Molina Clinical Policy
Hematopoietic Stem Cell Transplantation for Ewing's Sarcoma: Policy No. 272

Last Approval: 4/10/2024
Next Review Due By: October 2024

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

Ewing's Sarcoma (ES) is a small round cell tumor that originates in bone or soft tissue. ES is a part of the Ewing's Sarcoma Family of Tumors (ESFT) which includes Ewing tumor of bone, extraosseous Ewing, primitive neuroectodermal tumors, and Askin tumors, as all these malignancies derive from the same type of stem cell. ES is the second most common bone tumor in children and adolescents with a median age of 15 years old but can occur at any age. The most common osseous sites of ES are the lower extremities and pelvis, with the most common extraosseous sites being extremities and trunk. Approximately 25% of patients will have metastatic disease at diagnosis. Standard treatment of ESFT includes systemic chemotherapy in conjunction with either surgery or radiation, or both for local tumor control. The prognosis for patients with high-risk tumors treated with conventional chemotherapy, radiation and surgery remain poor, with long-term survival rates for patients with metastatic disease less than <35%. Dose-intensive chemotherapy regimens as well as Hematopoietic Stem Cell Transplantation (HSCT) have been investigated in patients with high-risk ESFT to improve survival. Classification of Ewing's Sarcoma is based on risk assignment (NCI 2022):

- **Low-Risk:** localized tumor when there is no spread beyond the primary site or regional lymph node involvement.
- **Intermediate-Risk:** tumor has spread to lungs.
- **Advanced-Risk:** tumor has spread beyond to bone, bone marrow and/or other tissue.

Hematopoietic Stem Cell Transplantation (HSCT) refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells, or platelets). HSCs are created in the bone marrow and are found there, in peripheral blood, and in high concentrations in umbilical-cord blood. Hematopoietic stem cell transplantation (HSCT) can be autologous (using the patient's own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed based on variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality (including graft rejection and graft-versus-host disease) also increases.

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.

Transplant Evaluation

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

Components of the transplant evaluation include:

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

2. Psychosocial evaluation and clearance:
    a. Absence of any history of medical treatment non-compliance; **AND**
    b. Member understands surgical risk and post procedure follow-up required; **AND**
    c. Adequate family and social support; **AND**
    d. No behavioral health disorders or psychosocial issues:
        i. If history of behavioral health disorder, no severe psychosis or personality disorder may be present;
        ii. Mood/anxiety disorder must be excluded, unless actively treated and controlled.

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 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:
        i. Lumbar puncture normal cytology; **OR**
        ii. Lumbar puncture with cytological exam abnormal, with 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: Human immunodeficiency virus (HIV); Epstein Barr virus; Hepatitis B virus; Hepatitis C virus; cytomegalovirus; rapid plasma reagin and/or fluorescent treponemal antibody:*

i. If HIV positive **ALL** of the following must be met:
   1. CD4 count >200 cells/mm-3 for >6 months; **AND**
   2. Human immunodeficiency virus 1 (HIV-1) ribonucleaic acid undetectable; **AND**
   3. On stable anti-retroviral therapy >3 months; **AND**
   4. 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 has a history of and/or current 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*; **AND**

12. 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 within the last 12 months; **AND**

13. Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated;*

OR

14. Prostate Specific Antigen, if history of prostate cancer or previously elevated prostate specific antigen with complete workup and treatment of abnormal results as indicated.*

* Participating Centers of Excellence may waive these criteria.

Criteria for Autologous HSCT

Hematopoietic Autologous Stem Cell Transplantation (HSCT) **may be considered medically necessary** and may be authorized for the treatment of Ewing's sarcoma when **ALL** the following criteria are met:

1. All transplant evaluation criteria are met; **AND**
2. Treatment meets **ONE** of the following:
   a. For initial treatment of high-risk Ewing's sarcoma (defined as metastatic disease, unfavorable tumor location [e.g., primary tumor site in the axial skeleton, including pelvis], larger tumor size, or older age of the Member); **OR**
   b. As salvage therapy for recurrent or refractory Ewing's sarcoma (defined as a tumor that does not achieve a complete remission after initial standard-dose chemotherapy).

