CIRCULAR OF INFORMATION
For the Use of Human Blood Components

HPC CORD BLOOD

Hematopoietic Progenitor Cells (HPC), Cord Blood

This product information addresses:

- **HPC, Cord Blood.**

The cord blood unit ID (CBU ID) is equivalent to the donor identification number (DIN).

Composition and properties

HPC, Cord Blood contains hematopoietic progenitor cells collected from the umbilical cord and placenta immediately after delivery of a baby. The cord blood is collected by gravity drainage into a sterile cord blood collection bag that contains a maximum of 29 mL of citrate-phosphate-dextrose (CPD) anticoagulant. The cord blood is buffy coat enriched (red cell and plasma reduced) by centrifugation. Cord blood units processed using the Sepax methodology (Cytiva) were processed using Hydroxyl Ethyl Starch (6% HES) prior to controlled rate freezing. Cord blood units processed by AXP®II (ThermoGenesis Corp.) were processed without Hydroxyl Ethyl Starch (HES). **HPC, Cord Blood** product may contain residual amounts of CPD anticoagulant. The cryopreservation solution is 10% dimethyl sulfoxide (DMSO) and 1% Dextran 40. The **HPC, Cord Blood** product is processed and cryopreserved within 48 hours of collection.

Notes: 1. CPD anticoagulant contains Acidum citricum monohydricum, Natrii citras dihydricus, Natrii dihydrogenophosphas dihydricus, Glucosum monohydricum

2. Please refer to the CBU Report for processing methodology used on each cord blood unit.

Quality Control Criteria

Quality Criteria that must be met for each **HPC, Cord Blood** Unit (CBU):

- ≥ $50x10^7$ Total Nucleated Cells (TNC)
- ≥ $1.25x10^6$ viable $CD34^+$ cells
- ≥ 85% viable nucleated cells at the time of cryopreservation

The pre-cryopreservation nucleated cell content of each unit of **HPC, Cord Blood** is provided on the final distribution label and accompanying documentation.

Prior to cryopreservation, the **HPC, Cord Blood** is tested for the following:

- ABO group
- Rh type
- Abnormal Hemoglobin
- HLA typing
- Quality Control Testing: Total Nucleated Cell (TNC) count, viable CD34+ cell content, cell viabilities (TNC, CD45 and CD34)
- Colony forming unit (CFU) assay testing is performed on a CBU sample post-processing. The CFU testing kits are indicated for “Research Use Only”.

Microbial culture testing is performed on a post-processing by-product sample consisting of plasma and red blood cells. The testing is carried out using a validated microbial detection system to detect microbial contamination (aerobic bacteria, anaerobic bacteria, and fungus).

Prior to distribution, an attached segment from the CBU is thawed and tested for TNC count, viable CD34+ cell content, cell viabilities (TNC, CD45 and CD34) and the CFU assay is performed. Our testing demonstrates a result range for CD34 Viability ≥70%.

A maternal sample has been tested and found non-reactive for:

- Antibodies and antigens to human immunodeficiency virus (HIV-1/2)
- Antibodies to hepatitis C virus (HCV), human T-cell lymphotropic virus, type I and II (HTLV-I/II), hepatitis B core antigen (HBcore)
- Hepatitis B surface antigen (HBsAg)
- Presence of viral RNA [HIV-1, HCV, and West Nile virus (WNV)]
- Presence of hepatitis B DNA [
- Syphilis
- Antibodies to *Trypanosoma cruzi* (*T. cruzi* or Chagas Disease) when increased Chagas risk is indicated on the *Cord Blood Medical History/Health Assessment Questionnaire*.

The maternal sample is tested for Cytomegalovirus (CMV) antibodies and can be found to be negative or positive.

Screening of mothers donating their child’s cord blood is performed using the *Cord Blood Medical History/Health Assessment Questionnaire*, in accordance with the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations.*

Packaging

The **HPC, Cord Blood** bag processed by Sepax methodology (Cytiva) is an 80/20 configuration consisting of 20mL and 5mL compartments. Cord blood units processed using the AXP® II methodology (ThermoGenesis Corp.) consist of a single 25mL compartment. The viability and potency of stored products are assessed through our current stability program.

