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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Multiple Myeloma

Multiple Myeloma (MM) is a hematological cancer affecting plasma cells. Plasma cells develop from B lymphocytes when foreign substances (antigens) enter the body and are responsible for producing antibodies (immunoglobulin) to fight infection and disease. MM is characterized by an overproduction of abnormal plasma

cells that adhere to the bone marrow and continue to proliferate, invading hard bone tissue and leading to bone destruction. Multiple lesions affecting the large bones of the body are common. Additionally, myeloma cells produce large numbers of inactive antibodies that crowd out normal functioning antibodies, and levels of functioning antibodies are often depressed in patients with MM. The clinical manifestations of MM include increased infection, diffuse osteoporosis, hypercalcemia, and renal damage. MM is generally considered a treatable but incurable disease. The diagnosis of myeloma requires 10% or more plasma cells on bone marrow examination (or biopsy-proven plasmacytoma), M protein in the serum or urine (except in patients who have true nonsecretory myeloma), and evidence of organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) believed secondary to the underlying plasma cell disorder. [31-32 42]

There are two staging systems used for Multiple Myeloma, the Durie-Salmon staging system and the International Staging System (ISS). The following table outlines the criteria for the staging [24]:

Stage	Durie-Salmon Staging Criteria	International Staging System (ISS) Criteria
I	All of the following: • Hb > 10g/dL • normal calcium • Skeletal survey: normal or single plasmacytoma or osteoporosis • Low M component production rate: ➢ Serum paraprotein level IgG< 5 g/dL ➢ Serum paraprotein level IgA< 3 g/dL • Urinary light chain excretion < 4 g/24h	Serum beta-2 microglobulin <3.5mg/L Serum Albumin ≥ 3.5g/dL
II	Neither stage I or III	Neither stage I or III
III	One or more of the following: • Hb < 8.5g/dL • high calcium > 12 mg/dL • Skeletal survey: Three or more lytic bone lesions • Low M component production rate: ➢ Serum paraprotein level IgG > 7g/dL ➢ Serum paraprotein level if IgA, > 5 g/dL • Urinary light chain excretion > 12g/24h	Serum beta-2 microglobulin <5.5mg/L
Note	Sub-classification criteria: A: Normal renal function: serum creatinine < 2 mg/dL B: Abnormal renal function: serum creatinine > 2 mg/dL	

Multiple Myeloma is also described as symptomatic or smoldering. Symptomatic multiple myeloma is defined as: [24]

- Calcium > 11.5 mg/dL
- Renal insufficiency: creatinine > 2 mg/dL
- Anemia: hemoglobin < 10 g/dL or 2 g/dL < normal
- Bone disease: lytic or osteopenic

Smoldering or asymptomatic multiple myeloma is defined by serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10 to 60 and the absence of myeloma defining events or amyloidosis. [24]

POEMS Syndrome

POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is characterized by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of the following features: osteosclerotic myeloma, Castleman disease (angiofollicular lymph node hyperplasia), increased levels of serum vascular endothelial growth factor (VEGF), organomegaly, endocrinopathy, edema, typical skin changes, and papilledema. The three major criteria for the diagnosis of POEMS syndrome are osteosclerotic bone lesions, elevated VEGF levels, and Castleman disease (angiofollicular lymph node hyperplasia). The six minor criteria for the diagnosis of POEMS syndrome are endocrine abnormalities, skin changes, organomegaly, extravascular volume overload, thrombocytosis/polycythemia, and papilledema.

Stem Cell Transplantation

Stem-cell transplantation 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 in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person'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 on the basis of 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 increase.

Tandem Transplantation:

Tandem transplantation refers to a planned second transplant or a subsequent second transplant that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant that is used as salvage therapy after failure of initial transplantation or relapsed disease.

RECOMMENDATION [1 23-29 30-37]

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 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.

Members must meet UNOS/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

Pre-Transplant Evaluation: [27 36] **Please see MCP-323 Pre-Transplant Evaluation for additional criteria and information.**

Criteria for transplant evaluation include all of the following:

- ❑ History and physical examination
- ❑ Psychosocial evaluation and clearance:
  - 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 has understanding of surgical risk and post procedure compliance and follow-up required
  - Adequate family and social support
- ❑ EKG
- ❑ Chest x-ray
- ❑ Cardiac clearance in the presence of any of the following:
  - o chronic smokers
  - o > 50 years age
  - o those with a clinical or family history of heart disease or diabetes
- ❑ Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- ❑ Neurological exam and clearance for transplant: [ONE]
  - o Normal exam by H&P
  - o Abnormal neurological exam with positive findings: [ONE]
    - ➢ Lumbar puncture normal cytology
    - ➢ Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- ❑ Performance Status : [ONE]
  - o Karnofsky score 70-100%; or
  - o Eastern Cooperative Oncology Group (ECOG) grade 0-2
- ❑ Lab studies:
  - o *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - o *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - ➢ CD4 count >200 cells/mm-3 for >6 months
      - ➢ HIV-1 RNA undetectable
      - ➢ On stable anti-retroviral therapy >3 months
      - ➢ No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
    - If abnormal serology need physician plan to address and/or treatment as indicated
  - o UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- ❑ *Colonoscopy (if indicated or if patient is 50 $\geq$ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated

