



Louisiana

Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenstrom's Macroglobulinemia

Policy # 00138

Original Effective Date: 01/28/2002

Current Effective Date: 05/11/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas is addressed separately in medical policy 00062.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to treat primary systemic amyloidosis to be **eligible for coverage**.**

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) as salvage therapy of chemosensitive Waldenstrom's macroglobulinemia (WM) to be **eligible for coverage**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat primary systemic amyloidosis to be **investigational**.*

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to treat Waldenstrom's macroglobulinemia (WM) to be **investigational**.*

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Background/Overview

Primary Amyloidosis

The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibits a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified by the type of amyloidogenic protein involved and by the distribution of amyloid deposits. In systemic amyloidosis, the unnatural protein is produced at a site that is remote from the site(s) of deposition, whereas, in localized disease, the amyloid light chain protein is produced at the site of deposition. Primary or amyloid light chain amyloidosis, the most common type of systemic amyloidosis, has an incidence similar to that of Hodgkin lymphoma or chronic myelogenous leukemia, estimated at 5 to 12 people per million annually. The median age at diagnosis is 60 years. The amyloidogenic protein in primary amyloidosis is an immunoglobulin light chain or light chain fragment produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in primary amyloidosis is typically low, ranging from 5% to 10%, this disease also may occur in association with multiple myeloma in 10% to 15% of patients. Deposition of primary amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

Treatment

Historically, this disease has had a poor prognosis, with median survival from diagnosis of approximately 12 months, although outcomes have improved with combination chemotherapy using alkylating agents and autologous hematopoietic cell transplantation (HCT). Emerging approaches include the use of immunomodulating drugs (eg, thalidomide, lenalidomide) and the proteasome inhibitor bortezomib. Regardless of the approach, treatment of primary amyloidosis aims at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. The therapeutic index of any chemotherapy regimen is a key consideration in the context of underlying organ dysfunction.

Hematopoietic Cell Transplantation

HCT refers to the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy.

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Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic [allo-] HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease.

Autologous HCT

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete response. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Allogeneic HCT

Immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allo-HCT. Compatibility is established by typing human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and the subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and

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organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility to opportunistic infections.

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains variable with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a clonal disorder of B lymphocytes that accounts for 1% to 2% of hematologic malignancies, with an estimated 1500 new cases annually in the United States. Symptoms include weakness, headaches, stroke-like symptoms (confusion, loss of coordination), vision problems, excessive bleeding, unexplained weight loss, and frequent infections. The median age of WM patients is 63 to 68 years, with men comprising 55% to 70% of cases. Median survival of WM ranges from 5 to 10 years, with age, hemoglobin concentration, serum albumin level, and β_2 -microglobulin level as predictors of outcome.

The Revised European American Lymphoma and World Health Organization classification and a consensus group formed at the Second International Workshop on Waldenström's Macroglobulinemia recognize WM primarily as a lymphoplasmacytic lymphoma with an associated immunoglobulin M (IgM) monoclonal gammopathy. The definition also requires the presence of a characteristic pattern of bone marrow infiltration with small lymphocytes demonstrating plasmacytic

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differentiation with variable cell surface antigen expression. The Second International Workshop indicated no minimum serum concentration of IgM is necessary for a diagnosis of WM.

Treatment

The goal of therapy for patients with WM is to achieve symptomatic relief and reduce organ damage without compromising quality of life. Treatment of WM is indicated only in symptomatic patients and should not be initiated solely on the basis of serum IgM concentration. Clinical and laboratory findings that indicate the need for therapy of diagnosed WM include a hemoglobin concentration less than 10 g/dL; platelet count less than 100,000/ μ L; significant adenopathy or organomegaly; symptomatic Ig-related hyperviscosity (>50 g/L); severe neuropathy; amyloidosis; cryoglobulinemia; cold-agglutinin disease; or evidence of disease transformation.