The polyvinyl chloride (PVC) used in the collection pack used to collect the cord blood unit complies with the European Pharmacopeia. The collection pack is licensed by Health Canada for use in Canada. The plasticizer is DEHP. **HPC, Cord Blood** could contain phthalates.

Storage and handling

The **HPC, Cord Blood** is stored at Canadian Blood Services’ Cord Blood Bank in liquid nitrogen at -196°C. The Cord Blood Bank does not assign a date of expiration to the product because Canadian Blood Services’ Cord Blood Bank monitors the viability and potency of stored product through a stability program. This process adheres to Canadian Safety of Human Cells, Tissues and Organs for Transplantation regulation Section 35. It is transported to

the Transplant Centers (TC) in a tamperproof insulated dry shipper.

All samples (maternal and cord) are stored at ≤ -150°C. Samples will be provided to TCs "AS IS" and Canadian Blood Services makes no warranties of merchantability or fitness for a particular purpose or test. Upon receipt the TC must inspect the dry shipper to ensure:

- The tamper-proof seal is intact.
- It is free of cracks, leaks and excessive condensation.

In the event that the dry shipper is damaged, please contact the Canadian Blood Services Stem Cell Registry immediately. Instructions for contacting the Canadian Blood Services Stem Cell Registry in the event of this or any other concern about the product or container are provided on the accompanying *CBU Receipt* form.

It is recommended that the TC adhere to the following instructions for receipt and handling of the dry shipper and **HPC, Cord Blood** product:

- TC must maintain the dry shipper in an upright position.
- TC must handle the dry shipper carefully, avoiding bumps, abrupt movements and extreme storage temperatures.
- To open dry shipper and access cryopreserved product, remove security seal and remove dry shipper lid. Handle the metal cassette containing the **HPC, Cord Blood** carefully to avoid damaging the product.
- The **HPC, Cord Blood** product must be removed from the dry shipper for storage at ≤ -150°C.
- TC must follow their institutional safety policies and procedures for handling cryopreserved cellular therapy products.

Action

The **HPC, Cord Blood** product contains hematopoietic progenitor cells, which are capable of repopulating the bone marrow, maintaining a population of self-renewing progenitors, as well as developing into mature cells of the blood and immune system.

Indications

The **HPC, Cord Blood** may be used in the treatment of a wide variety of malignant hematological and non-malignant diseases (e.g. leukemia, lymphoma, multiple myeloma, hemoglobinopathies, inherited metabolic disorders) and post chemotherapy for cancer treatment. Graft-versus-tumor effects may occur and aid in eradicating residual malignant disease in the recipient following unrelated allogeneic **HPC, Cord Blood** infusion.

Contraindications

Specific contraindications are determined by TC institutional policies and protocols. **HPC, Cord Blood** may be contraindicated for patients with known intolerance or hypersensitivity to DMSO, CPD, HES, or Dextran-40.

Warnings and precautions

The intended recipient must be properly identified before the infusion is started.

CAREFUL DONOR SELECTION AND AVAILABLE LABORATORY TESTS DO NOT ELIMINATE THE HAZARD OF TRANSMITTING INFECTIOUS DISEASE AGENTS FOR WHICH TESTING IS PERFORMED OR FOR PATHOGENS THAT ARE EITHER NOT RECOGNIZED OR FOR WHICH THERE IS NO DONOR SCREENING TEST.

HPC, Cord Blood may contain residual antibiotics if the cord blood donor was exposed to antibiotics in utero. Patients with a history of allergic reactions to antibiotics should be monitored for allergic reactions following administration of this product. There may be an effect on the reliability of the sterility test results if the cord blood donor was exposed to antibiotics in utero.

As manufacturing supplies associated with this product are not guaranteed to be latex-free, Canadian Blood Services' Cord Blood Bank cannot guarantee that this product is latex free.

Thawing and administration

Thawing, dilution/washing and infusion should be done in accordance with TC institutional safety policies and procedures for handling cryopreserved product. Further information may be found in Canadian Blood Services Cord Blood Recommendations for Preparation for Infusion. Copies will be provided upon request to the Canadian Blood Services Stem Cell Registry.

