Anthem

Medical Policy

Subject: Cellular Therapy Products for Allogeneic Stem Cell Transplantation
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Description/Scope

This document addresses stem cell therapy products such as omidubicel, (Omisirge®, Gamida Cell, Ltd. Boston, MA) for hematologic malignancies (blood cancers) which are amenable to stem cell transplantation. Omidubicel is the first U. S. Food and Drug Administration (FDA) approved stem cell therapy product for allogeneic stem cell transplantation.

Note: Please see the following related documents for additional information:

- TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation
- CG-TRANS-03 Donor Lymphocyte Infusion for Hematologic Malignancies after Allogeneic Hematopoietic Progenitor Cell Transplantation

Note: For additional stem cell transplant information and criteria, see the applicable transplant document:

- TRANS.00023 Hematopoietic Stem Cell Transplantation for Multiple Myeloma and Other Plasma Cell Dyscrasias
- TRANS.00024 Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome
- TRANS.00027 Hematopoietic Stem Cell Transplantation for Pediatric Solid Tumors
- TRANS.00028 Hematopoietic Stem Cell Transplantation for Hodgkin Disease and non-Hodgkin Lymphoma
- TRANS.00029 Hematopoietic Stem Cell Transplantation for Genetic Diseases and Aplastic Anemias
- TRANS.00030 Hematopoietic Stem Cell Transplantation for Germ Cell Tumors
- TRANS.00031 Hematopoietic Stem Cell Transplantation for Autoimmune Disease and Miscellaneous Solid Tumors
- TRANS.00034 Hematopoietic Stem Cell Transplantation for Diabetes Mellitus

Position Statement

Medically Necessary:

Use of ex-vivo expansion of cord blood stem cell products (for example, omidubicel) is considered **medically necessary** for individuals when the following criteria are met:

A. 12 years of age or older; **and**
B. Is a candidate for myeloablative allogeneic hematopoietic stem cell transplantation to treat a hematologic malignancy; **and**
C. The appropriate stem cell transplant criteria are met (see related policies above); **and**
D. Is eligible and planned for umbilical cord blood transplantation following myeloablative conditioning; **and**
E. Use is intended to reduce the time to neutrophil recovery and the incidence of infection.

Investigational and Not Medically Necessary:

Use of ex-vivo expansion of cord blood stem cell products (for example, omidubicel) is considered **investigational and not medically necessary** when the criteria above are not met and for all other indications.

Rationale

Umbilical cord blood (UCB) is one option for sourcing cells for hematopoietic transplantation, a potentially curative treatment option for a number of hematologic malignancies and oncologic disorders. Peripheral blood and bone marrow are also options for sourcing hematopoietic cells. UCB transplantations are typically reserved for individuals who do not have a human leukocyte antigen (HLA)-identical matched donor due to the increased risk of early treatment-related morbidity (delayed engraftment, graft failure and infections) and mortality (National Comprehensive Cancer Network [NCCN], 2023).

Omidubicel is a first-in-class, bone marrow transplant product that received Breakthrough Therapy Designation from the FDA and Orphan Drug Designation. On April 17, 2023 the FDA approved omidubicel for use in individuals (12 years and older) with hematologic malignancies who are planned for UCB transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection. FDA approval of omidubicel was primarily based on the pivotal phase 3 international, multi-center, randomized clinical trial (RCT; [NCT02730299]) that assessed safety and efficacy compared to standard UCB transplantation in participants with hematologic malignancies such as lymphoma, leukemia and myelodysplastic syndrome (Horwitz, 2021). The study's primary end point was time to neutrophil engraftment. Over the course of 3 years, (January 2017 to January 2020) 125 individuals ages 13 to 65 years (median age, 41 years) with hematologic malignancies were randomly assigned to omidubicel (n=62) versus standard UCB transplant (n=63; 33% single UCB grafts and 67% double UCB grafts). The majority of the 125 study participants were diagnosed with acute myeloid leukemia (AML; n=60) or acute lymphoblastic leukemia (ALL; n=41). Participants received myeloablative conditioning and prophylaxis for graft-versus-host disease (GVHD) prior to transplant. The treatment arms were well balanced with respect to diagnosis, disease severity, age, gender, and racial diversity; 44% of the study population were non-white participants. Per protocol, 10 participants in the omidubicel arm and 8 in the UCB transplant arm did not proceed to transplant; the final 'analyzed as treated' sample included 108 participants (omidubicel, n=52; UCB, n=56). The median follow-up was 10 months post-transplant. The study's primary outcome was met, with a significantly shorter time to neutrophil engraftment of 12 days (95% confidence interval [CI], 10-14 days) for the omidubicel arm compared to 22 days (95% CI, 19-25 days) for the control arm ($p<0.001$). The cumulative incidence of neutrophil engraftment was 96% in the omidubicel arm and 89% for UCB graft transplants ($p<0.001$). The omidubicel arm had marginally significant faster platelet recovery (55% vs 35% recovery by 42 days; $p=0.03$) and lower incidence of first grade 2 to 3 bacterial or invasive fungal infection (37% vs 57%; $p=0.03$). The cumulative incidence of first grade 3 viral infection during the first year after transplantation was also lower for those in the omidubicel arm (10% vs 26%; $p=0.02$). The omidubicel arm participants spent more time out of hospital during the first 100 days post-transplant (median, 61 vs 48 days; $p=0.005$) compared to the control transplant arm participants. The study was not powered to detect differences in mortality and did not demonstrate differences in GVHD nor survival between the study arms. At 210 days post-transplant, the non-

