Molina Clinical Policy
OMISIRGE (omidubicel-onlv): Policy No. 435

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Ohio Medicaid Members: The Ohio Transplant Consortium Approval eliminates the requirement of Corporate Transplant Team approval (pre-transplant evaluation) for Ohio Medicaid members. OAC 5160-2-65 (L) and will follow consortium recommendation.

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Acute Lymphocytic Leukemia (ALL)

Acute leukemias comprise a heterogeneous group of neoplastic disorders that arise from malignant transformation of blood-forming, or hematopoietic, stem cells. Malignant transformation typically involves chromosomal rearrangements (translocations), deletions, or additions, which disturb the normal control of cell division, allowing affected cells to multiply without restraint. Clones, or leukemic cells, arising from such transformation particularly influence the development of white blood cells or leukocytes, and rapidly proliferate in the bone marrow, replacing normal cells and causing anemia, thrombocytopenia, and granulocytopenia. After release into the blood stream, leukemic cells can infiltrate any organ or site and often spread to the liver, spleen, lymph nodes, central nervous system (CNS), and gonads, where they continue to grow and divide, resulting in tumors, inflammation, and/or organ damage and failure. One of two major types of acute leukemia, ALL involves stem cells that normally become lymphoblasts, the precursors of leukocytes known as lymphocytes. It is an aggressive type of leukemia characterized by the presence of too many lymphoblasts or lymphocytes in the bone marrow and peripheral blood; ALL can spread to the lymph nodes, spleen, liver, CNS, and other organs. Without treatment, ALL usually progresses quickly. (Stock & Estrov, 2022; [1-2] DynaMed, date unknown).

In 2022, there were an estimated 6,660 new cases and 1,560 deaths from ALL in the United States. ALL occurs in both children and adults, and it is the most common type of cancer in children. ALL is believed to arise from malignant transformation of B- or T-cell progenitor cells. The disease is characterized by the accumulation of lymphoblasts in the marrow or in various extramedullary sites. The World Health Organization (2022) classifies ALL as either B lymphoblastic leukemia or T lymphoblastic leukemia. B lymphoblastic leukemia is subdivided by the presence or absence of specific recurrent genetic abnormalities (t(9;22)), MLL rearrangement, t(12;21), hyperdiploidy, hypodiploidy, t(5;14), and t(1;19). Current treatment decisions rely on the immunophenotype (early-pre-B ALL, pre-B ALL, B-cell ALL, or T-cell ALL) and cytogenetics of affected cells. ([1] NCI, 2023; [2] NCI, 2023).

Chronic Myeloid Leukemia (CML)

Chronic Myelogenous Leukemia (CML or chronic granulocytic leukemia or chronic myeloid leukemia) is a disease of both the bone marrow and blood. It is classified as a myeloproliferative neoplasm. It most often occurs in middle-aged adults. CML is characterized by the fact that too many granulocytes (neutrophils, eosinophils, and basophils), and not enough red blood cells and platelets, develop from bone marrow myeloid stem cells. This can lead to anemia, infection, and problems with hemostasis. Signs and symptoms of CML may include night sweats, fever, exhaustion, and weight loss. It is thought that CML is due to a non-inherited genetic mutation called the on chromosome 22. The Philadelphia chromosome (Ph) results in the enzyme tyrosine kinase being produced in the bone marrow, and it is this enzyme that causes too many of the myeloid stem cells to take the path of converting into granulocytes, rather than red blood cells

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or platelets. CML can occur at any age, however it most often appears in adults with a median age of 60-65 years. There are three phases of the disease that consist of an initial (indolent) chronic phase, lasting a median of 3 years, which typically transforms into an accelerated phase, followed by a blast phase or "blast crisis," which is usually the terminal event. Conventional-dose regimens used for chronic-phase disease can induce multiple remissions and delay the onset of blast crisis to a median of 4–6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors. ([3] NCI, 2023; [4] NCI, 2023; [1] NMPD, date unknown).