Primary chemotherapeutic options in patients that may undergo autologous hematopoietic cell transplantation (HCT) often combine rituximab with other agents (eg, dexamethasone, cyclophosphamide, bortezomib, bendamustine), but other agents may also be used including purine analogues (cladribine, fludarabine). Plasma exchange is indicated for acute treatment of symptomatic hyperviscosity.

Conventional Preparative Conditioning for HCT

The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that develops after engraftment of allogeneic stem cells within patients' bone marrow space. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the patient to opportunistic infections.

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The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning for Allogeneic HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

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The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale/Source

Hematopoietic cell transplantation (HCT) refers to the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT).

For individuals who have primary amyloidosis who receive autologous HCT, the evidence includes a randomized controlled trial, nonrandomized comparative studies, and large case series. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined to less than 14% in current studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic (allo-) HCT, the evidence includes case reports. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. Evidence on the use of allo-HCT is sparse and has shown high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input and national and international clinical guidelines support the use of autologous HCT as a treatment of amyloidosis. For primary amyloidosis, allo-HCT is not recommended. Thus, autologous HCT may be considered medically necessary for primary amyloidosis, and allo-HCT for primary amyloidosis is considered investigational.

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Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease.

For individuals who have Waldenström macroglobulinemia who receive HCT, the evidence includes case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Several retrospective series have evaluated HCT for Waldenström macroglobulinemia. Analyses of registry data have found 5-year overall survival rates of 52% after allogeneic HCT and 68.5% after autologous HCT. The total number of patients studied is small and there is a lack of published controlled studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2011 and national and international clinical guidelines support the use of autologous HCT as salvage therapy for patients with chemosensitive Waldenström macroglobulinemia. Allogeneic HCT is recommended in the context of clinical trials. Thus, autologous HCT may be considered medically necessary as salvage therapy for patients with chemosensitive Waldenström macroglobulinemia. Allogeneic HCT for patients with Waldenström macroglobulinemia is considered investigational.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. There was support for the policy statements on hematopoietic stem transplantation in the treatment of amyloidosis.

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Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

The ASBMT (2015) issued guidelines on indications for autologous and allogeneic hematopoietic cell transplantation (HCT). ASBMT gave the rating of N (not generally recommended; neither evidence nor clinical practice supports the routine use) for the use of allogeneic HCT in the treatment of primary amyloidosis in adults. ASBMT gave a rating of C (standard of care; clinical evidence available) for the use of autologous HCT in the treatment of primary amyloidosis in adults.

British Committee for Standards in Haematology

The British Committee for Standards in Haematology developed guidelines on the management of light chain (primary) amyloidosis. Table 1 summarizes the recommendations from the 2015 guidelines on high-dose melphalan and autologous cell transplantation and allogeneic transplantation as treatments of primary amyloidosis.

Table 1. Recommendations on Use of High-Dose Melphalan, HDM-ASCT, and Allogeneic Transplant to Treat Primary Amyloidosis

Recommendation	GOR
HDM-ASCT recommended as “the preferred first line treatment for patients up to 65-70 years of age with estimated glomerular filtration rate (eGFR) >50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in bone marrow at time of transplant and lacking the contraindications....”	1c
HDM-ASCT recommended with any of the following: Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide >590 pmol/l and/or troponin-T > 0.06 ng/ml, severe autonomic neuropathy, significant gastrointestinal (GI) bleeding due to amyloid, ... recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status (>2).”	1c
“HDM-ASCT may be a treatment for selected patients up to 65-70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy.”	1c
“Reduced intensity allogeneic transplantation is generally not recommended as an upfront treatment due to high treatment-related mortality (TRM). However, selected fitter younger patients with limited organ involvement who have a matched sibling donor may be considered following relapse of their disease.”	1a

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GOR: grade of recommendation; HDM-ASCT: high dose melphalan autologous stem cell transplantation.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines on systemic light chain amyloidosis (v.1.2019) recommend assessing organ involvement based on amyloidosis consensus. Next patients should be evaluated for stem cell transplant candidacy. In patients eligible for stem cell transplant, stem cells may be collected, and transplant delayed for a later line of therapy. The dose of melphalan as part of stem cell transplantation can be adjusted based on factors such as age, presence/absence of cardiac involvement, and number of organs involved. In eligible patients, high-dose chemotherapy followed by autologous stem cell transplant has demonstrated higher response rates and improved overall survival compared with chemotherapy alone.

