77% (75% –	96% (92% - 100%)
Platelet Recovery at Day 100 (20,000/uL) (95% CI)	57% (51% –	-	92% (85% - 99%)
Platelet Recovery at Day 100 (50,000/uL) (95% CI)	46% (39% –	45% (42% –	83% (73% - 93%)

Erythrocyte Recovery at Day 100 (95% CI)	65% (58% –	-	-
Median time to Neutrophil Recovery	27 days	25 days	18 days
Median time to Platelet Recovery (20,000/uL)	90 days	-	41 days
Median time to Platelet Recovery (50,000/uL)	113 days	122 days	43 days
Median time to Erythrocyte Recovery	64 days	-	-

* HPC, Cord Blood (from multiple cord blood banks)
**Data from patients who received a suitable allograft (i.e., TNC dose $\geq 2.5 \times 10^7$/kg and HLA match > 3/6) with at least a single unit of CLEVECORD.
***All 91 patients had evaluable data for age, sex, and cell dose. Since not all of the 91 patients had evaluable data for all of the listed outcomes parameters, the numbers of patients treated (N) differ for the various listed outcomes parameters. Numbers of patients treated (N) for neutrophil recovery, platelet recovery $\geq$ 20k, platelet recovery $\geq$ 50k are: 76 (excludes patients who died prior to D42 and patients with missing data), 63 (excludes patients who died prior to D100 and patients with missing data), and 53 (excludes patients who died prior to D100 and patients with missing data), respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

CLEVECORD 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 W4215). The exact pre-cryopreservation nucleated cell content is provided in the accompanying records.

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

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients receiving CLEVECORD:

- 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 EQUIPMENT, REAGENTS, AND SUPPLIES

Equipment:

- Biological safety cabinet
- Water bath, 37°C ± 1°C
- Tube heat sealer compatible with polyvinyl chloride (PVC) plastic
- Scale
- Automated cell counter and/or microscope and cell count chamber for cell count and viability determination (optional)
- Thermogenesis canister opener
- Vapor phase liquid nitrogen (LN_2) freezer at -150°C or colder or a fully charged dry shipper. (The dry shipper equipment used for shipment of CLEVECORD can be used for temporary storage of the frozen product at the Transplant Center, if a LN_2 freezer or sufficient freezer space is not available.)
- Plasma extractor
- Centrifuge

Reagents:

- 5% Albumin (Human), USP
- Dextran 40 in Sodium Chloride Injection, USP

Supplies:

- Protective cryogloves
- Transplant processing two-bag set (for example, Pall Medical 791-03)
- Sterile plastic zip-lock bags
- Sterile disposable syringes: (5) 60 mL
- 18G injection needles
- 16G x 1½ injection needles
- Hemostats (optional)
- Alcohol prep pads
- Iodine swab sticks
- Sterile overwrap bag, if available

Forms:

- *Dry Shipper and HPC, Cord Blood Receipt* Form
- *Instructions for Receipt of Dry Shipper and HPC, Cord Blood at Transplant Center*

II RECEIPT INSTRUCTIONS

CLEVECORD is shipped frozen inside a steel canister placed inside a liquid nitrogen (LN_2) charged tank specifically designed to keep the temperature at or below -150°C (dry shipper). Dry shippers consist of a protective shipping container with a large rounded lid, carrying a LN_2 tank with a flat lid (see Figure 1). CLEVECORD must be stored at or below -150°C either in the LN_2 tank inside the dry shipper for short-term storage (up to 48 hours), or inside a LN_2-cooled storage device at the Transplant Center for storage greater than 48 hours. Recharge the tank with fresh LN_2 if CLEVECORD is to remain stored in the dry shipper for more than 48 hours.

