Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom’s Macroglobulinemia

Policy # 00138  
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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.

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 stem-cell transplantation (HSCT) to treat primary systemic amyloidosis to be eligible for coverage.

Based on review of available data, the Company may consider autologous hematopoietic stem-cell transplantation (HSCT) 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 stem-cell transplantation (HSCT) to treat primary systemic amyloidosis to be investigational.*

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

Background/Overview  
Primary Amyloidosis

Hematopoietic Stem-Cell Transplantation  
Hematopoietic stem-cell transplantation refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). 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 “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte...
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Antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigens 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.

Conventional Preparative Conditioning for Hematopoietic Stem-Cell Transplantation
The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., 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 (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM 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 effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic Hematopoietic Stem-Cell Transplantation
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 but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. Reduced-intensity conditioning 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 HSCT 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 the purposes of this policy, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.
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Primary Systemic 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 exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified on the basis of the type of amyloidogenic protein involved, as well as 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 protein is produced at the site of deposition. Light-chain amyloidosis (AL), the most common type of systemic amyloidosis, has an incidence similar to that of Hodgkin's lymphoma or chronic myelogenous leukemia, estimated at 5 to 12 people per million annually. The median age at diagnosis is approximately 60 years. The amyloidogenic protein in AL amyloidosis is an immunoglobulin (Ig) light chain or light-chain fragment that is produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in AL amyloidosis is typically low, ranging from 5–10%, this disease also may occur in association with multiple myeloma in 10–15% of patients. Deposition of AL amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

Historically, this disease has had a poor prognosis, with a median survival from diagnosis of approximately 12 months, although outcomes have improved with the advent of combination chemotherapy with alkylating agents and autologous HSCT. Emerging approaches include the use of immunomodulating drugs such as thalidomide or lenalidomide, and the proteasome inhibitor bortezomib. Regardless of the approach chosen, treatment of AL amyloidosis is aimed 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.

Waldenstrom's Macroglobulinemia
Hematopoietic Stem-Cell Transplantation
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Waldenstrom's Macroglobulinemia

Waldenstrom’s macroglobulinemia is a B cell malignancy that accounts for 1–2% of hematologic malignancies, with an estimated 1,500 new cases annually in the U.S. The median age of WM patients at presentation is 63 to 68 years, with men comprising 55–70% of cases. Median survival of WM ranges from 5 to 10 years, with age, hemoglobin concentration, serum albumin level, and beta-2 microglobulin level as predictors of outcome. The Revised European American Lymphoma (REAL) and World Health Organization
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(WHO) classification, and a consensus group formed at the Second International Workshop on WM recognize WM primarily as a lymphoplasmacytic lymphoma (LPL) 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 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 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 hemoglobin concentration less than 100g/L; platelet count less than 100 x 10^9/L; significant adenopathy or organomegaly; symptomatic IgM-related hyperviscosity (> 50g/L); severe neuropathy; amyloidosis; cryoglobulinemia; cold-agglutinin disease; or evidence of disease transformation. Primary chemotherapeutic options have included alkylating agents (chlorambucil, cyclophosphamide, melphalan), purine analogues (cladribine, fludarabine), and monoclonal antibody agents (rituximab), alone or in various combinations. Plasma exchange is indicated for acute treatment of symptomatic hyperviscosity.

**Rationale/Source**

**Primary Amyloidosis**

Conventional therapy for primary systemic amyloidosis usually combines oral melphalan with prednisone (MP), which has been shown to yield higher response rates and longer survival than colchicine or prior therapies. Median survival after MP (approximately 18 months) is longer than for untreated patients or those given older therapies (10–14 months), but more effective regimens have been sought. Combination therapy with vincristine, doxorubicin, and dexamethasone (VAD), a well-established regimen for myeloma, has been investigated. However, because of its toxicity, VAD therapy usually is limited to patients without peripheral neuropathy or cardiomyopathy, both common complications of amyloidosis. Because conventional regimens rarely cure systemic amyloidosis and because of the close biologic similarity to multiple myeloma, myeloablative chemotherapy with autologous HSCT was investigated for this disease.