Myelodysplastic Syndrome

Myelodysplastic syndromes (MDS) consist of a heterogeneous group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production and a varying risk of transformation to acute leukemia. Patients with MDS have reduced production of red blood cells, platelets, and mature granulocytes – abnormalities often result in anemia, bleeding, and increased risk of infection. MDS occur predominantly in older patients (≥ 60 years). The median age at diagnosis is approximately 70 years; however, patients as young as 2 years have been reported. Older men are more commonly affected by MDS. The isolated chromosome 5q deletion subtype (del5q) is more common in women. Signs and symptoms at presentation of MDS are nonspecific. Many patients are asymptomatic at diagnosis and only come to the provider's attention based upon abnormalities found on routine blood counts (e.g., anemia, neutropenia, and thrombocytopenia). Others present with symptoms or complications resulting from a previously unrecognized cytopenia (e.g., infection, fatigue). MDS is diagnosed based on an evaluation of the bone marrow and peripheral smear. The revised International Prognostic Scoring System (IPSS-R) should be used to incorporate information on bone marrow blast percentage, karyotype, and cytopenias for the purpose of stratifying the MDS into risk groups to guide management. Patients with a very low (≤1.5 points) or low (>1.5 to 3 points) IPSS-R score are primarily treated with supportive care or low intensity therapies such as azacitidine, decitabine, or immunosuppressive therapy. Patients with a high (>4.5 to 6 points) or very high (>6 points) IPSS-R score with a good performance status are primarily treated with combination chemotherapy or allogeneic hematopoietic cell transplantation (HCT) to alter the disease course. Treatment options for patients with an intermediate-risk (>3 to 4.5 points) IPSS-R score include those therapies used for patients with low- or very low-risk IPSS-R scores, and the more intensive therapies typically used for patients with high- or very high-risk IPSS-R scores. (Chao, 2022; Deeg & Sandmaier, 2022; Negrin, 2022; Sekeres & Platzbecker, 2022; Aster & Stone, 2021; Negrin, 2020; NLM, 2016; [3] DynaMed, date unknown; MSF, date unknown).

Acute Myeloid Leukemia (AML)

As in ALL, AML usually arises from the transformation of clones which disturb the normal control of cell division, allowing affected cells to multiply without restraint. After release into the blood stream, leukemic cells can infiltrate any organ or site and often spread to the liver, spleen, lymph nodes, CNS. Acute myeloid leukemia (AML) is also called acute myeloblastic leukemia, acute myelogenous leukemia, and acute nonlymphocytic leukemia (ANLL). AML is an aggressive disease in which too many myeloblasts or immature white blood cells are found in the bone marrow and blood. Two methods are commonly used to classify AML. The French American British (FAB) Cooperative Group classification is based on morphological-histochemical cell characteristics and identifies eight subtypes of AML and categorized as M0 - M7 ([2-7] NMDP, date unknown).

The World Health Organization (WHO, 2022) Classification System incorporates clinical, morphologic, immunophenotypic, cytogenetic and molecular markers that can be used to direct treatment that include five major subcategories of AML:

1. AML with recurrent genetic abnormalities;
2. AML with multilineage dysplasia;
3. Therapy-related AML and MDS;
4. AML not otherwise categorized; and
5. Acute leukemia of ambiguous lineage.

The National Cancer Institute ([5] NCI, 2023) notes that certain gene and cytogenetic abnormalities have been identified as high-risk for a poor prognosis with chemotherapy. These include internal tandem duplication of the FLT3 (FMS-related

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tyrosine kinase 3) gene, mutation of the tp53 gene, deletions of the long arms or monosomies of chromosomes 5 or 7; translocations or inversions of chromosome 3, t(6;9), t(9;22) and abnormalities of chromosome 11q23, t(10;11) translocation, t(1;22)(p13;q13) translocation, trisomy 8, and certain antigens/glycoproteins. Most children and adults with newly diagnosed AML undergo systemic multiagent chemotherapy designed to induce disease remission (induction therapy). These aggressive treatment approaches produce severe bone marrow aplasia and suppression of the hematopoietic system, which may lead to morbidity and mortality from infection or hemorrhage. Therefore, therapy is combined with appropriate supportive care involving early recognition and treatment of infection and, when necessary, red blood cell and platelet transfusions. With effective anticancer agents and appropriate supportive care, complete remission (CR) occurs in 75% to 90% of the children and 60% to 70% of the adults with AML. Even with treatment most patients relapse and die from leukemia. Among those who achieve first CR (CR1), disease-free survival has averaged only 40% at 5 years in children and overall survival with or without disease has averaged only 25% at ≥ 3 years in adults.