Important items to note are:

- Do not administer **HPC, Cord Blood** through a filter designed to remove leukocytes.
- **HPC, Cord Blood** may be filtered through a 170- to 260-micron filter designed to remove clots or clumps of cellular debris.
- Mix **HPC, Cord Blood** thoroughly before use.
- Do not irradiate **HPC, Cord Blood**.
- Do not add or infuse medications or solutions through the same tubing with **HPC, Cord Blood** with the exception of 0.9% Sodium Chloride, Injection (USP) or facility-approved solutions.
- Infusion rate is dependent on clinical factors and the product volume to be administered as per TC institutional policies and protocols.

If there is an unexpected delay in administration and the product must be held for later infusion, the Canadian Blood Services Stem Cell Registry should be contacted. Once thawed, **HPC, Cord Blood** product must not be re-cryopreserved

The Canadian Blood Services Stem Cell Registry tracks all CBU infusions with the assistance of our clinical partners. We require TCs to complete and return the *Thawing and Infusion Report* form to the Canadian Blood Services Stem Cell Registry as soon as possible.

Adverse events

Potential adverse events related to a cord blood infusion range in severity from minor with no sequelae to life-threatening. All adverse events occurring during infusion should be evaluated to determine whether or not the infusion can be safely continued or restarted. All adverse events suspected to be related to an infusion (whether during or after infusion of **HPC, Cord Blood)** should be reported to the Canadian Blood Services Stem Cell Registry and any applicable regulatory bodies. For further information, refer to the package insert that accompanies this product.

TABLE 1: The following adverse events have been described with infusion of cord blood products

Event	Symptoms and Signs	Etiology	Notes
DMSO toxicity	Cough, flushing, urticaria, hypertension, chest tightness and wheezing, nausea and vomiting, bradycardia and tachycardia.	Caused by residual DMSO in product.	Most common adverse event. May be minimized by washing product or pretreatment with antihistamines.[2]
Graft-versus-host disease (GVHD)	May affect skin, liver, lung, bowel, marrow and rarely other organs in varying degrees.	Viable T lymphocytes in CBU product engraft in the recipient and react against tissue antigens in the recipient.	Severely immunocompromised recipients are at greatest risk. May be acute or chronic.[3]
Allergic	Urticaria, pruritis; rarely facial or glottal edema.	Antibodies present in the donor or recipient plasma interact with atopic substances.	May respond to antihistamines or corticosteroids or epinephrine in severe cases.[2, 4]
Anaphylactic	Hypotension, bronchospasm, laryngospasm, with associated dyspnea.	IgA deficient patients with anti-IgA antibodies react with IgA in donor plasma. Patients with sensitivity to HES or DMSO in product also at risk.	Treatment includes –supportive care, fluids, corticosteroids, epinephrine; may require cardiorespiratory support. [2, 4]
Febrile non-hemolytic transfusion reactions (FNHTR)	Fever, (temperature increase of 1°C or more), chills.	Diagnosis of exclusion. A patient with fever should be evaluated for other more serious infusion reactions.	Antipyretics usually provide symptomatic relief. [2, 4]
Transfusion associated circulatory overload (TACO)	Pulmonary edema and dyspnea.	Due to excessive volume or excessively rapid infusion rates.	Unlikely due to small CBU volume. [2, 4]
Transfusion related acute lung injury (TRALI)	Acute respiratory distress occurs during or within 6 hours of infusion, hypoxia, new onset of hypoxemia, new bilateral lung infiltrates on chest X-ray and no evidence of circulatory overload.	Associated with the presence of leukocyte antibodies in the donor or recipient.	Treatment is supportive.[4]
Delayed hemolytic transfusion reactions (HTR)	Unexplained low grade fever, decrease in hemoglobin /hematocrit levels, mild jaundice, positive direct antiglobulin test, elevated lactate dehydrogenase (LDH) or bilirubin2-14 days post infusion.	Usually due to an anamnestic response of previously formed RBC antibodies.	Treatment is supportive. [2, 4]
Acute hemolytic transfusion reactions (HTR)	May be immediate including chills, fever, headache, low back pain, facial flushing, chest pain, rapid labored respiration, hypotension, disseminated intravascular coagulation, shock and kidney failure.	Due to ABO incompatibility or infrequently due to rare RBC antibodies. Rarely non immune due to mechanical/osmotic stress.	Treatment is supportive. [2, 4]
Bacterial contamination	Fever, chills, vomiting, severe hypotension, sepsis, shock.	Presence of bacteria or endotoxin in product causing infection or sepsis.	Supportive care, evaluation of blood cultures and aggressive therapy with broad spectrum antibiotics. Evaluate remaining product promptly by Gram's stain and microbial cultures. [2, 4]
Alloimmunization to antigens	Usually asymptomatic and does not cause physiologic changes.	May occur unpredictably after product administration.	Alloimmunization to white cells, platelets or plasma can be detected by specialized testing.[2]
Transmission of infectious disease	Variable according to infectious disease.	Unrecognized transmission that was not detected using the tests described outlined in the attached circular.	For estimate residual risk of transfusion-transmitted viral infection, see Reference 9.
Engraftment syndrome	Fever and rash in peri-engraftment period without other cause. Associated weight gain, hypoxemia, and pulmonary infiltrates in the absence of fluid overload or cardiac disease.	N/A	Treatment is supportive, steroid and ventilator support may be required.[7, 8]
Graft failure	Failure to achieve absolute neutrophil count >500/uL by day 42 post-transplant.	Primary cause is immunologic rejection.	May be fatal. [7, 8]
Malignancies of donor origin	Post-transplant lymphoproliferative disorder (PTLD), lymphoma-like disease favouring non-nodal sites, or leukemia of donor origin.	Thought to be donor lymphoid cells transformed by Epstein-Barr Virus (EBV).	Consider serial EBV monitoring of high risk groups.[7, 8]
Transmission of rare genetic diseases	Variable, depending on condition.	Unrecognized transmission of genetic disease or susceptibility to the development of disease with genetic basis due to abnormal expression or regulation of genes in the cells within the product.	Important clinical manifestations are rare. [5, 7]
Bleeding Due to Excess Anticoagulation	Bleeding or easy bruising.	Caused and/or exacerbated by trace or residual anticoagulant that is present in the collection bag at time of collection and/or administered to the mother prior to delivery and collection.	The collected CBU is processed and resuspended in a different solution before storage, making the amount of anticoagulant present in the product very low to negligible.