relapse mortality rate was 11% in the omidubicel arm and 24% in the control arm (p=0.09). This phase 3 study demonstrated the feasibility and clinical benefit omidubicel may provide as an alternative to standard UCB transplant for individuals in need of an HSCT who lack an HLA-identical matched donor.

In 2023, Lin and colleagues analyzed and published health-related quality of life (HRQL) measures from a post-hoc analysis of omidubicel's pivotal RCT (Lin, 2023a). The 108 participants who received a transplant completed HRQL questionnaires at screening and on days 42, 100, 180, and 365 post-transplantation. In the current study, 75 participants who completed key questionnaires at baseline and at least 1 follow-up visit were included in the analysis; the baseline characteristics of completing participants were well balanced between the study arms. Throughout the first year post-transplant, the omidubicel arm demonstrated significantly more improvement in physical, functional, and total Functional Assessment of Cancer Therapy-Bone Marrow Transplant scores ($p<0.05$). The HRQL improvements with omidubicel were observed as early as 42 days post-transplantation and were sustained through 1 year of follow-up. Across both study arms, adverse clinical outcomes, such as grade 3 viral infections and lower rates of engraftment, were associated with lower HRQL scores. This study demonstrates UBC transplant using omidubicel versus standard transplant methods, confers significant, clinically meaningful improvements in self-reported HRQL measures.

In 2023, Lin and colleagues published results from a planned, pooled analysis comprised of 105 study participants diagnosed with hematologic malignancies or sickle cell hemoglobinopathy from 5 multicenter (26 academic centers worldwide) clinical trials who underwent omidubicel transplantation. The median age was 42 years (2-62, range) and 39% (n=41) participants were non-white. The most common diagnosis-types were AML (41%), ALL (27%), MDS (12%) and sickle cell disease (8%). The 3-year estimated overall survival and disease-free survival were 62.7% (95% CI, 52.1 to 71.6%) and 56.4% (95% CI, 45.9 to 65.6%), respectively (median follow-up of 22 months). With up to 10 years of follow-up, omidubicel showed durable trilineage hematopoiesis. Serial quantitative assessments of CD3+, CD4+, CD8+, CD19+, CD116+CD56+, and CD123+ immune subsets revealed median counts remaining within normal ranges through 8 years of follow-up. Within the first year, secondary graft failure occurred in 5 participants (5%; 2 of which had sickle cell disease); no late cases were reported. The 3-year cumulative incidence of disease relapse was 22% and 2 participants were diagnosed with secondary hematologic malignancies (lymphoproliferative disorder at 17 and 20 months post-transplant). A single case of donor-derived myeloid neoplasm was reported at 40 months post-transplantation which also occurred in a control arm participant who received a standard UCB transplant. This study provides the first evidence of omidubicel's graft durability and safety over an extended period of follow-up.

In 2021, Parikh and colleagues published the results of a phase 1/2 study in 13 individuals with severe sickle cell disease who received omidubicel in combination with an unmanipulated UCB graft and 3 who received a single omidubicel graft (n=16; median age of 13 years). Grafts were minimally matched (4 of 6 HLA alleles). A median CD341 expansion of approximately 80-fold was observed and led to rapid neutrophil engraftment at a median of 7 days. The incidence of acute GVHD was high (69% grade 2 to 4 at 100 days post-transplant) but resolved in all 11 surviving study participants in the double-cord group. Event-free survival in the double-cord group was 85% (median follow-up 4 years). All 3 study participants in the single cord group were alive 1 year post transplantation. Overall, 13 of the 16 study participants were alive at study analysis with full donor engraftment and no evidence of sickle cell disease after transplant. Further study of omidubicel in the setting of severe sickle cell disease is warranted in the setting of a randomized controlled trial.

