

Application Type	Original Application
STN	125594/0
CBER Received Date	June 10, 2015
PDUFA Goal Date	September 9, 2016 (original date of June 9, 2016 extended 3 months by Major Amendment)
Division / Office	GMB/DCEPT/OCTGT (Clinical) TEB/DB/OBE (Statistical)
Priority Review	No
Reviewer Name(s)	Clinical: Steve Winitsky, M.D. Statistical: Stan Lin, Ph.D.
Review Completion Date / Stamped Date	August 15, 2016/August 15, 2016
Supervisory Concurrence	Ilan Irony, MD (Branch Chief, OCTGT) Wilson Bryan, MD (Division Director, OCTGT) Shiowjen Lee, PhD (Team Leader, OBE) Boguang Zhen, PhD (Branch Chief, OBE)
Applicant	Cleveland Cord Blood Center (CCBC)
Established Name	HPC, Cord Blood
(Proposed) Trade Name	CLEVECORD
Pharmacologic Class	Allogeneic Cord Blood
Formulation(s), including Adjuvants, etc.	Each Unit of CLEVECORD contains: <ul style="list-style-type: none"> Active ingredient: a minimum of 5.0×10^8 total nucleated cells (TNC) with a minimum of 1.25×10^6 viable CD34 cells Inactive ingredients: dimethyl sulfoxide (DMSO), citrate phosphate dextrose (CPD), hydroxyethyl starch, and Dextran 40
Dosage Form(s) and Route(s) of Administration	A cell suspension for intravenous use only
Dosing Regimen	Recommended minimum dose is 2.5×10^7 TNC/kg at cryopreservation
Indication(s) and Intended Population(s)	<p>CLEVECORD, 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.</p> <p>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.</p>
Orphan Designated (Yes/No)	No

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GLOSSARY

Table 1. Abbreviations and Glossary

AE	Adverse Event
ANC	Absolute Neutrophil Count
BLA	Biologics license application
CBER	Center for Biologics Evaluation and Research
CCBC	Cleveland Cord Blood Center
CDER	Center for Drug Evaluation and Research
CD34	A cluster of differentiation molecule present on certain cells within the human body
CI	Confidence interval (95%, unless otherwise specified)
CIBMTR	Center for International Blood and Marrow Transplant Research
CMC	Chemistry, manufacturing, and controls
COBLT	The Cord Blood Transplantation Study
Docket Data	Raw data submitted from multiple cord blood banks and cord blood organizations, such as NMDP, NYBC, and Duke University, to Dockets FDA-1997-N-0010 (Legacy Docket number 97N-0497), FDA-2006-D-0157 (Legacy Docket number 06D-0514), and FDA-2009-D-0490
DMSO	Dimethyl sulfoxide
GCP	Good Clinical Practices
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HPC-A	Hematopoietic progenitor cells, Apheresis
HPC-M	Hematopoietic progenitor cells, Marrow
HSCT	Hematopoietic stem cell transplantation
IND	Investigational New Drug application
NHLBI	National Heart, Lung and Blood Institute
NMDP	National Marrow Donor Program
NYBC	New York Blood Center
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee (CDER & CBER)
PI	Prescribing Information; Package Insert
PLT	Platelet
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategy
RMS/BLA	regulatory management system for the biologics license application
SAE	Serious adverse event
SCTOD	Stem Cell Therapeutic Outcomes Database
SOP	Standard Operating Procedure
Suitable Allograft	TNC dose at $\geq 2.5 \times 10^7/\text{kg}$ and HLA match at $\geq 4/6$
TNC	Total nucleated cells

1. Executive Summary

Cleveland Cord Blood Center (CCBC) applied for biologics licensure of CLEVECORD, HPC (Hematopoietic Progenitor Cell), Cord Blood, a cord blood product manufactured by the applicant. CLEVECORD is comprised of hematopoietic progenitor cells that are collected from the cord blood donor. The proposed indication is for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

The applicant did not conduct any clinical trials to study the efficacy or the safety of CLEVECORD. To support the safety and effectiveness of CLEVECORD, the applicant submitted their own retrospectively collected dataset (CCBC dataset) of 262 patients and referenced data contained in the Dockets (FDA-1997-N0010 and FDA-2006-D-0157), as well as published literature related to HPC, Cord Blood. The effectiveness of HPC, Cord Blood for hematopoietic reconstitution has been established by FDA analyses of the Docket data as well as the COBLT study and other published observational studies. A minimum effective cell dose of $\geq 2.5 \times 10^7$ cells/kg with a degree of human leukocyte antigen (HLA) match at 4/6 loci and above is defined as a suitable allograft for the purposes of this BLA review.

The efficacy of CLEVECORD is assessed in terms of hematopoietic reconstitution in patients who received a suitable cord blood allograft with CLEVECORD. In the 262-patient CCBC dataset, the clinical and statistical reviewers identified 91 patients who received a suitable allograft. Of these 91 patients, 59% (54/91) received one CCBC-manufactured cord blood unit combined with a second non-CCBC-manufactured cord blood unit, 39% (35/91) received only a single CCBC-manufactured cord blood unit, and 2% (2/91) received two CCBC-manufactured cord blood units. Transplantation of CLEVECORD, resulted in hematopoietic reconstitution, as demonstrated by neutrophil and platelet recovery. Neutrophil recovery is defined as the time from transplantation to an absolute neutrophil cell (ANC) count greater than 500 per microliter ($ANC > 500/\mu L$). Platelet recovery is defined as the time from transplantation to a platelet count greater than 20,000 per microliter ($> 20,000/\mu L$). The Docket data demonstrate that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery. Table 2 summarizes the efficacy data. The following CLEVECORD-related hematopoietic reconstitution outcomes were assessed and compared to the HPC, Cord Blood products that contributed to the Docket data and the COBLT study data: cumulative incidence of neutrophil recovery by Day 42, cumulative incidence of platelet recovery by Day 100, median time to platelet recovery, and median time to neutrophil recovery. While the data suggest favorable trends in favor of CLEVECORD, the following are important factors limiting any comparisons of the CCBC dataset to the COBLT and Docket datasets: incompleteness of information contained in the CCBC dataset; the relatively small size of the CCBC dataset; demographic differences between the CCBC and the Docket and COBLT study datasets; insufficient information about the

nature and severity of the diseases that comprised the primary indication for transplantation; and insufficient information about the conditioning regimens.

Despite the suggestion of favorable trends for hematopoietic reconstitution outcomes in the CCBC dataset, due to the deficiencies with the dataset, the reviewers conclude that the CCBC dataset can only serve as supportive data to supplement the primary evidence of effectiveness for HPC, Cord Blood that was demonstrated in the Docket data and the COBLT study. Because of the deficiencies in the CCBC dataset, the efficacy data obtained in patients who received a suitable allograft with CLEVECORD do not support a conclusion of superior effectiveness of CLEVECORD compared with the Docket data and the COBLT study.

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

Data Source	The COBLT Study*	Docket*	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) ($\times 10^7/\text{kg}$)	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% – 81%)	77% (75% – 79%)	96% (92% - 100%)
Platelet Recovery at Day 100 (20,000/uL) (95% CI)	57% (51% – 63%)	-	92% (85% - 99%)
Platelet Recovery at Day 100 (50,000/uL) (95% CI)	46% (39% – 51%)	45% (42% – 48%)	83% (73% - 93%)
Erythrocyte Recovery at Day 100 (95% CI)	65% (58% – 71%)	-	-
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.

***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 $\geq 20\text{k}$, platelet recovery $\geq 50\text{k}$ are: 76 (excludes 5 patients who died prior to D42), 63 (excludes 18 patients who died prior to D100), and 53 (excludes 18 patients who died prior to D100), respectively.

The CLEVECORDER data do not include information regarding immunologic reconstitution. However, based on the analyses of the Docket data and supported by the publicly available data, HPC, Cord Blood has demonstrated the ability of immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (See Section 12. Appendices).

The safety review of this BLA focuses on transplantation-related adverse events, including early death (prior to Day 100), infusion reactions, graft versus host disease (GVHD), and graft failure. Due to the above-mentioned deficiencies with the CCBC HPC, Cord Blood dataset, the assessment of these safety outcomes is based primarily on the Docket data, supplemented by the CCBC dataset, and taking into consideration the publicly available data. The point estimates for early death, primary graft failure, acute GVHD, and infusion reactions were lower among patients in the CCBC dataset who were reported to have received a suitable allograft compared to the Docket or the COBLT datasets (See Table 3).

