



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Donor Leukocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

**Policy #** 00027

**Original Effective Date:** 08/26/2002

**Current Effective Date:** 11/20/2013

*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 donor lymphocyte infusion (DLI) following allogeneic hematopoietic stem-cell transplantation (HSCT) that was originally considered medically necessary for the treatment of a hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse, or to convert a patient from mixed to full donor chimerism to be **eligible for coverage**.

*Note: Settings considered high risk for relapse include T cell depleted grafts or nonmyeloablative (reduced-intensity conditioning [RIC]) allogeneic hematopoietic stem-cell transplantation (HSCT).*

### **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 donor lymphocyte infusion (DLI) following allogeneic hematopoietic stem-cell transplantation (HSCT) that was originally considered investigational for the treatment of a hematologic malignancy to be **investigational**.\*

Based on review of available data, the Company considers donor lymphocyte infusion (DLI) as a treatment of nonhematologic malignancies following a prior allogeneic hematopoietic stem-cell transplantation (HSCT) to be **investigational**.\*

Based on review of available data, the Company considers genetic modification of donor lymphocytes to be **investigational**.\*

### **Background/Overview**

Donor lymphocyte infusion, also called donor leukocyte or buffy-coat infusion, is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a HSCT from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to the recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells.



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Approximately 40-60% of patients who receive a DLI develop graft-versus-host disease (GVHD), and the development of GVHD predicts a response to the DLI. A Blue Cross and Blue Shield Technology Evaluation Assessment on this subject was published in 1997. Treatment-related mortality after DLI is 5-20%. There does not seem to be a correlation between the type of hematologic malignancy for which the DLI was given and the development of GVHD. The risk of development of GVHD is related, in part, to DLI dose and therapy prior to DLI.

The timing of the use of DLI depends upon the disease indication and may be used in the setting of relapse after an allogeneic HSCT, as a planned strategy to prevent disease relapse in the setting of T cell depleted grafts or non-myeloablative conditioning regimens, or as a method to convert mixed to full donor chimerism. Management of relapse, which occurs in approximately 40% of all hematologic malignancy patients, is the most common indication for DLI.

The literature is heterogeneous for reporting methods of cell collection, timing of infusion (e.g., after chemotherapy, in early relapse), cell dose infused and cell subtype used. In addition, many studies include multiple diseases with little information regarding disease-specific outcomes; however, DLI is used in nearly all hematologic malignancies for which allogeneic HSCT is performed, including chronic myeloid leukemia, acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes, multiple myeloma and Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL).

## **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

The Center for Biologics Evaluation and Research (CBER) regulates the collection of blood and blood components used for transfusion or for the manufacture of pharmaceuticals derived from blood and blood components, such as clotting factors, and establishes standards for the products themselves. The CBER also regulates related products such as cell separation devices, blood collection containers and human immunodeficiency syndrome (HIV) screening tests that are used to prepare blood products or to ensure the safety of the blood supply. The CBER develops and enforces quality standards, inspects blood establishments and monitors reports of errors, accidents and adverse clinical events.

The CBER works closely with other parts of the Public Health Service (PHS) to identify and respond to potential threats to blood safety, to develop safety and technical standards, to monitor blood supplies and to help industry promote an adequate supply of blood and blood products.

Over a period of years, FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products:

- Blood donors are now asked specific and very direct questions about risk factors that could indicate possible infection with a transmissible disease. This "up-front" screening eliminates approximately 90 percent of unsuitable donors.
- The FDA requires blood centers to maintain lists of unsuitable donors to prevent the use of collections from them.
- Blood donations are tested for seven different infectious agents.

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In addition to strengthening these safeguards, FDA has significantly increased its oversight of the blood industry:

- The FDA inspects all blood facilities at least every two years, and "problem" facilities are inspected more often.
- Blood establishments are now held to quality standards comparable to those expected of pharmaceutical manufacturers.

While a blood supply with zero risk of transmitting infectious disease may not be possible, the blood supply is safer than it has ever been. As biological products, blood and blood products are likely always to carry an inherent risk of infectious agents. Therefore, zero risk may be unattainable. The role of FDA is to drive that risk to the lowest level reasonably achievable without unduly decreasing the availability of this life saving resource.

Centers for Medicare and Medicaid Services (CMS)  
There is no national coverage determination.

## **Rationale/Source**

Several review articles summarize studies that have reported the use of DLI as therapy for the treatment of hematologic malignancies after an allogeneic HSCT.

### Chronic Myelogenous Leukemia

Donor lymphocyte infusion has been found to be most effective in chronic myelogenous leukemia (CML), inducing a molecular complete remission (CR) in up to 80% of patients who relapse in chronic phase. Only a 12.5-33% response rate has been reported in patients in accelerated or blast phase. Response duration to DLI in patients with relapsed CML after HSCT is long-standing in the majority of patients.