International Workshops on Waldenström Macroglobulinaemia

The International Workshops on Waldenström Macroglobulinaemia (2017) published guidelines on the treatment of several paraproteinaemic neuropathies, one of which is primary, or amyloid light chain, amyloidosis. First-line treatment for eligible patients includes an autologous cell transplant preceded by a high-dose regimen combining rituximab with another agent such as purine analogue, bendamustine, or bortezomib.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services has determined that the evidence is adequate to conclude that, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan together with autologous stem cell transplantation can provide a net health benefit for Medicare beneficiaries of any age group with primary amyloidosis (110.23, formerly 110.8.1). This technique "is reasonable and necessary or Medicare beneficiaries of any age with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs, and,
- Cardiac left ventricular ejection fraction (EF) of greater than 45%."

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In addition, autologous HCT “must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy ... and/or radiotherapy used to treat various malignancies.”

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in December 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. Input indicated that autologous hematopoietic cell transplantation may be considered medically necessary as salvage therapy for Waldenström macroglobulinemia that is chemosensitive. Input was mixed on use of allogeneic hematopoietic cell transplantation, with comments suggesting the procedure be performed as part of a clinical trial.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on Waldenström macroglobulinemia (WM) and lymphoplasmacytic lymphoma (v.2.2019) indicate that, for patients with previously treated WM, stem cell transplantation may be appropriate in selected cases with either: high-dose therapy with autologous stem cell rescue or allogeneic cell transplant (myeloablative or nonmyeloablative). The Network noted that allogeneic cell transplantation “should ideally be undertaken in the context of a clinical trial.” For potential autologous cell transplantation candidates, the guidelines also provide suggested treatment regimens considered non-stem-cell toxic.

Mayo Clinic Cancer Center

In 2017, the Mayo Clinic Cancer Center updated its guidelines on the diagnosis and management of WM. The guidelines noted that patients who are potentially eligible for autologous hematopoietic cell transplantation (HCT; <70 years of age and with chemosensitive disease), should consider harvesting stem cells during first remission after a low tumor burden has been achieved. The

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guidelines recommended: “Autologous HCT should be considered for first or second relapse in transplant-eligible patients with chemosensitive disease, especially if the first remission duration is short (<2 years). Patients with refractory WM should not be offered [autologous HCT] (level 3, grade B).”

Eighth International Workshop on Waldenström’s Macroglobulinemia

In 2016, consensus recommendations from the Eighth International Workshop on Waldenström’s Macroglobulinemia were published. The panel concluded that autologous HCT is a treatment option for high-risk WM patients who are eligible for transplant. It further stated that autologous HCT should be offered at early relapses and is not as beneficial once patients have been exposed to more than 3 lines of therapy or in those with chemotherapy-refractory disease. Regarding allogeneic HCT, it stated that this treatment, “when appropriate, should preferably be considered in the context of clinical trials.”

Myeloma Foundation of Australian

In 2017, the Myeloma Foundation of Australia published practice guidelines on the treatment of patients with WM. The guidelines provided the following treatment recommendation for HCT: “Younger patients with good physical fitness should be considered for autologous and allogeneic stem cell transplantation at first or second relapse and should avoid stem cell-toxic therapies such as fludarabine (Level III, grade C).”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Currently unpublished trials that might influence this review are listed in Table 2.