Table 3. Summary of Safety, Frequencies of Major Adverse Events--A Comparison among CLEVECORDER; Docket; and COBLT Study Data for Patients with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$

Adverse Events	*Docket or COBLT	**CLEVECORDER
Early Mortality (Day 100)	25% (Docket)	18/91 (20%)
Primary Graft Failure	16% (Docket)	***3/76 (4%)
Acute GVHD	69% (Docket)	44/80 (55%)
Infusion Reactions	65% (COBLT)	****18/91 (8%)

*Pooled data from multiple blood banks

**Patients with a suitable allograft (N = 91); since not all 91 patients who received a suitable allograft had evaluable data for each of the listed outcomes parameters, the number of patients with evaluable data for each of the outcomes parameters are indicated by the denominators listed in this Table.

***The number of patients treated (N = 76) excludes 5 patients who died prior to D42.

****Due to insufficient information about the total number of patients with a suitable allograft who have evaluable data for infusion reactions, the number of patients listed reflects those who received a suitable allograft, which may underestimate the incidence of infusion reactions.

During her safety review of the Dockets and Public Information regarding HPC, Cord Blood, Dr. Donna Przepiorka generated and validated a mathematical model from the pooled dataset to identify patients with delayed engraftment (i.e., exceeding the expected upper 95% confidence limit for time to neutrophil recovery) for patients with hematological malignancies and receiving allografts with at least a 4 of 6 HLA antigen match and a TNC dose $\geq 2.5 \times 10^7/\text{kg}$. To further assess safety, this model was applied to the 60 patients who were reported to have received a suitable allograft with CLEVECORDER for treatment of a hematological malignancy. None (0%) of the 60 patients had neutrophil recovery times that exceeded the upper limit of the 95% confidence interval for the expected neutrophil recovery time. The delayed engraftment rate (0%) in patients receiving a suitable allograft with CLEVECORDER is comparable to the 5% of patients in the testing set of the Docket data who had neutrophil recovery times which exceeded the expected upper 95% confidence limit (See Section 12. Appendices: Safety Review of Dockets and Public Information by Donna Przepiorka, M.D., Ph.D.).

Given that the information about the incidence of adverse events after CLEVECORD administration is incomplete, and due to the above-mentioned deficiencies with the dataset, the reviewers conclude that the available safety data for patients who received a suitable allograft with CLEVECORD do not indicate a major variance with the safety profile of HPC, Cord Blood that is demonstrated in the Docket or the publicly available datasets. However, a determination of superiority for these safety outcomes in the CCBC dataset is not supported.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The active ingredient, indication, dosage form, dosing regimen, and route of administration of CLEVECORD, are not new because they are the same as for HEMACORD -- the first FDA-approved HPC Cord Blood product, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

Although the risks of conducting HPC, Cord Blood transplantation in conjunction with a preparative regimen for hematopoietic reconstitution are high, the diseases that affect the hematopoietic system for which cord blood transplantation is indicated are usually serious or life-threatening. Therefore, 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 type of hematopoietic progenitor cells.

There are no obvious safety issues related to CLEVECORD that warrant post-marketing requirements or commitments. However, to monitor the post-marketing safety of the product, the reviewers recommend, and the applicant has agreed to conduct, the following post-marketing surveillance if CLEVECORD is licensed in the United States:

- a. Implement a safety outcomes monitoring and analysis plan. This plan will include: 1) maintenance of an observational database to include, for all CLEVECORD units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences; 2) aggregate analyses of interval and cumulative adverse experience reports; and 3) safety outcomes analyses of interval and cumulative data that address early mortality, graft failure-related mortality, graft failure, time to neutrophil recovery, infusion-related events, and other adverse experiences. Reports will include a description of the population analyzed, results of the analyses, whether outcomes indicators were triggered and, if so, what actions were implemented as a result.
- b. Submit to FDA a 15-day "alert report" for each serious infusion reaction associated with administration of CLEVECORD.

Based on overall risk-benefit consideration of the Docket data referenced in this application, supplemented by the CCBC dataset, and taking into consideration the publicly available data, the FDA clinical and statistical reviewers recommend approval of CLEVECORD 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.

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

Because the risks of CLEVECORD and its preparative regimen can be mitigated and managed through the labeling of the product and pharmacovigilance plan, the reviewers do not recommend a Risk Evaluation and Mitigation Strategy (REMS), Postmarketing Requirement (PMR), or Postmarketing Commitment (PMC) for CLEVECORD.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The demographics of the evaluable population of the CCBC dataset that received a suitable allograft with CLEVECORD are listed in Table 4. For comparison, Table 4 lists the demographics for the Docket dataset, which provided primary evidence of safety and effectiveness of HPC, Cord Blood. A comparison between the subgroup of the CCBC dataset which received a suitable allograft and the Docket dataset demonstrates that the CCBC dataset contains a higher percentage of patients who were reported to be: older than 17 years of age (64% vs. 9%), male (55% vs. 40%) White (84% vs. 44%), and undergoing transplantation for a primary indication of hematologic malignancy (82% vs. 66%). Due to deficiencies with the CCBC dataset, which was small in size and had a large amount of missing data, no conclusions can be made about the correlation between demographics and clinical outcomes.

Table 4. Demographic Characteristics of Docket and CLEVECORD Patients

Patient Characteristics	Docket Patients (N=1299)	CLEVECORD Patients with a Suitable Allograft* (N=91)
Median Age (range)	7 (<1-66) yrs	38 (<1-68) yrs
Age Category		
<2yrs	393 (30%)	10 (11%)
2-16/17yrs	786 (61%)	23 (25%)
>16/17yrs	120 (9%)	58 (64%)
Unknown		
Sex		
Male	524 (40%)	50 (55%)
Female	389 (30%)	41 (45%)
Unknown	386 (30%)	
Ethnicity/Race		
White	573 (44%)	76 (84%)
African-American	90 (7%)	7 (8%)
Hispanic	129 (10%)	0 (0%)
Asian	28 (2%)	5 (5%)
Other	14 (1%)	2 (2%)
Unknown	465 (36%)	1 (1%)
Diagnosis		
Hematologic Malignancies	862 (66%)	75 (82%)
Inborn Errors of Metabolism	0 (0%)	0 (0%)
Immunodeficiency	93 (7%)	5 (6%)
Metabolic Disorders	134 (10%)	7 (8%)
Bone Marrow Failure	95 (7%)	1 (1%)
Hemoglobinopathy	8 (0.6%)	0 (0%)
Others	107 (8%)	3 (3%)

*Patients who received a unit/units having a TNC dose $\geq 2.5 \times 10^7$ cells/kg and HLA match 4/6 or greater

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

The proposed indication for this class of products is for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The risk-benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells. The categories of disorders for which hematopoietic and immunologic reconstitution is required include malignancies, metabolic disorders, marrow failure, hemoglobinopathy, immunodeficiency, and certain autoimmune disorders. These diseases are usually

serious, life-threatening, and with unmet medical needs. Please see the FDA reviews of the Docket information for malignant and non-malignant indications regarding the effect of hematopoietic and immunologic reconstitution on specific disease outcomes. (See Section 12. Appendices).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The FDA-approved therapies for hematological malignancies include various chemotherapy, immunotherapy, and targeted biologic agents. For some non-malignant indications, there are FDA-approved therapies including drugs, biologics, immunotherapy, and other standard supportive therapy. However, there are no FDA-approved, pharmacologically unrelated therapies for hematopoietic and immunological reconstitution as proposed in this BLA.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are several sources of stem cells for allogeneic hematopoietic stem cell transplantation (HSCT), including hematopoietic progenitor cells derived from bone marrow (HPC-M) and hematopoietic progenitor cells derived from peripheral blood apheresis (HPC-A). Use of unrelated cord blood has increased over the past 20 years with improved outcomes. Unrelated cord blood transplantation has extended the availability of allogeneic HSCT to patients who would not be eligible for this potentially curative approach because of lack of an HLA-identical bone marrow (HPC-M) or granulocyte colony-stimulating factor mobilized peripheral blood hematopoietic stem cell (PBSC, HPC-A) donor. Studies suggest that the total number of nucleated cells is the most important factor for engraftment, while favorable outcomes can occur in spite of some degree of HLA mismatch.