There are several large series reporting outcomes of patients with relapsed CML after receiving DLI. These studies comprise more than 500 patients, approximately half of whom had only molecular or cytogenetic relapse at the time of DLI. The cell doses varied among patients, with some patients receiving multiple DLI infusions and others planned dose escalations. Despite these variations, a molecular CR was achieved in 77% of patients (405 of 527) with overall survival (OS) at 3 or more years ranging from 53% to 95%.

The role of DLI in CML has recently changed as the use of tyrosine-kinase inhibitors (TKIs) has revolutionized the treatment of CML by keeping the disease under control instead of proceeding to HSCT. However, for patients who develop resistance to the TKIs or are unable to tolerate the adverse effects, HSCT and DLI may be an option to manage the disease.

National Comprehensive Cancer Network (NCCN) recommendations for treating CML (v4.2013) state that DLI can be considered an option for patients who do not achieve remission, are in cytogenetic relapse or have an increasing level of molecular relapse (category 2A).



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## Acute Leukemias, Myelodysplasia, and Other Myeloproliferative Diseases

### **Acute Myelogenous Leukemia**

Donor lymphocyte infusion for patients with relapsed acute myelogenous leukemia (AML) after allogeneic HSCT has resulted in overall remission rates ranging from 15% to 42%, with an OS of approximately 15-20%. (For comparison, a second HSCT in this group of patients results in 10-35% long-term survival with a treatment-related mortality of approximately 50%). Patients with lower initial disease burden, reduction in the tumor burden with chemotherapy prior to DLI, and favorable cytogenetics appear to have more benefit with DLI with relapsed AML after HSCT.

A large retrospective analysis from the European Blood and Marrow Transplant Group (EBMT) compared OS in 399 patients with AML with post-transplant relapse who either were treated with DLI (n = 171) or were not (n = 228). Patients who received DLI had an improved 2-year OS compared with those who did not, (21+/-3% versus 9 +/- 2%, respectively; p < 0.001).

The literature for myelodysplasia (MDS) and other myeloproliferative diseases treated with DLI either after relapse or for mixed chimerism consists of small sample sizes, inconsistent pre-DLI therapy, and varied DLI cell doses, making it difficult to draw definite conclusions on outcomes. However, it appears some patients attain durable remissions with DLI after post-transplant relapse.

Warlick and colleagues reported CR after DLI in 49% of 35 patients with relapsed non-CML, including AML and MDS, after allogeneic HSCT. Overall survival at 1 year was 30% and 19% at 2 years. The authors reported a lower-dose regimen of DLI was more tolerable and reduced GVHD occurrence to 25% compared to 66% with higher-dose DLI.

National Comprehensive Cancer Network guidelines do not address the use of DLI in the treatment of AML.

### **Acute Lymphoblastic Leukemia**

The graft-versus-tumor effect is thought to be less robust in patients with acute lymphoblastic leukemia (ALL) than in the myeloid leukemias. Small studies have reported response rates to DLI ranging from 0% to 20% and OS rates of less than 15%. By comparison, a second allogeneic HSCT provides a 5-year OS of approximately 15-20%, with a treatment-related mortality rate of approximately 50%.

The clinically evident graft-versus-leukemia effect of DLI requires weeks to months to become apparent, and, as ALL is a rapidly proliferating disease, DLI only is unable to control the disease without a significant reduction in leukemia burden prior to DLI. Management of patients with relapsed ALL leading to the best OS is with a combination of salvage chemotherapy and DLI. Although it is not clear whether DLI adds benefit to salvage chemotherapy, there are reports of long-term survivors with relapsed ALL who received both chemotherapy and DLI.

National Comprehensive Cancer Network recommendations for treating ALL (v1.2013) state that DLI can be considered an option for patients in relapse after allogeneic HSCT (category 2A).



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## **The Lymphomas**

Studies in which patients received DLI for lymphomas consist of small numbers of patients and various histologies (both HL and high- and low-grade NHL).

In general, the highest response rates have been seen in the indolent lymphomas. For NHL, there are too few patients reported with any single histologic subtype of lymphoma to give adequate information of the benefit of DLI for a specific lymphoma subtype.

The largest series reported for NHL (n = 21) using DLI showed response rates in 3 of 9 patients with high-grade NHL, 1 of 2 patients with mantle cell lymphoma, and 6 of 10 patients with low-grade disease.

A series of 14 patients with multiply relapsed HL who received RIC allogeneic HSCT and DLI showed a CR of 57% and survival at 2 years of 35%.

National Comprehensive Cancer Network guidelines do not address the use of DLI in the treatment of Hodgkin or non-Hodgkin lymphomas.

## Multiple Myeloma

Observational data suggest a graft-versus-tumor effect in multiple myeloma, as the development of GVHD has correlated with response in several analyses.

Allogeneic HSCT is currently considered investigational for this indication. Most patients with multiple myeloma who undergo HSCT receive an autologous HSCT. In addition, the overall role of HSCT for multiple myeloma is currently changing with the advent of new, highly active drugs like lenalidomide and bortezomib.

Five studies reporting the role of DLI in relapsed multiple myeloma consist of patients ranging in number from 5 to 63 with the highest response to DLI being reported as 62%, with approximately half of the responders attaining a CR. One confounding factor for high response rates for multiple myeloma treated with DLI is that corticosteroids used for treating GVHD have a known antimyeloma effect, which could potentially enhance response rates in these patients.

