Effective November 1, 2023, refer to CMS Manual 100-02, Chapter 16-General Exclusions from Coverage for services included in this policy.

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Stem-cell Therapy for Peripheral Arterial Disease

Policy #:183
Latest Review Date: January 2023
Category: Surgery
ARCHIVED EFFECTIVE 11/1/2023

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after March 24, 2020:

Blue Advantage will treat **injection or infusion of stem cells obtained from any source for the treatment of peripheral arterial disease, including critical limb ischemia**, as a **non-covered benefit** and as **investigational**.

Effective for dates of service February 26, 2018, through March 23, 2020, refer to LCD L34555.

Effective for dates of service prior to February 26, 2018:

Blue Advantage will treat the **injection or infusion of stem cells obtained from any source** for the treatment of peripheral arterial disease, including critical limb ischemia as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Peripheral Arterial Disease

Peripheral arterial disease (PAD) is a common atherosclerotic syndrome that is associated with significant morbidity and mortality. Critical limb ischemia (CLI) is the end stage of lower extremity PAD in which severe obstruction of blood flow results in ischemic pain at rest, ulcers, and a significant risk for limb loss.

A less-common cause of PAD is Buerger disease, also called thromboangitis obliterans, which is a non-atherosclerotic segmental inflammatory disease that occurs in younger patients and is associated with tobacco use. Development of PAD is characterized by narrowing and occlusion of arterial vessels and eventual reduction in distal perfusion.

Physiology

Two endogenous compensating mechanisms may occur with occlusion of arterial vessels, capillary growth (angiogenesis) and development of collateral arterial vessels (arterio-genesis). Capillary growth is mediated by hypoxia-induced release of chemo- and cytokines such as vascular endothelial growth factor (VEGF), and occurs by sprouting of small endothelial tubes from pre-existing capillary beds. The resulting capillaries are small and cannot sufficiently compensate for a large occluded artery. Arteriogenesis with collateral growth is, in contrast,

initiated by increasing shear forces against vessel walls when blood flow is redirected from the occluded transport artery to the small collateral branches, leading to an increase in the diameter of pre-existing collateral arterioles.

The mechanism underlying arterio-genesis includes the migration of bone marrow-derived monocytes to the perivascular space. The bone marrow-derived monocytes adhere to and invade the collateral vessel wall. It is not known if the expansion of the collateral arteriole is due to the incorporation of stem cells into the wall of the vessel or to cytokines released by monocytic bone marrow cells that induce the proliferation of resident endothelial cells. It has been proposed that bone marrow-derived monocytic cells may be the putative circulating endothelial progenitor cells. Notably, the same risk factors for advanced ischemia (diabetes, smoking, hyperlipidemia and advanced age) are also risk factors for a lower number of circulating progenitor cells.

Treatment
The standard therapy for severe, limb-threatening ischemia is revascularization aiming to improve blood flow to the affected extremity. If revascularization fails or is not possible, amputation is often necessary.

The rationale of hematopoietic stem-cell/bone marrow-cell therapy in PAD is to induce arteriogenesis by boosting the physiological repair processes. This requires large numbers of functionally active autologous precursor cells, and subsequently a large quantity of bone marrow (e.g., 240-500 mL) or other source of stem cells.

Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a role in the treatment of peripheral arterial disease. Stem cells can be administered in a variety of routes, derived from different progenitors, and be grouped with different co-factors, many of which are being studied in order to determine the best clinical option for patients. The primary outcome in stem-cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival, defined as time to major amputation and/or death from any cause. Other outcomes for critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the ankle-brachial index (ABI), transcutaneous oxygen pressure (TcO2), and pain-free walking. The ABI measures arterial segmental pressures on the ankle and brachium, and indexes ankle systolic pressure against brachial systolic pressure (normal range 0.95 – 1.2).

KEY POINTS:
The most recent update was performed through December 2, 2022.

Summary of Evidence
For individuals who have peripheral arterial disease who receive stem cell therapy, the evidence includes small randomized trials and systematic reviews. Relevant outcomes are overall survival, symptoms, and change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The current literature on stem cells as a treatment for critical limb ischemia due to peripheral arterial disease consists primarily of phase 2 studies using various cell preparation methods and methods of administration. A meta-analysis of the trials with the lowest

risk of bias has shown no significant benefit of stem cell therapy for overall survival, amputation-free survival, or amputation rates. Three RCTs have been published that used granulocyte-macrophage colony-stimulating factor mobilized peripheral mononuclear cells. The route of administration of the cell therapy and the primary outcomes differed between studies. In the trial that added cell therapy to guideline-based care, there were no significant differences in PFS and frequency of limb amputation at one year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms. Well-designed randomized controlled trials with a larger number of subjects and low risk of bias are needed to evaluate the health outcomes of these various procedures. Several are in progress, including multicenter randomized, double-blind, placebo-controlled trials. More data on the safety and durability of these treatments are also needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Heart Association and the American College of Cardiology

The 2016 guidelines from the American Heart Association and American College of Cardiology provided recommendations on the management of patients with lower-extremity PAD, including surgical and endovascular revascularization for critical limb ischemia. Stem cell therapy for PAD was not addressed.