First-in-class omidubicel has demonstrated clinically meaningful benefit, sustained durability and reasonable safety as an alternative to a standard UCB transplant in individuals with hematologic malignancies amendable to HSCT whom lack an HLA-identical matched UCB donor. Expanded access and long-term follow-up studies of the pivotal trial cohort are ongoing. There are also ongoing clinical trials of omidubicel for individuals diagnosed with non-Hodgkin lymphoma (n=99, [NCT05296525; primary completion estimated August 2024]).

Background/Overview

In 2019, there were an estimated 550,000 individuals living with a malignant hematologic (blood) cancer in the U.S. (Centers for Disease Control and Prevention [CDC], 2022). Most hematologic cancers originate in the bone marrow where blood is produced. The three most common types of blood cancers are leukemia, lymphoma and myeloma (American Society of Hematology, 2023).

Hematopoietic stem cell transplantation (HSCT) is an important treatment for hematologic diseases. While the number of individuals who could benefit from HSCT has increased due to advancements such as reduced intensity conditioning regimens that have made HSCT safer, the potential for transplant-associated morbidity and mortality remains significant. Most transplant centers use forums, boards or conferences where the treatment options of individual HSCT candidates are discussed (Majhail, 2015). The decision to transplant is unique to each individual and needs to include a specific risk-benefit analysis in partnership with the individual's physicians and other caregivers. Okamoto (2017) notes:

> The medical decision-making process for a transplant procedure is complex which requires assessing several factors besides the underlying indication for transplantation. Those include patient/disease factors, and transplant factors such as planed conditioning/graft vs host disease (GVHD) prophylaxis and stem cell source. Patient factors include their overall health and comorbidities, prior therapies, and how patients responded to those therapies, age, and disease/disease risk.

HSCT is a process which includes mobilization, harvesting, and transplant of stem cells after the administration of high dose chemotherapy (HDC) and/or radiotherapy. High-dose chemotherapy involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (e.g., opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

- *Autologous* - Stem cells can be harvested from the individual's own bone marrow prior to the cytotoxic therapy.
- *Allogeneic* - Stem cells harvested from a healthy, histocompatible donor.

Donor stem cells, either autologous or allogeneic, are most often collected from either the bone marrow or the peripheral blood. In addition, blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease. The most appropriate stem cell source for a particular individual depends upon his or her disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each individual must balance the risks of graft failure and re-infusion of malignant cells in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

Umbilical cord blood (UCB) transplantations are typically reserved for individuals who do not have a human leukocyte antigen (HLA)-identical matched donor due to the increased risk of early treatment-related morbidity (delayed engraftment, graft failure and infections) and mortality (National Comprehensive Cancer Network [NCCN], 2023). Ex vivo expansion of UCB stem cells prior to transplantation may help address this critical limitation. Omidubicel is an individualized cell product derived from a single banked UCB unit and consists of an ex vivo expanded $CD133^+$ fraction and a nonexpanded $CD133^-$ fraction. The active agent in the culture system, nicotinamide, is intended to inhibit cell differentiation and enhance the functionality of the cultured hematopoietic stem and progenitor cells.

Contraindications and Warnings

The current prescribing information for omidubicel (Omisirge, 2023) includes the following contraindications and black box warnings:

Contraindications:

Omidubicel is contraindicated in individuals with:

- Known sensitivity to dimethyl sulfoxide (DMSO), Dextran 40, gentamicin, human serum albumin or bovine material.

Black Box Warnings:

- Infusion reactions: Infusion reactions may be fatal. Monitor individuals during infusion and discontinue for severe reactions. Use is contraindicated in individuals with known allergy to dimethyl sulfoxide (DMSO), Dextran 40, gentamicin, human serum albumin, or bovine material.
- Graft versus Host Disease (GVHD): GVHD may be fatal. Administration of immunosuppressive therapy may decrease the risk of GVHD.
- Engraftment syndrome: Engraftment syndrome may be fatal. Treat engraftment syndrome promptly with corticosteroids.
- Graft failure: Graft failure may be fatal. Monitor individuals for laboratory evidence of hematopoietic recovery.

Definitions

Ablative: A very high dose of a treatment, calculated to kill a tumor or malignant cells.

Allogeneic: Tissue or cells taken from different individuals from the same species.

Aplastic anemia: Bone marrow is unable to make blood cells.

Ex vivo: Occurring outside of the living body. Refers to a medical procedure in which an organ, cells, or tissue are taken from a living body for a treatment or procedure, and then returned to the living body.

Graft-versus-host disease (GVHD): The condition that results when the immune cells of a transplant (usually of bone marrow) react against the tissues of the person receiving the transplant.

Hematologic malignancy: A cancer of the blood or bone marrow, such as leukemia or lymphoma.