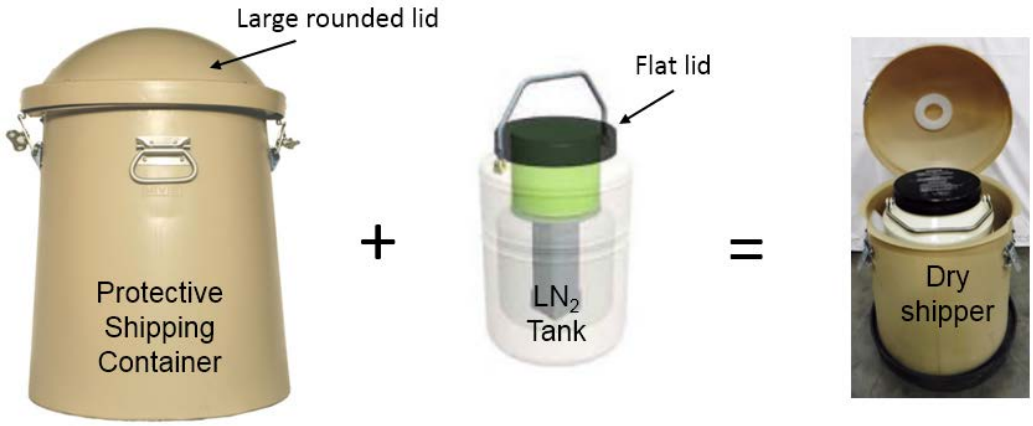

Figure 1: Dry shipper components and configuration

Use the following instructions to complete the *"Dry Shipper and HPC, Cord Blood Receipt Form"* confirming receipt of the CLEVECORD unit and verifying the identity of the unit for the intended recipient. Two trained transplant center staff members are required to receive and verify the CLEVECORD unit.

a. Inspect the dry shipper on receipt for tampering or damage.
b. Cut and remove the blue NMDP zip tie, any additional zip ties, and cellophane shipping wrap. Open the large rounded lid of the protective shipping container.
c. Inspect the temperature data logger which is located on top of the flat lid of the LN_2 tank inside of the dry shipper. Observe the temperature indicated on the data logger, and in Section 2 of the *Dry Shipper and HPC, Cord Blood Receipt Form* record if the indicated temperature is at or below -150°C.

   NOTE: After return of the dry shipper, the Cleveland Cord Blood Center will download the temperature recordings from the data logger. Upon request by the transplant center, a printout of the temperature readings will be provided by fax or email to validate that the CLEVECORD unit was maintained at or below -150°C at all times during shipment.

d. Remove the paperwork packet attached to the inside of the large rounded lid. Obtain the padlock combination enclosed in the packet. Use the padlock combination to remove the padlock from the flat lid on the LN_2 tank inside of the dry shipper.
e. Carefully remove the lid from the LN_2 tank by slight rotation and, using cryogenic gloves, quickly remove CLEVECORD enclosed in the metal canister(s). Immediately place the metal canister in a reservoir with LN_2 or in the vapor phase of a LN_2 freezer at a temperature at or below -150^0C (if available).
f. Place all packing materials back inside the LN_2 tank and replace the lid ensuring that the temperature probe extends to the bottom of the LN_2 tank and that the temperature probe wire is not kinked.
g. Carefully open the metal canister with the canister opening tool (included). Handle with caution to avoid damage to CLEVECORD cryobag.
h. Inspect the integrity of the cryobag.

   NOTE: If there is damage to the cryobag, return the cryobag to storage at or below -150°C (contain the cryobag in an overwrap if necessary). Consult with the transplant physician and contact Cleveland Cord Blood Center (CCBC).

i. Record the donor identification number (DIN) from the cryobag label on the *Dry Shipper and HPC, Cord Blood Receipt* Form. The DIN on CLEVECORD should include the CCBC Facility ID number (W4215). Large CLEVECORD products may be split into two cryobags, and the rotated flag characters after the DIN indicate the individual products, identified by flag codes 01 and 02.

j. Check that the CLEVECORD DIN agrees exactly with the DIN previously selected for the intended recipient. Verify the match and print and sign in Section 2, #11 on the *Dry Shipper and HPC, Cord Blood Receipt* Form.

k. Store CLEVECORD in a LN_2 freezer until ready to thaw for use.

l. Complete section 2 of the *Dry Shipper and HPC, Cord Blood Receipt* Form and fax to Cleveland Cord Blood Center at (216) 896-0320.

m. Re-attach the provided padlock to the flat lid of the LN_2 tank inside of the dry shipper and scramble the code for secured locking.

n. Secure the large rounded lid of the protective shipping container and follow instructions in Section VI. for return of the dry shipper.

NOTE: If there is any error or ambiguity with regard to the documentation or condition of the product, close the LN_2 tank to keep the product at or below -150°C. Immediately advise the staff of the Cleveland Cord Blood Center and the transplant physician. Do not proceed until the problem is resolved.