FDA has approved six HPC, Cord Blood products for the same indication as in this BLA. The six products are HEMACORD from New York Blood Center, Inc., approved in 2011; HPC, Cord Blood from ClinImmune Labs, approved in 2012; DUCORD from the Carolinas Cord Blood Bank (Duke University School of Medicine), approved in 2012; ALLOCORD from SSM Cardinal Glennon Children's Medical Center, approved in 2013; LifeSouth HPC, Cord Blood from LifeSouth Community Blood Centers, Inc., approved in 2013; and HPC, Cord Blood from Bloodworks, approved in 2016.

The CCBC product, HPC, Cord Blood is another preparation of HPC, Cord Blood produced under the same regulations and guidances as the six licensed products above.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

In 1996, two groups (Kurtzberg, Laughlin, et al. and Wagner, Rosenthal, et al.) first reported use of umbilical cord blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. Since then, the clinical use of umbilical cord blood as an alternative source of stem cells has been growing steadily. Over 10,000 unrelated-donor cord blood stem cell transplantations have been performed to date for a variety of diseases and conditions, such as hematological malignancies, immunologic disorders, and inborn errors of metabolism (American Academy of Pediatrics, 2007).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the BLA Submission

Pre-BLA meeting: 9/29/10

Original BLA submission: 6/10/15

BLA submission filed: 8/7/16

Mid-cycle meeting: 1/14/16

Amendments filed:

- 8/5/15
- 2/26/16
- 3/15/16
- 3/21/16
- 3/25/16
- 5/2/16
- 5/4/16
- 5/16/16
- 6/9/16
- 7/26/16

Major Amendment Letter: 5/13/16

Proprietary Name Acceptance Letter: 5/23/16

2.6 Other Relevant Background Information

On January 20, 1998 (63 FR 2985), FDA issued a notice in the Federal Register entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments", in which explained that it may be possible to develop product standards and establishment and processing controls for minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products intended for hematopoietic reconstitution, based on existing clinical trial data, or data developed shortly thereafter, demonstrating the safety and effectiveness of such cells. To provide a scientific basis for the proposed standards, the FDA requested the submission of comments proposing establishment controls, process controls, and product standards designed to ensure the safety and effectiveness of minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products derived from peripheral and cord blood for hematopoietic reconstitution. Submitted comments were to include supporting clinical and nonclinical laboratory data and other relevant information. A period of two years was provided, until January 20, 2000, for interested persons to submit supporting clinical data. At the request of industry, the comment period was reopened for 90 days until July 17, 2000 (65 FR 20825, April 18, 2000).

On February 27, 2003, the Biological Response Modifiers Advisory Committee (BRMAC) met to discuss issues related to the use of unrelated allogeneic hematopoietic

stem/progenitor cells derived from placental/umbilical cord blood for hematopoietic reconstitution, including the analysis of clinical outcome data submitted to FDA as well as information provided by guest experts regarding the safety and effectiveness of cord blood for hematopoietic reconstitution. On the basis of the submitted information, discussion of the BRMAC, and review of published literature on this subject, FDA determined that the data were sufficient to establish the safety and effectiveness of HPC-Cs for allogeneic transplantation in the treatment of hematologic malignancies.

On January 17, 2007 (72 FR 1999), the draft guidance for licensure of minimally manipulated cord blood entitled "Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies" became available. Additional discussion was held with the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) on March 30, 2007. The committee discussed access to HPC, Cord Blood units already in inventory and recommended additional clinical indications. In the process of finalizing the guidance, the FDA considered the recommendations of the CTGTAC, the public comments to the draft guidance, and additional data submissions.

In a Federal Register notice of October 20, 2009 (74 FR 53753), FDA announced the availability of the "Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications". In this notice of availability, the FDA also announced that it would end the period of phased-in implementation of IND and BLA requirements for HPC, Cord Blood. This announcement established a two-year implementation period, which ended October 20, 2011, by which all distribution of HPC, Cord Blood for clinical use in the United States would need to be done under an approved BLA or active IND.

The new, updated final guidance titled, "Guidance for Industry: Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System" was issued in March 2014. Among other changes, the indication contained in this guidance differs from the indications listed in the scope of the 2009 licensure guidance. This difference is a result of FDA's re-examination of the legacy Docket data and FDA's consideration of the proceedings of the September 2011 meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was accepted for filing by the review team because most elements required for review were satisfactory. The BLA was submitted on compact discs (CDs), which were loaded by FDA into the Electronic Document Room (EDR). The applicant did not submit paper copies. The main focus of the clinical and statistical review was the clinical outcomes data and adverse events.

The clinical dataset submission consists of data that contained narrative summaries and tables of safety and efficacy outcomes and Microsoft Excel files of the CLEVECORD data. Due to the voluntary nature of data collection, missing data occur in various

degrees for different variables. The major issues related to the data include the following:

Incompleteness

The dataset includes outcomes information consisting of neutrophil and platelet recovery, transplantation-related complications, and mortality. The dataset lacks information on diagnostic criteria for the diseases that comprised the primary indication for transplantation, as well as information about the conditioning regimens. The dataset does not contain case report forms (CRFs) for any patients, as it is based upon information collected incidentally in the course of the practice of medicine.

Missing Data

Missing data of different degrees have been described under each category of the outcome measures, which introduces interpretability issues for the results of the safety and efficacy analyses that the reviewers conducted using data from the CCBC dataset. For example, certain key efficacy analyses (e.g., recovery of platelets by Day 100) were conducted using only ~ 20% of the total dataset, due in large part to missing data.

Uncertainties

The main focus of the clinical review is the assessment of safety and efficacy outcomes in patients who received a suitable allograft (defined by administration of a minimum dose of cells per kg and the degree of HLA match between donor and recipient). However, there is uncertainty about the dose of HPC, Cord Blood that was administered to individual patients in the CCBC dataset, due to a lack of standardization of data collection and reporting for the voluntarily-collected dataset. There are uncertainties as to the number of patients who had evaluable data for infusion reactions.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Good Clinical Practices (GCPs) generally apply to clinical trials. No clinical trials were conducted by the applicant. Therefore, GCPs are not applicable for this BLA.

3.3 Financial Disclosures

The applicant referenced the Docket and publicly available data to support this BLA, therefore, the application does not rely on clinical trial data. Consequently, there are no financial disclosures submitted with the application.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see Chemistry, Manufacturing, and Controls (CMC) review of this BLA for details.

Donor Information

HPC, Cord Blood donations are screened to exclude potential donors with either a medical history of increased risk of infection or positive screening tests such as HIV, and hepatitis. Products are also screened for homozygous or double heterozygous hemoglobinopathy. Screens for genetic diseases that could be transmitted through

transplantation are conducted through maternal and family medical history questionnaires. CCBC does not exclude women taking antibiotics during labor and delivery, therefore, the labeling needs to warn transplant physicians to monitor for allergic reactions in recipients with history of allergy to certain antibiotics.

4.2 Nonclinical Pharmacology/Toxicology

The device components used in manufacturing and storage are cleared by FDA for cord blood processing, and the anticoagulant and diluents are approved by FDA. No additional studies of biocompatibility were required.

Dimethyl sulfoxide (DMSO) represents a potentially toxic component of CLEVECORD. Published studies report teratogenic responses caused by intraperitoneal administration of DMSO to rodents. Intravenous administration of DMSO to rodents caused hemolysis.

Please see the pharmacology/toxicology review of this BLA for details.

4.3 Clinical Pharmacology

4.3.1 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. However, the precise mechanism of action is unknown.

In patients with enzymatic abnormalities due to certain severe types of inborn disorders, mature leukocytes resulting from HPC, Cord Blood transplantation may synthesize enzymes that can improve cellular functions of some native tissues. However, the precise mechanism of action is unknown.

4.4 Statistical

The analyses of the CLEVECORD data are mainly based on a subset of patients who received a suitable allograft with at least one unit of CLEVECORD. Due to the voluntary nature of data collection, missing data occur in various degrees for different variables.

4.5 Pharmacovigilance

The applicant submitted a standard pharmacovigilance plan, and the reviewers determined that this is appropriate and sufficient for continued monitoring of the safety profile of CLEVECORD. In addition, the reviewers did not identify any safety concerns that are unknown for this class of product. Therefore, the BLA review does not include a Pharmacovigilance Plan Review from the Office of Biostatistics and Epidemiology.