**Autologous HSCT**

Initial results of autologous HSCT in uncontrolled patient series were published in 1998. Clinical response rates (50% to 60%) were nearly twice those reported for conventional therapy, and 2-year survival reportedly ranged from 56% to 68%. However, procedure-related mortality rates of 15% to 43% were substantially higher than those observed in myeloma patients, usually in cases that involved more than two organ systems or had symptomatic cardiac involvement.

A subsequent retrospective study analyzed outcomes of conventional therapy for primary amyloidosis in patients who would have been eligible for autologous HSCT. Inclusion required age younger than 70 years, cardiac interventricular septal thickness less than 15, left ventricular ejection fraction (LVEF) more than 55%, serum creatinine less than 2mg/dL, and direct bilirubin less than 2.0 mg/dL. Patients eligible for transplantation but managed conventionally reportedly had median survival of 42 months after conventional treatment, compared to median survival of only 18 months for all patients with primary amyloidosis. Survival
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of conventionally managed patients (n = 229) at 24 months was 61%, which was similar to 56% to 65% survival at 24 months after autologous HSCT.

In the same report, survival of 39 patients given autologous HSCT at their institution was compared with survival of a matched cohort (n = 78; 2 controls for each case) selected from their database of conventionally treated amyloidosis patients. Factors used to match patients were limited to age (within five years), gender, and number of involved organs. They reported similar survival of cases and controls at 6 (85% versus 83%), 12 (77% versus 74%), and 24 months (68% and 60%, all respectively).

A follow-up report to the matched-pair analysis cited above included a larger group of cases (n = 63) treated with autologous HSCT and used parameters measuring severity of organ involvement to select matched controls (n = 63). Factors used for matching were age, gender, time to presentation, LVEF, serum creatinine, cardiac septal thickness, nerve involvement, 24-hour urinary protein excretion, and serum alkaline phosphatase. At a median follow-up of 3.5 years from diagnosis for each group, 16 transplanted patients and 44 controls had died. Kaplan-Meier analysis showed significantly greater overall survival (OS) for those given autotransplants (p = 0.004). The survival rates for the high dose and standard treatment groups at 1, 2, and 4 years were 89% and 71%; 81% and 55%; and 71% and 41%, respectively.

In addition to longer survival, evidence suggests improvement in symptoms for amyloidosis patients treated with autologous HSCT. In a large retrospective series of amyloidosis patients eligible for transplant (n = 394), 63 patients declined treatment and 19 lost eligibility when they progressed before treatment started. Estimated median survival for 312 patients who initiated stem-cell mobilization was 4.6 years, but median follow-up was not reported. Of 181 evaluable patients (alive and followed-up for one year or more), 40% achieved complete hematologic response, defined as no evidence of plasma cell dyscrasia at one year after transplant. The authors reported functional improvement in at least one affected organ for 44% of evaluable patients: 66% of 73 patients with complete hematologic response, and 30% of 108 patients with an incomplete or no hematologic response. Among 277 patients who completed the transplant protocol, 36 (13%) died of treatment-related toxicity before day 100 post-transplant, 21 (8%) died between day 100 and one year, and 39 were alive but had not reached one year since transplant. This series included all patients transplanted between July 1994 and June 2002, of which one-half (n = 196) had three or more organs involved and 43% had some cardiac involvement. Median survival for those with cardiac involvement (n = 137) was significantly shorter (1.6 vs. 6.4 years, respectively; p < 0.001) than for those without cardiac involvement (n = 175).

