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.

Policy Guidelines

Coding
There are specific CPT category III codes for this therapy:

- **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.

These 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).

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.

Related Policies

- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions
- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)
- Progenitor Cell Therapy for the Treatment of Damaged Myocardium due to Ischemia

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these
instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

Six point-of-care concentrations of bone marrow aspirate have 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 SmartPreP® 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>
</tr>
<tr>
<td>MarrowStim Concentration System (MSC system)</td>
<td>Biomet Biologics, Inc</td>
<td>Warsaw, IN</td>
<td>12/18/2009</td>
<td>BK090008</td>
</tr>
<tr>
<td>PureBMC SupraPhysiologic Concentrating System</td>
<td>EmCyte Corporation</td>
<td>Fort Myers, Florida</td>
<td>5/30/2019</td>
<td>K183205</td>
</tr>
<tr>
<td>BioCUE Platelet Concentration Kit</td>
<td>Biomet Biologics, Inc</td>
<td>Warsaw, IN</td>
<td>5/26/2010</td>
<td>BK1000027</td>
</tr>
</tbody>
</table>

Food and Drug Administration product code: JQC.

**Rationale**

**Background**

**Peripheral Arterial Disease**

PAD is a common atherosclerotic syndrome 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 the hypoxia-induced release of chemokines and cytokines such as vascular endothelial growth factor and occurs by sprouting of small endothelial tubes from preexisting 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 preexisting 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 monocytes. Bone marrow cells that induce the proliferation of resident endothelial cells. It has been proposed that bone marrow-derived monocytes may be the putative circulating endothelial progenitor cells. Notably, the same risk factors for advanced ischemia (diabetes, smoking, hyperlipidemia, 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 peripheral arterial disease. Stems cell 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 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, transcutaneous oxygen pressure, and pain-free walking. 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).

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Stem Cell Therapy in Individuals With Peripheral Arterial Disease
Clinical Context and Therapy Purpose
The purpose of stem cell therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with PAD.

The question addressed in this evidence review is: Does stem cell therapy improve the net health outcome in patients with PAD?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with PAD.

Interventions
The therapy being considered is stem cell therapy. The rationale for hematopoietic cell or bone marrow cell therapy in PAD is to induce arteriogenesis by boosting the physiologic 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 another source of stem cells.
Comparators
Comparators of interest include conservative management, rehabilitation protocols or surgical intervention. 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.

Outcomes
The general outcomes of interest are overall survival, symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related morbidity, amputation rates, improved amputation-free survival, improved wound healing, ulcer healing, and pain-free walking distance. Follow-up at 3, 6, and 12 months is of interest for stem cell therapy to monitor relevant outcomes. Longer-term follow-up is also of interest.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

d. Studies with duplicative or overlapping populations were excluded.

At this time, the literature on stem cell therapy consists primarily of small RCTs, systematic reviews and meta-analyses, retrospective reviews, and case series. Systematic reviews, controlled studies, and the larger case series are described next.

Systematic Reviews
Rigato et al (2017) published a systematic review of autologous cell therapy for peripheral arterial disease. They identified 19 RCTs (837 patients), 7 nonrandomized controlled studies (338 patients), and 41 noncontrolled studies (1177 patients). There was heterogeneity across studies in setting, underlying diseases, types and doses of cells, routes of administration, and follow-up durations. Many studies were a pilot or phase 2 trials and were rated as low-quality. There was an indication of publication bias. A meta-analysis of all RCTs showed a significant reduction in amputation rates, improved amputation-free survival, and improved wound healing. However, when only the placebo-controlled trials (n=19) were analyzed the effects were no longer statistically significant, and analysis of only RCTs with low risk of bias (n=3) found no benefit of cell therapy.

