Subject: Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia (CML)		Original Effective Date: 7/25/14
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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

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (also referred to as CML or chronic granulocytic leukemia or chronic myeloid leukemia) is a disease of both the bone marrow and blood. It most often occurs in middle-aged adults. CML is characterized by the fact that too many granulocytes (neutophils, 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 increased bleeding from abrasions. 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 "Philadelphia chromosome". The Philadelphia chromosome 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 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.

Imatinib mesylate (Gleevec®), a selective inhibitor of the abnormal BCR-ABL TK protein, is considered the treatment of choice for newly diagnosed CML. While imatinib can be highly effective in suppressing CML in most patients, it is not curative and is ineffective in 20% to 30%, initially or due to development of BCR-ABL

mutations that cause resistance to the drug. Two other TK inhibitors (TKIs, dasatinib, nilotinib) have received marketing approval from the U.S. Food and Drug Administration (FDA) to treat CML following failure or patient intolerance of imatinib. However, allogeneic HSCT remains the only treatment capable of inducing durable remissions or cure in CML patients.

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.

Donor Lymphocyte Infusion

Following an allogeneic hematopoietic stem cell transplant, donor lymphocyte infusion is a form of adoptive immunotherapy and may be requested to induce a graft versus leukemia, or graft versus tumor, response without requiring the recipient to undergo additional high-dose chemotherapy. Donor lymphocytes are collected from the original donor through leukapheresis. This collection is an outpatient procedure for the donor. The lymphocytes are then either infused via vein into the recipient or are frozen for a more clinically appropriate time.

Pretransplant Evaluation

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

RECOMMENDATION

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 guidelines for transplantation and the diagnosis must be made by a *Specialist in the Disease* and or Transplant Surgeon.

Pre-Transplant Evaluation: 2-9 22 30 31

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)

- *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
- UDS (urine drug screen) if patient is current or gives a history of past drug abuse

❑ *Colonoscopy (if indicated or if patient is 50 ≥ 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 Allogeneic Stem Cell transplantation (HSCT) Transplantation: [1-9 30-32]

1. ***Hematopoietic Allogeneic stem-cell transplantation (HSCT)*** *ablative or non-myeloablative* from a human leukocyte antigen (HLA)-matched donor (i.e., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) or from cord blood when there are no matched sibling or unrelated donors (i.e. at least four out of six match of the HLA-A, HLA-B and HLA-DRB-1 markers) may be authorized in adults and children for the treatment of chronic myelogenous leukemia (CML) when ANY of the following criteria are met:

   ❑ All pre-transplant criteria are met; and

   ❑ In adults who are ≥ 18 years with any of the following clinical indications:
   - No hematologic response* after 3 months of oral tyrosine kinase inhibitor (TKI) {imatinib, dasatinib, nilotinib} therapy:

   Note: Complete hematologic response (CHR) is defined by a white blood cell count <10,000/microL with no immature granulocytes and <5 percent basophils on differential; platelet count <450,000/microL; and spleen not palpable [30]

OR

- No cytogenetic response*:

*<u>Note:</u> *Cytogenetic response is classified according to the percent Philadelphia chromosome positive cells into none (>95 percent), minimal (66 to 95 percent), minor (36 to 65 percent), major (1 to 35 percent), and complete (no Philadelphia chromosome positive cells). For patients with an inadequate number of metaphases, complete cytogenetic response can also be documented by FISH of blood interphase cell nuclei demonstrating <1 percent BCR-ABL1-positive nuclei of at least 200 nuclei* [30]

OR

- Those in cytogenetic relapse at 6, 12, or 18 months, after achieving initial hematologic remission after 3 months of imatinib therapy; or
- Progressing on an oral tyrosine kinase inhibitor (TKI) to accelerated phase: Defined by one or more of the following: [ONE] [9 30]
  - 10 to 19 percent blasts in the peripheral blood or bone marrow
  - Peripheral blood basophils ≥20 percent
  - Platelets <100,000/microL, unrelated to therapy
  - Platelets >1,000,000/microL, unresponsive to therapy
  - Progressive splenomegaly and increasing white cell count, unresponsive to therapy
  - Cytogenetic evolution (defined as the development of chromosomal abnormalities in addition to the Philadelphia chromosome)

