Miltenyi Biotec

Prevention of graft-versus-host disease (GVHD)

Understanding the role of *ex vivo* T cell depletion

Information for patients undergoing allogeneic stem cell transplantation in AML and their families

This informational brochure is intended for US patients undergoing allogeneic stem cell transplantation in acute myelogenous leukemia (AML) and their families.
It provides information about the causes of graft-versus-host disease and its prevention by *ex vivo* T cell depletion using the CliniMACS CD34 Reagent System. This brochure is not intended to replace conversations with your healthcare team. Your doctor and other healthcare providers are the most valuable resources for answering questions about your disease and *ex vivo* T cell depletion as a method of preventing graft-versus-host disease.

Content

Dear reader,

Note: Are some of the words or abbreviations used in this booklet unfamiliar to you? All words marked in bold are defined in the glossary found on page 18.

This booklet provides information to patients and their families about **allogeneic stem cell transplantation** for the treatment of acute myeloid leukemia (AML). It is intended to help you understand the rationale of allogeneic stem cell transplantation, **graft-versus-host disease (GVHD)**, and options for preventing graft-versus-host disease using ***ex vivo*** **T cell depletion**.

Allogeneic stem cell transplantation is a potential curative treatment option for certain forms of leukemia, including AML. The goal of a stem cell transplant is to encourage the repopulation of healthy blood cells in the patient's bone marrow by transferring healthy **stem cells** from a donor to the recipient. The newly introduced blood stem cells are tasked with the job of rebuilding the patient's blood and immune systems.

What are T cells?
T cells are a subset of white blood cells that play a large role in recognizing and defending your body against bacteria, viruses, and substances that appear foreign and harmful. The abbreviation "T" stands for thymus, the organ in which their final stage of development occurs.

A potentially serious complication that can occur after allogeneic stem cell transplantation is graft-versus-host disease, in which certain cells from the donor called **T cells** attack the patient's body. Managing this complication can be a serious challenge. Removal of the T cells from the donor's cells using a new FDA-approved system, the CliniMACS® CD34 Reagent System, has been shown to reduce this complication in AML patients receiving cells transplanted from a matched related sibling.

1. What is AML?

AML is a type of blood cancer. There are three main types of cells in the blood; **white blood cells**, **red blood cells**, and **platelets**. White blood cells are responsible for fighting infections and other diseases.

In patients with AML, the **bone marrow** makes a large number of immature white blood cells, called myeloid cells. These cells multiply uncontrollably, crowding out normal cells and interfering with the production of normal blood cells. This significantly increases the risk of infection and bleeding.

What type of blood cells are there and what are their functions?
See a summary of blood cell types and functions in the glossary at the back of this brochure.

What are the causes and risk factors of AML?
Ask your doctor and visit the Leukemia and Lymphoma Society website (www.lls.org) to find comprehensive disease information about AML.

2. How is AML treated?

Treatment of AML is usually divided into two phases:

- **Induction therapy:** The initial phase of treatment, designed to remove all detectable leukemia cells and treat the immediate disease.
- **Consolidation therapy:** Further treatment to destroy remaining leukemia cells and prevent the recurrence of the disease.

Induction therapy

The elimination of leukemic cells is usually accomplished using **chemotherapy**. This can be achieved with multiple drugs during a planned sequence of treatments.

The amount and type of chemotherapy given depends on several factors, including:

- Patient's age
- Disease stage
- Patient's physical condition
- Existence of other illnesses

If induction therapy is successful, no detectable leukemic cells will remain following this phase of treatment. This state is called a **complete remission**.

However, even if a complete remission has been achieved, there are often leukemic cells that linger in the bone marrow that can cause the disease to come back. When this happens, it is called relapse. Relapse can occur a few weeks, months, or years after a complete remission is achieved. For this reason, consolidation therapy is usually given to the patient to decrease the likelihood of relapse.

Consolidation therapy

Consolidation therapy can consist of chemotherapy alone, or chemotherapy followed by a stem cell transplant. The type of consolidation therapy recommended will depend on the probability of a relapse and the patient's ability to tolerate additional therapy.

For intermediate or high-risk AML, consolidation therapy options include chemotherapy with or without stem cell transplantation. The choice and intensity of treatment is dependent on the same factors described in the induction therapy section found on page 6.