II

References

1. CAN, Health Canada. Health Products & Food Branch, Safety of Human Cells, Tissues and Organs for Transplantation Regulations, SOR/2007-118 (last Amended on Feb 4, 2020).

2. AABB, FACT, ASBMT, et al. *Circular of information for the use of cellular therapy products*. Bethesda, MD: AABB, June 2021.

3. Acute Graft-versus-Host disease-Biologic Process, Prevention and Therapy. Zeiser R, Blazar BR. N Engl J Med. 2017 Nov 30;377(22):2167-2179. https://pubmed.ncbi.nlm.nih.gov/29171820/

4. Clarke G, Charge S, editors. *Clinical Guide to Transfusion*. Canadian Blood Services; 2019. Available online at https://professionaleducation.blood.ca.

5. CAN/CSA-Z900.1-17 Cells, tissues and organs for transplantation: General Requirements, Canadian Standards Association, (November 2017).

6. CAN/CSA-Z900.2.5-17 Lymphohematopoietic cells for transplantation, Canadian Standards Association, (November 2017).

7. ClinImmune Labs, University of Colorado Blood Bank, Package Insert, HPC Cord Blood. Revised 06/12.

8. New York Blood Centre, Inc. Package Insert, HEMACORD. Available online at http://www.fda.gov/downloads/Biologics BloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM279612.pdf

9. Circular of Information, RBC Blood Cells LR SAGM Added, Canadian Blood Services.

The *Circular* as a whole or in part cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described
HPC, Cord Blood when used for its intended purpose. Attention to the specific indications for cellular therapy products is needed to prevent
Inappropriate infusion.

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This Circular of Information is an extension of the product container label for minimally manipulated unrelated cord blood units, ***HPC, Cord Blood****. The Circular of Information provides general information to the medical practitioner that administer* ***HPC, Cord Blood****.*
This product, its labeling, and the process by which it was manufactured and distributed, conform to the Safety of Human Cells, Tissues and Organs for Transplantation Regulations[1], issued by Health Canada.
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