Hematopoietic progenitor cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow. Cells may be obtained from bone marrow, peripheral blood or umbilical cord blood.

Hematopoietic stem cells: Cells that give rise to distinct daughter cells, one cell that replicates the stem cell and one cell that will further proliferate and differentiate into a mature blood cell; also called progenitor cells.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

Leukemia: A type of cancer found in your blood and bone marrow caused by the rapid production of abnormal white blood cells.

Lymphoma: A type of blood cancer that affects the lymphatic system (removes excess fluids from your body and produces immune cells).

Myeloma: A cancer of the plasma cells (white blood cells that produce disease- and infection-fighting antibodies in your body).

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
38999	Unlisted procedure, hemic or lymphatic system [when specified as use of an ex-vivo expansion of cord blood stem cell product such as omidubicel]
HCPCS	
C9399	Unclassified drugs or biologicals [when specified as an ex-vivo expansion of cord blood stem cell product such as omidubicel]
J3490	Unclassified drugs [when specified as an ex-vivo expansion of cord blood stem cell product such as omidubicel]
J3590	Unclassified biologics [when specified as an ex-vivo expansion of cord blood stem cell product such as omidubicel]
ICD-10 Procedure	
XW133C8	Transfusion of omidubicel into peripheral vein, percutaneous approach, new technology group 8
XW143C8	Transfusion of omidubicel into central vein, percutaneous approach, new technology group 8
ICD-10 Diagnosis	
C81.00- C96.9	Malignant neoplasms of lymphoid hematopoietic and related tissue
D46.0-D46.9	Myelodysplastic syndromes

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

References

Peer Reviewed Publications:

1. Horwitz ME, Stiff PJ, Cutler C, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. Blood. 2021; 138(16):1429-1440.
2. Lin C, Sajeev G, Stiff PJ, et al. Health-related quality of life following allogeneic hematopoietic cell transplantation with omidubicel versus umbilical cord blood. Transplant Cell Ther. 2023a; 29(1):52.e1-52.e9.
3. Lin C, Schwarzbach A, Sanz J, Montesinos P, et al. Multicenter long-term follow-up of allogeneic hematopoietic cell transplantation with omidubicel: A pooled analysis of five prospective clinical trials. Transplant Cell Ther. 2023b; 29(5):338.e1-338.e6.
4. Okamoto S. Current indication for hematopoietic cell transplantation in adults. Hematol Oncol Stem Cell Ther. 2017 Jun 30. pii: S1658-S13876.
5. Parikh S, Brochstein JA, Galamidi E, et al. Allogeneic stem cell transplantation with omidubicel in sickle cell disease. Blood Advances. 2021; 5(3):843-852.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Society of Hematology (ASH). Blood Cancers. 2023. Available at: https://www.hematology.org/education/patients/blood-cancers. Accessed on June 2, 2023.
2. Centers for Disease Control and Prevention. USCS: Hematologic Cancer Incidence, Survival and Prevalence. 2022. Available at: https://www.cdc.gov/cancer/uscs/pdf/USCS-DataBrief-No30-September2022-h.pdf. Accessed on June 01, 2023.
3. Gamida Cell ltd. Evaluation of Safety and Efficacy of Allo GDA-201 NK Cells in Patients With Relapsed/Refractory B Cell NHL. NLM Identifier: NCT05296525. Last updated on March 10, 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT05296525. Accessed June 5, 2023.
4. Gamida Cell ltd. Stem Cell Transplantation With NiCord® (Omidubicel) vs Standard UCB in Patients With Leukemia, Lymphoma, and MDS. NLM Identifier: NCT02730299. Last updated on November 15, 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT02730299. Accessed June 5, 2023.
5. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015; 21(11):1863-1869.
6. National Cancer Institute. Blood-Forming Stem Cell Transplantation. Reviewed August 12, 2013. Available at: http://www.cancer.gov/cancertopics/factsheet/Therapy/bone-marrow-transplant. Accessed on June 01, 2023.
7. NCCN Clinical Practice Guidelines in Oncology®. © 2023 National Comprehensive Cancer Network, Inc. Hematopoietic Cell Transplantation (HCT). V1.2023. Revised March 31, 2023. For additional information: http://www.nccn.org/index.asp. Accessed on June 02, 2023.

Websites for Additional Information

1. American Cancer Society. Available at: http://www.acs.org./. Accessed on June 02, 2023.
2. American Society for Transplantation and Cellular Therapy. Patient Education. Available at: https://www.astct.org/learn/patient-education. Accessed on June 01, 2023.

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Cellular Therapy
Cord Blood Stem Cell Therapy Product
Omidubicel (Omisirge)

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.