3. What is a stem cell transplant?

How does allogeneic stem cell transplantation differ from autologous stem cell transplantation?
There are two main types of stem cell transplants – allogeneic and autologous. An allogeneic stem cell transplant is a procedure in which a patient receives blood-forming stem cells from a donor. In contrast, for an autologous stem cell tranpslant, the patient provides his own stem cells for the procedure. Blood stem cells collected from the patient while he is in remission are stored and then returned following conditioning chemotherapy or radiation.

Autologous stem cell transplantation may be used as a consolidation therapy. However, for some patients **allogeneic stem cell transplantation** provides the best chance for a cure.

The rationale for allogeneic stem cell transplantation is two-fold. A chemotherapy or radiation-based treatment before transplantation, called **conditioning**, enables the elimination of the harmful leukemic cells. An undesirable effect however is the destruction of the patient's immune and blood building systems.

Therefore, the first goal of allogeneic stem cell transplantation is to replace the patient's blood and immune system with a healthy one from a donor. The second goal and major advantage of this approach is that newly generated immune cells attack residual leukemic cells, called the **graft-versus-leukemia (GvL) effect**. This makes the disease less likely to return.

How does it work?

In an allogeneic stem cell transplant, stem cells are donated by a healthy individual whose tissue and blood cell type are compatible to the patient. Frequently, the donor is a sibling with an identical tissue type. Other immediate family members can also serve as stem cell donors. Following a successful stem cell transplant, the bone marrow is repopulated with blood stem cells from the healthy donor, which will rebuild the patient's blood and immune systems. This step is critical for the effective treatment of AML.