National Comprehensive Cancer Network recommendations for treating multiple myeloma (v2.2013) state that DLI can be considered an option for patients who do not respond or are in relapse after allogeneic HSCT (category 2A).

## Genetic Modification of Donor Lymphocytes

There are inadequate data to permit conclusions regarding the use of genetic modification of donor lymphocytes. In an effort to control GVHD, a group in Italy explored using genetically modified lymphocytes engineered to express the suicide gene thymidine kinase of herpes simplex virus. These lymphocytes were infused into 23 patients with various hematologic malignancies who relapsed after an allogeneic HSCT. Six patients died of progressive disease within 4 weeks of infusion. Eleven patients experienced disease response (CR in 6 and partial remission in 5). Three patients remained alive in CR at a median of 471 days.

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Twelve patients were evaluable for GVHD, 3 of whom developed acute or chronic GVHD, which was successfully treated with ganciclovir.

## Ongoing Clinical Trials

A search of online site ClinicalTrials.gov on April 12, 2013 identified 31 open and active Phase II studies that list DLI as an intervention component.

## Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 1 academic medical center and 5 Blue Distinction Centers for Transplant 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 general agreement with the policy statements, although 2 reviewers disagreed with the policy statement on the use of DLI in non-hematopoietic malignancies; one thought it was investigational and also medically necessary and the other did not think this was investigational or medically necessary. One reviewer suggested adding Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease as another medically necessary indication for DLI. One reviewer commented on an evolving technique for use of ex-vivo expansion of donor lymphocytes.

## Summary

Donor lymphocyte infusion, also called donor leukocyte or buffy-coat infusion, is a type of therapy in which T lymphocytes from the blood of a donor are given to a patient who has already received a HSCT from the same donor. The DLI therapeutic effect results from a graft-versus-leukemic or graft-versus-tumor effect due to the recognition of certain antigens on the cancer cells by the donor lymphocytes and the resultant elimination of the tumor cells.

The response rates to DLI for relapsed hematologic malignancies following an allogeneic HSCT are best in CML, followed by the lymphomas, multiple myeloma and acute leukemias, respectively. Other than CML, clinical responses are most effective when chemotherapy induction is used to reduce the tumor burden prior to DLI.

Donor lymphocyte infusion is used in nearly all hematologic malignancies that relapse after a prior allogeneic HSCT, as a planned strategy to prevent disease relapse in a setting of high-risk of disease relapse (e.g., after a reduced-intensity allogeneic HSCT), and to convert mixed to full donor chimerism. Future directions are focused on enhancing the antitumor effect of the donor T cells while decreasing the toxicities related to GVHD from DLI.

Therefore, DLI may be considered medically necessary following an allogeneic HSCT that was considered medically necessary for the treatment of a hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse, or to convert a patient from mixed to full donor chimerism. Donor lymphocyte infusion is considered investigational following an allogeneic HSCT for the treatment of a hematologic malignancy that was originally considered investigational.

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Data on the use of DLI in the treatment of non-hematologic malignancies following a prior allogeneic HSCT are limited, and therefore, use of DLI in this circumstance is considered investigational. Data on the genetic modification of donor lymphocytes are also limited. Therefore, genetic modification of donor lymphocytes is considered investigational.

## 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)<sup>®</sup>†, copyright 2012 by the American Medical Association (AMA). 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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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	38242
HCPCS	No code
ICD-9 Diagnosis	201.00 thru 201.98, 2002.00 thru 202.98, 203.00 thru 203.82, 204.00 thru 204.92, 205.10 205.11, 206.00 thru 209.92, V59.09
ICD-9 Procedure	99.09, 99.72

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07/18/2002	Medical Policy Committee review
08/26/2002	Managed Care Advisory Council approval
08/31/2004	Medical Director review
09/21/2004	Medical Policy Committee review. Format revision. No substance change to policy.
09/27/2004	Managed Care Advisory Council approval
08/03/2005	Medical Director review
08/16/2005	Medical Policy Committee review. No change to coverage eligibility.
08/24/2005	Managed Care Advisory Council approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
05/02/2007	Medical Director review

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05/23/2007	Medical Policy Committee approval. Background section was added to the policy. Based on review of available data, the Company considers donor leukocyte infusion as a treatment of other malignancies that have relapsed after a prior marrow-ablative allogeneic SCT to be investigational was added.
11/05/2008	Medical Director review
11/18/2008	Medical Policy Committee approval. No change to coverage eligibility.
11/12/2009	Medical Policy Committee approval
11/18/2009	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/04/2010	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. Title changed to "Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant." References extensively revised/added. Policy statements modified to indicate that donor lymphocyte infusion would be considered eligible for coverage "following an allogeneic-hematopoietic stem cell transplantation that was considered eligible for coverage for the treatment of a hematologic malignancy that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse, or to convert a patient from mixed to full donor chimerism.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	11/2014

\*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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