OR

- Progressing on a TKI to Blast crisis (myeloid or lymphoid): Defined by any of the following: [ONE] [9 30]
  - ≥20 percent peripheral blood or bone marrow blasts
  - Large foci or clusters of blasts on the bone marrow biopsy
  - Presence of extramedullary blastic infiltrates (eg, myeloid sarcoma, also known as granulocytic sarcoma or chloroma)

OR

- Intolerance to TKI

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

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

2. A second or repeat ***Hematopoietic Allogeneic stem cell transplantation*** *(ablative or non-myeloablative)* may be authorized only one time for members with CML who meet all of the above criteria for transplant and have any of the following: [ONE]

   ❑ primary graft failure indicated by no signs of engraftment* by 42 days after the transplant; or
   ❑ failure to engraft*

   ***Note:** Engraftment is defined as the first 3 consecutive days on which the absolute neutrophil count (ANC) exceeds 5 x 10^9/L or > ANC500 at any time after transplantation.*[3]

Criteria for Donor Lymphocyte Infusion (DLI): [9 30]

3. ***Donor lymphocyte infusion (DLI)***, ***collection and cryopreservation*** may be authorized following a medically necessary allogeneic hematopoietic stem cell transplant:

   ❑ For incomplete chimerism and disease relapse in the setting of incomplete chimerism (defined as incomplete donor stem cell grafting in the recipient's bone marrow); and
   ❑ Donor lymphocytes must be collected from the original hematopoietic stem cell donor

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.

COVERAGE EXCLUSIONS [6 31]

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

SUMMARY OF MEDICAL EVIDENCE [10-29]

The published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of CML in selected individuals. However, improved outcomes have not been demonstrated for autologous HSCT compared with conventional chemotherapy in individuals with CML therefore the role of autologous HSCT for this indication has not been established. A summary of the most relevant medical evidence is outlined below.

Saussele et al (2010) from the German CML study group presented overall survival data of a prospective multiarm trial (n=84) of first line treatment with allogeneic stem cell transplantation in selected low-risk CML patients, advanced disease, or as planned second-line therapy after imatinib failure. Excellent outcomes were achieved with a 3-year projected overall survival of 91% after allogeneic transplantation in chronic phase. 59% achieved OS in advanced disease. 88% achieved complete molecular remission and, when a matched-pair

analysis was performed of transplanted CML patients in first chronic phase versus matched non-transplantation patients derived from the imatinib-responsive group, 3-year survivals were equivalent. [10]

In a retrospective study by Hehlman (2007) patients with Philadelphia chromosome negative, and/or breakpoint cluster-Abelson (BCR-ABL) positive chronic phase chronic myelogenous leukemia (CML) were randomized to hematopoietic stem-cell transplantation (HSCT) as first-line therapy (n=135) or best available drug treatment (n=219). Survival was superior for patients who received drug treatment compared to HSCT (p=.049), with outcomes most pronounced in low-risk patients (p=.032). [11]

Results of several case series and retrospective clinical studies involving adult patients suggest that stable engraftment can occur and that treatment-related mortality is decreased with the use of non-myeloablative or reduced-intensity conditioning with allogeneic HSCT [12-17] Disease-free survival (DFS) ranges from 40% to 85% at three-to- five-years. Graft-versus-host disease (GVHD) remains the most significant concern after non-myeloablative HSCT; morbidity and mortality from this complication can be reduced by careful patient selection. [27] Additionally, nine studies compiled in a recent, non-systematic review indicates that outcomes achieved with RIC allogeneic transplants have been similar to those with conventional allotransplants, with overall survival (OS) rates ranging from 35% at 2.5 years to 85% at 5 years among patients in chronic phase 1 at transplant. [20]