If documentation and product are acceptable, but your facility either has no LN_2 freezer, or insufficient LN_2 storage space for the frozen CLEVECORD product, the CCBC dry shipper can be used for temporary storage. Inform CCBC that return of the dry shipper will be delayed for purpose of temporary product storage on site.

If storage for more than 48 hours is required, add fresh LN_2 to the tank inside the dry shipper to keep the product frozen until a completely satisfactory resolution for long-term storage and / or use of the frozen product has been reached. Confirm the temperature probe and data logger are properly installed as per step II.f, to ensure continued temperature monitoring.

III PREPARATION

a. Coordination with the clinical team
   i. Confirm the transplant infusion time in advance, and adjust the start time for 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 procedure for DMSO removal and volume reduction (Section VI.3) should be followed.

b. Prepare the water bath and verify that the temperature is 37°C ± 1°C.

c. Record the manufacturer information, lot number and expiration date (if applicable) of all reagents and disposables. Use only sterile materials when processing the CLEVECORD product.

d. Preparation of Dextran 40/Albumin solution.

NOTE: Use aseptic technique in a Biological Safety Cabinet for all processing steps, including all open-container processing and all spiking of container ports.

   i. Combine 100 mL Dextran 40 solution and 100 mL 5% albumin solution in a

sterile 300 mL transfer bag. Clamp the tubing with a hemostat. Prepare fresh solution on the day of transplant and store at 15-25°C.

ii. Fit one (1) 60 mL syringe with an 18 gauge needle and draw 25 mL Dextran-40/Albumin solution from the 300 mL transfer bag.

iii. Fit two (2) 60 mL syringes with 18 gauge needles and draw 60 mL Dextran-40/Albumin solution from the 300 mL transfer bag into each syringe.

e. Prepare a portable container with LN_2 for storage of the frozen CLEVECORD product

f. With product and recipient files at hand, locate and remove the frozen product from storage in the LN_2 freezer, or dry shipper, and verify product identity, labeling, accuracy of information, and container integrity. Two trained members of laboratory staff are required for this verification process.

g. Remove any segment attached to the unit, place into a 2 mL cryovial and store in either vapor or liquid phase of nitrogen (at or below -150°C).

h. Immediately transfer the product from LN_2 storage into the portable LN_2 container. Rest in vapor phase for 5-10 minutes prior to further manipulation.

IV PROCEDURE

Two different procedures for preparation of CLEVECORD for infusion are provided. The first procedure, referred to as the "Dilution" procedure is for dilution of thawed product, yielding ~170 mL product volume for infusion (Section IV.2 below). The second procedure, referred to as the "Dilution and Volume Reduction" procedure, involves centrifugation of thawed and diluted product, followed by supernatant removal, yielding a reduced (25-35 mL) product volume, amenable to infusion in pediatric patients (Section IV.3 below).

1. Thaw

a. Use cryoprotective gloves. Apply personal protective gear.

b. Open canister with the canister opening tool. Handle carefully to avoid damage to the cryobag containing the frozen CLEVECORD unit. Carefully examine the cryobag for breaks or cracks.

c. Remove the CLEVECORD cryobag from the canister.

d. Wipe the external surface of the cryobag with isopropyl alcohol.

e. Place the CLEVECORD cryobag into a clean plastic zip-lock bag. Let the air out of the zip-lock bag, and close it tightly. Use a sterile plastic zip-lock bag if available.

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

f. Place the plastic zip-lock bag containing the frozen CLEVECORD cryobag into the water bath pre-warmed at 37°C ± 1°C.

g. Document the start time of the thawing procedure.

h. Gently and carefully agitate the cryobag in the water bath to accelerate thawing and resuspension of the cells. Use your fingers to massage the bag to ensure uniform distribution of heat.

i. Watch closely for any cracks or breaks, as shown by red cells leaking from the cryobag into the plastic zip-lock bag.

j. If any leakage is seen, keep the leakage site upright to prevent further leaking while continuing to gently agitate the cryobag until the product is slushy. If feasible, point clamp the site of leakage with a hemostat. (See section VII EMERGENCY RECOVERY PROCEDURE IN THE EVENT OF A CONTAINER FAILURE for procedures for emergency recovery of the thawed cord blood cells).
k. If no leakage is seen, remove the plastic zip-lock bag from water bath when the product is completely slushy (i.e., when all visible ice-crystals have disappeared).
l. Document the stop time of the thawing procedure.