However, a post-marketing safety outcomes monitoring and analysis plan, and expedited reporting of serious infusion reactions, will be useful to monitor the post-marketing safety of the product. The applicant has agreed to a post-marketing safety outcomes monitoring and analysis plan, and will submit post-marketing expedited reporting of serious infusion reactions, as recommended by FDA.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

5.1.1 Scope of Efficacy Review

The efficacy review of CLEVECORDER focuses on its ability to achieve hematopoietic reconstitution, based primarily on the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data (including the COBLT Study). Hematopoietic reconstitution is demonstrated by neutrophil and platelet recovery after transplantation. The ability of CLEVECORDER to reconstitute the immune system and erythrocytes can be reliably extrapolated from FDA reviews of the Docket and public data (See Section 12. Appendices).

5.1.2 Scope of Safety Review

The safety review focuses mostly on transplantation-related adverse events, including infusion reactions, death within the first 100 days after transplantation (100-day mortality), and graft-versus-host disease (GVHD). The safety review is based primarily on the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data. The applicant did not report any cases of engraftment syndrome, malignancies of donor origin, or transmission of serious infection or rare genetic diseases.

5.1.3 Controls

The CLEVECORDER data are collected from uncontrolled clinical experience. The FDA reviews of the Docket and public data, which are the primary data to support the safety and efficacy of CLEVECORDER, serve as references for both efficacy (hematopoietic reconstitution) (See Section 12. Appendices) and safety (transplantation-related adverse events) (See Section 12. Appendices) of this review.

5.1.4 Statistical Considerations

Conduct of descriptive statistical analyses is the primary statistical methodology used in this review. This clinical BLA review is a collaborative review by the clinical and statistical review teams.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following documents serve as the basis for this review:

- BLA 125594 submission, original submission
- FDA reviews of the Docket information (FDA- 1997- N- 0010, Legacy Docket number 97N- 0497 and FDA- 2006- D- 0157, Legacy Docket number 06D- 0514)
- FDA review of the COBLT Study (data available from the National Heart, Lung, and Blood Institute (NHLBI) via its data-sharing portal at <https://biolincc.nhlbi.nih.gov/home/>)

The following FDA reviews are included as Appendices:

- Safety Review of Docket and Public Information (Appendix 12.1) – This review contains the primary evidence of efficacy and safety to support this BLA.
- Efficacy Review (Non-Oncology) – Docket and Public Information (Appendix 12.2)
- Efficacy Review (Oncology) – Docket and Public Information (Appendix 12.3)

5.3 Table of Studies/Clinical Trials

The applicant did not conduct any clinical trials to support this BLA. The materials used in this review include primarily the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data. The reviewers are unable to verify the information in the dataset because there are no case report forms (CRFs) for any patients.

5.4 Consultations

None.

5.4.1 Advisory Committee Meeting

On September 22, 2011, the Cellular, Tissue, and Gene Therapies Advisory Committee discussed the BLA for HEMACORD, which was the first-in-class BLA. No Advisory Committee Meeting was held for this BLA because the review team did not identify any novel concerns.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed

- a. American Academy of Pediatrics, 2007, Cord blood banking for potential future transplantation. *Pediatrics* 119(1): 165-170.
- b. Kurtzberg, J, M Laughlin, ML Graham, et al., 1996, Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. *N Engl J Med* 335:157-166B
- c. Wagner, JE, J Rosenthal, R Sweetman, et al., 1996, Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. *Blood* 8:795-802.
- d. Yellowlees, P, C Greenfield, N McIntyre, 1980, Dimethyl sulfoxide-induced toxicity. *Lancet* 2:1004-1006.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The applicant did not conduct any clinical trials to study the efficacy or the safety of CLEVECORDER.

7. INTEGRATED OVERVIEW OF EFFICACY

The assessment of efficacy is based primarily on the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data. The data available for review are descriptive. They are voluntarily reported, and records are not always complete. A suitable allograft is defined as $\geq 2.5 \times 10^7$ cells/kg and HLA match 4/6 or more.

Of 262 patients treated with CLEVECORDER, the reviewers identified 91 patients as having received a suitable allograft based on the reported dose of TNC/kg and the degree of HLA match in the original dataset submitted in the BLA application. Of these 91 patients, 59% (54/91) received one CCBC-manufactured cord blood unit combined with a second non-CCBC-manufactured cord blood unit, 39% (35/91) received only a single CCBC-manufactured cord blood unit, and 2% (2/91) received two CCBC-manufactured cord blood units. The remainder (i.e., 171 patients) of the patients in the CCBC dataset either did not meet the criteria for minimum cell dose and/or HLA match, or did not have reported data for one or both of these parameters. Thus, most safety and efficacy analyses in this review are based on data from patients who received a suitable allograft (n = 91).

Transplantation of CLEVECORDER resulted in hematopoietic reconstitution, indicated by neutrophil, platelet and erythrocyte recovery. The Docket data and the publicly available data demonstrate that hematopoietic recovery varies with the degree of HLA match and the dose of TNC/kg.

The CLEVECORDER data do not include information to evaluate immunologic reconstitution following CLEVECORDER transplantation. However, based on the Docket and publicly available data, HPC, Cord Blood has demonstrated a benefit in immunologic reconstitution for patients transplanted for primary immunodeficiency as well as for other malignant and nonmalignant disorders (See Section 12. Appendices).

7.1 Indication

CLEVECORDER, is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

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

7.1.1 Methods of Integration

Published data and the Docket data were reviewed independently and compared to data from CLEVECORDER for this review.

7.1.2 Demographics and Baseline Characteristics

Demographics (for CLEVECORD):

The demographics of patients who received a suitable allograft with CLEVECORD are shown in Table 5. The median age (38 vs. 7 years) for patients in the CCBC dataset was substantially higher than the Docket dataset, which reflects the substantially higher proportion of adult patients in the CCBC dataset (i.e., 64% of CCBC dataset patients who received a suitable allograft were reported as older than 17 years of age vs. 9% in the Docket). A comparison between the subgroup of the CCBC dataset which received a suitable allograft and the Docket dataset demonstrates that the CCBC dataset contained a higher percentage of patients who were reported to be: male (55% vs. 40%) White (84% vs. 44%), and undergoing transplantation for a primary indication of hematologic malignancy (82% vs. 66%).

Table 5. Demographic Characteristics of Docket and CLEVECORD Patients

Patient Characteristics	Docket Patients (N=1299)	CLEVECORD Patients with a Suitable Allograft* (N=91)
Median Age (range)	7 (<1-66) yrs	38 (<1-68) yrs
Age Category		
<2yrs	393 (30%)	10 (11%)
2-16/17yrs	786 (61%)	23 (25%)
>16/17yrs	120 (9%)	58 (64%)
Unknown		
Sex		
Male	524 (40%)	50 (55%)
Female	389 (30%)	41 (45%)
Unknown	386 (30%)	
Ethnicity/Race		
White	573 (44%)	76 (84%)
African-American	90 (7%)	7 (8%)
Hispanic	129 (10%)	0 (0%)
Asian	28 (2%)	5 (5%)
Other	14 (1%)	2 (2%)
Unknown	465 (36%)	1 (1%)
Diagnosis		
Hematologic Malignancies	862 (66%)	75 (82%)
Inborn Errors of Metabolism	0 (0%)	0 (0%)
Immunodeficiency	93 (7%)	5 (6%)
Metabolic Disorders	134 (10%)	7 (8%)
Bone Marrow Failure	95 (7%)	1 (1%)
Hemoglobinopathy	8 (0.6%)	0 (0%)
Others	107 (8%)	3 (3%)

*Patients who received a unit/units having a TNC dose $\geq 2.5 \times 10^7$ cells/kg and HLA match 4/6 or greater

7.1.3 Subject Disposition

Not Applicable.

7.1.4 Analysis of Primary Endpoint(s)

There is no pre-specified primary endpoint because no clinical trial was conducted. However, this review uses neutrophil and platelet recovery as the indicators of hematopoietic reconstitution.

Primary graft failure is defined as failure to achieve an absolute neutrophil count (ANC) $> 500/\mu\text{L}$ by Day 42. Patients who do not have evaluable data for neutrophil recovery by Day 42, due to death prior to Day 42, or for platelet recovery by Day 100, due to death prior to Day 100, are not included in the analyses of neutrophil and platelet recovery. Information about neutrophil recovery prior to the date of death is listed separately for patients who died prior to Day 42, and information about platelet recovery prior to the date of death is listed separately for patients who died prior to Day 100.

