FEP 8.01.55 Stem Cell Therapy for Peripheral Arterial Disease

Description
Critical limb ischemia due to peripheral arterial disease results in pain at rest, ulcers, and significant risk for limb loss. Injection or infusion of stem cells, either concentrated from bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is being evaluated for the treatment of critical limb ischemia.

The primary outcome in stem cell therapy trials regulated by the U.S. Food and Drug Administration (FDA) is amputation-free survival. Other outcomes for critical limb ischemia include the Rutherford criteria for limb status, healing of ulcers, the Ankle-Brachial Index, transcutaneous oxygen pressure, and pain-free walking. The Rutherford criteria include ankle and toe pressure, level of claudication, ischemic rest pain, tissue loss, nonhealing ulcer, and gangrene. The Ankle-Brachial Index measures arterial segmental pressures on the ankle and brachium and indexes ankle systolic pressure against brachial systolic pressure (normative range, 0.95-1.2 mm Hg). An increase more than 0.1 mm Hg is considered clinically significant. Transcutaneous oxygen pressure is measured with an oxymonitor; a normal range is 70 to 90 mm Hg. Pain-free walking may be measured by time on a treadmill or, more frequently, by distance in a 400-meter walk.

OBJECTIVE
The objective of this evidence review is to evaluate whether stem cell therapy improves the net health outcome in patients with peripheral arterial disease.

POLICY STATEMENT
Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of stem cells from concentrated bone marrow, expanded in vitro, stimulated from peripheral blood, or from an allogeneic source, is considered investigational.

BENEFIT APPLICATION
Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).
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**FDA REGULATORY STATUS**

Two point-of-care concentration of bone marrow aspirate has been cleared by the Food and Drug Administration through the 510(k) process and summarized in Table 1.

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

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Location</th>
<th>Date Cleared</th>
<th>510(k) No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The SmarkPReP2® Bone Marrow Aspirate Concentrate System, SmartPReP Platelet Concentration System</td>
<td>Harvest Technologies</td>
<td>Lakewood, CO</td>
<td>12/06/2010</td>
<td>K103340</td>
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<tr>
<td>MarrowStim Concentration System</td>
<td>Biomet Biologics, Inc</td>
<td>Warsaw, IN</td>
<td>12/18/2009</td>
<td>BK090008</td>
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</table>

FDA product code: JQC.

**RATIONALE**

**Summary of Evidence**

For individuals who have PAD who receive stem cell therapy, the evidence includes small randomized trials, systematic reviews, and case series. The relevant outcomes are overall survival, symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related morbidity. The current literature on stem cells as a treatment for critical limb ischemia 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. Two RCTs have been published that used granulocyte 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.

For individuals who have peripheral arterial disease who receive stem cell therapy, the evidence includes small randomized trials, systematic reviews, retrospective reviews, and case series. The 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 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. Two randomized controlled trials have been published that used granulocyte 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 progression-free survival 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.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Heart Association and 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 peripheral arterial disease (PAD), including surgical and endovascular revascularization for critical limb ischemia (CLI). Stem cell therapy for PAD was not addressed.

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 favour 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.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


FEP 8.01.55 Stem Cell Therapy for Peripheral Arterial Disease

### POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2013</td>
<td>New Policy</td>
<td>Treatment of peripheral arterial disease, including critical limb ischemia, with injection or infusion of cells concentrated from bone marrow aspirate is considered investigational.</td>
</tr>
<tr>
<td>September 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review. References 3, 4, 6, 10, 12, 13, and 15 added. Some reordered. Policy statement unchanged.</td>
</tr>
<tr>
<td>September 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review, references 5, 14 added; policy statement unchanged.</td>
</tr>
<tr>
<td>September 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review, references 4, 9, and 23 added; policy statement unchanged.</td>
</tr>
<tr>
<td>June 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through November 7, 2017; references 3, 4, 7, 9, 14, 15 and 17 added. Policy statement unchanged.</td>
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<tr>
<td>March 2019</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 29, 2018; references 4, 8 and 16 added. Policy statement unchanged.</td>
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