AND

3. The requesting transplant recipient is free from **ALL** the following absolute contraindications:
   a. Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery.
   b. Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
   c. Systemic and/or uncontrolled infection
   d. AIDS (CD4 count < 200cells/mm3)
   e. Unwilling or unable to follow post-transplant regimen:
      i. Documented history of non-compliance
      ii. Inability to follow through with medication adherence or office follow-up.
   f. Chronic illness with one year or less life expectancy

g. Limited, irreversible rehabilitation potential
h. Inadequate social/family support
i. Active, untreated substance abuse or misuse (including significant and/or daily cannabis use) requires formal substance use disorder evaluation with clear and unambiguous documentation of:
    i. A reasonable expectation that the member can adequately comply with a complex, post-transplant plan of care; **AND**
    ii. The member is free from addiction for at least 6 months.

AND

4. The requesting transplant recipient is carefully evaluated and potentially treated for any of the following relative contraindications. (Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation).
    a. Smoking, requires documentation supporting free from smoking for 6 months; **OR**
    b. Active peptic ulcer disease; **OR**
    c. Active gastroesophageal reflux disease; **OR**
    d. Cerebrovascular accident (CVA) with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months; **OR**
    e. Obesity with body mass index of >30 kg/m^2 **OR**
    f. Chronic liver disease such as Hepatitis B/C/D or cirrhosis, requires consultation by a gastroenterologist or hepatologist; **OR**
    g. Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation.

Criteria for Subsequent Autologous HSCT

Hematopoietic Autologous Stem Cell Transplantation (HSCT) **may be considered medically necessary** and may be authorized after the first prior stem cell transplantation has occurred only one time for members with Ewing's sarcoma who meet **ALL** of the above criteria for transplant and have **ANY** of the following:

1. Primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; **OR**
2. Failure to engraft*; **OR**
3. A suitable allogeneic donor has been identified if applicable (applies to allogeneic only).

*NOTE: Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 0.5 x 10^9/L or > ANC500 at any time after transplantation. ([1] NMDP, n.d.).

Continuation of Therapy

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

1. If Molina Healthcare has authorized prior requests for transplantation, **ALL** the following information is required for medical review:
    a. Presence of no absolute contraindication as listed above; **AND**
    b. History and physical within the last 12 months; **AND**
    c. Kidney profile within the last 12 months; **AND**
    d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
    e. Psychosocial evaluation or update within the last 12 months; **AND**
    f. Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.
2. If authorized prior requests for transplantation were obtained from another insurer, **ALL** the following information is required for medical review:
    a. Authorization letter/documentation from previous insurer; **AND**
    b. Presence of no absolute contraindication as listed above; **AND**
    c. History and physical within the last 12 months; **AND**
    d. Cardiac update if history of cardiac disease within two years (≥ 50 years of age); **AND**
    e. Psychosocial evaluation or update within the last 12 months; **AND**
    f. Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

Limitations and Exclusions

1. Autologous HSCT when the above criteria are not met.
2. A second or repeat autologous HSCT due to persistent, progressive, or relapsed disease.
3. Allogeneic HSCT.
4. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant is not covered.

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

The published medical evidence and outcomes for HSCT for Ewing Sarcoma is limited to information from international bone marrow transplant registries and case series from individual institutions comparing treatment outcomes that suggest a survival benefit with the use of high dose chemotherapy followed by autologous HSCT. Several uncontrolled trials demonstrate improved or equivalent survival outcomes with autologous HSCT.

Ratko et al. (2012) conducted a comparative effectiveness review on the use of HSCT in the pediatric population. The report was published by the Blue Cross and Blue Shield Association Technology Evaluation Center for the Agency for Healthcare Research and Quality (AHRQ). Conclusions for Ewing Sarcoma Family of Tumors (ESFT) indicated the following: Low strength evidence on overall survival suggests no benefit with single HSCT compared to conventional therapy for the treatment of high-risk ESFT. The body of evidence on overall survival with tandem HSCT compared to single HSCT for the treatment of high-risk ESFT and overall survival is insufficient to draw conclusions.