Neutrophil and Platelet Recovery

Although the point estimates for cumulative incidence of neutrophil recovery by Day 42, cumulative incidence of platelet recovery by Day 100, median time to platelet recovery, and median time to neutrophil recovery suggest favorable trends for CLEVECORDER, compared to the Docket and COBLT data, due to the deficiencies with the observational dataset, the reviewers conclude that these results are comparable, and not superior, to those reported in the Docket or the COBLT study (Table 2 and Table 6).

Table 6. Hematopoietic Reconstitution after Infusion with CLEVECORDER: Time to, or Cumulative Incidence of, Neutrophil (ANC) and Platelet (PLT) Recovery

Hematopoietic Reconstitution Parameter	Description	Outcomes for Patients with Suitable Allograft
Time to ANC recovery	Median time (days) to ANC>500 k/uL	18 days
Cumulative incidence of ANC recovery	ANC>500k/uL by Day 42	96% (92%-100%) N=76
Time to Plt recovery(>20k)	Median time (days) to Plt>20k/uL	41 days
Cumulative incidence of Plt recovery (>20k)	Plt>20k/uL by Day 100	92% (85%-99%) N=63
Time to Plt recovery (>50k)	Median time (days) to Plt>50k	43 days
Cumulative incidence of Plt recovery (>50k)	Plt>50k/uL by Day 100	83% (73%-93%) N=53

Neutrophil reconstitution after transplantation with CLEVECORDER is further described in Table 7. Of all 186 patients with hematopoietic recovery data who received at least a single unit of CLEVECORDER, 94% achieved neutrophil recovery by Day 42. The median time required for neutrophil recovery by Day 42 was 19 days.

Table 7. Neutrophil Reconstitution of CLEVECORDER: Time to, or Cumulative Incidence of ANC Recovery

All Patients with Hematopoietic Recovery Data		Patients with a Suitable Allograft*
N (Total)	186**	91***
ANC>500 μ L by Day 42 (%)	94%	96%
Median time to ANC>500 μ L by Day 42 (range)	19 days	18 days
Primary graft failure rate	6%	4%

*Patients who received a unit/units having a TNC dose $\geq 2.5 \times 10^7$ /kg and HLA match 4/6 or more

**Excludes 10 patients who died prior to D42.

***Excludes 5 patients who died prior to D42.

Primary Graft Failure

Primary graft failure was reported in 6% within the population of patients in the CLEVECORDER dataset who received at least a single unit of CLEVECORDER and who had evaluable hematopoietic reconstitution data. The rate of primary graft failure among patients receiving a suitable allograft was 4% (3/76) (see Table 7). The analysis of primary graft failure excludes data from five patients who died prior to Day 42. Of these five patients, one had recovery of ANC > 500 on D29 and died on (b) (6). The four patients who did not achieve ANC recovery prior to death by D42 died on Days (b) (6). The incidence of primary graft failure by HLA match and TNC dose in patients who received a suitable allograft with CLEVECORDER is shown in Table 8. If the data from four patients who lived at least 14 days post-transplant but who died prior to Day 42 are included in the analysis of primary graft failure, the reported incidence of primary graft failure (i.e., 6 occurrences of primary graft failure among 80 evaluable patients) would be 8% (95% CI: 2 – 14), which is comparable to the 16% incidence of primary graft failure in the Docket dataset.

Table 8. CLEVECORDER: Primary Graft Failure by HLA Match and TNC Dose

HLA Match	TNC Dose ($\times 10^7$ /kg)		
	2.5 to <5	5 to <10	>10
4/6	0/23 (0%)	1/8 (13%)	0/2 (0%)
5/6	2/24 (8%)	0/14 (0%)	0/5 (0%)
6/6	0/6 (0%)	0/4 (0%)	0/5 (0%)

Platelet Recovery

Platelet recovery in patients who received a suitable allograft with CLEVECORDER is described in Table 9. Of the patients with evaluable data, 92% (58/63) of patients achieved a platelet count higher than 20,000/ μ L by Day 100, and 83% (44/53) achieved a platelet count higher than 50,000/ μ L by Day 100, following transplantation. The median time times to platelet recovery with higher than 20,000/ μ L and higher than 50,000/ μ L are 41 days (range 18 – 119) and 43 days (range 39 – 121), respectively. For the analysis of platelet count recovery > 20,000/ μ L by Day 100, 18 patients did not have evaluable data, due to death prior to Day 100, and were excluded from the analysis. Of

these 18 patients who experienced early death, four recovered a platelet count of at least 20,000/ μ L prior to death (i.e., prior to death, these four patients met the platelet recovery endpoint on Days 29, 37, 40, and 47). For the analysis of platelet count recovery > 50,000/ μ L by Day 100, 18 patients did not have evaluable data, due to death prior to Day 100, and were excluded from the analysis. Of those 18 patients who experienced early death, two recovered a platelet count of at least 50,000/ μ L prior to death (i.e., the two patients met the endpoint on Days 41 and 47).

Table 9. Platelet Recovery in Patients who Received a Suitable Allograft with CLEVECORDER: Time to, or Cumulative Incidence of Platelet Recovery

Hematopoietic Reconstitution Parameter	Patient Outcome
Platelets > 20,000/ μ L by Day 100	92%
Median time to Plt >20,000/ μ L (range)	41 days (19 – 119)
Platelets \geq 50,000/ μ L by Day 100	83%
Median time to Plt > 50,000/ μ L (range)	43 days (39 -121)

Neutrophil Recovery, HLA matching and TNC Dose

Analysis of the Docket data indicated that the TNC dose and degree of HLA match are inversely associated with the time to neutrophil recovery (See Section 12. Appendices).

During her review of the Docket and publicly available information regarding HPC, Cord Blood, Dr. Donna Przepiorka generated and validated a mathematical model from the pooled dataset to identify patients with delayed engraftment (i.e., exceed the expected upper 95% confidence limit for time to neutrophil recovery) for patients with hematological malignancies and receiving allografts with at least 4 of 6 HLA antigen match and a TNC dose of $>2.5 \times 10^7$ cells/kg.

This model was used to compare the efficacy of CLEVECORDER to the efficacy of HPC, Cord Blood in the Docket experience, with regard to assessing for delayed neutrophil recovery. The reviewers identified a total of 60 patients who received a suitable allograft (HLA match $\geq 4/6$, dose $\geq 2.5 \times 10^7$ /kg) with CLEVECORDER for a primary indication of hematologic malignancy and who had evaluable data for neutrophil recovery. None (0%) of the 60 patients had neutrophil recovery times that exceeded the upper limit of the 95% confidence interval for the expected neutrophil recovery time. Due to deficiencies with the CCBC dataset, the reviewers conclude that the delayed engraftment rate (0%) in patients receiving a suitable allograft with CLEVECORDER is comparable to the 5% of patients in the testing set of the Docket data who had neutrophil recovery times which exceeded the expected upper 95% confidence limit, and

that a determination of superiority for the rate of delayed engraftment is not supported. The comparison of hematopoietic recovery in the COBLT, Docket, and CLEVECORDER datasets is shown in Table 10.

Table 10. Comparison of Hematopoietic Recovery for Patients in the COBLT Study, Docket, and CLEVECORDER Datasets

Data Source	COBLT Study*	Docket and Public Data*	CLEVECORDER**
Design	Single-arm, prospective	Retrospective	Retrospective
Number of Patients	324	1299	91***
Median Age (range)	4.6 (0.7-52.2) yrs	7.0 (<1-65.7) yrs	38 (<1-68) yrs
Median TNC Dose (range) (x10 ⁷ /kg)	6.7 (2.6-38.8)	6.4 (2.5-73.8)	4.6 (2.9 – 45.0)
Neutrophil Recovery by Day 42 (ANC>500/μL) (95% CI)	76% (71%-81%)	77% (75%-79%)	96% (92% - 100%)
Platelet Recovery by Day 100 (>20,000/μL)	57% (51%-63%)	--	92% (85% - 99%)
Median Time to Neutrophil Recovery	27 days	25 days	18 days
Median Time to Platelet Recovery	90 days	--	41 days **

*HPC, Cord Blood from multiple cord blood banks

**Data from patients who received a suitable allograft.

***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) with data for neutrophil recovery, platelet recovery ≥ 20k, platelet recovery ≥ 50k are: 76 (excludes 5 patients who died prior to D42), 63 (excludes 18 patients who died prior to D100), and 53 (excludes 18 patients who died prior to D100), respectively.

7.1.5 Other Endpoint(s)

None.

7.1.6 Persistence of Efficacy

The BLA submission does not include data on the duration of the therapeutic effect.