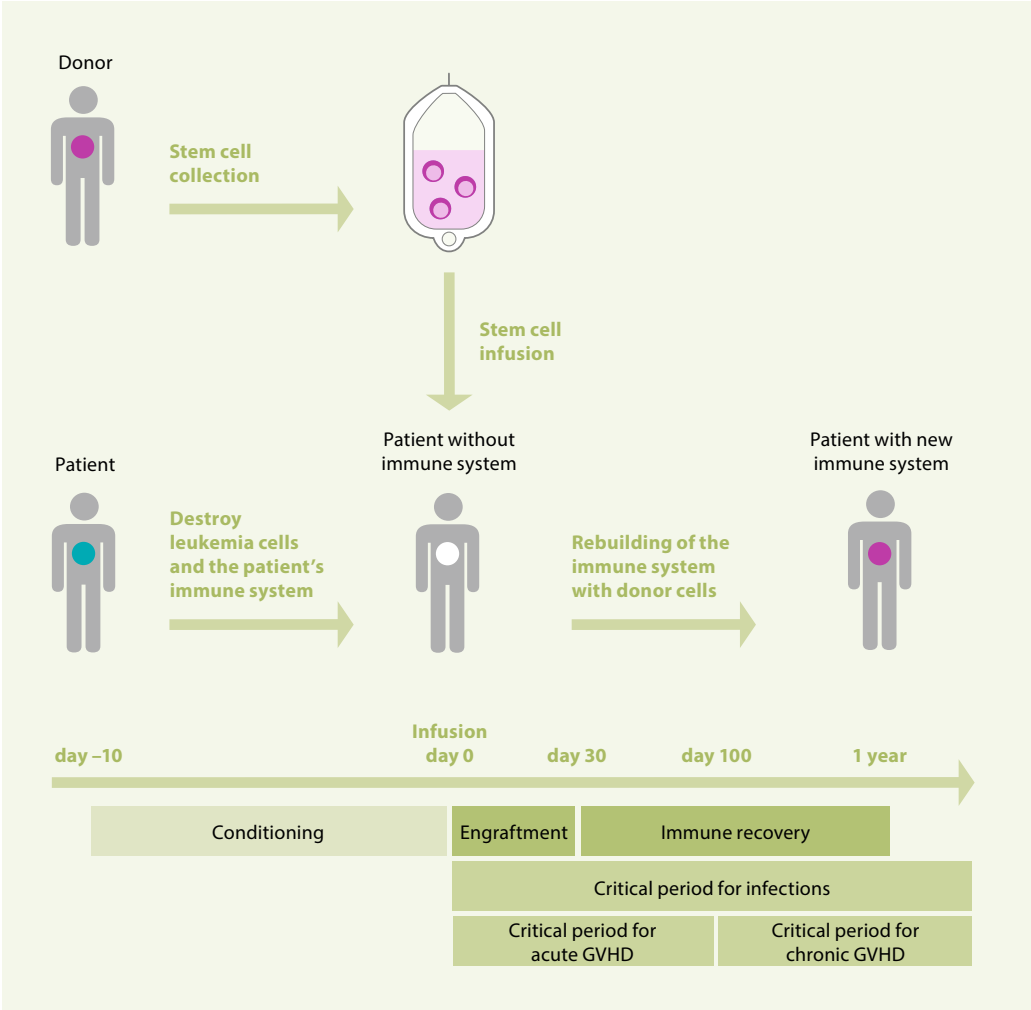

Figure 1: Overview of the process for allogeneic stem cell transplantation.

Why are stem cells transplanted?

Stem cells can be collected from **bone marrow**, the blood stream **(peripheral blood stem cells)**, or **umbilical cord blood**. Harvesting stem cells from bone marrow was the original collection method and has the longest history in stem cell transplantation. Frequently "bone marrow transplantation" is used as the umbrella term for stem cell transplantation. The transplanted cells are called the **"graft"**.

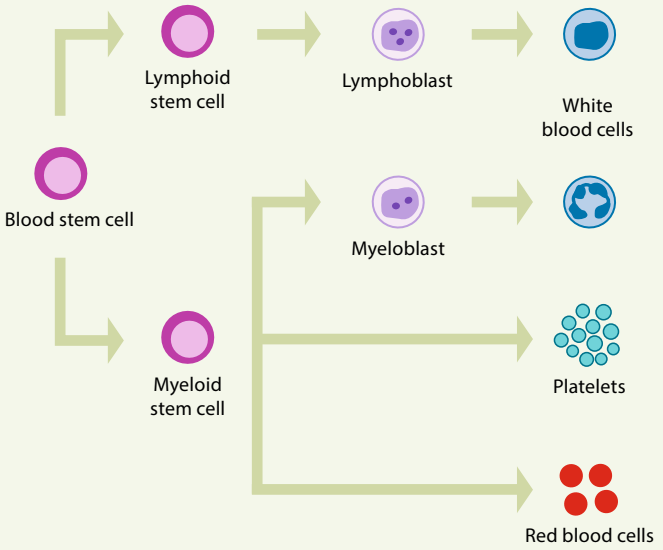

Figure 2: Blood cell development. A blood stem cell goes through several steps to become a white blood cell, platelet, or red blood cell.

Our blood cells develop from a small number of precursor bone marrow cells called blood stem cells. Blood stem cells will develop into white blood cells, red blood cells, or platelets in the presence of specific chemical signals.

- **White blood cells** are cells of the immune system whose function is to fight infections caused by bacteria, viruses, and fungi.
- **Red blood cells** carry oxygen from the lungs to the cells in the body.
- **Platelets**, also called thrombocytes, are pieces of cells that seal damaged blood vessels and help blood to clot. Both functions are important in stopping bleeding.

4. What is GVHD?

Although allogeneic stem cell transplantation is a potentially curative treatment option for AML, it is also associated with the risk of several serious side effects. One potential complication is a disease called graft-versus-host disease (GVHD).

GVHD often occurs following stem cell transplantation as the donor stem cells grow and repopulate the body's immune system. While not every patient develops GVHD, the literature suggests that nearly half of those that undergo an allogeneic stem cell transplant will. A specific type of donor white blood cells, called T cells, identify the patient's body as foreign and attack it.

Normally, these T cells are performing their job correctly by protecting the body from abnormal cells, such as virus-infected or tumor cells. However, in the course of GVHD the transplanted T cells also react against the patient's tissue, resulting in tissue and organ damage.

In severe cases of GVHD, damage can occur in different parts of the body, including the liver, skin, mucosa, and gastrointestinal tract. Symptoms can include rashes, intestinal inflammation, severe diarrhea, nausea, and vomiting.

GVHD is divided into two categories: acute and chronic. Whereas acute GVHD is normally observed within the first 100 days after transplantation, chronic GVHD occurs after 100 days and in some cases, may occur years after transplantation as a long-term side effect of the treatment.

GVHD can be mild, moderate, or severe. In a small percentage of patients, it can even become life threatening. When GVHD becomes a **chronic disease**, it is frequently accompanied by a dramatic decrease in the patient's quality of life.