NOTE: The recommended expiration time of thawed CLEVECORD is 4 hours from the end time of thaw in step IV.1.1, if stored at 15-25°C.

m. Gently dry the outside of the bag, disinfect it with alcohol, and place it inside a Biological Safety Cabinet.
n. Proceed to either Section IV.2 for the Dilution procedure or Section IV.3 for the Dilution and Volume Reduction procedure.

2. Dilution (~170 mL volume for infusion)

a. Perform all steps in a Biological Safety Cabinet using aseptic technique
b. Obtain a Transplant Processing Two-Bag Set (See Figure 2).
c. Heat seal the tubing between Transplant and Transfer bags (between port on Infusion bag and SC-1). Discard the Transfer bag and connecting tubing.
d. Label the transplant bag with the CLEVECORD DIN and the name of the recipient, or according to institutional standard practice.
e. Confirm that all clamps are closed.
f. Remove the thawed CLEVECORD cryobag from the zip-lock bag. Using an iodine swab stick, disinfect the covers of both ports on the cryobag.
g. Disinfect scissors with alcohol and cut off the hermetically sealed covers to the spike ports on the cryobag.
h. Disinfect the cut surfaces of the two spike ports using an iodine swab stick and insert the two spikes of the transplant set.
i. Attach the 60 mL syringe with 25 mL Dextran-40/Albumin solution to female Luer lock. Open PC-1, PC-2 and PC-3 and then slowly add 25 mL of Dextran-40/Albumin solution to the thawed CLEVECORD product. Mix by gentle massage.
j. Close PC-3. Allow 5 minutes at 15-25°C for equilibration with the CLEVECORD cryobag and Transplant set placed flat on a clean surface.
k. Open PC-4. Transfer the diluted CLEVECORD from the cryobag to the Transplant bag. Close PC-1 and PC-2.
l. Attach the first syringe containing 60 mL Dextran-40/Albumin solution to the Luer lock. Open PC-1, PC-2, and PC-3. Transfer the 60 mL solution to the freezing bag. Close PC-3 and open PC-4. Transfer 60 mL Dextran-40/Albumin solution to the Transplant bag. Gently massage the Transplant bag in order to mix the CLEVECORD cell suspension.
m. Repeat step (l) using the second syringe containing 60 mL Dextran-40/Albumin solution. The final volume should approximate 170 mL (25 mL CLEVECORD unit and (25 + 60 + 60 =) 145 mL Dextran-40/Albumin solution).
n. Seal tubing between PC-4 and IP-1 and disconnect. Discard the spikes, Luer lock and connecting tubing.
o. Aseptically attach an 18 gauge needle to a 60 mL syringe, insert into port IP-1 and remove a 5 mL aliquot for quality control testing.

p. Place the Transplant bag inside a sterile overwrap bag and place flat inside a bin at ambient temperature (15-25°C).
q. Transport the CLEVECORD product to the clinical transplant site per the facility's SOP.

NOTE: The recommended expiration time of thawed CLEVECORD is 4 hours from the end time of thaw, if stored at 15-25°C.

