

Policy Number	RX501.197
Policy Effective Date	10/01/2026

Omidubicel-only

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

EXCEPTION: For members residing in the state of Arkansas, § 23-79-147 relating to off-label prescription drug coverage, requires any plan that covers prescription drugs to provide for the coverage of any anticancer chemotherapeutic regimen ("drug") approved by the U.S. Food and Drug Administration (FDA) when that drug has been recognized as safe and effective for treatment of that specific type of cancer in standard reference compendia, (the American Hospital Formulary Service Drug Information, the National Comprehensive Cancer Network Drugs and Biologics Compendium, The Elsevier Gold Standard's Clinical Pharmacology), or has been recognized as safe and effective for treatment of that specific type of cancer in two [2] articles from medical literature that have not had their recognition of the drug's safety and effectiveness contradicted by clear and convincing evidence presented in another article from medical literature, or other authoritative compendia as identified by the Secretary of the United States Department of Health and Human Services. This coverage must include medically necessary services associated with the administration of the drug, provided that such services are covered by the insurance policy. However, coverage is never required where the FDA has recognized a use to be contraindicated. This applies to the following: Fully Insured Group, Student, Small Group, Mid-Market, Large Group, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

EXCEPTION: New Mexico: For plans delivered, or issued for delivery or renewal on or after January 1, 2025, NMSA 1978 §59A-22B-8 (SB 135) prohibits step therapy requirements before authorizing coverage for medication approved by the U.S. Food and Drug Administration (FDA) that is prescribed for the treatment of an autoimmune disorder, cancer, or a substance use disorder, pursuant to a medical necessity determination, except in cases in which a biosimilar, interchangeable biologic or generic version is available. Any approved step therapy exception may be continued for no less than the duration of the therapeutic effect of the drug. This does not prevent a requirement of a member trying biosimilars, interchangeable biologics or generics of a prescription drug before providing coverage for the equivalent brand name prescription drug. This applies to the following: fully insured group business; Individual and Family Market plans, both on- and off-exchange; the State's Medicaid Plan; and the mandatory coverage for IBAC plans (i.e., State of New Mexico, Public Schools Insurance Authority, Albuquerque Public Schools and the New Mexico Retiree Health Care Authority).

EXCEPTION: For members residing in the state of Louisiana, R.S. 22:999 prohibits excluding coverage for a drug prescribed for the treatment of cancer even where the FDA has not approved the product for that indication so long as that drug is recognized for treatment of the covered indication in a standard reference compendia or in substantially accepted peer reviewed medical literature. Coverage requirement also includes all medically necessary services related to the administration of the product. Coverage is not required where use of the product for the prescribed indication is contraindicated. "Medical literature" means scientific studies published in a journal specified by the United States Department of Health and Human Services pursuant to Section 1861(t)(2)(B) of the Social Security Action, 107 Stat. 591 (1993), 42 U.S.C. 1395x(t)(2)(B), as amended. "Standard reference compendia" means authoritative compendia as identified by the secretary of the United States Department of Health and Human Services.

EXCEPTION: For members residing in the state of Louisiana, R.S. 22:1054.1 requires coverage for a minimum initial treatment period of not less than three months for medically necessary drugs prescribed for the treatment of metastatic or unresectable tumors or other advanced cancers even where the drug is not FDA approved to treat the specific tumor type or a cancer of the location of the body afflicted so long as the drug is FDA approved for the treatment of cancer with the specific genetic mutation. Continued coverage of the prescribed drug shall be provided after the initial treatment period if the treating physician certifies the prescribed drug is medically necessary for the treatment of the patient's cancer based on documented improvement of the patient. Coverage may be denied only if an alternative treatment has proven to be more effective in published randomized clinical trials and is not contraindicated in the patient.