A subsequent report based on the dataset from the large retrospective series outlined in the preceding paragraph provided an analysis of outcomes of risk-adjusted myeloablative melphalan and autologous HSCT in patients aged 65 years and older versus outcomes in those younger than 65 years, with up to 10 years of follow-up. Patients younger than 65 years with LVEF of 45% or greater and adequate stem-cell yield (n = 280; median age 55 years, range 29–64 years) received melphalan 200mg/m²; those aged 65 years and older, those with reduced LVEF (40–45%), or those with lower stem-cell yield (n = 65; median age 68 years, range 65–79 years) received risk-adjusted melphalan 140mg/m². No difference was observed in early treatment-related mortality (10.3% in patients 65 years or older vs. 13.4% in those younger than 65 years, p = 0.665). A trend toward a lower rate of hematologic complete response (CR, defined as the
absence of clonal plasma cells in the bone marrow by immunohistochemical staining and of monoclonal gammopathy by immunofixation electrophoresis of serum and urine) was observed in the older patients (27.6% for patients 65 years or older) versus 13.4% in those younger than 65 years (p = 0.882). However, the median survival after autologous HSCT did not differ according to age (4.0 years for patients aged 65 years and older vs. 4.85 years for those younger than 65 years; log-rank p = 0.28).

A registry analysis of 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers included 37 (35%) patients who received a transplant for initial therapy of amyloidosis, while 27 (25%) received a transplant after two or more prior therapies. With a median follow-up of 30 months after transplant, OS at one and three years was 66% (95% confidence interval [CI]: 56–75%) and 56% (95% CI: 45–66%), respectively. For those with no or one organ involved at transplant, survival at one year was 72% (95% CI: 61–82%), while for those with two or more organs involved, survival at one year was 54% (95% CI: 38–70%). Survival at one year also was greater for those without (69%; 95% CI: 58–79%) than with (56%; 95% CI: 37–74%) cardiac involvement. Treatment-related mortality at 30 days was 18% (95% CI: 11–26%), mostly among patients with cardiac and/or multiple organ involvement.

Long-term survival and outcomes were evaluated in a series of 80 patients with AL amyloidosis who were treated with myeloablative full-dose or risk-adjusted melphalan according to a risk-based protocol and underwent autologous HSCT. All patients had a histologic diagnosis of amyloidosis with evidence of plasma cell dyscrasia and met eligibility criteria for autologous HSCT in clinical protocols. Patients (median age 56 years, range 29–71 years) received risk-adjusted melphalan 100mg/m² (n = 37) or full-dose melphalan 200mg/m² (n = 43) followed by autologous HSCT 24–72 hours after completion of the conditioning regimen. Treatment-related mortality was reported in 11 (14%) cases, 6 of whom had received risk-adjusted melphalan, while 5 received the full-dose regimen. Median survival for all 80 patients was 57 months; 18 (23%) were alive ten or more years after undergoing autologous HSCT. Hematologic CR (defined above) was assessed in 63 (79%) surviving patients at one year following treatment. Thirty-two of those patients (51%) achieved a hematologic CR; among those, median survival had not been reached at the time the report was prepared for publication. In contrast, the median survival for patients who failed to achieve a CR was 50 months, with a 6% estimated probability of survival at 10 years (p < .001 vs. patients with CR).

In a series of 282 consecutive patients with AL amyloidosis who underwent autologous HSCT, investigators sought to determine whether or not a hematologic CR, as determined by normalization of serum and urine monoclonal protein levels, provides an adequate surrogate marker for OS. All patients had AL histologically verified with Congo red tissue stain, and received risk-adjusted melphalan conditioning based on the presence of numbers of organs involved, creatinine level, age, and cardiac involvement. One third (n = 93) of the patients received risk-adjusted melphalan (100 or 140mg/m²) and 67% (n = 189) received full-dose melphalan (200mg/m²). The mortality at day 100 was 11%, with 28% of the cohort dead by the time this report was prepared. Ninety-three (33%) patients achieved a CR, 108 (38%) had a partial response (PR), and 36 (13%) had no response (NR) to autologous HSCT. Kaplan-Meier analysis showed that median survival was reached only in the NR group, compared with the CR and PR groups after more than 80 months of follow-up (log-rank p < 0.001 for NR vs. CR and PR). An analysis (landmark analysis) focused on patients who survived for at least six months after autologous HSCT included 86 patients in the CR group, 91 who had PR, and 36 NR patients. This analysis showed that the survival curve differences remained
significant between response groups as in the overall cohort, with a median survival of 40 months reached only in the NR group.