Since undetected minimal residual disease is a major cause of relapse, patients in CR usually undergo a second phase and, often, a third phase of multiagent chemotherapy known as consolidation therapy and intensification therapy, respectively, which frequently employ different agents and/or higher doses than used in induction therapy to eradicate residual disease. High-dose chemotherapy may be administered for this purpose but also ablates normal marrow (myeloablation), thereby destroying the hematopoietic system.

Hodgkin Lymphoma

Lymphomas are neoplasms of the lymphatic system, a network of blood-filtering tissues that help fight infection and disease found in the lymph nodes, spleen, thymus gland, adenoids, tonsils, and bone marrow. Lymphomas affect lymphocytes which are specialized white blood cells responsible for immunity. Hodgkin lymphoma spreads in an orderly manner, typically from one group of lymph nodes to another. Symptoms include swollen lymph nodes (particularly where the lymphoma originates), fever, night sweats, fatigue, and weight loss ([6,7] NCI, 2023; CDC, 2018).

Hodgkin lymphoma is marked by the presence of Reed-Sternberg cells which are large, abnormal lymphocytes (a type of white blood cell) that can contain more than one nucleus. The two types of Hodgkin lymphoma are classical and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Most cases are the classical type which includes four subtypes: nodular sclerosing; mixed cellularity; lymphocyte-depleted; lymphocyte-rich classic. Among non-classical types, NLPHL is rare and typically grows slower than classic Hodgkin lymphoma. This type presents as a swollen lymph node in the neck, chest, armpit, or groin; many have no additional signs or symptoms of cancer at diagnosis. Treatment typically differs from classic Hodgkin lymphoma. ([6,7] NCI, 2023).

Being in early or late adulthood, being male, past Epstein-Barr (EBV) infection, and a family history of Hodgkin lymphoma can increase the risk of adult Hodgkin lymphoma. Among children and adolescents diagnosed with Hodgkin lymphoma, the nodular-sclerosing type is often diagnosed in older children and adolescents and typically presents as a chest mass at diagnosis. Mixed cellularity Hodgkin lymphoma is typically diagnosed in those age 10 and under; it presents as lymph nodes in the neck and there is a connection to EBV infection. Lymphocyte-rich classic Hodgkin lymphoma is rare in children; upon viewing under a microscope, tissue samples include Reed-Sternberg cells as well as normal lymphocytes and other blood cells. Lymphocyte-depleted Hodgkin lymphoma is also rare in children and is typically found in adults and adults with HIV/AIDS. Microscope analysis shows large, oddly shaped cancer cells and few normal lymphocytes and other blood cells. ([6,7] NCI, 2023).

This form is usually curable in some patients who receive prompt treatment. In 2021, there were 8,830 new cases diagnosed in the United States; this accounts for 0.5% of all new cancer cases. An estimated 960 people died in 2021 (0.2% of all cancer deaths). The five-year relative survival rate for Hodgkin lymphoma is 88.3%. ([6,7] NCI, 2023). Rates of new diagnoses of Hodgkin lymphoma (per 100,000 people) are slightly higher in males (2.8) than females (2.3). By age, rates are highest in those ages 80-84 (4.1), ages 20-24 (4.0), ages 25-29 (3.8), ages 75-79 (3.8), ages 70-74 (3.6). By race and ethnicity, new diagnoses are highest in White (2.6), Black (2.5), and Hispanic (2.2) populations. (CDC, 2018).

Omisirge (Omidubicel-onlv)

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Omisirge (Omidubicel-onlv) is an ex vivo expanded hematopoietic progenitor cell and non-expanded myeloid and lymphoid cell product derived from a single umbilical cord blood unit. Omidubicel-onlv utilizes the small molecule nicotinamide to inhibit differentiation and to increase the migration, bone marrow homing and engraftment efficiency of hematopoietic progenitor cells. Omidubicel-onlv is cryopreserved and composed of the cultured fraction (CF) and non-cultured fraction (NF) of the same unit of cord blood. The CF is the ex vivo expanded, umbilical cord blood derived hematopoietic CD34+ progenitor cells. For some high-risk hematologic malignancies, allogeneic hematopoietic stem cell transplantation (HSCT) is the only potential curative treatment; however, about 40% of patients do not receive transplant due to many factors, including inability to find a matched donor. For those patients able to receive HSCT, they may develop complications such as graft-versus-host disease, infection and increased early treatment-related morbidity and mortality due to delayed hematopoietic and immunologic recovery. Omidubicel-onlv addresses these challenges by providing rapid and durable engraftment by expanding hematopoietic stem and progenitor cells leading to faster neutrophil recovery after myeloablative conditioning. There are approximately 2000-2500 patients in the United States with blood malignancies that are eligible for transplant, but unable to find a donor. (Horwitz et al., 2021).