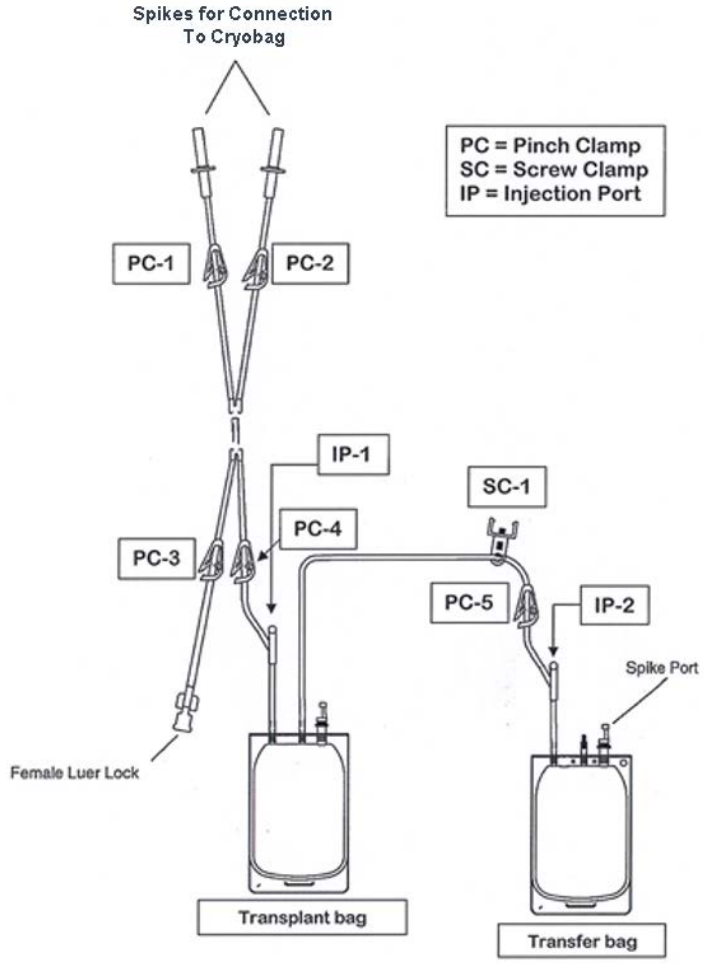

Figure 2: Transplant Processing Two-Bag Set

3. Dilution and Volume Reduction (~25-35 mL volume for infusion)

a. Perform all steps in a Biological Safety Cabinet using aseptic technique.
b. Obtain a Transplant Processing Two-Bag Set (See Figure 2).
c. Label both bags of the Two-Bag Set with the assigned CLEVECORD DIN.
d. Confirm that all clamps are closed.
e. Using an iodine swab stick, disinfect the covers of both ports on the thawed cryobag.
f. Disinfect scissors with alcohol and cut off the hermetically sealed covers to the spike ports on the thawed cryobag.
g. Disinfect the cut surfaces of the two spike ports using an iodine swab stick and insert the two spikes of the Two-Bag Set.
h. Attach Syringe 1 with 25 mL Dextran-40/Albumin solution to female Luer lock. Open PC-1, PC-2 and PC-3 and then slowly add 25 mL of Dextran-40/Albumin solution to the thawed CLEVECORD cryobag and mix.
i. Slowly and gently push and pull the syringe plunger to mix the CLEVECORD and

Dextran-40/Albumin solutions; repeat three to four times.

j. Transfer the entire volume back into the cryobag. Close PC-3. Allow 5 minutes at 15-25°C for equilibration, with the CLEVECORD cryobag and Transplant set placed flat on a clean surface.

k. Open PC-4. Transfer the diluted CLEVECORD unit from the cryobag into the Transplant bag. Close PC-1 and PC-2.

l. Attach Syringe 2 containing 60 mL with Dextran-40/Albumin solution to the Luer lock. Open PC-3. Transfer the 60 mL solution via the cryobag into the diluted CLEVECORD in the Transplant bag. Gently massage the Transplant bag in order to mix the CLEVECORD cell suspension.

m. Repeat step (l.) using Syringe 3 containing 60 mL Dextran-40/Albumin solution. The final volume should now approximate 170 mL (25 mL CLEVECORD unit and (25 + 60 + 60 =) 145 mL Dextran-40/Albumin solution)

n. Close PC-3 and open PC-1 and PC-2. Pass the 170 mL diluted CLEVECORD suspension back and forth between the transplant bag and the cryobag two or three times to pass as many cells from the cryobag into the Transplant bag. Close PC-4.

o. Seal tubing between PC-4 and IP-1 and disconnect. Discard the spikes, Luer lock and connecting tubing.

p. Confirm PC-5 and SC-1 are closed. Place the Transplant Processing Two-Bag set in a sterile overwrap bag and in a centrifuge bucket.

q. Fully support the Transplant Processing Two-Bag set with thawed product with inserts to prevent formation of creases during centrifugation.

r. Balance carriers and centrifuge for 20 min at 400 x g at 10°C without brake.

s. After centrifugation, carefully remove the centrifuged Transplant Processing Two-Bag set from the centrifuge bucket. Be careful not to disturb the cells in the bottom of the bag. Record the date/time removed from the centrifuge.

t. Hang the Transplant Bag in a plasma extractor. Slowly close the door to the plasma extractor.

u. Open PC-5 and use SC-1 to adjust the flow of supernatant. Very slowly transfer most of the supernatant into the Transfer bag.

v. Empty the tubing between the bags by transferring air from the Transfer bag to Transplant Bag.

w. Close PC-5.

x. Aseptically attach an 18 gauge needle to a 60 mL syringe, insert into port IP-1 and remove a 5 mL aliquot for quality control testing.

y. Place the Transplant bag inside a sterile overwrap bag and place flat inside a bin at ambient temperature (15-25°C).

z. Transport the CLEVECORD product to the clinical transplant site per the facility's SOP.