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Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01251575	Sirolimus, Cyclosporine, and Mycophenolate Mofetil in Preventing Graft-versus-Host Disease in Treating Patients with Blood Cancer Undergoing Peripheral Blood Stem Cell Transplant	80	Dec 2019
NCT02844361	Comparison of ASCT and Conventional Chemotherapy in High Risk Waldenström Macroglobulinemia (BDH-WM03)	70	May 2020

NCT: national clinical trial.

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7. Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood.* May 15 1998;91(10):3662-3670. PMID 9573002

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Policy History

Original Effective Date: 01/28/2002

Current Effective Date: 05/11/2020

12/06/2001 Medical Policy Committee review

01/28/2002 Managed Care Advisory Council approval

06/24/2002 Format revision. No substance change to policy.

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06/01/2004 Medical Director review

06/15/2004 Medical Policy Committee review. Format revision. Rationale and Source added. Clinical criteria revision. Primary amyloidosis eligible for coverage.

06/28/2004 Managed Care Advisory Council

06/07/2005 Medical Director review

06/21/2005 Medical Policy Committee Review Policy revision; investigational status for: 1) HDC with allogeneic SCS for primary systemic Amyloidosis or Waldenstrom's Macroglobulinemia and 2) HDC with autologous SCS in cases where Patient Selection Criteria are not met.

07/15/2005 Managed Care Advisory Council approval

06/07/2006 Medical Director review

06/21/2006 Medical Policy Committee approval. Format revisions, FDA /Governmental, Rationale/Source

09/05/2007 Medical Director review

09/19/2007 Medical Policy Committee approval. No change in policy statement.

09/09/2008 Medical Director review

09/17/2008 Medical Policy Committee approval. Criteria removed from policy.

04/02/2009 Medical Director review

04/15/2009 Medical Policy Committee approval. Investigational statement for when criteria are not met removed from the policy. No change to coverage eligibility.

09/03/2009 Medical Policy Committee approval

09/16/2009 Medical Policy Implementation Committee approval. Title changed from "High-Dose Chemotherapy with Hematopoietic Stem Cell Support to Treat Primary Amyloidosis or Waldenstrom's Macroglobulinemia" to Hematopoietic Stem Cell Support to Treat Primary Amyloidosis or Waldenstrom's Macroglobulinemia "Hematopoietic Stem Cell Transplantation for Primary Amyloidosis or Waldenstrom's Macroglobulinemia." No change to coverage eligibility.

09/09/2010 Medical Policy Committee review

09/15/2010 Medical Policy Implementation Committee approval. Changed the language in the coverage section from high-dose chemotherapy with stem cell support to hematopoietic stem-cell transplantation. Coverage eligibility unchanged.

09/01/2011 Medical Policy Committee review

09/14/2011 Medical Policy Implementation Committee approval. "Based on review of available data, the Company may consider autologous hematopoietic stem-cell

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transplantation as salvage therapy of chemosensitive Waldenstrom macroglobulinemia to be eligible for coverage” was added to the coverage statement. “Autologous hematopoietic stem cell transplantation” was changed to “Allogeneic hematopoietic stem cell transplantation” in the investigational statement for the treatment of Waldenstrom macroglobulinemia.

- 10/11/2012 Medical Policy Committee review
- 10/31/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 10/03/2013 Medical Policy Committee review
- 10/16/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 11/06/2014 Medical Policy Committee review
- 11/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
- 10/29/2015 Medical Policy Committee review
- 11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 11/03/2016 Medical Policy Committee review
- 11/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 11/02/2017 Medical Policy Committee review
- 11/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. The word Stem removed from title and policy.
- 11/08/2018 Medical Policy Committee review
- 11/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 11/07/2019 Medical Policy Committee review
- 11/13/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 04/02/2020 Medical Policy Committee review

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04/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2021

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150

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ICD-10 Diagnosis	C88.0, E85.0-E85.9
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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