Patients with AL amyloidosis and cardiac involvement were treated in a series from Mayo Clinic. A total of 187 patients of median age 57 years received high-dose melphalan (HDM) followed by autologous HSCT. The median time from diagnosis to HSCT was about 4 months, and median estimated follow-up from diagnosis was 65 months (95% CI: 61, 74 months). The median estimated OS for all 187 patients was 66 months (95% CI: 42, 83 months). Overall, hematologic and cardiac responses were observed in 66% and 41% of patients, respectively. Overall, 30 (16%) patients died within 100 days of treatment; 29 of those deaths were considered to be the result of therapy.

A series of 421 consecutive patients treated with high-dose melphalan and autologous HSCT at a single referral center compared outcomes for patients with and without a CR. Treatment-related mortality was about 11% overall (5.6% in the last 5 years). By intention-to-treat (ITT) analysis, the CR rate was 34% and the median event-free survival (EFS) and OS were 2.6 and 6.3 years, respectively. Eighty-one patients died within the first year after HSCT and were not evaluable for hematologic and organ response. Of 340 evaluable patients, 43% achieved CR and 78% of them experienced an organ response. For CR patients, median EFS and OS were 8.3 and 13.2 years, respectively. Among the 195 patients who did not obtain CR, 52% achieved an organ response, and their median EFS and OS were 2 and 5.9 years, respectively. Thus, treatment of selected AL patients with HDM and autologous HSCT resulted in a high organ response rate and long OS, even for those patients who did not achieve CR. These results are compatible with others cited above.

Several additional retrospective and prospective series have been reported on the use of autologous HSCT in patients with AL. Results from these series are consistent with others that suggest autologous HSCT is feasible and beneficial in selected patients with AL.

One randomized multicenter trial involving eight centers from the Myelome Autogreffe (MAG) and Intergroupe Francophone du Myelome (IFM) Intergroup has been reported in which conventional chemotherapy with melphalan plus dexamethasone was compared with myeloablative melphalan followed by autologous HSCT in patients with AL amyloidosis. Patients between 18 and 70 years of age had a histologic diagnosis of AL amyloidosis and either a complete hematologic response characterization of amyloid deposits or evidence of a monoclonal Ig protein in the serum or urine or a monoclonal staining pattern of bone marrow plasma cells and had received no more than two courses of any chemotherapy regimen. They were randomly allocated, stratified according to age (younger than 65 years or 65 years or older) and according to the affected organ system (cardiac, renal, neurological, or other). Of note, approximately two thirds of the patients had two or more organs affected. Patients in the melphalan plus dexamethasone group (n = 50) received monthly courses of dose-adjusted (according to cytopenic status) oral melphalan, 10mg/m² of body-surface area, on days 1 to 4 plus oral dexamethasone, 40mg/day on days 1 to 4, for up to 18 courses if no severe adverse events occurred. In the autologous HSCT patients (n = 50), hematopoietic stem cells were obtained from peripheral blood with granulocyte colony-stimulating factor mobilization. Melphalan was administered intravenously on day 0, and stem cells were infused on day two, with the dose reduced from 200mg/m² to 140mg/m² for patients aged 65 years or older and for those with
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an LVEF less than 30%, a calculated creatinine clearance less than 30mL/min, or severe liver disease. According to ITT analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 PR (28%) in the melphalan-dexamethasone recipients versus 11 CR (22%) and 7 PR (14%) in the autologous HSCT group (p = 0.11). At publication of the study, the median follow-up for the entire cohort was 24 months, and for survivors it was 36 months; 20 patients in the melphalan-dexamethasone group had died versus 31 in the autologous HSCT group. Among 65 patients who could be evaluated, the ITT median survival for patients assigned to melphalan plus dexamethasone was 56.9 months, versus 22.2 months in the autologous HSCT group (p = 0.04). Survival rates and duration were significantly better in responders (CR plus PR) compared to NR (p < 0.0001). Analysis of patients who survived for at least six months and who received their assigned treatment, showed no significant difference in survival rates in patients assigned to melphalan plus dexamethasone compared to autologous HSCT, with neither group reaching median survival after 80 months (p = 0.38).