EXCEPTION: For members residing in the state of Arkansas, § 23-79-147 relating to cancer drug step therapy, requires any policy that covers prescription drugs and which provides coverage for the treatment of metastatic cancer to not limit or exclude coverage under the health benefit plan for a drug approved by the United States Food and Drug Administration that is on the prescription drug formulary of the insurance policy by mandating that a covered person with metastatic cancer undergo step therapy unless the preferred drug is consistent with best practices and have an approved indication for the treatment of metastatic cancer or associated conditions by US FDA or the National Comprehensive Cancer Network Drugs and Biologics Compendium or based on evidence-based, peer-reviewed, recognized medical literature. This applies to the following: Fully Insured Group, Student, Small Group, Mid-Market, Large Group, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

Omidubicel-only (Omisirge®) **may be considered medically necessary** for any of the following indications:

- Individuals 12 years of age or older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infections;
- Individuals 6 years of age or older with severe aplastic anemia following reduced intensity conditioning.

Omidubicel-only (Omisirge®) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

The product label of omidubicel recommends that patients be treated under the supervision of a physician experienced in the treatment of hematologic malignancies or severe aplastic anemia at centers with expertise in hematopoietic stem cell transplantation.

The product label contains several boxed warnings:

- Infusion reactions: Fatal infusion reactions may occur. Individuals should be monitored during infusion and discontinue for severe reactions. The use of omidubicel is

contraindicated for individuals with a known allergy to dimethyl sulfoxide, Dextran 40, gentamicin, human serum albumin, or bovine material.

- Graft versus host disease (GVHD): Fatal GVHD may occur. The administration of immunosuppressive therapies may decrease the risk of GVHD.
- Engraftment syndrome: Fatal engraftment syndrome may occur. Engraftment syndrome should be treated promptly with corticosteroids.
- Graft failure: Fatal graft failure may occur. Patients should be monitored for hematopoietic recovery using laboratory evidence.
- Autoimmune cytopenias: Autoimmune cytopenias have occurred following treatment of severe aplastic anemia. Blood counts should be monitored prior to and after infusions.

Description

Diagnoses

Hematologic Malignancies

Hematologic malignancies are a heterogeneous group of diseases characterized by distinct biological subtypes, marked by cellular, immunophenotypic, and genetic profile variations.

Severe Aplastic Anemia

Severe aplastic anemia (SAA) is a rare, life-threatening blood disorder where the bone marrow fails to produce enough red blood cells, white blood cells and platelets.

Treatment

Therapeutic approaches may involve immunosuppressive therapy, hematopoietic cell transplantation, and in cases where a suitable matched donor is unavailable, umbilical cord blood may serve as a source of hematopoietic stem and progenitor cells for transplantation. Ex vivo expansion strategies using nicotinamide have been investigated to expedite hematopoietic recovery and enhance cell volume without inducing differentiation or cellular stress commonly associated with culturing hematopoietic progenitor cells outside their natural environment. Omidubicel is a modified allogeneic hematopoietic progenitor cell therapy derived from cord blood utilizing a proprietary nicotinamide enrichment technology.

Hematopoietic Stem Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or the umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility

is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Umbilical Cord Blood Grafts

Umbilical cord blood (UCB) transplant utilizes blood remaining in the umbilical cord and placenta following the birth of a child. This provides a source of hematopoietic stem and progenitor cells (HSPCs) for allogeneic HCT for individuals who lack an HLA-matched related or unrelated donor. In recent years the demand for UCB transplantation has increased due to: a lack of suitable HLA-matched unrelated donors, this is especially true in individuals who are not of Northern European descent; attrition of donors; timing constraints with identifying and typing a candidate as well as harvesting; and the increased incidence of GVHD when HLA-mismatched donor cells are used. Advantages of using UCB grafts include rapid cell procurement, lower incidence of chronic GVHD, and less stringent HLA-matching requirements. UCB transplantation is typically reserved for patients without an HLA-matched donor and should be performed in centers with expertise in this procedure. Patients without an HLA-matched donor may also be candidates for HCT from a haploidentical, or half HLA-matched, related donor.