7.1.7 Product-Product Interactions

The BLA submission does not include data regarding the effect of concomitant medications, devices, or therapies on the efficacy of the CLEVECORDER product.

7.1.8 Additional Efficacy Issues/Analyses

None.

7.1.9 Efficacy Conclusions

Based primarily on the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data, CLEVECORDER can function as an alternative source of hematopoietic progenitor cells for hematopoietic and immunologic reconstitution in patients with diseases affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment (See Section 12. Appendices).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The applicant did not conduct any clinical trials to assess the safety of CLEVECORDER. The safety analysis of CLEVECORDER is based primarily on the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant did not conduct any clinical trials to evaluate the safety of CLEVECORDER.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see Table 4 for the demographic characteristics of the dataset for patients who received a suitable allograft with HPC, Cord Blood. Table 11 describes the dose exposure and cord blood unit characteristics for the population of patients who received a suitable allograft with CLEVECORDER.

Table 11. CLEVECORDER Unit Characteristics and Dose Exposure

Unit Characteristics	CLEVECORDER Patients with Suitable Allograft
Number of Patients	N=91
HLA Match Level	
4/6	33 (36%)
5/6	43 (47%)
6/6	15 (17%)
Not Reported	0 (0%)

8.2.3 Categorization of Adverse Events

The safety review focuses on the adverse events that are primarily transplantation-related, including infusion reactions, death within 100 days after transplantation (Day-100 mortality), graft versus host disease (GVHD), engraftment syndrome, malignancies of donor origin, and transmission of serious infection and rare genetic diseases. The

incidences of these adverse events are compared, where possible, with those obtained from the safety review of the Docket information (See Section 12. Appendices).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

This is not applicable, because no clinical trial was conducted.

8.4 Safety Results

8.4.1 Deaths

As shown in Table 12, eighteen out of 91 patients (i.e., 20%) who received a suitable allograft with CLEVECORD experienced early mortality (prior to Day 100). Table 12 compares the demographic characteristics for patients who experienced early death after receiving a suitable allograft with CLEVECORD to the Docket data. The size of the CCBC dataset is insufficient to draw conclusions about the interaction between demographics and early mortality; however, the limited data categorizing early mortality outcomes by demographic characteristics appear to be comparable to the experience in the Docket data (See Section 12. Appendices).

Table 12. Early Mortality with Demographic Characteristics of CLEVECORD

	Docket Dataset Patients with TNC $\geq 2.5 \times 10^7/\text{kg}$	CLEVECORD Patients with a Suitable Allograft	
	Percentage of Patients who Died Prior to Day 100 by Category	Number of Patients by Category (N=91)	Percentage of Patients who Died Prior to Day 100 by Category (N=18)
Demographic			
Age			
<2 yrs	22.3%	10	2 (20%)
2-16/17 yrs	27.4%	23	1 (4%)
≥ 17 yrs	48.6%	58	15 (26%)
Sex			
Male	18.1%	50	7 (14%)
Female	27.0%	41	11 (27%)
Race/Ethnicity			
White	22.3%	76	15 (20%)
African American	28.9%	7	1 (14%)
Hispanics	18.9%	0	0 (0%)
Asian	19.4%	5	1 (20%)
Other	31.3%	2	1 (50%)
Unknown		1	0 (0%)
Diagnosis			
Hematologic malignancies	46.5%	75	16 (21%)
Inborn error of metabolism	32.0%	0	0 (0%)
Primary Immunodeficiency	17.7%	5	1 (20%)
Metabolic disorder		7	0 (0%)
Bone marrow failure	23.4%	1	0 (0%)
Hemoglobinopathy		0	0 (0%)
Others		3	1 (33%)

Table 13 shows the causes of death after transplantation. As shown in Table 13, the most common causes of early death (by Day 100) for patients who received a suitable allograft with CLEVECORD were primary disease, pulmonary toxicity, infection, graft failure, and organ failure. Available data from the Docket dataset showed that the most common causes of death by Day 100 after transplantation for those who received a dose of TNC $\geq 2.5 \times 10^7/\text{kg}$ were infection, organ failure, and primary disease. Graft failure was the cause of early death in 2.5% of patients in the Docket dataset. In the limited CLEVECORD Blood dataset, the incidence of overall death, the incidence of early death, and the primary causes of death appear to be similar to the experience in the Docket data.

Table 13. Causes of Death after Transplantation in the CLEVECORD and Docket Datasets

	CLEVECORD Dataset				Docket Dataset	
	All Patients with graft dose reported who have evaluable data for mortality N=224		Patient with a Suitable Allograft N=91		Patient with a Suitable Allograft N=1289	
Causes of Death	Total Deaths N=89 (39%)	Deaths ≤ Day 100 N=35 (14%)	Total Deaths N= 35 (38%)	Deaths ≤ Day 100 N=18 (20%)	Total Deaths N=631 (49%)	Deaths ≤ Day 100 N=328 (25.3%)
Graft failure (n%)	3 (1%)	3 (1%)	2 (2%)	2 (2%)	48 (4%)	33 (3%)
Organ failure (n%)	10 (5%)	5 (2%)	5 (5%)	2 (2%)	115 (8.9%)	84 (7%)
Infection (n%)	8 (4%)	4 (2%)	3 (3%)	2 (2%)	170 (13%)	101 (8%)
GVHD (n %)	6 (3%)	1 (<1%)	3 (3%)	1 (1%)	72 (6%)	39 (3%)
Primary disease (n%)	21 (9%)	6 (3%)	9 (10%)	4 (4%)	168 (13%)	39 (3%)
2nd Malignancy (n%)	3 (1%)	1 (<1%)	-	-	4 (<1%)	0
Prior malignancy (n%)	-	-	-	-		
Hemorrhage (n%)	5 (2%)	1 (<1%)	4 (4%)	1 (1%)		
Pulmonary toxicity (n%)	2 (1%)	-	4 (4%)	2 (2%)		
Unknown (n%)	26 (12%)	12 (5%)	4 (4%)	-		
Other (n%)	5 (2%)	2 (1%)	1 (1%)	4 (4%)		

Table 14 shows the product characteristics for patients who experienced early mortality in the CCBC dataset. The small size of the CCBC dataset does not allow for conclusions to be drawn regarding the interaction between product characteristics and early mortality. The higher number of early deaths in patients who received multiple units of HPC, Cord Blood reflects that the majority of patients in the CCBC dataset were adult patients who received more than one unit of HPC, Cord Blood.

Table 14. Early Mortality Interactions with Product Characteristics for Patients (N = 91) who Received a Suitable Allograft with CLEVECORD

Product Characteristics	Percentage of Deaths ≤ Day 100 after Transplantation by Category, N=18
Number of Cord Blood Units	
Single Unit	4 (22%)
Multiple Units	13 (72%)
Not Reported	1 (6%)
Degree of HLA Match	
4/6	5 (28%)
5/6	11 (61%)
6/6	2 (11%)
Not Reported	-

8.4.2 Nonfatal Serious Adverse Events

Primary graft failure

Primary graft failure is defined as failure to achieve ANC > 500/μL by Day 42. Immunological rejection is the primary cause of graft failure and may be fatal. Patients who do not have evaluable data for neutrophil recovery by Day 42, due to death prior to Day 42, are not included in the analysis of primary graft failure. Of the 76 patients who received a suitable allograft with CLEVECORD and had evaluable data for neutrophil recovery by Day 42, 3/76 (4%) patients experienced primary graft failure (see Table 7). If the data from four patients who lived at least 14 days post-transplant but who died prior to Day 42 are included in the analysis of primary graft failure, the reported incidence of primary graft failure (i.e., 6 occurrences of primary graft failure among 80 evaluable patients) would be 8% (95% CI: 2 – 14), which is comparable to the 16% incidence of primary graft failure in the Docket dataset.

Infusion Reactions

Infusion reactions are defined as adverse events occurring within 24 hours after transplantation. The causes of infusion reactions may include reactions to hemolyzed HPC, Cord Blood, allergic or anaphylactic reactions to any component of HPC, Cord Blood, or bacterial contamination.

The applicant received voluntary reports of infusion reactions in patients who received at least a single unit of CLEVECORD. Of the 262 patients who received at least a single unit of CLEVECORD and of the 91 patients who received a suitable allograft with CLEVECORD, the percentages of patients who had a reported infusion reaction are 16% and 20%, respectively (see Table 15). Of note, since there is insufficient information to characterize the size of the evaluable database for infusion reactions, the incidence of infusion reactions among patients receiving CLEVECORD that is reported in Table 15 may underestimate the true event rate for infusion reactions in the dataset. Based on the available data, no new safety issues regarding the incidence and nature of infusion reactions are identified in the CCBC dataset compared to the COBLT dataset.