These randomized trial data suggest that autologous HSCT may be no more efficacious than conventional chemotherapy in prolonging survival among patients with AL amyloidosis. However, the results are limited by the size of the study, a lack of assessor blinding or allocation concealment, and a large attrition post-randomization. Thus, among 50 patients assigned to autologous HSCT, 13 (26%) did not receive the planned treatment (1 declined, 2 had insufficient stem-cell harvest, 10 died before treatment), whereas 7 of 50 (14%) assigned to melphalan plus dexamethasone did not receive planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received incorrect treatment). Therefore, even though this was a randomized trial, the results are not sufficient to change the coverage statement given the body of evidence available from other, albeit nonrandomized, studies.

Allogeneic HSCT
Data on the use of allogeneic SCT to treat AL amyloidosis are sparse, with no systematic evaluation in a clinical trial. Concerns about the use of allogeneic SCT include high treatment-related mortality (more than 40%), morbidity secondary to GVHD, and questions about the efficacy of a proposed GVM effect on low-grade plasma cell dyscrasias.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from no physician specialty societies and 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. 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. There was support for the coverage statements regarding HSCT in the treatment of amyloidosis.

Summary
Chemotherapy for the treatment of AL amyloidosis was introduced in 1972 in the form of melphalan and prednisone. Median survival with this regimen was typically 12 to 18 months, with therapy remaining unchanged until the introduction of autologous HSCT. The use of autologous HSCT for AL amyloidosis rapidly eradicates the amyloidogenic light chain produced by the clonal plasma cell populations, which is
the proximal cause of pathology and subsequent death. This has extended survival rates to a reported 53% at 10 years in patients with a CR to treatment. Transplant-related mortality rates have declined, from as high as 40% to 7% in current studies. Therefore, autologous HSCT is an important option for patients who are deemed eligible, and it is considered eligible for coverage. Data on the use of allogeneic HSCT are sparse and it remains investigational.

**National Comprehensive Cancer Network Guidelines**
The 2014 National Comprehensive Cancer Network (NCCN) published guidelines specific for AL amyloidosis. Optional treatments include autologous HSCT as primary therapy for systemic amyloidosis; however, they caution that the optimal therapy is not established and that such treatment would best be performed in a clinical trial.

**National Cancer Institute Physician Data Query Database**
A search of the National Cancer Institute clinical trials Physician Data Query (PDQ®) database in January 2014 identified one active Phase II study (NCT00681044): High-Dose Melphalan and Stem Cell Transplant in Treating Patients With Immunoglobulin Deposition Disease or Light-Chain Deposition Disease. The purpose of the study is:

- To assess the tolerability of HDM and autologous stem-cell transplantation in patients with Ig deposition disease or light-chain deposition disease.
- To determine the hematologic response rate in patients treated with this regimen.
- To determine the predictability of early free light-chain response for heme response in patients treated with this regimen.
- To determine organ or clinical response in patients treated with this regimen.
- To determine OS of these patients.

**Waldenstrom’s Macroglobulinemia**
A 2002 International Workshop summarized clinical experience (combined n = 49) using autologous HSCT for WM. These were all small feasibility studies that reported response rates but lacked data on survival and other long-term outcomes. A total of 9 (18%) achieved complete response (CR) and 39 (80%) achieved partial response (PR), but data on the durability of these responses were unavailable.

A consensus panel from the Second International Workshop on Waldenstrom’s Macroglobulinemia recommended that autologous HSCT may be considered for selected patients with refractory or relapsing disease, but allogeneic transplants should be used only in the context of a clinical trial. Another recent review agreed that the role of autologous HSCT for WM was not fully defined, although its empirical use might be appropriate for some patients with relapsed or refractory disease. This review also considered allogeneic transplants for WM to be investigational therapy.