Omisirge (Omidubicel-onlv) was FDA (Food and Drug Administration) approved on April 17, 2023, for adult and pediatric patients 12 years and older with hematologic malignancies (ALL, CML, AML, MDS, and Hodgkin Lymphoma) planned for umbilical cord blood transplantation (UCBT) following a myeloablative conditioning regimen.

RELATED POLICIES

MCP-118: Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia (ALL)
MCP-119: Hematopoietic Stem Cell Transplantation for Acute Myelogenous Leukemia (AML)
MCP-143: Hematopoietic Stem Cell Transplantation for Aplastic Anemia
MCP-188: Hematopoietic Stem Cell Transplantation for Chronic Lymphoblastic Leukemia (CLL)
MCP-187: Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia (CML)
MCP-272: Hematopoietic Stem Cell Transplantation for Ewing's Sarcoma
MCP-194: Hematopoietic Stem Cell Transplantation for Germ Cell Tumors
MCP-125: Hematopoietic Stem Cell Transplantation for Hodgkin's and Non-Hodgkin's Lymphoma
MCP-265: Hematopoietic Stem Cell Transplantation for Immunodeficiency Disorders
MCP-256: Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses (MPS)
MCP-122: Hematopoietic Stem Cell Transplantation for Multiple Myeloma
MCP-309: Hematopoietic Stem Cell Transplantation for Myelodysplastic Syndromes
MCP-193: Hematopoietic Stem Cell Transplantation for Neuroblastoma
MCP-324: Hematopoietic Stem Cell Transplantation for Primary Myelofibrosis
MCP-209: Hematopoietic Stem Cell Transplantation for Sickle Cell Anemia
MCP-283: Hematopoietic Stem Cell Transplantation for Wilms Tumor

COVERAGE POLICY

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be reviewed by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, State regulations, and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Pre-Transplant Evaluation

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Please see *MCP-323 Pre-Transplant Evaluation* for additional criteria and information.

Criteria for transplant evaluation include:

1. History and physical examination; **AND**

2. Psychosocial evaluation and clearance:
   a. No behavioral health disorder by history or psychosocial issues:
      - If history of behavioral health disorder, no severe psychosis or personality disorder;
      - Mood/anxiety disorder must be excluded or treated;
      - Member understands surgical risk and post procedure compliance and follow-up required.

   AND
   b. Adequate family and social support.

AND

3. EKG; **AND**

4. Chest x-ray; **AND**

5. Cardiac clearance in the presence of any of the following:
   a. Chronic smokers; **OR**
   b. Members > 50 years age; **OR**
   c. Those with a clinical or family history of heart disease or diabetes.

AND

6. Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease; **AND**

7. Neurological exam and clearance for transplant including **ONE** of the following:
   a. Normal neurologic exam; **OR**
   b. Non-life limiting neurological impairment that does not preclude transplant and not caused by hematologic malignancy (e.g., diabetic peripheral neuropathy); **OR**
   c. Abnormal neurological exam with positive findings including **ONE** of the following:
      - Lumbar puncture normal cytology; **OR**
      - Lumbar puncture with cytological exam abnormal, however central nervous system disease treated prior to clearance.

AND

8. A Performance Status that includes **ONE** of the following:
   a. Karnofsky score 70-100%; **OR**
   b. Eastern Cooperative Oncology Group (ECOG) Grade 0-2.

AND

9. Lab studies that include:
   a. Complete blood count; kidney profile (blood urea nitrogen, creatinine); electrolytes; calcium; phosphorous; albumin; liver function tests; and coagulation profile (prothrombin time, and partial thromboplastin time);*
   b. Serologic screening for: HIV (Human Immunodeficiency Virus); Epstein Barr virus (EBV); Hepatitis virus B (HBV); Hepatitis C (HCV); cytomegalovirus (CMV); rapid plasma reagin (RPR) and/or fluorescent treponemal antibody (FTA):*
      - If HIV positive **ALL** of the following must be met:
        i. CD4 count >200 cells/mm-3 for >6 months; **AND**

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ii. Human Immunodeficiency Virus 1 (HIV-1) ribonucleic acid undetectable; **AND**
iii. On stable anti-retroviral therapy >3 months; **AND**
iv. No other complications from Acquired Immunodeficiency Syndrome (AIDS) (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm).

c. Urine drug screen if Member is current or gives a history of past drug abuse.