NOTE: The recommended expiration time of thawed CLEVECORD is 4 hours from the end time of thaw, if stored at 15-25°C.

V QUALITY CONTROL

Perform quality control assays per transplant center policies and procedures using the aliquot of thawed product obtained in step IV.2.o. or IV.3.x. Recommended assays include:

- Nucleated Cell count
- Viability test
- Viable $CD34^+$ cell count
- Colony Forming Unit

- Microbial cultures (aerobic, anaerobic and fungal)

VI ADMINISTRATIVE REQUIREMENTS

1. Prepare a written summary of the procedure, including:
   a. CLEVECORD ID number
   b. Date of receipt of CLEVECORD unit
   c. Liquid nitrogen storage temperature
   d. Date of thaw, including whether and at what stage leaks or cracks occurred
   e. Date and time CLEVECORD unit 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 test 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 the Cleveland Cord Blood Center at (216) 896-0320
4. Return the dry shipper to the Cleveland Cord Blood Center. The return address is:

   Cleveland Cord Blood Center
   25001 Emery Road, Suite 150
   Cleveland, OH 44128
   Phone: (216) 896-0360
   Fax: (216) 896-0320

VII EMERGENCY RECOVERY PROCEDURE IN THE EVENT OF A CONTAINER FAILURE

1. General Precautions

Use standard procedures and trained personnel to perform post-thaw sampling and/or bag rescue. As cryobags can be very fragile, handle the frozen cord blood bag with extreme care at every step including opening the metal containers, inspecting, thawing and/or washing. Perform all steps on lab benches, under biological safety cabinet, or another surface to prevent inadvertent drop of the frozen unit. To facilitate thawing, gradually remove the CLEVECORD unit from the liquid phase of the LN_2 storage area, suspending in the vapor phase for at least five minutes prior to bringing the container to room temperature. Wipe the external surface of the cryobag with isopropyl alcohol before it is placed inside a sterile zip-lock bag. This will allow the cell laboratory to potentially recover the product in the case of an unexpected leak or container failure during thawing, dilution or volume reduction.

2. Emergency Recovery

   a. If the CLEVECORD cryobag is observed to be cracked when removed from the LN_2 storage container, or if cracks or leaks occur during thawing, immediately notify Cleveland Cord Blood Center by phone at (216) 378-3032 or (216) 896-0493. Notify the transplant physician and transplant team and the laboratory director as soon as possible.
   b. The transplant physician or team will determine whether to use or discard the CLEVECORD product and whether any additional HPC, Cord Blood units should be

requested.

c. If the transplant physician or team decides that the product in the leaking cryobag could be used, the CLEVECORD unit may be recovered as follows:

    i. Obtain sterile sampling cups, sterile pipettes and syringes.
    ii. Open a sterile sampling cup and set cup in working space to receive contents of zip-lock bag.
    iii. If any contents remain within the broken CLEVECORD cryobag, remove the contents from the cryobag using sterile syringes.
    iv. Wash all contents out of the CLEVECORD cryobag and transfer contents in a new transfer bag (Rescue Bag).
    v. Using a sterile syringe, transfer 20 mL from the Dextran-40/Albumin solution in the 300 mL transfer bag into a sterile sample cup.
    vi. Using a sterile pipette, obtain 3 mL of Dextran-40/Albumin solution from the sample cup and inject into the zip-lock bag containing the remaining CLEVECORD cryobag contents that leaked when thawing.
    vii. Using a different sterile pipette, remove the CLEVECORD and Dextran-40/Albumin solution from the zip-lock bag and place in a sterile sample cup.
    viii. Repeat steps vi and vii until all remaining CLEVECORD is transferred to the sterile sample cup.
    ix. Using a sterile 20-mL syringe, draw the contents from the sterile sampling cup into the syringe. Inject the solution into the Rescue Bag.
    x. Repeat until all of the contents from the sample cup are transferred into the Rescue Bag.
    xi. Mix Rescue Bag well by inverting 180° for 10 to 15 times.
    xii. Continue with Step k in Section IV.1.

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