Warlick et al. (2012) reported outcomes of 306 patients with CML treated with myeloablative or RIC preparative regimens before allogeneic HSCT at the Center for International Blood and Marrow Transplant Research. Although age, disease status, prior treatment (including TKI and autologous transplant), and strength of donor match differed between the treatment groups, a statistical model indicated a potential association between use of RIC preparatory regimen and increased survival (when compared with traditional myeloablative regimens). Relapse and disease-free survival were similar across age cohorts. [21]

A 2012 comparative effectiveness review published by the Agency for Healthcare Research and Quality (AHRQ) on the use of HSCT in the pediatric population considered allogenic HSCT for the treatment of CML. The review cited the risk of disease relapse with interruption in TKI therapy, which complicates the decision to proceed to allogeneic HSCT. The review concluded that evidence demonstrating benefit or harm of HSCT versus standard therapies or disease natural history was insufficient for most pediatric indications. [19]

A 2016 cohort study was designed to compare the outcomes of imatinib (n=292) versus allo-HSCT (n=141) for CML, the clinical data of these patients being retrospectively analyzed so as to compare the event free survival (EFS) and overall survival (OS) between these two groups with patients in the chronic phase (CP) and advanced phases, including accelerate (AP) and blast phases (BP). Patients treated with imatinib (278 in the CP) demonstrated superior EFS, OS, 5-year EFS and 5-year OS rates of 88.5% versus 70.0% (P<0.05), 93.2% versus 80.0% (P<0.05), 84% versus 75.0% (P<0.05) and 92% versus 79.0% (P<0.05), respectively, to those treated with allo-HSCT (120 patients in the CP). (2) Both treatments resulted in similar survival, with EFS and OS rates of 42.9% versus 47.6% (P>0.05), 42.9% versus 57.1% (P>0.05), respectively, for imatinib (14 patients in the AP and BP) and allo-HSCT (21 patients in the AP and BP). [26]

Professional Organizations [2-9]

National Comprehensive Cancer Network (NCCN): The NCCN Guidelines (2018) for Chronic Myelogenous Leukemia [9] recommend consideration of allogeneic bone marrow transplant for treatment of CML for individuals with high-disease risk score upon diagnosis. Since response rates with tyrosine kinase inhibitors (TKIs) have been favorable as an initial treatment options (first and second line therapies) for chronic phase CML, HCT is no longer recommended as a first-line treatment option for chronic phase CML. The NCCN has published the following recommendations for allogeneic HCT in individuals:

- who have an inadequate, no response or progress while on TKIs; and
- who have T315I and other BCR-ABL1 mutations and are unresponsive or intolerant to all TKIs; and
- who have progression of CML to accelerated or blast phase on tyrosine kinase inhibitor therapy

Survival rates are better for individuals transplanted in chronic phase versus those with advanced disease. Five year survival for individuals with chronic, accelerated and blast crisis phases treated with matched-related transplants are approximately 75%, 40% and 10% respectively.

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 A 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-9	Description: [For dates of service prior to 10/01/2015]
205.10-205.11	Chronic myeloid leukemia

ICD-10	Description: [For dates of service on or after 10/01/2015]
C92.10-C95.12	Chronic myeloid leukemia BCR/ABL-positive code range
C92.20-C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative code range

RESOURCE REFERENCES

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Professional Society Guidelines

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Review/Revision History:

7/25/14: Policy created

6/2/15: Updated pre-transplant criteria, continuation of therapy, absolute and relative contraindications and coding sections.

12/16/15: Policy reviewed, no changes

6/15/16: Policy reviewed, no changes

7/27/17: Updated professional society guidelines, references and summary of medical evidence sections.

7/10/18: Policy reviewed, no changes