AND

10. Colonoscopy (if indicated or if Member is age ≥ 45) with complete workup and treatment of abnormal results as indicated; an initial screening colonoscopy after initial negative screening requires a follow-up colonoscopy every 10 years).*

AND

11. Gynecological examination with Pap smear for women ages ≥ 21 to ≤ 65 years of age or if indicated (not indicated in women who have had a total abdominal hysterectomy or a total vaginal hysterectomy) within the last three years with complete workup and treatment of abnormal results as indicated.*

Within the last 12 months:

1. Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre- or post-transplant; **AND**
2. Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated; * **AND**
3. Prostate Specific Antigen (PSA) if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated.*

* Participating Centers of Excellence may waive these criteria.

Criteria for Omisirge (Omidubicel-onlv)

Omidubicel-onlv **may be considered medically necessary** for members who meet criteria for umbilical cord blood transplant when the following criteria are met.

1. All applicable pre-transplant criteria are met; **AND**
2. Documentation of a hematologic malignancy without symptoms of CNS disease (e.g., Acute Lymphocytic Leukemia, Chronic Myeloid Leukemia, Myelodysplastic Syndrome, Acute Myeloid Leukemia, Hodgkin Lymphoma, Non-Hodgkin lymphoma, Acute Lymphoblastic leukemia etc.); **AND**
3. Member is between 12 years old and 65; **AND**
4. Member does not have an allogeneic human leukocyte antigen (HLA) matched donor OR had allogeneic hematopoietic stem cell transplantation in the past; **AND**
5. Favorable Karnofsky/Lansky Performance Status; **AND**
6. Member does not have an active or uncontrolled infection of any kind; **AND**
7. Member does not have any other documented current active non-hematologic malignancy; **AND**
8. Member does not have known hypersensitivity to dimethyl sulfoxide (DMSO), Dextran 40, gentamicin, human serum albumin, or bovine products; **AND**
9. For Women of child-bearing potential: Documentation or attestation that member is not pregnant or lactating.

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Continuation of Therapy

This is only approved for one time use.

For Members with Significant or Daily Cannabis Use

1. Documentation of compliance with a physician prescribed and managed program of abstinence, and a reasonable expectation that the Member will be abstinent from cannabis use during the transplant and immediate post-transplant time-period. Daily cannabis use is an absolute contraindication for both transplant and pre-transplant evaluation unless there is a state mandate applicable for medical cannabis use and transplants, and there is documentation of Member compliance with a physician prescribed plan of care for prescribed cannabis use.
2. If the Member's cannabis use follows a formal, State-based program for managed medical cannabis, the request should include:
   - Documentation of the Plan of Care for medical cannabis (including the medical decision making that supports the use of medical cannabis); **AND**
   - Transplant Provider agreement with the Plan of Care (including agreement to be accountable for managing the Member's use of medical cannabis).

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Omisirge (Omidubicel-onlv) was studied in a phase 3 (P0501), randomized, open label trial in patients aged 12 to 65 years with high-risk hematologic malignancies who were also candidates for myeloablative allogeneic HSCT. Patients were randomized (n=125) to receive either Omisirge (n=62) or a standard umbilical cord blood graft (n=63). All patients received myeloablative preparative regimens and graft versus host disease prophylaxis with tacrolimus or cyclosporin plus mycophenolate mofetil. The primary endpoint was time to neutrophil engraftment.