Global Vascular Guideline

In 2019, a Global Vascular Guideline on management of chronic limb-threatening ischemia summarized the available literature on therapeutic angiogenesis for various etiologies. The guideline was a joint venture of the Society for Vascular Surgery, the European Society for Vascular Surgery, and the World Federation of Vascular Societies. Based on a moderate level of evidence, the guideline recommended that therapeutic angiogenesis in patients with chronic limb-threatening ischemia should be limited to the context of a clinical trial (strong recommendation). The authors noted that Phase 3 clinical trials are planned or underway so additional data may be forthcoming in the future.

European Society of Cardiology

The 2011 European Society of Cardiology guidelines on the diagnosis and treatment of PAD did not recommend for or against stem cell therapy for PAD. However, in 2017, updated guidelines, published in collaboration with the European Society of Vascular Surgery, stated: “Angiogenic gene and stem cell therapy are still being investigated with insufficient evidence in favor of these treatments.” The current recommendation is that stem cell/gene therapy is not indicated in patients with chronic limb-threatening ischemia (class of recommendation: III; level of evidence: B).

U.S. Preventive Services Task Force Recommendations

Not Applicable.

KEY WORDS:

Critical Limb Ischemia, Peripheral Arterial Disease, Peripheral Artery Disease, Bone marrow concentrate, Harvest, Hematopoietic stem cells, Limb Ischemia, Monocytes, Mononuclear cells, SmartPrep, Stem cells, RESTORE-CLI, PROVASA, MarrowStim™, Ixmyelocel-T, Arthrex Angel System Kit, Magellan® Autologous Platelet Separator System, PureBMC SupraPhysiologic Concentrating System, BioCUE Platelet Concentration Kit, ART BMC, ART BMC Plus System, PXP®-1000 System

APPROVED BY GOVERNING BODIES:

Several point-of-care concentrations of bone marrow aspirate has been cleared by the Food and Drug Administration through the 510(k) process and summarized below.

FDA Approved Point-of-Care Concentration of Bone Marrow Aspirate Devices

Device	Manufacturer	Location	Date Cleared	510(k) No.
The SmartPrep Bone Marrow Aspirate Concentrate System, SmartPrep Platelet Concentration System	Harvest Technologies	Lakewood, CO	12/06/2010	K103340
MarrowStim Concentration System (MSC system)	Biomet Biologics, Inc. (now Zimmer Biomet)	Warsaw, IN	12/18/2009	BK090008
PureBMC SupraPhysiologic Concentrating System	EmCyte Corporation®	Fort Myers, Florida	5/30/2019	K183205
Arthrex Angel® System Kit	Arthrex, Inc.	Naples, Florida	5/23/2018	BK180180
Magellan® Autologous Platelet Separator System	Arteriocyte Medical Systems (Medtronic)	Memphis, TN	11/09/2004	BK040068
BioCUE® Platelet Concentration Kit (now BioCUE® Blood and Bone Marrow Aspiration (bBMA) Concentration Kit)	Biomet Biologics, Inc. (now Zimmer Biomet)	Warsaw, IN	5/26/2010	BK100027

ART BMC/ART BMC PLUS	SpineSmith Holdings, LLC (now Ceiling Biosciences)	Austin, TX	Not available	Not available
PXP® System (now PXP®-1000)	ThermoGenesis Corp.	Rancho Cordova, CA	7/10/2008	K081345

Food and Drug Administration product code: JQC.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT codes:

0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest.
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest.
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy.

The CPT codes were constructed to allow reporting of the complete procedure and harvesting by a single physician (**code 0263T**) or separate reporting when the cell harvesting and therapy injections are performed by separate physicians (**0264T and 0265T**).

REFERENCES:

1. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. Mar 01 2018; 39(9): 763-816.
2. Benoit E, O'Donnell TF, Jr., Iafrati MD et al. The role of amputation as an outcome measure in cellular therapy for critical limb ischemia: implications for clinical trial design. J Transl Med 2011; 9:165.
3. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. Jun 2019; 69(6S): 3S-125S.e40.
4. Fadini GP, Agostini C, Avogaro A. Autologous stem cell therapy for peripheral arterial disease meta-analysis and systematic review of the literature. Atherosclerosis 2010; 209(1):10-17.
5. Gao W, Chen D, Liu G, et al. Autologous stem cell therapy for peripheral arterial disease: a systematic review and meta-analysis of randomized controlled trials. 2019 May 21.
6. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. Mar 21 2017; 69(11):e71-e126.
7. Gupta PK, Krishna M, Chullikana A, et al. Administration of Adult Human Bone Marrow-Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells in Critical Limb Ischemia Due to Buerger's Disease: Phase II Study Report Suggests Clinical Efficacy. Stem Cells Transl Med. Mar 2017; 6(3):689-699.
8. Horie T, Yamazaki S, Hanada S, et al. Outcome From a Randomized Controlled Clinical Trial- Improvement of Peripheral Arterial Disease by Granulocyte Colony-Stimulating Factor-Mobilized Autologous Peripheral-Blood-Mononuclear Cell Transplantation (IMPACT). Circ J. Jul 25 2018;82(8):2165-2174.
9. IOM (Institute of Medicine). 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press.
10. Lawall H, Bramlage P, Amann B. Treatment of peripheral arterial disease using stem and progenitor cell therapy. J Vasc Surg 2011; 53(2):445-453.
11. McDermott MM, Ferrucci L, Tian L, et al. Effect of Granulocyte-Macrophage Colony-Stimulating Factor With or Without Supervised Exercise on Walking Performance in Patients With Peripheral Artery Disease: The PROPEL Randomized Clinical Trial. JAMA. Dec 05 2017; 318(21): 2089-2098.
12. Moazzami B, Mohammadpour Z, Zabala ZE, et al. Local intramuscular transplantation of autologous bone marrow mononuclear cells for critical lower limb ischemia. Cochrane Database Syst Rev. Jul 08 2022; 7(7): CD008347.