In a meta-analysis of RCTs, Xie et al (2018) reviewed published evidence evaluating the safety and efficacy of autologous stem cell therapy in critical limb ischemia (CLI). Cell therapy increased the probability of angiogenesis (relative risk=5.91, confidence interval [CI]: 2.49-14.02, p<0.0001), ulcer healing (relative risk=1.73, CI: 1.45-2.06, p<0.00001), and a reduction in amputation rates (relative risk=0.59, CI: 0.46-0.76, p<0.00001). Compared with the control group, significant improvement in the cell therapy group was also seen in ankle-brachial index (mean difference=0.13, CI=0.11-0.15, p<0.00001), transcutaneous oxygen tension (mean difference=12.22, CI=5.03-19.41, p=0.0009), and pain-free walking distance (mean difference=144.84, CI=53.03-236.66, p=0.002).

Gao et al (2019) reviewed 27 RCTs and found that 1186 patients and 1280 extremities were included. A majority of studies showed a high-risk of bias. Meta-analysis indicated that autologous stem cell therapy was more effective than conventional therapy on the healing rate of ulcers. There was also a significant improvement in Ankle-Brachial Index (ABI) total carbon dioxide, and pain-free walking distance while the significant reduction was shown in amputation rate and rest pain scores. However, the result presented no significant improvement in major limb salvage.
Table 2. Systematic Reviews of Trials Assessing Autologous Cell Therapy for PAD

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Literature Search</th>
<th>Studies</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao (2019)</td>
<td>May 2019</td>
<td>27</td>
<td>Patients with PAD or CLI who received autologous stem cell therapy</td>
<td>1186</td>
<td>RCTs</td>
<td>Pooled analysis of 27 RCTs showed a significant improvement in ABI, total carbon dioxide, and pain-free walking distance while significant reduction was shown in amputation rate and rest pain scores.</td>
</tr>
<tr>
<td>Rigato (2017)</td>
<td>Jul 2016</td>
<td>67</td>
<td>Patients with severe intractable PAD or CLI who received autologous cell therapy</td>
<td>2352</td>
<td>RCTs, cohort</td>
<td>Pooled analysis of 19 RCTs showed a reduction in amputation rates, improved amputation-free survival, and improved wound healing</td>
</tr>
<tr>
<td>Xie (2018)</td>
<td>Jan 2018</td>
<td>23</td>
<td>Patients with PAD or CLI who received autologous stem cell therapy</td>
<td>1118</td>
<td>RCTs</td>
<td>Pooled analysis of 18 studies showed a reduction in amputation rate, ulcer healing, and pain-free walking distance (n=612)</td>
</tr>
</tbody>
</table>

ABI: Ankle-Brachial Index; CLI: critical limb ischemia; PAD: peripheral arterial disease, RCT: randomized controlled trial.

Autologous stem cell therapy for peripheral arterial disease: a systematic review and meta-analysis of randomized controlled trials.

The following discussion concerns some RCTs included and not included in the meta-analyses. A number of these RCTs were described as pilot or phase 2 studies.

Concentrated Bone Marrow Aspirate (Monocytes and Mesenchymal Stem Cells-MSCs) Intramuscular Injection

Prochazka et al (2010) reported on a randomized study of 96 patients with CLI, and foot ulcers. Patient inclusion criteria were CLI as defined by an ABI score of 0.4 or less, ankle systolic pressure of 50 mm Hg or less or toe systolic pressure of 30 mm Hg or less, and failure of basic conservative and revascularization treatment (surgical or endovascular). Patients were randomized to treatment with bone marrow concentrate (n=42) or standard medical care (n=54). The primary endpoints were major limb amputation during the 120 days posttreatment, and degree of pain and function at 90- and 120-day follow-ups. At baseline, the control group compared with the treatment group had a higher proportion of patients with diabetes (98.2% vs 88.1%), hyperlipidemia (80.0% vs 54.8%), and ischemic heart disease (76.4% vs 57.1%), respectively. Additionally, the control group had a higher proportion of patients (72% vs 40%) with the University of Texas Wound Classification stage DIII (deep ulcers with osteitis). For the 42 patients in the treatment group, there was a history of 50 revascularization procedures; 46 of 54 patients in the control group had a history of revascularization procedures. All 42 patients in the bone marrow group finished 90 days of follow-up, and 37 of 54 patients in the control group finished 120 days of follow-up. Differences in lengths of follow-up for the primary outcome measure were unexplained. Five patients in the bone marrow group and eight in the control group died of causes unrelated to the therapy during follow-up. At follow-up, the frequency of major limb amputation was 21% in patients treated with bone marrow concentrate and 44% in controls. Secondary endpoints were assessed only in those treated with bone marrow concentrate. In the treatment group with salvaged limbs, toe pressure and Toe-Brachial Index score increased from 22.66 to 25.63 mm Hg and from 0.14 to 0.17, respectively. Interpretation of
results is limited by unequal baseline measures, lack of blinding, differences in lengths of follow-up, differences in losses to follow-up, and differences in follow-up measures for the two groups.