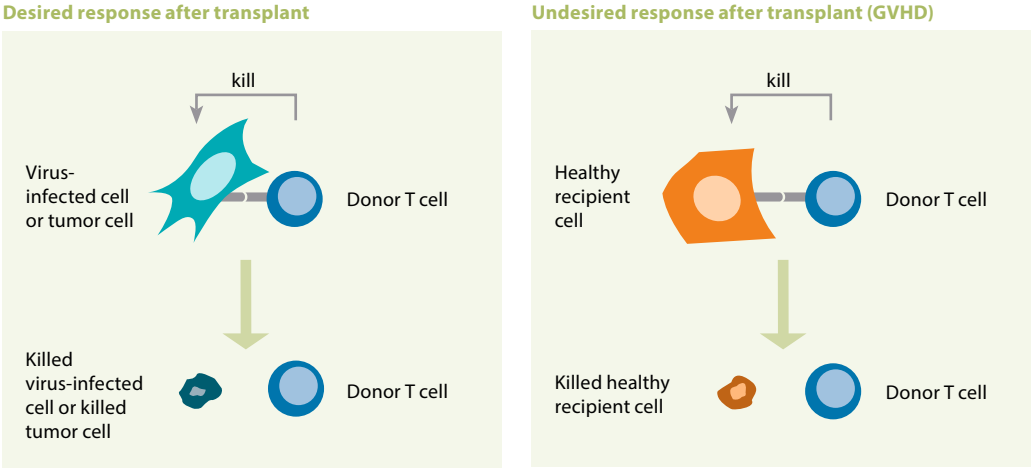

Figure 3: T cells defend the body against virally infected or tumor cells in a normal immune response. When transplanted to a patient, donor T cells may attack the patient's tissue and cause organ damage resulting in a disease called GVHD.

5. Is it possible to prevent GVHD?

What is *ex vivo* T cell depletion?
T cells can be removed from the transplant with the use of a medical device. By collecting the donor blood stem cells, the most important players in the transplant, all other cells, including T cells, are depleted. The highly purified stem cells are then given to the patient.

Different approaches are used to prevent the development of GVHD. Matching of the patient and donor tissue types and immune systems is the first step to avoid an undesired immune response. In addition, **GVHD prophylaxis** can be accomplished with various methods to reduce the activity of T cells from the donor graft.

Immunosuppressive drugs are commonly used to inhibit the activity of the patient's immune system, including the donor T cells. These drugs are used as prophylaxis for GVHD. Unfortunately, immunosuppressive drugs can have severe side effects.

Another viable option for GVHD prophylaxis is the removal of donor T cells prior to transplantation in a process called ***ex vivo* T cell depletion**. Removal of the T cells takes place *ex vivo*, meaning outside the patient's body. This is accomplished by processing donor cells using an FDA-approved medical device before transplantation to the patient.

Magnetic cell separation – a method for *ex vivo* T cell depletion

Cell types of the human body can be identified by the molecules they bear on their surface. Human blood stem cells are often characterized by a protein marker they bear on their surface called **CD34**. By coupling a magnetic particle (comprised of iron and dextran, a sugar molecule) to an antibody that is capable of binding very specifically to the CD34 surface marker, stem cells can be separated from

other cells when placed in a magnetic field within the medical device.

The preparation of a T cell-depleted graft for transplantation involves a series of steps.

- Collection of blood stem cells from the donor
- Incubation with the anti-CD34 magnetic particle
- Passage through a magnetic field
- Retention of the blood stem cells within the magnetic field, while all other donor cells are removed, including potentially harmful T cells
- Removal of the magnetic field and collection of the highly purified stem cells for transplantation

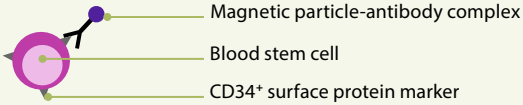

Figure 4: A magnetic particle is coupled to an antibody that can recognize human stem cells expressing the CD34 surface marker.

Magnetic enrichment of blood stem cells is performed with the CliniMACS CD34 Reagent System, a medical device to select and enrich CD34-positive cells from donor **apheresis** products *ex vivo*, meaning outside of the human body.