Eligible patients were 12 to 65 years of age with high-risk hematologic malignancies who were candidates for myeloablative allo-HSCT, had an available UCB unit HLA–matched at four or more loci (HLA-A and -B at the antigen level, and DRB1 at the allele level) with a total nucleated cell (TNC) count ≥1.8 × 109, a TNC dose of ≥1.5 × 107 cells/kg, a CD34+ cell count of ≥8 × 106, and available backup UCB. This unit was designated for use before the random assignments were made and was required to be used in both arms of the study. The minimum specifications of Omisirge were a total nucleated viable cell count of 8.0 × 108 cells and CD34+ cell count of 5.6 × 107. A total of 52 patients were transplanted with Omisirge at a median CD34+ cell dose of 9.0 × 106 cells/kg (range 2.1–47.6 × 106 cells/kg); 56 patients were transplanted in the UCBT group with one or two cord blood units (66% received two cord blood units); among patients for whom the post-thaw cell dose was reported (n = 42), the median CD34+ cell dose was 0.2 × 106 cells/kg (range, 0.0–0.8 × 106 cells/kg). Multiple conditioning regimens were used, including total body irradiation–based or chemotherapy-based options. Demographic and baseline patient characteristics were similarly distributed among the treatment groups. The efficacy of Omisirge was established based on time to neutrophil recovery following transplantation and the incidence of Blood and Marrow Transplant Clinical Trials Network Grade 2/3 bacterial or Grade 3 fungal infections through Day 100 following transplantation. Table 2 provides a summary of the study's design.

Efficacy

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Patients who received Omisirge (Omidubicel-onlv) had a median time to neutrophil engraftment of 12 days in comparison to 22 days for patients that received a standard UCB graft. In the Omnisirge (Omnidubicel-onlv) group, patients had faster platelet recovery (55% vs. 35%), a lower incidence of bacterial and invasive fungal infections (37% vs. 57%) and had less in-hospital days within the first 100 days post-transplant (median, 61 vs. 48) in comparison to the control group. The cumulative incidence of neutrophil engraftment by Day 42 following transplantation in the Omisirge group (as-treated population, n = 52) was 96%, with a median time to engraftment of 10 days (95% CI, 8 to 13 days) compared with 89% for patients in the standard UCBT group (n = 56) with a median time to engraftment of 20 days (95% CI, 18 to 24 days) (P <0.001). The cumulative incidence of platelet engraftment by Day 42 for patients assigned to Omisirge was 55% compared to 35% for patients assigned to standard UCBT (P = 0.028). For the patients transplanted with Omisirge, the cumulative incidence of platelet engraftment by Day 100 was 83%, with a median time to engraftment of 37 days (95% CI, 33–42 days), compared to 73%, with a median time to engraftment of 50 days (95% CI, 42–58 days), for standard UCBT (P = 0.023). Full donor chimerism (defined as >90% in the whole blood fraction) was observed at Day 30 and Day 100 after transplantation in all but two Omisirge recipients; one experienced early relapse and the other experienced primary graft failure. Six standard UCBT recipients experienced graft failure on Day 42. The remaining evaluable standard UCBT recipients had full donor chimerism on Day 30 and Day 100 after transplantation.

Among patients who received a transplant who were randomly assigned to Omisirge (n = 59) or standard UCBT (n = 58), the incidence of Grade 2 to 4 acute graft-versus-host disease (aGVHD) at Day 100 was similar, at 56% versus 43%, respectively (13% difference: 95% CI, −6% to 30%; P = 0.18). The incidence of Grade 3 or 4 aGVHD at Day 100 was also similar in the Omisirge and standard UCBT groups, at 14% versus 21%, respectively (−7% difference; 95% CI, −21% to 7%; P = 0.33). The cumulative incidence of all chronic GVHD (cGVHD) at 1 year was 35% for the Omisirge group and 29% for the controls (6% difference; 95% CI, −14% to 25%; P = 0.57). The 1-year cumulative incidence of moderate to severe cGVHD was 27% for the Omisirge group and 21% for the controls (6% difference; 95% CI, −11% to 24%; P = 0.49).

Patients in the Omisirge group spent a median of 61 days (range, 0–89 days) out of the hospital in the first 100 days following transplant. In the standard UCBT group, patients spent a median of 48 days out of the hospital in the first 100 days after transplant (range, 0–84 days) (P value for difference = 0.005). Additionally, the median time from transplant to discharge from the hospital was 27 days in the Omisirge group versus 35 days in the standard UCBT group, respectively (P = 0.005).

The cumulative incidence of first Grade 2 or 3 bacterial or invasive fungal infections was 37% and 57% for Omisirge and standard UCBT recipients, respectively (P = 0.03). The rate of first Grade 3 viral infection within the first year after transplantation was 10% among Omisirge recipients and 26% for standard UCBT recipients, respectively (P = 0.02).