Ex Vivo Expansion With Omidubicel

UCB transplantation is limited by the cell doses that can be achieved in recipients with high body weight and is also associated with delayed engraftment, higher risk for graft failure, higher rates of infectious complications, and higher costs for procurement. Omidubicel is a blood-based stem cell therapy derived from a single allogeneic UCB unit. The therapy uses a proprietary expansion technology based on nicotinamide, proposed to enable donor cells to grow while maintaining their functionality, increase homing to the recipient's bone marrow, and retention of engraftment capacity. Omidubicel is designed to accelerate the rate of neutrophil recovery and lower the risk of infection in patients with hematologic malignancies planning allogeneic hematopoietic stem cell transplant (HSCT) but lacking a matched sibling or unrelated donor source.

Regulatory Status

According to the U.S. Food and Drug Administration (FDA), cord blood stored for potential use by a patient unrelated to the donor meets the definitions of “drug” and “biological products.” As such, products must be licensed under a biologics license application or an investigational new drug application before use. Facilities that prepare cord blood units only for autologous and/or first- or second-degree relatives are required to register and list their products, adhere to Good Tissue Practices issued by the FDA, and use applicable processes for donor suitability determination.

In April 2023, Omisurge® (omidubicel-only) was approved by the FDA for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for

umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

In December 2025, Omisirge® (omidubicel-only) was approved by the FDA for use in adults and pediatric patients 6 years and older with severe aplastic anemia following reduced intensity conditioning and for whom a compatible donor is not available. (1)

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Omidubicel for Hematologic Malignancies

Clinical Context and Therapy Purpose

The purpose of omidubicel in individuals with hematologic malignancies is to provide a treatment option that is an improvement over standard allogeneic umbilical cord blood (UCB) transplantation in individuals who lack a matched sibling or matched unrelated donor source.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals 12 years of age or older with hematologic malignancies planning to undergo UCB transplantation following myeloablative conditioning.

Interventions

The therapy being considered is omidubicel.

Comparators

Comparators of interest include standard of care UCB transplantation.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, treatment-related mortality, treatment-related morbidity, and quality of life.

Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Lin et al. (2023) published a pre-planned, pooled analysis of long-term follow-up data from 5 multicenter clinical trials evaluating allogeneic hematopoietic cell transplantation with omidubicel in patients with hematologic malignancies (3 trials, n=97) and sickle cell hemoglobinopathy (2 trials, n=8) (Table 1). (2) Patients had a median age of 42 years, were 48% female and 39% non-white or Hispanic. Most transplantations consisted of single cord units (88%) and had an HLA matching of 4/6 (72%) (Table 2). Primary graft failure occurred in 5 (5%) patients and 1 patient died before engraftment. The pooled population had a median follow-up of 22 months (range 0.3 to 122.5 months) with a 3-year estimated overall survival and disease-free survival rate of 62.7% and 56.4%, respectively (Table 3). The 3-year cumulative incidence of chronic GVHD was 36.6%, while the 3-year cumulative incidence of disease relapse in all patients was 22.2%. The most common causes of death were relapse (n=16), infection (n=11), and acute GVHD (n=6). Secondary malignancies occurred in 3 patients (2 lymphoproliferative disorders and 1 donor-derived myelodysplastic syndrome).

Table 1. Comparison of Trials/Studies Included in SR & M-A

Study	Lin et al. (2023)
Horwitz et al. (2021) (3)	●
Horwitz et al. (2019) (4)	●
Horwitz et al. (2014) (5)	●

Parikh et al. (2021) (6)	●
NCT2504619, unpublished (closed early due to sponsor decision)	●

NCT: national clinical trial; M-A: meta-analyses; SR: systematic review.

Table 2. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Lin et al. (2023) (2)	2011-2021	5	Pediatric or adults with hematologic malignancies or sickle cell hemoglobinopathy undergoing UCB transplantation with omidubicel	105 (1 to 52)	4 single arm studies and 1 RCT	3 years

M-A: meta-analyses; RCT: randomized controlled trial; SR: systematic review; UCB: umbilical cord blood.

Table 3. SR & M-A Results

Study	Overall Survival (95% CI)	Disease-Free Survival (95% CI)	Chronic GVHD (95% CI)	Relapse (95% CI)
Lin et a. (2023) (2); N=105 (5 studies)				
1 year	~71%	~65%	~34%	~18%
3 years	62.7% (52.1% to 71.6%)	56.4% (45.9% to 65.6%)	36.6% (26.9% to 46.2%)	22.2% (14.5% to 31.1%)
5 years	~58%	~56%	~38%	~24%

~indicates estimated from figure.