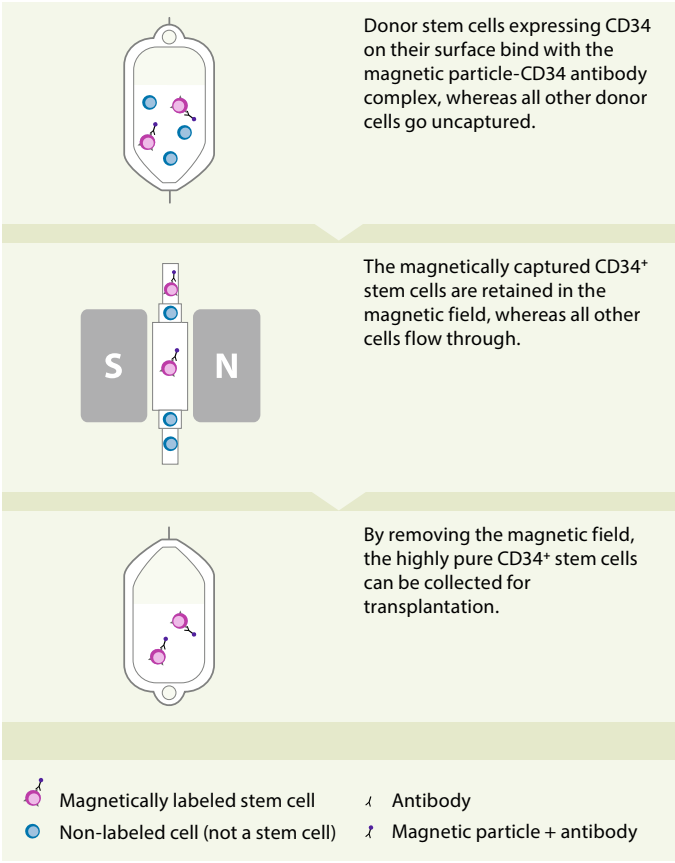

Figure 5: The principle of magnetic stem cell enrichment.

The CliniMACS CD34 Reagent System – clinical outcome

The enrichment of CD34-positive stem cells with the CliniMACS CD34 Reagent System is an FDA-approved method for GVHD prophylaxis for patients with acute myeloid leukemia (AML) in first **complete remission** undergoing allogeneic stem cell transplantation from a **matched-related donor**. Infusion of highly purified blood stem cells eliminates the need for pharmacologic GVHD prevention therapies in these patients.

The depletion of T cells with the CliniMACS CD34 Reagent System results in a low risk of both acute and chronic GVHD for patients with AML in first complete remission undergoing allogeneic SCT from a matched related donor.

The low risk of acute and chronic GVHD by *ex vivo* T cell depletion has been demonstrated in a clinical study conducted by the Bone Marrow Transplantation Clinical Trials Network (BMT CTN 0303).

How can I learn more about the clinical data?

Ask your doctor about the BMT CTN 0303 study that was conducted to evaluate *ex vivo* T cell depletion as GVHD prophylaxis and showed low rates of chronic GVHD in patients receiving T cell-depleted transplants.

6. Glossary

Allogeneic – Taken from a different individual.

Allogeneic stem cell transplantation – A patient receives blood-forming stem cells from a donor.

AML – Acute Myeloid Leukemia (also known as acute myelogenous leukemia) is a cancer of the blood and bone marrow, caused by an overgrowth of immature blood cells.

Apheresis – The withdrawal of donor blood using an automated collection device that spins blood into various layers. During collection, the stem cell-containing layer is seperated from plasma, platelets, and red blood cells. The cells in this layer are retained while all other cells are returned to the donor in the same procedure.

Autologous stem cell transplantation – A patient provides his own stem cells for transplantation. Blood stem cells are collected from the patient while he is in remission and given back following chemotherapy.

Bone marrow – Tissue that fills the cavities of the bones. It contains blood stem cells, the precursors of white blood cells, red blood cells, and platelets. All blood cells originate in the bone marrow.

CD34 – A protein on the surface of blood stem and progenitor cells.

Chemotherapy – Treatment of cancer with chemotherapeutic agents which kill rapidly dividing cells, a characteristic of cancer cells. Unfortunatley all cells that divide rapidly are killed, like hair follicles or digestive tract cells, causing side effects like hair loss and mucositis. It is often used with other treatments, such as radiation and stem cell transplantation.

Chromosomal abnormalities – Chromosomes are the structures that hold your genes. Alteration in their number or structure is called a chromosomal abnormality.

Chronic disease – A long-lasting condition that can be controlled but not cured.