Benoit et al (2011) reported on a U.S. Food and Drug Administration-regulated, double-blind pilot RCT of 48 patients with CLI who were randomized 2:1 to bone marrow concentrate using the SmartPReP system or to iliac crest puncture with an intramuscular injection of diluted peripheral blood.8 At a 6-month follow-up, the differences in the percentages of amputations between the bone marrow concentrate group (29.4%) and diluted peripheral blood group (35.7%) were not statistically significant. In a subgroup analysis of patients with tissue loss at baseline (Rutherford 5), intramuscular injection of bone marrow concentrate resulted in a lower amputation rate (39.1%) than placebo (71.4%). Power analysis indicated that 210 patients were needed to achieve 95% power in a planned pivotal trial.

Intramuscular injection with a combination of bone marrow mononuclear cells (BM-MNCs) and gene therapy with a vascular endothelial growth factor plasmid were tested in a 2015 European RCT assessing 32 patients.9 Controls in this trial were treated pharmacologically, and therefore the groups were not blinded to treatment. Several objective measures were improved in the BM-MNC group but not in the control group. They included ABI scores, development of collateral vessels measured with angiography, and healing rates of ischemic ulcers. Amputations were performed in 25% of patients in the BM-MNC group and in 50% of patients in the control group.

Gupta et al (2017) evaluated the efficacy and safety of intramuscular adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeutics Research, Bangalore, India) in a phase II prospective, open-label dose-ranging study.10 Ninety patients were nonrandomly allocated to 3 groups: 1 million cells/kg body weight (n=36), 2 million cells/kg body weight (n=36), and standard of care (SOC; n=18). Compared with the SOC group, greater reduction in rest pain and healing of ulcers were seen in the 2 million cells/kg body weight group (0.3 units per month [standard error (SE): 0.13], CI: -0.55 to -0.05, p=0.0193 and 11.0% decrease in size per month [SE: 0.05%], CI: 0.80-0.99, p=0.0253, respectively) and in the 1 million cells/kg body weight group (0.23 per month [SE: 0.13], CI: -0.49 to 0.03, p=0.081 and 2.0% decrease in size per month [SE: 0.06%], CI: 0.87-1.10, p=0.6967, respectively). Limitations of this study included the geographically and ethnically homogenous cohort and a lack of clearly defined methods for cohort selection. Additionally, patients in the cell administration groups had lower ankle-brachial pressure index values and larger ulcers indicating potential investigator bias to allocate more severe patients to the treatment groups.

Section Summary: Concentrated Bone Marrow Aspirate (Monocytes and MSCs) - Intramuscular Injection
RCTs, a non-randomized comparative study and a retrospective chart review have been published.8 There is preliminary evidence of benefit to the use of intramuscular concentrated bone aspirate injection outcomes in CLI patients.