CI: confidence interval; GVHD: graft versus host disease; N: number; M-A: meta-analyses; SR: systematic review.

Pivotal Trial

A randomized trial (Study P0501, NCT02730299) by Horwitz et al. (2021) investigated omidubicel compared to standard unmanipulated UCB transplantation. Participants included pediatric and adult patients with high-risk hematologic malignancies who were candidates for myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) but did not have a readily available matched sibling or unrelated donor (Table 4). (3, 7) All participants had a UCB unit, HLA matched at 4 or more loci and underwent standard myeloablative conditioning. Patients had a median age of 41 years (range 13-65 years) and included the following cancer types: 48% acute myeloid leukemia (AML), 33% acute lymphoblastic leukemia (ALL), 7% myelodysplastic syndrome (MDS), 5% chronic myeloid leukemia (CML), 4% lymphoma, and 3% other rare leukemias. Participants were randomized 1:1 to receive either omidubicel (n=62) or standard UCB transplantation (n=63) and were stratified on the treatment center, disease risk index, age, and the intent to perform a single or double UCB transplantation. The median follow-up time for all participants was 10 months post-transplantation (range 1 to 19 months); 10 individuals randomized to the omidubicel group and 8 randomized to UCB transplant alone

did not proceed to transplant and were not part of the 'as treated' analyzed population. A single primary endpoint of time to neutrophil engraftment was defined and had 90% power to detect a difference with the selected sample size. Secondary outcomes included the incidence of platelet engraftment on day 42 post-transplant, days alive out of the hospital in the first 100 days post-transplant, and first grade 2 or 3 bacterial or invasive fungal infections within 100 days post-transplant. Several additional outcomes, including safety, infection rate, non-relapse-related mortality (NRM), OS, disease-free survival (DFS), and acute and chronic GVHD, were also reported (Table 5).

The primary outcome of time to neutrophil engraftment favored participants treated with omidubicel over standard of care. The time to neutrophil recovery and the incidence of platelet engraftment also favored the omidubicel-treated arm. The rate of acute grade 2 to 4 GVHD at 100 days (13% difference; 95% confidence interval [CI], -6% to 30%; $p=.18$) or chronic GVHD at 1 year (6% difference; 95% CI, -21% to 7%; $p=.33$) were similar between groups. No significant differences were observed for the rate of relapse at 15 months follow-up (8% difference; $p=.32$), OS (hazard ratio [HR], 0.57; 95% CI, 0.3 to 1.1; $p=.09$), DFS (HR, 0.79; 95% CI, 0.45 to 1.38; $p=.4$), NRM (11% vs. 24%; $p=.09$), or treatment failure (HR, 0.79; 95% CI, 0.45 to 1.38; $p=.4$). The incidence of first grade 2 or 3 bacterial or invasive fungal infection (according to Bone Marrow Transplant & Clinical Trials Network infection severity grading) was significantly lower in patients treated with omidubicel compared to standard UCB ($p=.03$). The authors also found a significant reduction in the incidence of first grade 3 viral infections reported in the omidubicel group ($p=.02$) as well as some other stratified analyses by infection type and grade. More deaths were reported in the standard UCB group ($n=18$) compared to the omidubicel group ($n=11$) with GVHD accounting for 4 deaths in each group. Participants allocated to omidubicel also showed a quicker time to discharge from the hospital than those in the standard of care comparator (27 days vs. 35 days; $p=.005$). The incidence of treatment-related serious adverse events was similar between omidubicel (40%) and standard UCB (41%) groups. Study limitations include: a short median follow-up period for outcomes such as OS, DFS, NRM, and some adverse effects, not being powered to detect differences in important clinical outcomes, and a lack of blinding for participants and investigators.