CliniMACS CD34 Reagent System – An FDA-approved medical device to select and enrich CD34-positive cells from donor apheresis products.

Complete remission – No leukemia cells are detectable in a period of time after treatment.

Conditioning – The destruction of the patient's blood and immune system before the transplantation of blood stem cells.

Consolidation therapy – Treatment after induction therapy to destroy any remaining leukemia cells and prevent the recurrence of the disease.

Engraftment – The process in which the transplanted stem cells find their way to the bone marrow and begin to produce new blood cells.

***Ex vivo* –** Outside the body.

***Ex vivo* T cell depletion** – The removal of T cells from the graft before transplantation.

Graft – Cells transplanted to the patient.

Graft-versus-host disease (GVHD) – A serious complication after allogeneic stem cell transplantation in which transplanted cells identify the patient's body as foreign and attack it, resulting in organ damage. Acute GVHD is normally observed within the first 100 days after transplantation, whereas chronic GVHD occurs after 100 days.

GVHD prophylaxis – Attempts to prevent GVHD from developing. Different methods are used to prevent donor T cells from attacking the patient's body, like T cell depletion or immunosuppressive drugs.

Graft-versus-leukemia effect (GvL) – The activity of newly generated immune cells that attack residual leukemic cells.

Immunosuppressive drugs – Agents that inhibit or prevent the activity of the immune system.

Induction therapy – Initial phase of chemotherapy used to remove all detectable leukemia cells and treat the immediate disease.

Matched-related donor – A related person that is chosen to donate his cells for an allogeneic stem cell transplantation and whose tissue type matches that of the patient. A close match between the donor and the patient reduces the likelihood of GVHD.

Myeloid cells – Precursor cells in the bone marrow that develop into white blood cells.

Peripheral blood stem cells (PBSC) – Blood stem cells that moved from the bone marrow into the blood stream and can be collected from there by apheresis.

Platelets – Small cells (thrombocytes) that aggregate at blood vessel injures and seal the vessel to stop bleeding. Normal platelet counts are 150,000–450,000/mm^3. Below 150,000/mm^3, increased bruising and bleeding occur in a condition called thrombocytopenia. Spontaneous bleeding occurs if platelet counts drop below 20,000/mm^3 – which is particularly dangerous if bleeding occurs in the brain or blood leaks from the intestine or stomach.

Red blood cells – Carry oxygen from the lungs to all of the cells in the body. A blood test (hematocrit) shows the percentage of blood composed of red blood cells. The normal range is about 35% to 50% for adults. Percentages below this level indicate anemia, which can lead to pale skin, chills, fatigue, and shortness of breath.

Relapse – The recurrence of cancer.

Remission – See complete remission.

Stem cells – Can differentiate into many different cells. Blood stem cells develop into red blood cells, white blood cells, or platelets in the presence of specific chemical signals. Following a successful stem cell transplant, the bone marrow is repopulated with healthy blood stem cells to rebuild the patient's blood and immune systems.

T cells – A subgroup of white blood cells responsible for defending the body against virally infected or tumor cells. When transplanted to a patient, donor T cells may attack the patient's tissue and cause organ damage, resulting in a disease called graft-versus-host disease.

Umbilical cord blood – A sample of blood taken from a newborn baby's umbilical cord blood. It contains a rich source of stem cells, which could be used in the treatment of over 75 different diseases, including leukemia, lymphoma, and anemia.

White blood cells – Fight infections caused by bacteria, viruses, and fungi. T cells and neutrophils are subgroups which are critical in fighting infections. Infection risk increases when the absolute neutrophil count drops below 1,000/mm^3 in a condition called neutropenia. The greatest danger is at levels below 500/mm^3.

Humanitarian Device
Authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this use has not been demonstrated.

Indications for Use
The CliniMACS® CD34 Reagent System is indicated for processing hematopoietic progenitor cells collected by apheresis (HPC, Apheresis) from an allogeneic, HLA-identical, sibling donor to obtain a $CD34^+$ cell-enriched population for hematopoietic reconstitution following a myeloablative preparative regimen without the need for additional graft versus host disease (GVHD) prophylaxis in patients with acute myeloid leukemia (AML) in first morphologic complete remission.

Contraindications
Do not use $CD34^+$ cells prepared with CliniMACS CD34 Reagent System in patients with known hypersensitivity to murine (mouse) proteins or iron-dextran.

Rx only

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