Table 15. Incidence of Infusion Reactions in Patients who Received an Infusion of CLEVECORD and who Received an Infusion of HPC, Cord Blood in the COBLT Study

	Patients who Received ≥ 1 CLEVECORD Unit N=262*	Patients who Received ≥ 1 CLEVECORD Unit with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$ and HLA $\geq 4/6$ N=91**	COBLT Infusions with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$ Number of Infusions Assessed: N=442
Percentage of Infusions with Reported Reactions	16% (41/262)	20% (18/91)	65.4%
Signs and symptoms reported: Number (%) of patients with this event			
Hypertension	33 (13%)	16 (17%)	48.0%
Hypotension	2 (1%)	2 (2%)	
Hypoxia	3 (1%)	3 (3%)	2%
Nausea	9 (3%)	2 (2%)	12.7%
Headache	2 (1%)	0 (0%)	
Tachycardia	3 (1%)	2 (2%)	
Vomiting	6 (2%)	1 (1%)	14.5%
Chest Pain	3 (1%)	1 (1%)	
Fever, Chills	1 (< 1%)	1 (1%)	0.9%
Rigor mild	1 (< 1%)	1 (1%)	
Hives	1 (< 1%)	1 (1%)	
Bradycardia	0 (0%)	0 (0%)	10.4%
SOB	1 (< 1%)	0 (0%)	
Other	10 (4%)	1 (1%)	

*Due to insufficient information about the total number of patients who have evaluable data for infusion reactions, the reported percentage is calculated using the total number of patients who received at least a single unit of CLEVECORD as the denominator, which may underestimate the rate of infusion reactions.

**Due to insufficient information about the total number of patients with a suitable allograft who have evaluable data for infusion reactions, the reported percentage is calculated using the total number of patients who received a suitable allograft with CLEVECORD as the denominator, which may underestimate the rate of infusion reactions.

Graft-versus-Host Disease (GVHD)

GVHD is a common complication after unrelated cord blood transplantation, induced by immune T cells in donor cord blood that recognize the recipient as “foreign” and attack the host’s body cells. While the donor T-cells can cause undesirable systemic immune reactions, those T-cells can have a desirable graft-versus-tumor effect if the transplantation is used to treat cancer such as leukemias. Acute GVHD is defined as occurring within the first 100 days post-transplant, attacking predominantly liver, skin, mucosa, and gastrointestinal tract. Acute GVHD is classified by severity from grade 1 to

4. Chronic GVHD occurs after 100 days post-transplant, involving different immune cell subsets, cytokines, and host targets.

Data for acute GVHD in the CCBC dataset was available for 80 patients who received a suitable allograft with CLEVECORD. Of these 80 patients, 44 (55%) experienced acute GVHD, which appears to be comparable to the incidence of acute GVHD in the Docket dataset, in which 69% of patients who received a TNC dose $\geq 2.5 \times 10^7/\text{kg}$ experienced acute GVHD (See Table 16).

Table 16. Incidence of Acute GVHD in the CLEVECORD and Docket Datasets

	Acute GVHD in CLEVECORD Dataset		Docket Data	
	Total reported N = 262	Patients with a Suitable Allograft N = 80	Patients reported (N=1381)	Patients with a TNC Dose $\geq 2.5 \times 10^7/\text{kg}$ (N=1182)
No	76 (29%)	36 (45%)	451 (33%)	369 (31%)
Yes	117 (45%)	44 (55%)	930 (67%)	813 (69%)
Unknown	69 (26%)			
Grade				
1	20 (8%)	9 (11%)	347 (25%)	315 (27%)
2	53 (20%)	21 (26%)	314 (23%)	276 (23%)
3	26 (10%)	7 (9%)	176 (13%)	149 (13%)
4	14 (5%)	7 (9%)	93 (7%)	73 (6%)
Unknown	4 (2%)	0 (0%)	347 (25%)	369 (31%)

In the CLEVECORD dataset, of the 82 patients who received a suitable allograft and have evaluable data for chronic GVHD, 15 (18%) developed chronic GVHD. This is comparable to the percentage (20%) of patients in the overall CLEVECORD dataset who were reported to have experienced chronic GVHD (see Table 17).

Table 17. Incidence of Chronic GVHD after Infusion with CLEVECORD

		All Patients	Patients with a Suitable Allograft
Total Reported (Yes or No)		197	82
Of Those Reported	Yes	40/197 (20%)	15/82 (18%)
	Limited	16/40 (40%)	7/15 (47%)
	Extensive	24/40 (60%)	8/15 (53%)
	Not Indicated	-	-

Engraftment Syndrome

Engraftment syndrome manifests 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. The treatment of choice to ameliorate the symptoms is systemic corticosteroids.

No information regarding engraftment syndrome was submitted in the BLA. To support the safety of CLEVECORDER, the reviewers took into consideration information on engraftment syndrome based on the Docket data, and on the publicly available data (See Appendix 12.1).

Malignancies of Donor Origin, Transmission of Serious Infection and Rare Genetic Diseases

There are no reports of possible transmission of malignancy, serious infection, or genetic disease from the donor material in the CLEVECORDER dataset; to support the safety of CLEVECORDER, the reviewers took into consideration information from the Docket data, and the publicly available data (See Appendix 12.1).

8.4.3 Study Dropouts/Discontinuations

Not applicable.

8.4.4 Common Adverse Events

Please see section 8.4.2 for details.

8.4.5 Systemic Adverse Events

Please see section 8.4.2 for details.

8.5 Additional Safety Evaluations

None.

8.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events has been discussed in the safety review of the Docket and public information (See Section 12. Appendices). Therefore, this review does not include analysis of dose dependency for adverse events.

8.5.2 Time Dependency for Adverse Events

See 8.4 for analyses of total death and death at Day 100 post-transplantation.

8.5.3 Product-Demographic Interactions

See Dr. Przepiorka's review of Docket and public information (Appendix 12.1) for analyses of product-demographic interactions regarding safety (graft failure) and efficacy (neutrophil recovery) by age, gender, and race/ethnicity.

8.5.4 Product-Disease Interactions

The BLA submission does not include data to assess the product-disease interactions.

8.5.5 Product-Product Interactions

The BLA submission does not include data to assess any product-product interactions.

8.5.6 Human Carcinogenicity

The BLA submission does not include data regarding human carcinogenicity.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

See Dr. Przepiorka's review of Docket and public information (Appendix 12.1) for information on overdose of HPC, Cord Blood products. CCBC did not provide information on overdose of their product. CLEVECORDER prepared for infusion contains 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. Toxic overdose of DMSO has been reported in a subject undergoing autologous HPC – bone marrow transplantation (Yellowlees, Greenfield, et al. 1980). There is no report in the literature of a DMSO overdose related to HPC, Cord Blood transplantation.

The BLA submission does not include data regarding the abuse potential, withdrawal, and rebound of CLEVECORDER.

8.5.8 Immunogenicity (Safety)

CLEVECORDER is an allogeneic cord blood hematopoietic progenitor cell therapy for use in an unrelated recipient. An appropriate preparative regimen using chemotherapy and/or total body irradiation is required for engraftment. As a result, clinical complications related to both immunogenicity and the preparative regimens are major safety concerns. Please see Sections 8.4.1 and 8.4.2 of this review for details.

8.5.9 Person-to-Person Transmission, Shedding

Transplantation of CLEVECORDER may result in the development of malignancies of donor origin in the recipient, transmission of serious infection and rare genetic diseases from the donor to the recipient. No such cases were reported in this BLA. Please see Appendix 12.1 for more details.

8.6 Safety Conclusions

Based primarily on the Docket data, supplemented by the CLEVECORDER data, and taking into consideration the publicly available data, the risks associated with CLEVECORDER transplantation are serious and potentially fatal. The adverse events include early death, infusion reactions, graft versus host disease (GVHD), and graft failure.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

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

9.1.2 Use During Lactation

There is no information regarding the presence of CLEVECORDER 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 CLEVECORDER Blood and any potential adverse effects on the breastfed infant from HPC Cord Blood or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

CLEVECORDER has been used in pediatric patients with disorders affecting the hematopoietic system that are inherited, acquired, or resulted from myeloablative treatment (See Sections 7 and 8 of this review for more details).