A supplementary analysis using the same RCT population as the Horwitz trial investigated the health-related quality of life (QOL) for trial participants and prospectively collected data on 3 instruments: the Functional Assessment of Cancer Therapy-General instrument, the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) and the EuroQol 5-Dimension 3-Level tests. (8) Participants were asked to complete these QOL measures at 42, 100, 180 and 365 days post-transplantation. This study used the 'as treated' population, so only 108 of the original 125 participants were eligible, and of those 75 participated (37 in the omidubicel group and 38 in the standard UCB group) by completing 1 or more assessments. Notably, an assessment comparing characteristics of those who participated in the QOL study and those that did not found that the excluded patients had a significantly lower ($p<.001$) incidence of platelet engraftment (54.6% vs. 90.7%) more days in the hospital (66.3 days vs. 43.6 days) and lower 1 year overall survival (42.4% vs. 82.7%). On the FACT-G test, the total FACT-G score was significantly better in the omidubicel versus unmanipulated cord blood

transplantation ($p=.01$) with mean differences ranging from 6 to 6.9 points. This exceeded the minimally important clinical difference (MICD) of 5 at all time points follow-up through 1 year. On the FACT-G subscale of physical wellbeing, a significant difference ($p=.02$) also favored the omidubicel group but significant or MICD was observed for the domains of social/family and emotional quality of life measures on FACT-G. Similarly, the mean change in scores on the FACT-BMT total score also favored the omidubicel group ($p=.01$) and exceeded the MCID of 7 at all follow-up assessments (range 7.2 to 10 points). No significant difference between groups was observed on the EQ-5D-3L index ($p=.06$). Another secondary analysis of the same 'as treated' patient population ($n=108$) focused on hospitalization and healthcare utilization. The authors found that the average hospital length of stay for primary transplantation was shorter in omidubicel recipients compared to UCB (mean, 27.7 days vs. 39.7 days; $p<.001$) as was the total hospital length of stay within the first 100 days post-transplantation (mean, 41.2 days vs. 50.8 days; $p=.027$). (9)

Table 4. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Horwitz (2021) (3)	US, EU, Brazil, Israel, Singapore, and the UK	33	2014-2020	Pediatric or adult participants with hematologic malignancies with no matched sibling or matched unrelated adult donor	62	63

EU: European Union; RCT: randomized controlled trial; UK: United Kingdom; US: United States.

Table 5. Summary of Key RCT Results

Study	Neutrophil Engraftment	Platelet Engraftment	aGVHD	Non-relapse Mortality	Bacterial or Fungal Infection	Viral Infection
Horwitz et al. (2021) (3)	<i>Median time to neutrophil engraftment (days)</i>	<i>Cumulative incidence of platelet engraftment at day 42 after assignment</i>	<i>aGVHD (Grade 2 to 4) at day 100 after assignment</i>	<i>Cumulative incidence of non-relapse mortality at 210 days after assignment</i>	<i>Incidence of first grade 2 or 3 bacterial or invasive fungal infections at 100 days after assignment</i>	<i>Incidence of first grade 3 viral infections at 100 days after assignment</i>
N	125	125	125	125	125	125
Omidubicel transplant	10 (96% neutrophil engraftment)	55%	56%	11%	37%	10%

Standard UCB transplant	20.5 (89% neutrophil engraftment)	35%	43%	24%	57%	26%
Diff (95% CI); p-value	-10.5 days; <.001	20% (3% to 35%); .028	13% (-6% to 30%); .18	-13%; .09	-20%; .03	-16%; .02

aGVHD: acute graft versus host disease; CI: confidence interval; N: number; RCT: randomized controlled trial; UCB: umbilical cord blood.

The purpose of the study limitations tables (see Tables 6 and 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 6. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Horwitz et al. (2021) (3)					1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 7. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Horwitz et al. (2021) (3)	3. Allocation concealment unclear	1,2. Study not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Studies

Tables 8 and 9 describe the characteristics and results of nonrandomized studies, respectively.

