MEDICAL POLICY

POLICY TITLE	STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE
POLICY NUMBER	MP-2.089

Original Issue Date (Created):	**11/1/2012**
Most Recent Review Date (Revised):	**2/10/2021**
Effective Date:	**8/1/2021**

I. POLICY

Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source is considered **investigational** as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Cross-reference:

MP-2.033 Recombinant and Autologous Platelet Derived Growth Factors as Treatment of Wound Healing and Other Non-Orthopedic Conditions
MP-2.080 Orthopedic Applications of Stem Cell Therapy Including Allograft and Bone Substitute Products used with Autologous Bone Marrow

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital BlueCross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual MP-8.01.55 Stem-Cell Therapy for Peripheral Arterial Disease. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

Peripheral arterial disease is a common atherosclerotic syndrome 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. Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a role in the treatment of PAD.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is a common atherosclerotic syndrome that is associated with significant morbidity and mortality. A less-common cause of PAD is Buerger disease (also called thromboangitis obliterans), which is a nonatherosclerotic segmental inflammatory disease that occurs in younger patients and is associated with tobacco use. The development of PAD is characterized by narrowing and occlusion of arterial vessels and eventual reduction in distal perfusion. Critical limb ischemia 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.

Physiology

Two endogenous compensating mechanisms may occur with occlusion of arterial vessels, capillary growth (angiogenesis) and development of collateral arterial vessels (arteriogenesis). 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 arteriogenesis 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

Use of autologous stem cells freshly harvested and allogeneic stem cells are reported to have a role in the treatment of PAD. 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, and pain-free walking. The ABI measures arterial segmental pressures on the ankle and brachium and indexes ankle systolic pressure against brachial systolic pressure (normative range, 0.95 to 1.2 mm Hg).

Regulatory Status

Six point-of-care concentrations of bone marrow aspirate have been cleared by the FDA through the 510(k) process and are summarized in Table 1.

Table 1. FDA Approved Point-of-Care Concentration of Bone Marrow Aspirate Devices

Device	Manufacturer	Location	Date Cleared	510(k) No.
The SmarktPReP2® Bone Marrow Aspirate Concentrate System, SmarktPReP Platelet Concentration System	Harvest Technologies	Lakewood, CO	12/06/2010	K103340
MarrowStim Concentration System (MSC system)	Biomet Biologics, Inc	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	Biomet Biologics, Inc.	Warsaw, IN	5/26/2010	BK1000027

ART BMC System	SpineSmith Holdings, LLC	Austin, TX	Not available	Not available
PXP® System	ThermoGenesis Corp.	Rancho Cordova, CA	07/10/2008	K081345

U.S. Food and Drug Administration product code: JQC.

IV. RATIONALE

TOP

SUMMARY OF EVIDENCE

For individuals who have peripheral arterial disease (PAD) who receive stem cell therapy, the evidence includes small randomized trials and systematic reviews. Relevant outcomes are overall survival, symptoms, 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 CLI due to PAD 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 randomized controlled trials (RCTs) have been published that used granulocyte colony-stimulating factor (GM-CSF)-mobilized peripheral blood mononuclear cells (PBMNC). The route of administration of 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 progression-free survival and frequency of limb amputation at 1 year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms. Well-designed RCTs 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 that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

N/A

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the

applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

TOP

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

CPT Codes®								
0263T	0264T	0265T						

IX. REFERENCES

TOP

1. *Lawall H, Bramlage P, Amann B. Treatment of peripheral arterial disease using stem and progenitor cell therapy. J Vasc Surg. Feb 2011; 53(2): 445-53. PMID 21030198*
2. *Fadini GP, Agostini C, Avogaro A. Autologous stem cell therapy for peripheral arterial disease meta-analysis and systematic review of the literature. Atherosclerosis. Mar 2010; 209(1): 10-7. PMID 19740466*

3. *Rigato M, Monami M, Fadini GP. Autologous Cell Therapy for Peripheral Arterial Disease: Systematic Review and Meta-Analysis of Randomized, Nonrandomized, and Noncontrolled Studies. Circ Res. Apr 14 2017; 120(8): 1326-1340. PMID 28096194*
4. *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. PMID 29977308*
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. Stem Cell Res Ther. May 21 2019; 10(1): 140. PMID 31113463*
6. *Prochazka V, Gumulec J, Jaluvka 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. PMID 20529449*
7. *Benoit E, O'Donnell TF, 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. Sep 27 2011; 9: 165. PMID 21951607*
8. *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): 325-31. PMID 25995748*
9. *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. PMID 28297569*
10. *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): 851-60. PMID 25567765*
11. *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): 83-9. PMID 26511056*
12. *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). Circ Cardiovasc Interv. Feb 01 2011; 4(1): 26-37. PMID 21205939*
13. *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. Oct 2011; 54(4): 1032-41. PMID 21684715*

14. *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. Jun 2012; 20(6): 1280-6. PMID 22453769*
15. *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. Dec 25 2013; 310(24): 2631-9. PMID 24247554*
16. *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. PMID 29141087*
17. *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. PMID 29877199*
18. *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. PMID 27851992*
19. *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. PMID 28826846*
20. *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. PMID 31159978*
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. PMID 21873417*
22. *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 arteriesEndorsed 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. PMID 28886620*
23. *Blue Cross Blue Shield Association Medical Policy Reference Manual 8.01.55, Stem Cell Therapy for Peripheral Arterial Disease, Feburary, 2021.*

POLICY TITLE	STEM CELL THERAPY FOR PERIPHERAL ARTERIAL DISEASE
POLICY NUMBER	MP-2.089

X. POLICY HISTORY

TOP

MP-2.089	**CAC 6/26/2012 New Policy. Adopted BCBSA.** Stem-cell therapy for the treatment of peripheral arterial disease is considered investigational.
	7/26/13 Admin coding review complete
	CAC 9/24/13 Consensus. No change to policy statements. Added FEP variation to reference the policy manual. Added rationale section.
	CAC 9/30/14 Consensus. No change to policy statements. References updated**.**
	CAC 9/29/15 Consensus review. No change to the policy statement. Reference and rationale update. Coding Reviewed
	CAC 9/27/16 Consensus review. No change to the policy statement. References and rationale updated**.** Variations reformatted**.** Coding reviewed.
	CAC 11/28/17 Consensus review. Policy statement updated to describe specific sources of stem cells. Procedure remains investigational. Rationale and references updated. Coding reviewed.
	8/16/18 Consensus review. No change to policy statements. References updated. Rationale condensed.
	6/3/2019 Consensus review. Policy statement unchanged. References updated.
	7/10/2020 Consensus Review. Policy statement unchanged. FEP statement updated. Benefit Variation statement updated. Product Variation Statement updated. Coding checked, no changes. References reviewed, updated.
	2/10/21: Consensus Review. Policy statement unchanged. Background, rationale and references updated. Coding reviewed.

Top