13. Peeters Weem SM, Teraa M, den Ruijter HM, et al. Quality of life after treatment with autologous bone marrow derived cells in no option severe limb ischemia. Eur J Vasc Endovasc Surg. Jan 2016; 51(1):83-89.
14. Poole J, Mavromatis K, Binongo JN et al. Effect of progenitor cell mobilization with granulocyte-macrophage colony-stimulating factor in patients with peripheral artery disease: a randomized clinical trial. JAMA 2013; 310(24):2631-2639.
15. Powell RJ, Comerota AJ, Berceli SA et al. Interim analysis results from the RESTORE-CLI, a randomized, double-blind multicenter phase II trial comparing expanded autologous bone marrow-derived tissue repair cells and placebo in patients with critical limb ischemia. J Vasc Surg 2011; 54(4):1032-1041.
16. Powell RJ, Marston WA, Berceli SA et al. Cellular therapy with Ixmyelocel-T to treat critical limb ischemia: the randomized, double-blind, placebo-controlled RESTORE-CLI trial. Mol Ther 2012; 20(6):1280-1286.
17. Procházka V, Gumulec J, Jalůvka F, et al. Cell therapy, a new standard in management of chronic critical limb ischemia and foot ulcer. Cell Transplant. 2010; 19(11): 1413-24.
18. Pu H, Huang Q, Zhang X, et al. A meta-analysis of randomized controlled trials on therapeutic efficacy and safety of autologous cell therapy for atherosclerosis obliterans. J Vass Surg. Apr 2022; 75(4): 1440-1449.e5.
19. Rigato M, Monami M, Fadini GP. Autologous cell therapy for peripheral arterial disease: systematic review and meta-analysis of randomized, nonrandomized, and non-controlled studies. Circ Res. Apr 14 2017; 120(8):1326-1340.
20. Skora J, Pupka A, Janczak D, et al. Combined autologous bone marrow mononuclear cell and gene therapy as the last resort for patients with critical limb ischemia. Arch Med Sci. Apr 25 2015; 11(2):325-331.
21. Tendera M, Aboyans V, Bartelink ML, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology(ESC). Eur Heart J. Nov 2011; 32(22): 2851-906.
22. Teraa M, Sprengers RW, Schutgens RE, et al. Effect of Repetitive Intra-Arterial Infusion of Bone Marrow Mononuclear Cells in Patients With No-Option Limb Ischemia: The Randomized, Double-Blind, Placebo-Controlled Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) Trial. Circulation. Mar 10 2015; 131(10):851-860.
23. Valentine EA, Ochroch EA. 2016 American College of Cardiology/American Heart Association guideline on the management of patients with lower extremity peripheral artery disease: perioperative implications. J Cardiothorac Vasc Anesth. Oct 2017; 31(5):1543-1553.
24. Walter DH, Krankenberg H, Balzer JO et al. Intraarterial administration of bone marrow mononuclear cells in patients with critical limb ischemia: a randomized-start, placebo-controlled pilot trial (PROVASA). Circulation interventions 2011; 4(1):26-37.
25. Xie B, Luo H, Zhang Y, et al. Autologous Stem Cell Therapy in Critical Limb Ischemia: A Meta-Analysis of Randomized Controlled Trials. Stem Cells Int. 2018;2018:7528464.

POLICY HISTORY:

Adopted for Blue Advantage, May 2011
Available for comment May 25 – July 11, 2011
Medical Policy Group, May 2012
Medical Policy Group, May 2013
Medical Policy Group, June 2014
Medical Policy Group, May 2015
Medical Policy Group, February 2016
Medical Policy Group, August 2017
Medical Policy Group, February 2018
Medical Policy Group, April 2020: Reinstated policy effective March 24, 2020.
Medical Policy Group, January 2021
Medical Policy Group, January 2022
Medical Policy Group, January 2023
Medical Policy Group, November 2023: Archived effective 11/1/2023.