Horwitz et al. (2019) evaluated omidubicel (n=36) compared to a cohort of matched historical controls (n=146) from The Center for International Blood and Marrow Transplant Research (CIBMTR) database in patients with high-risk hematologic malignancies and no matched sibling or unrelated donor matches for allogeneic HSCT. (4) The median follow-up of omidubicel recipients was 14 months (range, 5 to 36 months). Neutrophil engraftment was higher in the omidubicel recipients (94%) compared to the historical control group (85%) and showed a significantly higher rate of engraftment (Table 9). Time to platelet engraftment showed a similar trend. The 2-year cumulative incidence of NRM was 24% (95% CI, 11% to 39%) for patients treated with omidubicel and showed a significantly reduced risk of NRM compared to standard UCB (HR, 0.41; 95% CI, 0.19 to 0.88; p=.02). The cumulative rate of relapse at 2 years was 33% (95% CI, 16% to 52%); relapse showed conflicting findings in a multivariate analysis with one showing a significant between-group difference and the other showing no difference depending on which variables were adjusted for in the model. DFS was similar between the omidubicel (DFS, 43%; 95% CI, 24% to 60%) and historical control groups (DFS, 45%; 95% CI, 37% to 53%; p=.77). Omidubicel (OS, 51%; 95% CI, 33% to 67%) and historical control (OS, 48%; 95% CI, 40% to 56%; p=.72) did not differ on rates of 2-year overall survival. No differences were observed in the rate of acute GVHD or the incidence of chronic GVHD at 2-years post-transplantation between the 2 groups.

Horwitz et al. (2025) reported results of a multicenter expanded access program (EAP). (10) In this study, 29 patients with hematologic malignancies were treated with omidubicel. Results were compared to cohorts from the phase 3 study (NCT02730299). The EAP patient characteristics were similar to the phase 3 trial with the exception of the inclusion of patients up to 73 years of age. EAP patients had similar time to hematopoietic recovery to omidubicel-treated patients in the phase 3 study which was shorter than UCB-treated patients. Grade 2 to 4 GVHD was also similar between patients in the EAP and patients in the phase 3 study. Infections were numerically lower among patients in the EAP study compared with either cohort from the phase 3 study. There was no statistically significant difference between cohorts in DFS, disease relapse, or OS at 1 year.

Table 8. Summary of Key Nonrandomized Trials or Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Control	Follow-Up
Horwitz et al. (2019) (4)	Prospective cohort w/ historic control	US, Italy, Netherlands, Singapore, Spain	2013-2017	Pediatric or adult participants with hematologic malignancies with no matched sibling or matched unrelated adult donor	Omidubicel (n=36)	Standard UCB [Historic] (n=146)	2 years
Horwitz et al. (2025) (10)	Prospective cohort with historic control	US	2020-2023	Patients ≥12 years with hematologic malignancies with no matched sibling or matched unrelated adult donor	Omidubicel (n=11)	Omidubicel [Historic from phase 3 study] (n=52) Standard UCB [Historic from phase 3 study] (n=56)	Median 11.8 mos

mos: months; n: number; UCB: umbilical cord blood; US: United States.

Table 9. Summary of Key Nonrandomized Trials or Observational Comparative Study Results

Study	Time to Neutrophil Engraftment (days), Median	Platelet Engraftment (days), Median	aGVHD	OS	DFS
Horwitz et al. (2019) (4)	182	182	182 (at day 100 grade 2 or 4 aGVHD)	182	182
Omidubicel	11.5 (95% CI, 9 to 14)	34 (95% CI, 32 to 42)	44% (95% CI, 28% to 60%)	51% (95% CI, 33% to 67%)	43% (95% CI, 24% to 60%)
Standard UCB [Historic]	21 (95% CI, 20 to 23)	46 (95% CI, 42 to 50)	56% (95% CI, 47% to 64%)	48% (95% CI, 40% to 56%)	45% (95% CI, 37% to 53%)
HR/Diff/OR/RR (95% CI)	Diff, -9.5; p<.001	Diff, -12; p<.001	HR, 0.7; p=.20	HR, 0.7; p=.22	HR, 0.72; p=.24

