MEDICAL POLICY

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

Effective Date:	5/1/2023

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 general 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 Blue Cross. Please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. 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

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

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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 chemokines 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	Biomet	Warsaw, IN	12/18/2009	BK090008

Concentration System (MSC system)	Biologics, Inc.			
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

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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

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N/A

VI. BENEFIT VARIATIONS

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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 Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross'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 Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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:

Procedure Codes								
0263T	0264T	0265T						

IX. REFERENCES

TOP

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X. POLICY HISTORY

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MP-2.089	**CAC 6/26/2012 New Policy. Adopted BCBSA.** Stem-cell therapy for the treatment of peripheral arterial disease is considered investigational.

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	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.
	3/4/2022: Consensus Review. Policy statement unchanged. Background, FEP, and references updated. No coding changes.
	1/26/2023 Consensus review. Background and references updated. No changes to coding.

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