

## Corporate Medical Policy

### Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis

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<b>Origination:</b>	2/2001
<b>Last CAP Review:</b>	11/2019
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<b>Last Review:</b>	11/2019

#### Description of Procedure or Service

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##### **Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (HSCT) 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 antigens (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.

##### **Conventional Preparative Conditioning for HSCT**

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

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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 HSCT**

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. 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 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 reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

## **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 around 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 about 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 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.

## **Related Policies:**

# Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis

Hematopoietic Stem-Cell Transplantation for CLL and SLL

Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas

Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

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**BCBSNC will provide coverage for Hematopoietic Stem-Cell Transplantation for Primary Systemic Amyloidosis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

**Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**Some health benefit plans may exclude benefits for transplantation.**

## When Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis is covered

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Autologous hematopoietic stem-cell transplantation may be considered **medically necessary** to treat primary systemic amyloidosis.

## When Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis is not covered

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1. When the medical criteria listed above are not met.
2. Allogeneic hematopoietic stem-cell transplantation is considered **investigational** to treat primary systemic amyloidosis.

## Policy Guidelines

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Refer to the individual member's benefit booklet for prior review requirements.

For individuals who have primary amyloidosis who receive autologous hematopoietic cell transplantation (HCT), the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloidogenic light chain (AL) 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 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, from as high as 40% to less than 14% in current studies. Therefore, autologous

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HCT is an important 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 HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Evidence on the use of allogeneic HCT is sparse, and the available evidence shows 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 2016, 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.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## **Scientific Background and Reference Sources**

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### **Bone Marrow Transplant for Primary Amyloidosis or Waldenstrom Macroglobulinemia**

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 2/25/2004

Specialty Matched Consultant Advisory Panel - 11/2004

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 7/20/06

Specialty Matched Consultant Advisory Panel - 11/2006

National Comprehensive Cancer Network (NCCN). 2008. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma V.2.2009. Retrieved 9/17/08 from [http://www.nccn.org/professionals/physician\\_gls/PDF/myeloma.pdf](http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf) BCBSA

Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 9/11/08

Specialty Matched Consultant Advisory Panel - 11/2008

### **Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia**

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 8/13/2009

# Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis

National Comprehensive Cancer Network (NCCN). 2010. NCCN Clinical Practice Guidelines in Oncology: Waldenstrom Macroglobulinemia/lymphoplasmacytic lymphoma Retrieved 9/2/10 from [http://www.nccn.org/professionals/physician\\_gls/PDF/waldenstroms.pdf](http://www.nccn.org/professionals/physician_gls/PDF/waldenstroms.pdf)

Medical Director – 9/2010

Specialty Matched Consultant Advisory Panel – 11/2010

## **Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis**

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 2/10/2011

Specialty Matched Consultant Advisory Panel – 11/2011

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 2/9/12

Medical Director – 4/2012

Specialty Matched Consultant Advisory Panel – 12/2012

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 2/14/2013

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 2/13/2014

Specialty Matched Consultant Advisory Panel – 11/2014

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 2/12/2015

National Comprehensive Cancer Network (NCCN). 2015. NCCN Clinical Practice Guidelines in Oncology: Systemic Light Chain Amyloidosis V.1.2016. Retrieved 10/23/15 from [http://www.nccn.org/professionals/physician\\_gls/pdf/amyloidosis.pdf](http://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf)

Specialty Matched Consultant Advisory Panel – 11/2015

Specialty Matched Consultant Advisory Panel – 11/2016

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 12/8/2016

Specialty Matched Consultant Advisory Panel – 11/2017

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 12/14/2017

Specialty Matched Consultant Advisory Panel – 11/2018

BCBSA Medical Policy Reference Manual [Electronic Manual]. 8.01.42, 1/17/2019

Specialty Matched Consultant Advisory Panel – 11/2019

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## **Policy Implementation/Update Information**

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### **Bone Marrow Transplant for Primary Amyloidosis or Waldenstrom Macroglobulinemia**

- 12/29/04 New policy. Split primary amyloidosis from policy SUR6090.14/Multiple Myeloma and added Waldenstrom macroglobulinemia to new policy's content. Specialty Matched Consultant Advisory Panel review 11/29/2004. Added Policy statement indicating that "Bone Marrow Transplant for Waldenstrom Macroglobulinemia is considered investigational." Added new indication to "When Covered" indicating that "High-dose chemotherapy with autologous stem-cell support may be considered medically necessary to treat primary systemic amyloidosis." Notice given 12/23/2004. Effective date of policy 3/3/2005.
- 12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/2006. No changes to policy statement. Rationale updated in "Policy Guidelines" section. References added.
- 12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/2008. Added "2. High-dose chemotherapy with allogeneic stem-cell support is considered investigational to treat primary systemic amyloidosis." to the "When not covered" section. Updated rationale in the "Policy Guidelines" section. Notice given 12/22/08. Effective date 3/30/09. References added. (btw)
- 6/22/10 Policy Number(s) removed (amw)

### **Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia**

- 1/4/11 Policy name changed from Bone Marrow Transplant for Primary Amyloidosis or Waldenstrom Macroglobulinemia to Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis or Waldenstrom Macroglobulinemia. "Description" section revised. Changed wording in policy statement and throughout the policy from "high dose chemotherapy with stem-cell support" to "hematopoietic stem-cell transplantation" as appropriate. Removed the following statement from the "Benefits Application" section; "Services for or related to the search for a donor are not covered." No change to policy statement. Updated "Policy Guidelines" section. Specialty Matched Consultant Panel review 11/29/2010. References added. (btw)

### **Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis**

- 1/10/12 "Waldenstrom Macroglobulinemia" removed from policy name and throughout policy as appropriate. This topic is discussed in a separate policy entitled Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia. Specialty Matched Consultant Advisory Panel review 11/30/2011. (btw)
- 2/21/12 Added new 2012 CPT code, 38232, to Billing/Coding section. (btw)
- 5/1/12 Policy Guidelines updated. Reference added. Medical Director review 4/17/12. (btw)
- 12/28/12 Specialty Matched Consultant Advisory Panel review 12/4/2012. No change to policy intent. Added new 2013 CPT code, 38243 to Billing/Coding section. (btw)

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- 4/1/13 Reference added. (btw)
- 12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. Policy Guidelines updated. No change to policy intent. (btw)
- 4/15/14 Reference added. (btw)
- 12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)
- 3/31/15 Reference added. (lpr)
- 12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. Reference added. No change to policy statement. (lpr)
- 12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. Updated Policy Guidelines. Reference added. No change to policy intent. (lpr)
- 12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)
- 1/12/18 Reference added. (lpr)
- 12/14/18 Specialty Matched Consultant Advisory Panel review 11/28/2018. No change to policy statement. (lpr)
- 12/31/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. Reference added. No change to policy statement. (lpr)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.