Intra-Arterial Injection
The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation trial was a randomized, double-blind, placebo-controlled study (2015) from Europe (NCT00371371).11 This foundation-supported trial evaluated the clinical effects of repeated intra-arterial infusion of BM-MNCs in 160 patients with nonrevascularizable CLI. Patients received a repeated intra-arterial infusion of BM-MNCs or placebo (autologous peripheral blood erythrocytes) into the common femoral artery. The primary outcome measure (rate of major amputation after 6 months) did not differ significantly between groups (19% for BM-MNCs vs 13% controls). Secondary outcomes of QOL, rest pain, ABI score, and transcutaneous oxygen pressure improved to a similar extent in both groups, reinforcing the need for placebo control in this type of trial. Results from a long-term follow-up analysis of 109 of the participants found improvements in self-reported QOL persisted for a median of 35 months in both groups, who remained blinded to treatment assignment.12 The percentages of patients undergoing amputation also remained similar in the 2 groups (25.9% for the BM-MNC group vs 25.3% for the control group).
Results from the multicenter Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease trial (2011) were reported. In this double-blind, phase 2 trial, 40 patients with CLI who were not candidates or had failed to respond to interventional or surgical procedures were randomized to intra-arterial administration of BM-MNC or placebo. The cell suspension included hematopoietic, mesenchymal and other progenitor cells. After three months, both groups were treated with BM-MNC in an open-label phase. Twelve patients received additional treatment with BM-MNC between 6 months and 18 months. The primary outcome measure (a significant increase in the ABI score at 3 months) was not achieved (from 0.66 at baseline to 0.75 at 3 months). Limb salvage and amputation-free survival rates did differ between groups. There was a significant improvement in ulcer healing (ulcer area, 1.89 cm² vs 2.89 cm²) and reduced pain at rest (an improvement on a 10-point visual analog scale score of >3 vs 0.05) following intra-arterial BM-MNC administration, respectively.

Section Summary: Concentrated Bone Marrow Aspirate (Monocytes and MSCs) - Intra-Arterial Injection

Two RCTs have been published 11,12. The RCTs did not find support for their respective primary outcome measures; the rate of major amputation after six months or a significant increase in the ABI score at three months.

Adverse Events

Jonsson et al (2012) reported a high incidence of serious adverse events in patients treated with peripheral blood mononuclear cells, causing the investigators to terminate the study.14. Of nine patients, two had myocardial infarction believed to be related to the bone marrow stimulation, one of whom died. Another patient had a minor stroke one week after stem cell implantation.

Expanded Monocytes and MSCs

Interim and final results from the industry-sponsored phase 2, randomized, double-blind, placebo-controlled RESTORE-CLI trial, which used cultured and expanded monocytes and MSCs derived from bone marrow aspirate (ixmyelocel-T), were reported by Powell et al (2011, 2012).15,16. Seventy-two patients with CLI received ixmyelocel-T (n=48) or placebo with sham bone marrow aspiration (n=24) and were followed for 12 months. There was a 40% reduction in any treatment failure (due primarily to differences in doubling of total wound surface area and de novo gangrene), but no significant differences in amputation rates at 12 months.

Granulocyte-Macrophage Colony-Stimulating Factor Mobilization

Poole et al (2013) reported on the results of a phase 2, double-blind, placebo-controlled trial of GM-CSF in 159 patients with intermittent claudication due to PAD.17. Patients were treated with subcutaneous injections of GM-CSF or placebo three times weekly for four weeks. The primary outcome (peak treadmill walking time at 3 months) increased by 109 seconds (296 to 405 seconds) in the GM-CSF group and by 68 seconds (308 to 376 seconds) in the placebo group (p=0.08). Changes in the physical functioning subscale score of the 36-Item Short-Form Health Survey and distance score of the Walking Impairment Questionnaire were significantly better in patients treated with GM-CSF. However, there were no significant differences between the groups in ABI score, Walking Impairment Questionnaire distance or speed scores, claudication onset time, or 36-Item Short-Form Health Survey Mental Component or Physical Component Summary scores. The post hoc exploratory analysis found that patients with more than a 100% increase in progenitor cells (CD34-positive/CD133-positive) had a significantly greater increase in peak walking times (131 seconds) than patients who had less than 100% increase in progenitor cells (60 seconds).