The median follow-up of all patients was 10 months after transplantation (range, 1–19 months). Using ITT (intention to treat) analysis, the cumulative incidence of nonrelapse mortality (NRM) at 210 days after random assignment was 11% for the Omisirge group and 24% for the control group (P = 0.09). The cumulative incidence of disease relapse at 15 months after random assignment was 25% for the Omisirge group and 17% for the control group (P = 0.32). During the time from random assignment to transplantation, relapse was reported in four patients in the Omisirge group and four patients in the standard UCBT group. Among these, relapse prevented two patients in the Omisirge group and three patients in the standard UCBT group from receiving a transplant by Day 90.

The adjusted hazard ratio (HR) for treatment failure (relapse or death, inverse of relapse-free survival [RFS]) with Omisirge versus standard UCB was 0.79 (95% CI, 0.45–1.38; P = 0.4). The adjusted HR for mortality with Omisirge versus standard UCBT was 0.57 (95% CI, 0.3–1.1; P = 0.09). The 1-year GVHD-free RFS for the Omisirge group was 36% compared to 45% for standard UCBT (P = 0.56).

Safety

Fatal adverse reactions occurred in 17% of patients treated with Omisirge (Omidubicel-onlv), including infection (6%), acute GvHD (6%), veno-occulsive disease (VOD)/sinusoidal obstruction syndrome (SOS) (2%), thrombotic

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thrombocytopenic purpura (TTP)/thrombotic microangiopathy (TMA) (2%), and pulmonary hemorrhage (2%). Fatal adverse reactions occurred in 29% of subjects treated with UCB, including infection/sepsis (11%), respiratory disorders (11%), GvHD (5%), and VOD/SOS (2%). Infusion reactions occurred in 56% of patients that received Omisirge (Omidubicel-onlv) and 71% of patients that received UCB. The most common infusion reactions were hypertension, mucosal inflammation, arrythmia, and fatigue. Infections (Grades 1-3) following transplantation with Omisirge (Omidubicel-onlv) vs. UCB for viral infections were 75% versus 80%, bacterial infections 65% versus 80% and fungal infections 21% versus 27% respectively. Acute and chronic GvHD occurred following treatment with OMISIRGE. Moderate to severe chronic GvHD was reported in 23% of patients in the Omisirge (Omidubucel-onlv) arm versus 20% in the control arm. Primary graft failure (defined as failure to achieve an absolute neutrophil count greater than or equal to 0.5 Gi/L by Day 42 after transplantation) occurred in 2% of patients treated with Omisirge (omnidubicel-onlv), compared to 11% of patients receiving UCB. Disease relapse occurred in 21% of patients treated with Omisirge (Omidubicel-onlv) compared to 13% of patients that received standard UCB. Other adverse reactions reported ≥ 10% incidence include pain, mucosal inflammation, hypertension, and gastrointestinal toxicity. (Horwitz, 2021; Omisirge PI, 2023).

SUPPLEMENTAL INFORMATION

OTHER SPECIAL CONSIDERATIONS:

Omisirge (Omidubicel-onlv) has a black box warning for infusion reactions, graft versus host disease (GvHD), engraftment syndrome and graft failure. Infusion reactions, GvHD, engraftment syndrome and graft failure may be fatal. Monitor patients during infusion and discontinue if severe reactions occur. Administration of immunosuppressive therapy may decrease the risk of GvHD. Treat engraftment syndrome promptly with corticosteroids. Monitor patients for laboratory evidence of hematopoietic recovery.

There is no available data regarding the use of Omisirge (Omidubicel-onlv) in pregnancy and lactation. Pregnant and lactating members were explicitly excluded from study populations. Pregnancy status of females with reproductive potential should be verified prior to starting the conditioning regimen for Omisirge (Omnidubicel-onlv).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Code

CPT	Description
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

HCPCS (Healthcare Common Procedure Coding System) Code

HCPCS	Description
C9399	Unclassified drugs or biologicals [when specified as Omisirge (Omidubicel-onlv)]

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

6/14/2023 New policy. Independent Review Organization Peer Review on May 18, 2023, by a practicing, board-certified physician with a

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specialty in Pathology - Hematology, Internal Medicine, Medical Oncology.

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APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*