In 2004, a consensus panel from the Third International Workshop on WM suggested autologous HSCT may be considered for eligible patients with primary refractory or relapsing disease but that allogeneic transplants should be cautiously approached, only in the context of a clinical trial. However, the review article does not cite evidence to support the recommendations. The panelists also concluded that it was not possible to recommend a particular first-line therapeutic approach; rather, the choice should be made on
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the basis of individual patient considerations. A retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) registry analysis of HSCT (autologous, n = 10, allogeneic, n = 26) for WM reported 3-year OS rates of 46% (95% CI: 27–65%) for allogeneic HSCT recipients and 70% (95% CI: 40–93%) for autologous HSCT patients. Although the CIBMTR results appear favorable, it should be noted that patients in this report were heavily pretreated, highly heterogeneous in terms of disease characteristics and risk factors, and received a variety of conditioning regimens, including myeloablative and RIC, between 1986 and 2002. These data, taken together, are insufficient to form conclusions about the potential clinical efficacy of HSCT for WM. Subsequent additional review articles are in general agreement with this position.

Kyriakou et al. reported on 158 adult patients with WM reported to the European Group for Blood and Marrow Transplantation (EBMT) between January 1991 and December 2005. Median time from diagnosis to autologous HSCT was 1.7 years (range, 0.3 to 20.3 years), 32% of the patients experienced treatment failure with at least 3 of therapy, and 93% had sensitive disease at the time of HSCT. Median follow-up for surviving patients was 4.2 years (range: 0.5 to 14.8 years). Nonrelapse mortality was 3.8% at 1 year. Relapse rate was 52.1% at 5 years. Progression-free survival (PFS) and OS were 39.7% and 68.5%, respectively, at 5 years and were significantly influenced by number of lines of therapy and chemoresistance at HSCT. The authors conclude that autologous HSCT is a feasible procedure in young patients with advanced WM but that it should not be offered to patients with chemoresistant disease and to those who received more than 3 lines of therapy.

Kyriakou and colleagues also reported on a retrospective analysis of a smaller group of patients who had allogeneic HSCT for WM. A total of 86 patients received allogeneic HSCT by using either myeloablative conditioning (MAC; n = 37) or RIC (RIC; n = 49) regimens. The median age was 49 years (range: 23 to 64 years); 47 patients had received 3 or more previous lines of therapy, and 8 patients had experienced failure on a prior autologous HSCT. A total of 59 patients (68.6%) had chemotherapy-sensitive disease at the time of allogeneic SCT. Median follow-up of the surviving patients was 50 months. The overall response rate was 75.6%. The relapse rates at 3 years were 11% for MAC and 25% for RIC. Overall survival at 5 years was 62% for MAC and 64% for RIC, respectively. The occurrence of chronic GVHD was associated with a lower relapse rate. The authors concluded that allogeneic SCT can induce durable remissions in a selected population of young and heavily pretreated patients who have WM.

Little additional published evidence is available on use of autologous HSCT for WM, as summarized in 2 recent review articles. No randomized trials have been reported.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received from no physician specialty societies and 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. 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. The input indicated that autologous HSCT may be considered medically necessary as salvage therapy in WM that is chemosensitive. The input was mixed for use of allogeneic HSCT, with comments about this being performed as part of a clinical trial.
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Summary
In summary, based on the literature and clinical input, autologous HSCT may be considered medically necessary as salvage therapy for chemosensitive WM. Allogeneic HSCT for WM is considered investigational.

National Comprehensive Cancer Network Guidelines
The 2014 NCCN guidelines indicate that selected cases of WM may be treated with autologous or allogeneic HSCT, but the latter only in a clinical trial.

National Cancer Institute Physician Data Query Database
No current study is specifically focused on HSCT for WM. Five Phase III studies are active that may involve patients with WM.


References
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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 transplantation as salvage therapy of chemo-sensitive 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
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
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2015 by the American Medical Association (AMA).

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CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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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