Horwitz et al. (2025) (10)			Grades 2 to 4, %	1 year OS, %	
Omidubicel [EAP] (n=29)	12 (range, 7 to 35)	33.5 (range, 24 to 58)	63	87	76
Omidubicel [Historic] (n=52)	10 (range, 6 to 35)	37 (range, 21 to 80)	60	77	65
Standard UCB [Historic] (n=56)	20.5 (range, 13 to 40)	50 (range, 21 to 120)	44	64	61
Omidubicel [EAP] vs Omidubicel [Historic]; Diff (p-value)	2 (NS)	3.5 (NS)	3 (NS)	10 (NS)	11 (NS)
Omidubicel [EAP] vs Standard UCB [Historic]; Diff (p-value)	8.5 (.0002)	16.5 (.0012)	19 (NS)	23 (NS)	15 (NS)

aGVHD: acute graft versus host disease; CI: confidence interval; Diff: difference; DFS: disease free survival; EAP: expanded access program; HR: hazard ratio; n: number; NS: not statistically significant; OR: odds ratio; OS: overall survival; RR: relative risk; UCB: umbilical cord blood; vs: versus.

Section Summary: Omidubicel for Hematologic Malignancies

For individuals who have hematologic malignancies and undergo omidubicel-modified UCB transplant, the evidence includes 3 cohort studies with historic controls, one RCT with 2 supplementary analyses, and 1 pooled analysis of long-term follow-up data. The RCT found that compared to patients treated with standard UCB, omidubicel-treated patients had a significantly lower time to neutrophil and platelet engraftment, neutrophil recovery, as well as a significant reduction in the incidence of first grade 2 or 3 invasive fungal or bacterial infections and grade 3 viral infections. Differences in OS, DFS, NRM, treatment failure, the rate of acute or chronic GVHD, and treatment-related adverse events were not observed between groups. Supplementary analyses found that omidubicel-treated participants were likelier to have improved scores on several quality-of-life measures and have lower average hospitalization times within the first 100 days of transplant. The evidence from the non-randomized studies suggests that compared to standard UCB, omidubicel showed a faster time to neutrophil and platelet engraftment and a lower rate of bacterial infections compared to historic controls, but no differences in the rates of engraftment failure, acute or chronic GVHD, OS, or DFS. A pooled, patient-level analysis utilizing data predominantly from the RCT and 4 other studies found that rates of OS, DFS, GVHD, and relapse were durable through 3 years of follow-up, although this analysis included a minority of patients with sickle cell hemoglobinopathy.

Practice Guidelines and Position Statements

American Academy of Pediatrics

The American Academy of Pediatrics issued a position statement in 2017 concerning cord blood banking and selection, but the statement contained no discussion of ex vivo expansion. (11)

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines on hematopoietic cell transplantation (v3.2026) state that if a myeloablative conditioning regimen is planned for a recipient of umbilical cord blood, omidubicel-only has been shown to shorten the time to engraftment and reduce the risk of some infections (Grade 2A). (12) NCCN guidance on acute lymphoblastic leukemia (v3.2026), acute myeloid leukemia (v5.2026), B-cell lymphomas (v4.2026), chronic myeloid leukemia (v2.2027), myelodysplastic syndromes (v3.2026), and Hodgkin lymphoma (v2.2026) do not provide recommendations on the use of omidubicel or ex vivo expansion of cord blood more generally. (13-18)

American Society for Transplantation and Cellular Therapy

The American Society for Transplantation and Cellular Therapy published guidelines on the indications for hematopoietic cell transplantation and immune effector cell therapy in 2020; these guidelines did not provide recommendations on the use of omidubicel or ex vivo expansion of cord blood. (19)

Omidubicel For Severe Aplastic Anemia (1)

The efficacy of Omisirge in patients with severe aplastic anemia (SAA) was evaluated in study 17-H-0091 (NCT 03173937), an open-label, single center study. The study enrolled patients with SAA who had intolerance or failure to respond to immunosuppressive therapy and availability of at least one $\geq 4/8$ human leukocyte antigen (HLA)-matched (HLA-A, B, C and DR loci) cord blood unit. Patients were excluded if there was availability of an HLA identical (12/12) matched related or unrelated donor.