- ❑ *GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- ❑ 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
- ❑ *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- ❑ *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 Hematopoietic Stem Cell Transplantation:

- ❑ ***Autologous hematopoietic cell transplant (AuSCT)*** may be considered medically necessary to treat multiple myeloma (MM) or POEMS syndrome for individuals with either of the following: [ONE]
  - Diagnosis of Durie-Salmon Stage II or III multiple myeloma and one of the following:
    - A partial response to post induction therapy defined as a 50% decrease either in measurable paraprotein (serum and/or urine) or in bone marrow infiltration sustained for at least 1 month; or
    - Relapsed disease post induction therapy defined as increased M proteins in serum and urine; or
    - Refractory disease post induction chemotherapy defined as disease that is unresponsive to post induction chemotherapy
  - Diagnosis of disseminated POEMS syndrome defined as diffuse sclerotic lesions or disseminated bone marrow involvement

- ❑ ***A second autologous hematopoietic cell transplantation*** may be considered medically necessary for the treatment of responsive MM or POEMS syndrome that has relapsed after a durable complete or partial remission following an autologous transplantation

- ❑ ***Allogenic Hematopoietic Stem Cell Transplantation*** may be considered medically necessary to treat multiple myeloma for individuals with early relapse (less than 24 months) after primary therapy that included an autologous HCT

- ❑ ***Tandem hematopoietic cell transplant*** may be considered medically necessary for individuals with active multiple myeloma and the first and second transplantation should be within a 6-month period for either of the following: [ONE]
  - Autologous-autologous tandem hematopoietic cell transplant; or
  - Initial autologous hematopoietic cell transplant followed by reduced-intensity conditioning allogeneic hematopoietic cell transplant

AND

- ❑ The requesting transplant recipient should not have any of the following **absolute contraindications**:
  - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  - Systemic and/or uncontrolled infection
  - AIDS (CD4 count < 200cells/mm3)
  - Unwilling or unable to follow post-transplant regimen
    - ◊ Documented history of non-compliance
    - ◊ Inability to follow through with medication adherence or office follow-up
  - Chronic illness with one year or less life expectancy
  - Limited, irreversible rehabilitation potential
  - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
  - No adequate social/family support

- ❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
  - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
  - Smoking, documentation supporting free from smoking for 6 months
  - Active peptic ulcer disease
  - Active gastroesophageal reflux disease
  - CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
  - Obesity with body mass index of >30 kg/m^2 may increase surgical risk
  - Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
  - Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

CONTINUATION OF THERAPY

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

- ❑ If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
  - Psychosocial evaluation or update within the last 12 months;

- 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.

❑ If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
- Authorization letter/documentation from previous insurer;
- Presence of no absolute contraindication as listed above;
- History and physical within the last 12 months;
- Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
- Psychosocial evaluation or update within the last 12 months;
- 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

1. Autologous (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant
3. Allogeneic hematopoietic cell transplant to treat POEMS syndrome
4. Tandem hematopoietic cell transplant for POEMS syndrome

SUMMARY OF MEDICAL EVIDENCE [3-26]

The published medical evidence and outcomes for hematopoietic stem cell transplantation for multiple myeloma and POEMS syndrome in children and adults in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information.

Professional Society Guidelines:
Several professional society organizations have recommended that Autologous SCT is the preferred method of treatment following primary therapy for eligible patients and is an option for treatment of primary progressive or refractory disease post induction treatment. [27-33]

The National Marrow Donor Program: The NMDP recommends that individuals with multiple myeloma referred for consultation for HSCT when the following characteristics are present: After initiation of therapy and at first progression. [27]

The National Comprehensive Cancer Network Guidelines (NCCN Guidelines): [28] The guidelines for Multiple Myeloma recommend the following:

- Autologous Transplant for active (symptomatic) myeloma proceeding after induction therapy to high-dose therapy and stem cell transplant.
- Additional treatment post-autologous cell transplant may include a second autologous cell transplant on or off clinical trial depending on the time interval between the preceding stem cell transplant and documented progression.

- Tandem transplant is recommended for active (symptomatic) myeloma for response or stable disease.
- Allogeneic Transplant is recommended for active (symptomatic) myeloma and may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably in a clinical trial. Current data do not support mini-allografting alone. The same recommendation is applied to post-autologous cell transplant scenarios for progressive disease and response or stable disease.
- For patients treated with or without a prior transplant, allogeneic cell transplant is also a recommended option for transplant candidates with relapse or progressive disease.

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
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
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
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
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic

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

ICD-10	Description: [For dates of service on or after 10/01/2015]
C90.0	Multiple Myeloma

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REVIEW/REVISION HISTORY

12/12/2012: New Policy

8/12/2015: Policy reviewed and updated with revisions made to the pre-transplant criteria, minor revision to the criteria to include upper age limit of 78, and criteria for Allogenic Stem Cell Transplantation was added. Guideline and reference sections were updated.
12/14/16, 6/22/17: Policy reviewed, no changes
9/13/18: Policy reviewed, no criteria changes, reference section updated.
6/19/19: Added criteria for POEMS Syndrome. For MM removed age limitation, revised the criteria for first, second and tandem stem cell transplant based on updated professional society guidelines, updated references. General recommendation and summary of medical evidence sections were condensed for ease of application.
6/17/20, 6/9/21: Policy reviewed, no changes to criteria, updated guidelines and references.