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The active ingredient, indication, dosage form, dosing regimen, and route of administration of CLEVECORDER are not new because they are the same as for HEMACORDER, manufactured by New York Blood Center. Therefore, this application does not trigger PREA.

9.1.4 Immunocompromised Patients

CLEVECORDER has been used in immunocompromised patients due to either the preparative regimen prior to transplantation or the underlying disease(s). Adverse events associated with its use are discussed in Section 8 of this review.

9.1.5 Geriatric Use

Clinical studies of HPC, Cord Blood (from multiple cord blood banks) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, administration of CLEVECORDER to patients aged 65 and over should be cautious, reflecting this demographic subset's greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or use of other drug therapy.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None.

10. CONCLUSIONS

Based primarily on the Docket data, supplemented by the CLEVECORDER data, and considering the publicly available data, we conclude that CLEVECORDER is capable of hematopoietic and immunologic reconstitution in conjunction with an appropriate preparative regimen. CLEVECORDER can function as an alternative source of hematopoietic progenitor cells for transplantation to treat diseases affecting the hematopoietic system.

CLEVECORDER transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The risks associated with 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, include early death, infusion reactions, GVHD, and graft failure.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 18 provides a detailed assessment of risk-benefit considerations for CLEVECORDER.

Table 18. Risk-Benefit Considerations for CLEVECORD

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment Etiology categories include hematological malignancies, metabolic disorders, marrow failure, hemoglobinopathy, immunodeficiency, and autoimmune disorders Unrelated donor hematopoietic progenitor cell transplantation procedures require potentially toxic preparative regimens in order to achieve hematopoietic and immunologic reconstitution 	<ul style="list-style-type: none"> Hematological malignancies and marrow failure are life-threatening diseases Metabolic disorder, hemoglobinopathy, immunodeficiency, and autoimmune disease are a group of serious disorders, and can be life-threatening if severe and at late-stage.
Unmet Medical Need	<ul style="list-style-type: none"> Chemotherapy, immunotherapy, and targeted biologic agents have significant adverse event potential Other therapies include hematopoietic stem cells (HSC) from the sources of HLA-matched related or unrelated bone marrow transplant, HLA-matched related cord blood transplant, or granulocyte colony-stimulating factor mobilized peripheral blood donor The above HSC sources are limited and HPC, Cord Blood provides wider source of HSC for allogeneic HSC transplant. 	<ul style="list-style-type: none"> Not all patients have, or can use, available HSC sources from autologous or allogeneic bone marrow or peripheral blood. In such situations, cord blood fills an unmet medical need by providing a reasonable option for hematopoietic transplantation.
Clinical Benefit	<ul style="list-style-type: none"> A single-arm prospective study (COBLT) and retrospective reviews of an observational database in the dockets and public data have demonstrated the effectiveness of class of HPC, Cord Blood as defined by hematopoietic reconstitution. The total nucleated cell dose and the degree of HLA match were associated with the time to neutrophil recovery Retrospective analyses of the CLEVECORD database demonstrated comparable results of hematopoietic reconstitution as compared with the COBLT and Docket data 	<ul style="list-style-type: none"> HPC, Cord Blood can be effectively used in patients who have disorders affecting the hematopoietic system and who have life-threatening or serious diseases but have failed standard therapy and no available other HSC sources for transplant The effect of the HPC, Cord Blood is related to the numbers of TNC in the cord blood HPC, Cord Blood can provide a broader and prompt source of HSC Effectiveness may vary depending on age of the patients, type and stage of disease, and comorbidity
Risk	<p>Based on Docket and COBLT data,</p> <ul style="list-style-type: none"> All-cause mortality rate of 30% at 100 days post-transplant as result of infection, primary disease, pulmonary causes, multi-organ failure, and GVHD Acute GVHD in 69% of population, which may benefit for malignant patients as Graft versus tumor effect Infusion reactions in 65% of population (COBLT), including hypertension, nausea, vomiting, sinus bradycardia, fever, sinus tachycardia, allergy, hypotension, hemoglobinuria, and hypoxia Primary Graft failure in 16% of population 	<ul style="list-style-type: none"> The overall risks of the HPC, Cord Blood transplantation along with a myeloablative preparative regimen can be serious and fatal Standard approved chemotherapy or biologics should be considered first If failed standard therapy, other HSC source such as autologous or matched bone marrow or cord blood or peripheral cells should be considered Type of the disease such as hematological malignancies vs. non-oncological disease, stages of the disease, patient health conditions (age, comorbidities, functional status) should be considered when considering using CLEVECORD

<p>Risk Management</p>	<ul style="list-style-type: none"> • The risk of fatal infusion reactions, GVHD, engraftment syndrome and graft failure are addressed in the black box warning of the Prescribing Information for HPC, Cord Blood class • Risks of infusion reactions, malignancies of donor origin, transmission of serious infections or rare genetic disease are addressed under Warning and Precaution of the PI. • Risk/benefit assessment should include analyzing disease type and stage, risk factors, number of the TNC and level of HLA match, other available treatment or types of HSCs. • Post-market: clinical outcome data collection; adverse events reporting: serious and unexpected 	<p>Labeling information and post-marketing pharmacovigilance monitoring should suffice for risk management; no REMS or PMR is necessary</p>
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11.2 Risk-Benefit Summary and Assessment

Transplantation of CLEVECORDER resulted in hematopoietic reconstitution, indicated by neutrophil and platelet recovery.

Based on the Docket data and supported by the publicly available data, HPC, Cord Blood has demonstrated the ability to reconstitute the immunologic system in patients transplanted for primary immunodeficiency, as well as for other malignant and nonmalignant disorders (Section 12, Appendices).

CLEVECORDER transplantation for hematopoietic and immunologic reconstitution is a potentially life-saving treatment for certain diseases affecting the hematopoietic system; however, the risks are serious and potentially fatal. The risks associated with CLEVECORDER include early death, infusion reactions, GVHD, engraftment syndrome, and graft failure. 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.

11.3 Discussion of Regulatory Options

No major safety and efficacy concerns were identified from the clinical and statistical review to warrant a complete response action for the CLEVECORDER BLA. The overall risks of CLEVECORDER can be mitigated in labeling. There are no unexpected or special risks identified from the BLA review to trigger a REMS, PMC or PMR. A post-marketing plan to monitor for safety, as proposed by the applicant, should be sufficient to monitor the safety of CLEVECORDER.

11.4 Recommendations on Regulatory Actions

The reviewers recommend approval of CLEVECORDER for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with a preparative regimen appropriate for treatment of the patient's disease and for hematopoietic and immunologic reconstitution in patients with hematopoietic system-affecting diseases that are inherited, acquired, or result from chemotherapy and/or radiation intended to treat their disease.

11.5 Labeling Review and Recommendations

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed. Labeling for HPC, Cord Blood is primarily class labeling. Therefore, the labeling of CLEVECORD follows the format of labeling of previously approved HPC, Cord Blood products.

11.6 Recommendations on Postmarketing Actions

The risks of CLEVECORD and its related preparative regimen can be mitigated and managed through the labeling of CLEVECORD and a post-marketing safety monitoring plan. No unexpected safety issues are identified in this BLA review that warrant post-marketing requirements or commitments. The reviewers do not recommend Risk Evaluation and REMS nor PMR or PMC for CLEVECORD.

The review team recommended, and the applicant agreed, to do the following:

1. Implement a safety outcomes monitoring and analysis plan. This plan will include a) maintenance of an observational database to include, for all CLEVECORD units released, information including but not limited to, time to neutrophil recovery, graft failure, survival, cause of death, infusion reactions, and other adverse experiences, b) aggregate analyses of interval and cumulative adverse experience reports, and c) safety outcomes analyses of interval and cumulative data that address early mortality, graft failure-related mortality, graft failure, time to neutrophil recovery, infusion-related events, and other adverse experiences. Reports will include a description of the population analyzed, results of the analyses, whether outcomes indicators were triggered and, if so, what actions were implemented as a result.
2. Submit a 15-day "alert report" for each serious infusion reaction associated with administration of CLEVECORD.

12. APPENDICES

Appendix 12.1 Safety Review: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Donna Przepiorka, MD, PhD

Appendix 12.2 Clinical Efficacy Review, Nonmalignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: John E. Hyde, Ph.D., M.D.

Appendix 12.3 Clinical Efficacy Review, Malignant Indications: Hematopoietic Progenitor Cells-Cord Blood; Primary Reviewer: Maura O'Leary, M.D.