In total, 17 patients were treated with Omisirge, among them 14 patients were treated with Omisirge alone and three patients were treated with both Omisirge and haploidentical CD34+ cells. The minimum specifications of Omisirge were a Total Nucleated Viable Cell (TNVC) count of 8.0×10^8 cells and CD34+ cell count of 9.2×10^7 . The fourteen patients who were transplanted with Omisirge alone were included in the efficacy evaluation. The median CD34+ cell dose of Omisirge was 9.5×10^6 cells/kg (range, 2.3 - 21.4 cells/kg). All patients received reduced intensity conditioning which included cyclophosphamide, fludarabine, total body irradiation (TBI) and horse-ATG (equine anti-thymocyte globulin). GVHD prophylaxis was administered according to institutional guidelines.

The demographic characteristic of the population included the following: median age was 17 years (range: 6 – 45), 10 patients (59%) were male, 6 patients (35%) were Black, 3 patients (18%) were White, 5 patients (29%) were Asian, and 3 patients (18%) were of “other races” or “unknown”. Twenty-nine percent of patients identified as Hispanic or Latino. Median absolute neutrophil count at baseline was $0.3 \times 10^9/L$ (range, 0.0 – 1.0) and median platelet count at

baseline was $35 \times 10^9/L$ (range, 10-89). Hematopoietic stem cell transplantation (HSCT) specific comorbidity index was ≥ 3 in 76% and 0-2 in 24% of patients. Twelve percent of patients received 4/8 HLA match, 59% 5/8 HLA match, 18% 6/8 HLA match, 6% 7/8 HLA match and 6% 8/8 HLA match.

The primary efficacy outcome measure was the incidence of early and sustained neutrophil recovery, defined as absolute neutrophil count (ANC) ≥ 500 cells/ μL for 3 consecutive measurements on different days by Day 26, maintained at Days 42 and 100 posttransplant. Other secondary efficacy outcomes were neutrophil recovery (days to first of three consecutive ANC ≥ 500 cells/ μL), red blood cell (RBC) transfusion independence (days to 30-day transfusion independence), platelet recovery $\geq 20,000/\mu L$ (days to first of 3 consecutive platelet count of 20,000/ μL with no preceding transfusion in 7 days) and platelet transfusion independence (days to 30-day platelet transfusion independence).

The efficacy results are summarized in Table 10 below.

Table 10. Efficacy Results from Study 17-H-0091

Efficacy Outcome	N=14
Patients with early and sustained neutrophil recovery at 100 days n (%) (95% CI) ¹	12 (86%) (57%, 98%)
Time to neutrophil recovery ² Median days (min - max) ³	11 (7 – 20)
Time to RBC transfusion independence Number patients who achieved (%) Median days (min - max) ³	12 (86%) 58.5 (42 – 446)
Time to platelet 20,000/ μL recovery Number patients who achieved within a year (%) Median days (min – max) ³	12 (86%) 31.5 (20 – 197)
Time to platelet transfusion independence No. patients who achieved (%) Median days (min - max) ³	11 (79%) 53.0 (43 – 93)

¹ 95% CI was calculated by the Clopper-Pearson method.

² Time to neutrophil recovery was defined as ANC ≥ 500 cells/ μL for 3 consecutive measurements on different days.

³ Based on patients who achieved the events.

CI: Confidence interval; max: Maximum; min: Minimum; N/n: number; RBC: red blood cells.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 11.

Table 11. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT03173937	Unrelated Umbilical Cord Blood Transplantation for Severe Aplastic Anemia and Hypo-plastic MDS Using CordIn(TM), Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells to Expedite Engraftment and Improve Transplant Outcome	37	Mar 2032

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3406

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

Policy History/Revision	
Date	Description of Change
10/01/2026	New medical document. Omidubicel-only (Omisirge®) may be considered medically necessary for any of the following indications: • Individuals 12 years of age or older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infections; • Individuals 6 years of age or older with severe aplastic anemia following reduced intensity conditioning. Omidubicel-only (Omisirge®) is considered experimental, investigational and/or unproven for all other non-Food and Drug Administration approved indications.