Horie et al (2018) reported an RCT of 107 patients with PAD characterized as Buerger disease that evaluated the efficacy and safety of GM-CSF-mobilized peripheral blood mononuclear cell transplantation compared with SOC.18. Participants were randomized to guideline-based SOC or SOC plus intramuscular weight-based peripheral blood mononuclear cell administration. After
disease progression or completion of a 1-year follow-up, 17 patients in the control group underwent cell therapy. Furthermore, 21 patients underwent revascularization after completion of the protocol treatment period or after discontinuation of the study (12 in the cell therapy group, 9 in the control group; 18 patients underwent percutaneous transluminal angioplasty, 2 had bypass surgery, and 1 had thrombectomy). Serious adverse events occurred in 20% of the cell therapy group compared with 11.3% of the control group (p=0.28). Leukopenia, alkaline phosphatase elevation, and hyperuricemia were determined to be adverse events related to GM-CSF administration. This study was limited to a small number of advanced cases (Fontaine stage IV cases (20.4%)), a high-risk group of hemodialysis patients and the high number of patients who did not complete treatment (cell therapy group: 38.5% control group: 50.9%).

McDermott et al (2017) reported an RCT of 210 patients with PAD that evaluated whether GM-CSF combined with supervised treadmill exercise improves 6-minute walk distance (6MWT) compared with exercise alone and compared with GM-CSF alone and to determine whether GM-CSF alone improves 6MWT more than placebo and whether exercise improves 6MWT more than an attention control intervention. Supervised exercise consisted of treadmill exercise three times weekly for six months. Participants were randomized to 1 of 4 groups: supervised exercise +GM-CSF (exercise +GM-CSF) (n=53), supervised exercise +placebo (exercise alone) (n=53), attention control +GM-CSF (GM-CSF alone) (n=53), attention control +placebo (n=51). The attention control consisted of weekly educational lectures by clinicians for six months. The primary outcome was change in 6MWT distance at a 12-week follow-up, with a minimum clinically important difference of 20 meters. 93% of patients completed a 12-week follow-up. At 12-week follow-up, exercise +GM-CSF did not significantly improve 6MWT distance more than exercise alone (p=.61) or more than GM-CSF alone (Hochberg-adjusted p =.052). GM-CSF alone did not improve a 6MWT more than attention control +placebo (p =.91). Exercise alone improved a 6MWT compared with attention control +placebo (Hochberg-adjusted p =.02).

### Table 3. Key Characteristics RCT Intramuscular GM-CSF PBMNCs for CLI

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horie (2018)</td>
<td>Japan</td>
<td>17</td>
<td>2009-2013</td>
<td>Patients with PAD, Fontaine classification II-IV (n=107)</td>
<td>Intramuscular GM-CSF, single dose of 200μg/m² per day for 4 days (n=52)</td>
<td>Guideline based Standard of care¹ (n=55)</td>
</tr>
<tr>
<td>Poole et al (2013)</td>
<td>(n=159)</td>
<td>subcutaneous GM-CSF three times weekly for four weeks</td>
<td></td>
<td>placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CLI: critical limb ischemia; GM-CSF: granulocyte-macrophage colony-stimulating factor; PAD: peripheral arterial disease; PBMNC: peripheral blood mononuclear cell; RCT: randomized controlled trial.

¹Includes the use of lipid, antihypertensive, antidiabetic, antithrombotic drugs, exercise, and prostanoids.

### Table 4. Results of RCT Intramuscular GM-CSF PBMNCs for CLI - 1 Year Follow-Up

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>PFS (95% CI)</th>
<th>Frequency of major limb amputation</th>
<th>New ulcer or gangrene</th>
<th>Serious AE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horie (2018) Impact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Therapy group</td>
<td>0.42 (0.13-1.36)</td>
<td>6.0%</td>
<td>18%</td>
<td>20.0</td>
</tr>
<tr>
<td>Control group</td>
<td>0.62 (0.28-1.36)</td>
<td>5.7%</td>
<td>15.1%</td>
<td>11.3</td>
</tr>
<tr>
<td>p-value</td>
<td>0.07</td>
<td>1.00</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

AE: adverse events; CI: confidence intervals; CLI: critical limb ischemia; GM-CSF: granulocyte-macrophage colony-stimulating factor; PBMNC: peripheral blood mononuclear cell; PFS: progression-free survival; RCT: randomized controlled trial.