Ferrari et al. (2011) conducted a large study and reported results of the Italian Sarcoma Group/Scandinavian Sarcoma Group III protocol, a multicenter, multi-country clinical trial involving 300 participants with Ewing family of tumors. At a median follow-up of 64 months, five-year overall survival (OS) and event-free survival (EFS) were 75% and 69%, respectively. Five-year EFS for those treated with high-dose therapy (HDT) were 75% for good responders and 72% for partial responders, and 33% for partial responders who did not receive HDT.

Ladenstein et al. (2010) conducted a large study named the EURO-EWING-Intergroup-EE99 R3 trial enrolled 281 patients with primary disseminated metastatic Ewing sarcoma. Patients were treated with six cycles of vincristine, ifosfamide, doxorubicin, and etoposide followed by high-dose therapy and autologous stem cell transplant and after a median follow-up of 3.8 years, event-free survival (EFS) and overall survival (OS) at 3 years for all 281 patients were 27% +/- 3% and 34% +/- 4% respectively. Factors such as the presence and number of bone lesions, primary tumor volume greater than 200 mL, and age older than 14 years, additional pulmonary metastases, and bone marrow involvement were identified as independent prognostic factors.

Gardner et al. (2008) reported on 116 individuals with Ewing sarcoma who underwent autologous HSCT (80 [69%] as first-line therapy and 36 [31%] for recurrent disease) between 1989 and 2000. Five-year probabilities of PFS in individuals who received HSCT as first-line therapy were 49% (95% CI, 30-69%) for those with localized disease at diagnosis and 34% (95% CI, 22-47%) for those with metastatic disease at diagnosis. For those with localized disease at diagnosis and recurrent disease, 5-year probability of PFS was 14% (95% CI, 3-30%). It was concluded that PFS rates after autologous HSCT were comparable to rates seen in those with similar disease characteristics treated with conventional therapy.

McTiernan et al. (2006) conducted a case series of 33 individuals with recurrent or progressive Ewing sarcoma and reported treatment outcomes of hematopoietic stem cell transplants with different preparatory regimens. Two of the individuals received autologous bone marrow, 1 received autologous bone marrow and stem cells, 29 received autologous peripheral blood stem cells, and 1 received an allogeneic bone marrow transplant due to an unsuccessful

autologous harvest. Event-free survival was 42.5% (95% CI, 26-59%) at 2 years and 38.2% at 5 years (95% CI, 21-55%). Although this treatment demonstrated the potential for long-term survival with high-dose therapy (HDT) for recurrent or refractory Ewing sarcoma, it was associated with significant toxicity. One treatment-related death was reported, and 2 participants experienced grade IV infections.

National and Specialty Organizations

The **National Marrow Donor Program (NMDP)** has published the following guidance: *Disease-Specific HCT Indications and Outcomes Data; Engraftment; HLA Matching; Patient Eligibility for HCT; Transplant Consultation Timing; and Treatment Before Transplant.* ([1-6] NMDP n.d.).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

Code	Description
	Collection Codes
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38243	Hematopoietic progenitor cell (HPC); HPC boost

HCPCS (Healthcare Common Procedure Coding System) Code

Code	Description
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

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

04/10/2024 Correction to ANC value in coverage section. Annual review scheduled for October 2024.

10/12/2023	Policy reviewed, changes to criteria include age for colonoscopy reduced to 45 years, addition of non-life limiting neurological impairment criteria and substance abuse to absolute contraindications, and removal of abnormal serology criteria and cannabis use section. Overview, Summary of Medical Evidence, and References sections updated. IRO peer reviewed by practicing physician board certified in Hematology Oncology August 2023.
10/12/2022	Policy reviewed, no changes to criteria, included section on marijuana use.
10/13/2021	Policy reviewed, no changes to criteria, updated references.
09/16/2020	Policy reviewed, no changes to criteria, updated references.
09/18/2019	Policy reviewed, no changes to criteria, updated references.
03/08/2018	Policy reviewed, no changes to criteria, updated references.
06/22/2017	Policy reviewed, no changes to criteria, updated references.
05/03/2016	New policy.

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