Three RCTs have been published. 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 PFS and frequency of limb amputation at one year of follow-up. There was a substantial rate of subsequent surgical intervention in both arms.
Summary of Evidence
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. Three randomized controlled trials have been published that used granulocyte colony-stimulating factor mobilized peripheral mononuclear cells. 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 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.

Supplemental Information
Practice Guidelines and Position Statements

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

European Society of Cardiology
The European Society of Cardiology (2011) 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01049919</td>
<td>MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia (CLI) in Subjects With Severe Peripheral Arterial Disease (PAD) (MOBILE)</td>
<td>152</td>
<td>May 2020</td>
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<tr>
<td>NCT03304821</td>
<td>Granulocyte-Macrophage Stimulating Factor (GM-CSF) in Peripheral Artery Disease: the GPAD-3 Study</td>
<td>176</td>
<td>Jun 2022</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT02834858</td>
<td>Umbilical Cord Mesenchymal Stem Cell Infusion for Diabetes-Related Vascular Complications</td>
<td>240</td>
<td>December 2019</td>
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<tr>
<td>NCT02685098</td>
<td>A Clinical and Histological Analysis of Mesenchymal Stem Cells in Amputation (CHAMP)</td>
<td>16</td>
<td>September 2025</td>
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<tr>
<td>NCT03339973a</td>
<td>Allogenic ABCB5-positive Stem Cells for Treatment of PAOD</td>
<td>76</td>
<td>March 2020</td>
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<tr>
<td>NCT03809494a</td>
<td>HemaTrate™ in the Treatment of Critical Limb Ischemia</td>
<td>350</td>
<td>January 2026</td>
</tr>
<tr>
<td>NCT02805023a</td>
<td>Assessing the Feasibility of BCG101 in the Treatment of PAD and CLI (EnEPC-CU)</td>
<td>30</td>
<td>December 2019</td>
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<tr>
<td>NCT02551679a</td>
<td>ACP-01 in Patients with Critical Limb Ischemia</td>
<td>95</td>
<td>December 2020</td>
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<tr>
<td>NCT01483989a</td>
<td>An Efficacy and Safety Study of Ixmyelocel-Tin Patients With Critical Limb Ischemia (CLI) (REVIVE)</td>
<td>594</td>
<td>Apr 2014 (last update posted Aug 2018)</td>
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<tr>
<td>NCT01245335a</td>
<td>Pivotal Study of the Safety and Effectiveness of Autologous Bone Marrow Aspirate Concentrate (BMAC) for the Treatment of Critical Limb Ischemia Due to Peripheral Arterial Disease</td>
<td>97</td>
<td>Nov 2015</td>
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<tr>
<td>NCT02538978a</td>
<td>Safety and Effectiveness of the SurgWerks™-CLI Kit and VXPTM System for the Rapid Intra-operative Aspiration, Preparation and Intramuscular Injection of Concentrated Autologous Bone Marrow Cells into the Ischemic Index Limb of Rutherford Category 5 Non-Reconstructable Critical Limb Ischemia Patients</td>
<td>224</td>
<td>Mar 2019 (last update posted 2016 not yet recruiting)</td>
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<tr>
<td>NCT01679990a</td>
<td>A Phase II, Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled, Parallel-Groups Study to Evaluate the Safety and Efficacy of Intramuscular Injections of Allogeneic PLX-PAD Cells for the Treatment of Subjects With Intermittent Claudication (IC)</td>
<td>172</td>
<td>April 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

References


Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td></td>
<td>0263T</td>
<td>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</td>
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<td>0264T</td>
<td>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</td>
</tr>
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<td>0265T</td>
<td>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</td>
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</table>

HCPCS

None

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>01/11/2013</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>06/30/2015</td>
<td>Coding update</td>
</tr>
<tr>
<td>01/01/2016</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>09/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>04/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>04/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>03/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
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</table>
Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member’s illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 35077 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.